Cases and Tools in Biotechnology Management

# Cases and Tools in Biotechnology Management

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# Contents

PART I

# MAIN BODY

# 1. Zenify Your Presentation example

**Zenify Your Presentation**
**BUS*6050 Management Communications • May 2017**
**Dr. Trent Tucker • University of Guelph • @ProfTucker**

The purpose of this document is to provide additional information and resources about improving your presentations using the ideas of Garr Reynolds and others. It is also designed as a document to accompany the presentation versus the usual 6-thumbnails to a page PowerPoint "notes" you often see! I have to practice what I preach!

## Resources:

I'll be presenting ideas from Garr Reynolds' books and website, namely:

- Presentation Zen: Simple ideas on presentation design and delivery (2nd edition, 2012)
- The Naked Presenter: Delivering powerful presentations with or without slides (2011)
- Presentation Zen Design: Simple design principles and

techniques to enhance your presentations (2nd edition, 2014). Most of the references in this document come from "PZD2".

I'd suggest adding Reynolds' @presentationzen handle to the list of people you follow on Twitter. His website: www.presentationzen.com is a good source of information and ideas. His document, www.garrreynolds.com/Presentation/pdf/presentation_tips.pdf, is an excellent summary of the key ideas from his books. Finally, spend an hour online and watch his **Authors@Google** talk at: www.youtube.com/watch?v=DZ2vtQCESpk—well worth the time.

*A YouTube element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/bio16610w18/?p=57*

Here are some other resources I find extremely useful:

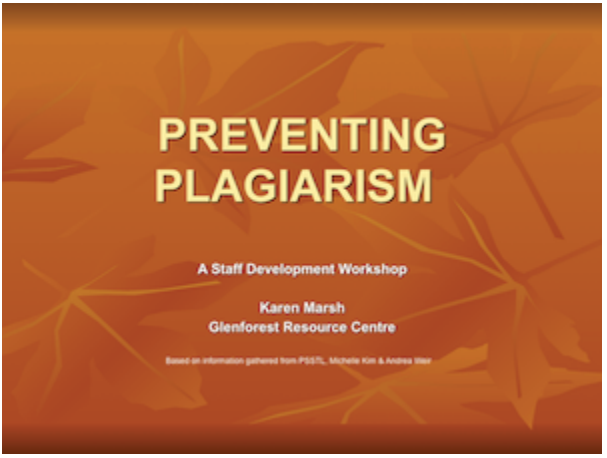
- • Slide:ology—the art and science of creating great presentations (Nancy Duarte, 2008)
  • Resonate: Present visual stories that transform audiences (Nancy Duarte, 2010)
  • Harvard Business Review HBR Guide to Persuasive Presentations (Nancy Duarte, 2012)
  • The Cognitive Style of PowerPoint (Edward Tufte, 2003) from edwardtufte.com website.

The presentation I'm going to "Zenify" is entitled "Preventing Plagiarism" and was authored by Karen Marsh of Glenforest Secondary School in Mississauga (Peel District School Board). It can be found online at: schools.peelschools.org/sec/glenforest/SiteCollectionDocuments/combattingplagiarism.ppt. Karen has kindly granted me permission to subject her work to the "Zenification" process.

## Less is More

A recurring theme in Reynolds' work is simplify. "Simplify as much as you can—but no more" is design principle #12 (PZD2, p. 17). He makes observations like "simplicity is our guiding principle" and "if you can do it with less, then do it with less" (ibid). This idea is reinforced with his design principle #8: "Think communication—not decoration," further reinforced by the suggestion that we "minimize or eliminate that which is excess" (PZD2, p. 15).

The following four slides from my presentation illustrate this "Less is More" philosophy applied to the title slide of the presentation…


PREVENTING
PLAGIARISM
A Staff Development Workshop
Karen Marsh
Glenforest Resource Centre

(A)


Preventing Plagiarism
Staff Development Workshop • Karen Marsh

(B)


(C)


(D)

(A) This is the original slide. The presentation used PowerPoint's "Maple" theme throughout. The maple leaves in the background don't add anything to the meaning or the topic and distract the viewer. The extremely small (Arial, 10pt) text which reads "Based on information gathered from PSSTL, Michelle Kim & Andrea Weir" at the bottom of the slide can be removed. The information can still be conveyed by the speaker, but doesn't have to reside on a slide.

(B) For this first zenification, I used a stock photo image of a classroom chalkboard. This connotes an academic setting–the image

reinforces the message rather than detracts from it like the leaves did. The background colours, blue and black–while 'cold'–connote an authoritative and professional tone. The title, subtitle, and presenter information from the original slide remain, but additional information like affiliation has been removed. The title text has been changed from an aggressive ALL CAPS style to a softer Title Case style.

(C) Another stock photo of the same classroom, this time with natural light flowing in. It has a 'warmer' feel to it than the blue classroom, a lighter tone for this talk. I also changed the font to "Chalkduster" to give it a more homey / 'classroom-y' feel. Choose images and graphics that reinforce the messages you wish to communicate. Start with the end in mind–what is it you are trying to convey–and work all of the slides for this purpose.

(D) This version of the title slide is simple and elegant. What is the purpose of a title slide? It is on the screen as people come into the room so they know they are in the right place. It introduces the topic and presenter–nothing more. This bare-bones approach meshes with that purpose. ? There is no right or wrong way to zenify a presentation–these are applications of Reynolds' ideas to an existing slide deck–however, it all gets back to "what is the purpose of my presentation?"

# 2. Sign-up for LifeScanner Live Case topic...

Use the following document to sign-up for the LifeScanner Live Case topic of your choice. Please limit team size to a maximum of **four people**.

| | | |
|---|---|---|
| Supply Chain | Price Point | Customer Development |
| Louis, Arsalan, Allan, Rashmi | TBD | Felix, Matt, Kevin |
| Competition | White-Label | Education |
| Viola, Maham, Amna, Adrienne | Cherry, Aman, Naheen | Madison, Tanisha, John, Luka |
| Wildlife Crime | Bootstrap the Business | Customer Engagement |
| TBD | TBD | TBD |

# 3. Turing Pharmaceuticals: a glimpse into controversial drug pricing.

## Turing Pharmaceuticals: a glimpse into controversial drug pricing.

By Michel Saba

### Introduction

In 2015, an act of greed hidden under the mask of good samaritanism backfired and resulted in the whole planet talking about controversial drug pricing. Martin Shkreli, the CEO of Turing Pharmaceuticals at the time, was under the spotlight of global media after he greatly increased the price of an antiparasitic drug prescribed to people with compromised immune systems (including those living with HIV). For several years, the story uncovered many flaws in the pharmaceutical industry. Although increased prices were attributed to crucial drug research that needed funding, the public quickly realized there was a missing piece to the puzzle. The scope of this controversy widened to Big Pharma which resulted in many bigger questions being asked.

## Turing Pharmaceuticals

Turing Pharmaceuticals was a Swiss-incorporated company founded on the 24th of February 2015 by Martin Shkreli. Their first acquisitions were from Retrophin (a company previously founded by Shkreli): an intranasal formulation of ketamine, an oxytocin nasal solution, and Vecamyl. During the same year (August 5th), Turing raised millions of dollars in Series A funding (United States Securities and Exchange Commission, 2015a) which was presumably used to acquire the rights to Daraprim (pyrimethamine) from Impax Laboratories on August 7 (United States Securities and Exchange Commission, 2015b). Daraprim is an antiparasitic drug approved by the FDA in 1953 (AIDSinfo Database). It targets toxoplasmosis and is mainly given to patients with a compromised immune system. This includes HIV and cancer patients as well as the elderly. After its acquisition, Turing pharmaceuticals increased the price of Daraprim from $13.50 a pill to $750 (a %5455 increase). As a result, the cost of treatment using Daraprim increased to $336,000 or $634,500 (IDSA and HIVMA, 2015) depending on the patient's weight (below or above 60 kg respectively).

The news media wave that was started by Healio (2015) and USA Today (Rushton, 2015) was instantly picked up by global media. What started off as the scrutiny of Shkreli's decision extended to that of Pharmaceuticals' drug pricing policies.

## Stakeholders

Many groups were affected by this price hike. First and foremost, the patients who were dependent on this drug were those who were most affected. Although the disease is not very common in the US (only 2,000 patients), Daraprim is a generic drug and unfortunately

the only one available with its function. This means that people in need of Daraprim either had to deal with the costs or turn to other alternatives that are not as effective. To make matters worse, individuals who do not have insurance usually have other barriers to healthcare (such as transportation and stigma) (Healio, 2015)

Consequently, this affected other groups such as insurance companies who cover those costs. Following such a price increase, those companies increase their rates and therefore society as a whole ends up indirectly paying for it via more expensive insurance plans. Moreover, the fact that the drug was less affordable meant that hospitals had low inventory for the drug and there was, therefore, high demand for it. This was a similar situation when considering assistance programs (Georgia Aids Assistance Program) which informed those who used their services that they lacked the supply of the drug.

Additionally, the stock market was also affected by Shkreli's decision. After the news went viral, Hillary Clinton addressed the issue on Twitter, mentioning her intentions of taking on drug market pricing. This resulted in a decrease in biotech stocks, which affected multiple pharmaceutical companies (Egan, 2015).

Although Turing pharmaceuticals claimed they did not intend to decrease their prices, they stated that they were developing a corrective plan to ensure that patients had access to Daraprim (Healio, 2015). This included a 50% discount to hospitals treating patients with toxoplasmosis.

## Price Justification

These events begged the question: what is the reasoning behind these price hikes? What is the justification?

Renowned biotech writers such as Andrew Pollack at the New York Times (2015a) and John Carroll at FierceBiotech (2015a; 2015b) not only questioned the actions of pharmaceutical companies but also criticized their "generic" responses. When asked why Turing Pharmaceuticals increased the price of Daraprim, Martin Shkreli (as well as other Turing Pharma representatives) explained that the money gained would be allocated to research and development revolving around the treatment of toxoplasmosis. While the statement itself makes sense, it seems that it was not an honest one but only the umbrella under which pharma greed stands under. Wendy S. Armstrong, the vice chair of HIVMA, said that "this is not an infection where we have been looking for more effective drugs". The drug was already effective, requiring only one pill a day, and having very manageable side effects (Healio, 2015). On the other hand, Shkreli mentioned how Daraprim is underpriced relative to its peers and questioned why other companies were not being criticized for having done the same act. The issue with this response was that the peers Shkreli was referring to, were treatments to diseases such as cystic fibrosis and cancer. One cannot compare Daraprim to those drugs since the former is a generic drug (the patent expired in 1953) while the latter is still under ongoing patents. Moreover, these drugs are a product of recent research, while Daraprim has been very effective for many decades. No drug has yet been released as an alternative/improvement to Daraprim which further supports the hollowness of the argument given by Turing. It is becoming more apparent that such valuations of drugs might not be of pure developmental causes. This is supported by statements from Shkreli on twitter (Carroll, 2015b) and during a Forbes Healthcare Summit (Forbes, 2015): "This is a great business decision that also benefits all of our stakeholders"; "my shareholders expect me to make the most profit [...] that's what people [in healthcare] are afraid to say". Although immoral, Martin Shkreli's actions had a silver lining. Had he been political with his responses and had answered with the usual

"no comment" or "our prices reflect the value we generate to our patients", the events would have progressed very differently. There wouldn't have been such an explosion of public outcry, and big pharma could have passed somewhat unnoticed. But Shkreli didn't hold back and the public's attention has since then been focused on the drug pricing process.

Inspecting other pharmaceutical companies, it is obvious that many treatments of serious diseases are quite expensive: Gilead Sciences produces a Hepatitis C drug that sells for $1,000 a pill; Kalydeco, a cystic fibrosis drug from Vertex, surmounts $300,000 in yearly treatments; Celgene's Revlimid costs around $150,000 for patients combating cancer. These charges are staggering either because the company owns the patent and therefore is the only one capable of selling that specific drug (no competition means no decrease in prices) or because there is some sort of unspoken agreement between companies where they set prices at a certain level so that all companies benefit. The latter is best explained by an anonymous statement from a director of multiple sclerosis drug development: "we all look at each other and keep pace with each other". Meaning that, aside from the obvious fact that there is a substantial amount of money being spent on research and development, valuations are set at what the market is willing to pay. Prices are hiked to the point of maximal possible profit where all companies would benefit while avoiding harmful public attention. This ceased to be the case when Martin flew a bit too close to the sun. When politicians started getting involved, initiatives to increase transparency of company expenditures began to gain traction. Both Clintons took their concerns to the public. As mentioned earlier, Hillary Clinton stated her desire to tackle big pharma followed by concrete actions to amend drug policies (Staton, 2015). Moreover, at a pharmaceutical event, Bill Clinton made a speech to executives in Philadelphia appealing for them to "explain, explain, explain and

disclose, disclose, disclose". He said this would allow the public to better understand pharma's stand on high prices (given that pharma is granted the benefit of the doubt regarding R&D spending) but also allow better policy results. Consequently, multiple bills were put forth with the objective to increase cost transparency. This would allow the public, insurers and the government to examine and justify said spendings. This includes developmental costs, money spent on manufacturing and marketing, pricing history, profits, and assistance program funding (Pollack, 2015b). More importantly, these bills would not only require these reports but would also allow companies (i.e. insurance) and the government to act upon the information. That being, it would allow an insurance company to deny the purchase of a drug in the case of missing information, or even allow the government to set a maximum price for a drug. Although pharmaceutical companies are required to disclose payments spent on doctors to conduct research, give speeches and consult, these mentioned bills did not pass. Government officials stated the bills did not have sufficient support or that it was "not ready for prime time". As ridiculous as that may sound, we cannot condemn big pharma without having concrete proof of funds misuse. What if, the information was indeed misleading? Since the developmental costs of drug research ignored the money spent on drugs that did not make it to market. Unfortunately, we cannot be sure until we get a glimpse behind big pharma's closed curtains.

This brings us to a real head-scratching moment. In order to gain insight into pharmaceutical expenditures, we must use the law to gain access. That being, the government must be on the public's side in order to have law reforms. In our case, the government is backing such bills yet is still failing to have them passed. As it turns out, there are people "above" the government: puppeteers that pull the right strings to get their way, big pharma's way.

## Political Lobbying

For around ten years, Big Pharma has spent around $2.5 billion to lobby the government regarding issues that include drug pricing (OpenSecrets, 2018). For instance, the industry supported presidents on the condition that lower drug prices would not be negotiated, or even made sure that Obamacare did not include any drug pricing reforms (allegedly; Morgan, 2018). Of course, this cost a lot of money. PhRMA (Pharmaceutical Research and Manufacturers of America) and BIO (Biotechnology Innovation Organization), which are trade associations representing the US' largest drug manufacturers and biotech companies, were involved in $277 million spent in 2017 alone for federal government lobbying (OpenSecrets, 2018).

This is not limited to trade organizations as there are many individual companies that support the cause. For example, Mylan, an American drug manufacturer, lobbies issues regarding drug pricing in order to maintain profits. Their interests are reflected in their price increases over the past couple of year. Ironically, these increases are very similar to those of Turing Pharmaceuticals, yet were not covered as extensively by the media. This company had increased the price of an asthma drug by 4,014% over a year, the price of a heart medication by 573% over a year, the price of a cancer drug by 100% over two years, and the price of the EpiPen by 500% over seven years (Morgan, 2018). Again, the increased price of the EpiPen did not result in an improved product, even though company officials might say the money was allocated to the development of other drugs. Moreover, when considering such drugs that are required by law in schools, it is taxpayers that end up having to pay the price.

Drug pricing lobbying is a major issue in the united states. A study by CREW (Citizens for Responsibility and Ethics in Washington) found that there were around 153 companies lobbying drug pricing in 2017 alone (a four-time increase over the past couple of years; Morgan,

2018). Among the 153 companies, 22 were among Forbes' top 25 largest pharma/biotech companies on the planet (including the previously mentioned Gilead Sciences; Jurney, 2016).

## Conclusion

There is fortune in all misfortune. Although the increased price of Daraprim had wide negative consequences, it allowed us to take a step back and see the bigger picture. The public realized that the lawful drug increase was a symptom and not the disease. We find through evidence that with the use of large amounts of money, the U.S. government is being swayed by Big Pharma in order to subdue drug pricing bills. It is an ugly truth that needed to be known in order to start making reforms. Many government officials have taken a stance against such events but have not yet succeeded. As time goes by, there will certainly be some changes that could satisfy both parties. As a final note, citizens need to be more attentive of how large companies are involved in the government.

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PART II

# PART I • TOOLS

Tools to help Masters in Biotechnology students with presentations, business data management, case analysis, etc.

# 4. Chapter 1 • Presentations

Presenting data and information is a valuable skill...

# 5. Quick Start Guide for Bloomberg® Professional

Kevin Romanick, Felix Rheude, Matthew Guilleman

## General Information

### *Purpose of the Quick Start Guide*

The purpose of this quick start guide is to provide the information necessary for students to gain access to a Bloomberg® terminal, and to find company and market information necessary for building a business case related to biotechnology. Finally, stepwise instructions are provided for exporting data to be used in external softwares such as Excel.

### *Company Information*

Bloomberg® was founded in 1981 by Michael Bloomberg. The company describes itself as "global information and technology

company" (Bloomberg® Finance L.P. 2018). The company provides online information about finance, economics and news regarding compliance, research and legal regulatory (Forbes Media LLC 2017). This Quick Start Guide focuses on the division "Bloomberg® Professional", which provides specific financial information about companies and markets worldwide. The provided information are available in both real-time and historic numbers.

## *Terminals*

Access to the Bloomberg® Professional Program is only given through Bloomberg® Terminals. The University of Guelph has a total of 11 terminals (Library University of Guelph 2017). They can be found in the Data Research Centre on the second floor in the McLaughlin Library as well as in Day Hall Rm. 101 (Library University of Guelph 2017). Whereas the terminals in the library are accessible for everyone during the opening hours of the library, the ones in the Day Hall are only accessible by key granted from the main office of the Department of Economics and Finance (Library University of Guelph 2017).

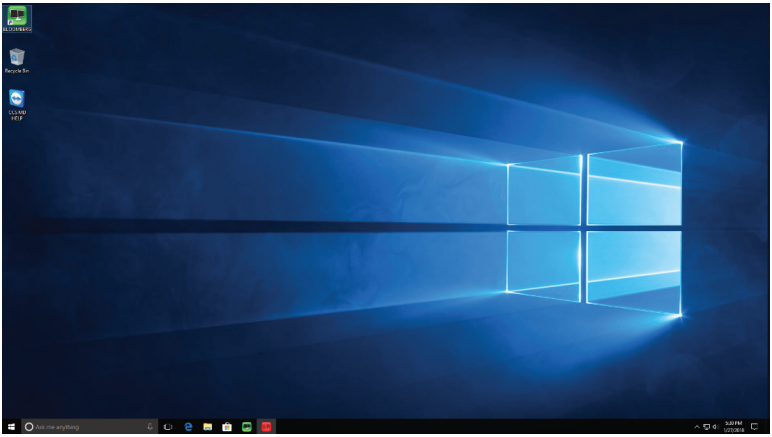
Day Hall Access:

To gain access to Day Hall you must have your card activated to be able to open the doors. Sharon Lee will be able to do this for you. Her office is located on the 7th floor of McKinnon. If you inform her of your name program, and why require access she will provide you with access the following day.

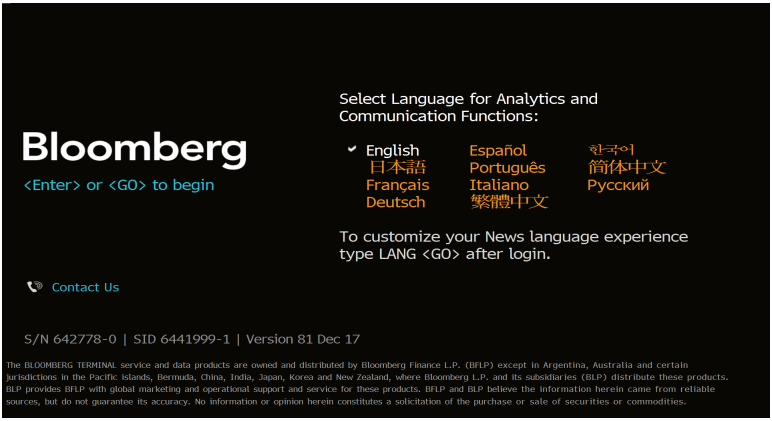
Sharon Lee's contact info and office number can be found at:https://www.uoguelph.ca/business/people/sharon-lee

*Picture 1 & 2: Day Hall at University of Guelph and McLaughlin Library at University of Guelph*

# First steps

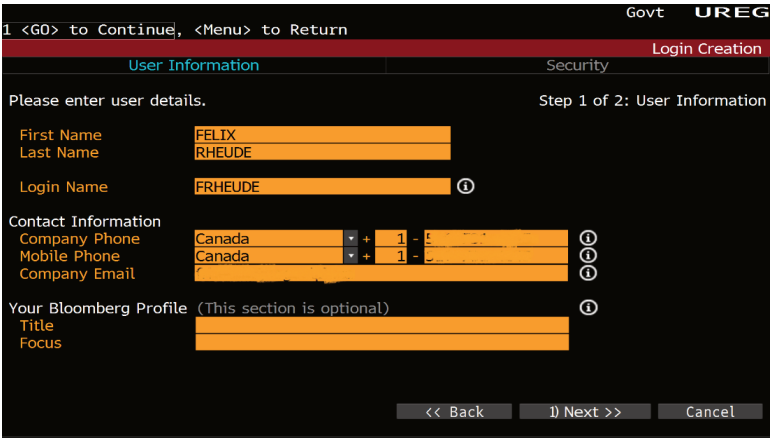


*Picture 3: Desktop of the Bloomberg terminal with the button  to start Bloomberg in the top left corner*



*Picture 4: Starting screen of the Bloomberg Professional program*

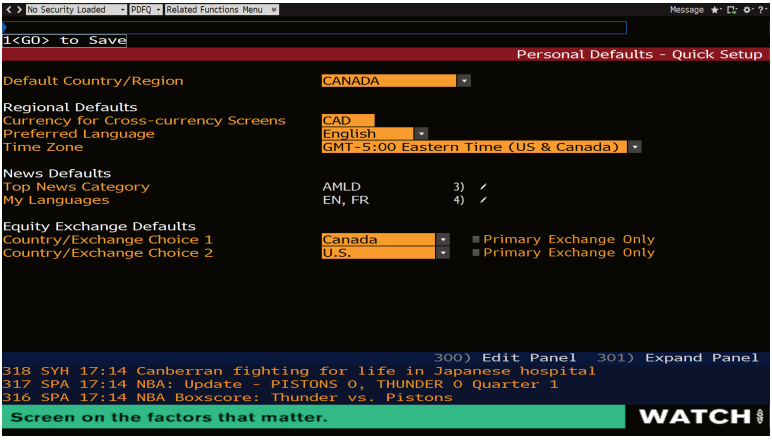
Before having access to the terminal, students have to make their own accounts. Therefore students have to enter their name, email-address, country and phone number.

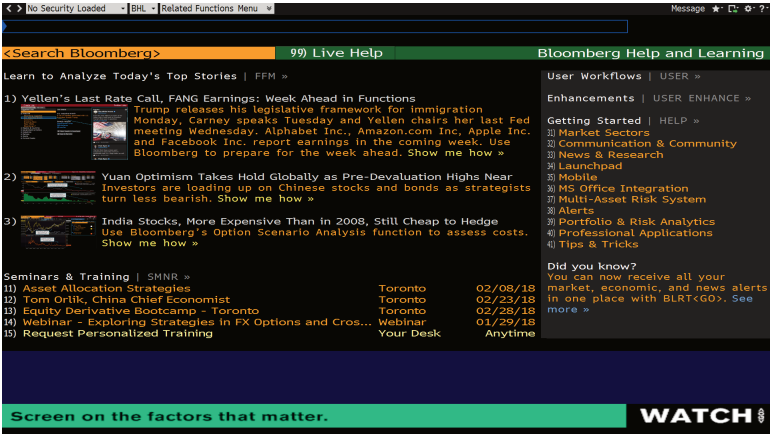



*Picture 5: Required information to create an account in Bloomberg*

After entering these details, a text message will be sent to the phone with a short numerical code to verify their account.

After these steps the following screens show up.




*Picture 6,7: Starting screens of Bloomberg after login. In the upper part of the pictures the command line can be seen.*

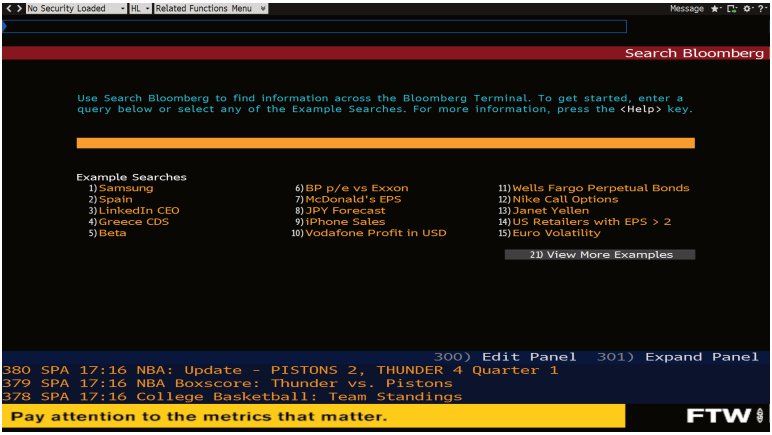
# Search functions of Bloomberg

In the upper part of this screen a command line can be seen. This command line can be used to find

1. Functions
2. Securities
3. Further information

Provided by Bloomberg®, functions are applications, which show "analysis and information on securities, sections, regions and more" (Bloomberg® Finance L.P. 2012). Securities on the other hand, are stocks and bonds, which can be analyzed using the Bloomberg® tools.

The third option, is the preferred method in this report. When entering "HL" in the command line, the comprehensive help search function opens (Bloomberg® Finance L.P. 2012). By entering the company name (e.g. Monsanto) or the market (e.g. Biotechnology) information about these search keywords are displayed.




*Picture 8: Command Line after entering "HL" to get to the comprehensive help search function opens*

A short video by Matthew Minnis describing how to use basic commands and perform basic searches on the Bloomberg® terminal is available at Youtube.

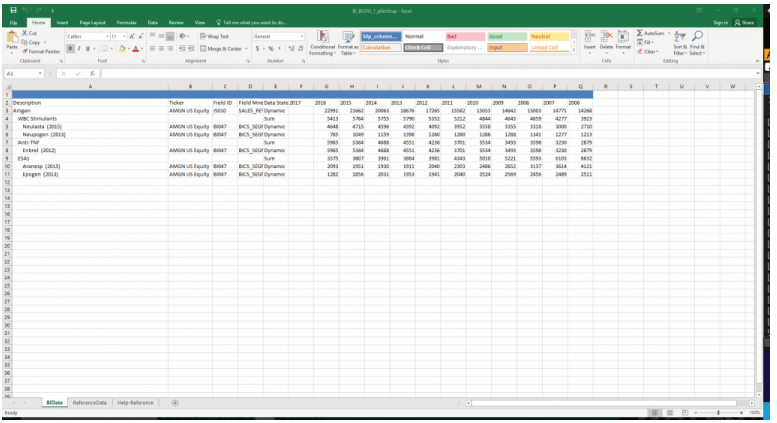
## Exporting Data

After the desired information is found, the data can be exported to Excel following these steps.

1. In the left corner select "91) Actions"
2. Select "Export to Excel;"
3. Select all the rows with a checkmate to download
4. Select "91) Export" in the left corner
5. All checkmated information will be shown in an excel

spreadsheet





*Picture 9, 10, 11, 12: Screens following step 1 to 5. Exporting data to Excel using Bloomberg®*

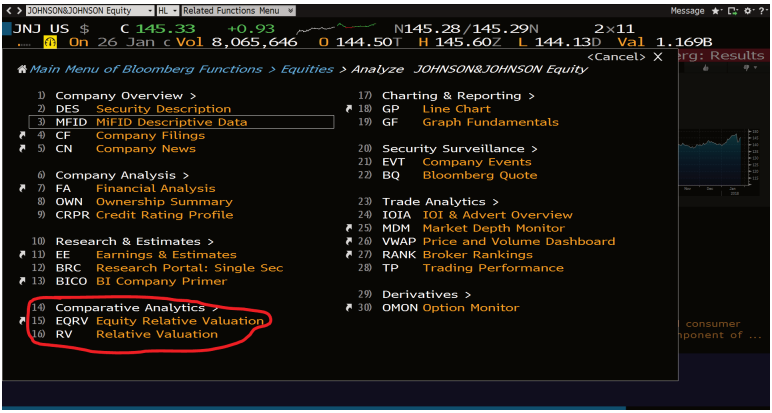
It is important to know that these excel data cannot be used on computers without Bloomberg® Professional application.

## Industry and Company Analysis Tools

Bloomberg® is a powerful tool for conducting a market and competitor analysis. To conduct a market analysis, enter the company of interest into the comprehensive search function (HL). In this example, we use Johnson & Johnson as the company of interest.

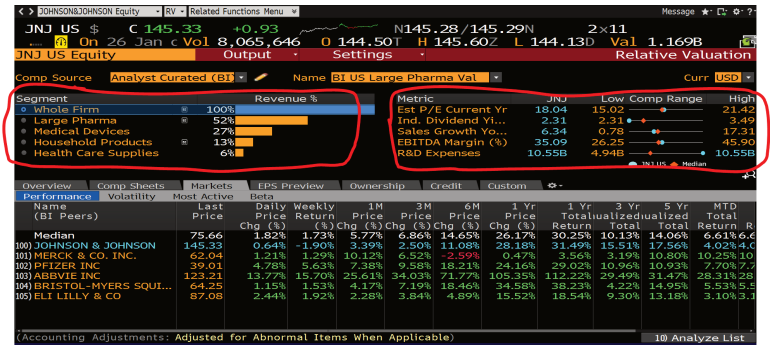

*Picture 13: Initiating company and industry analyses.*

Select the desired company from the search results and select the desired function from the main menu. To conduct a market analysis, select Relative Valuation from the comparative analytics subheading.




*Picture 14: Main menu options for conducting market analyses.*

Explore the industry information presented in the Relative Valuation section. Product segments are provided on the upper left screen, while company performance metrics are presented on the upper right screen.



*Picture 15: Product segments and performance metrics.*

Three short videos by FinTute are extremely helpful when trying to learn the fundamentals of company analysis and industry analysis. These can be found at the following links:

- Company Analysis

    1. Part 1
    2. Part 2

- Industry Analysis

    1. Video 1

## Finding Financial Information

When using the comprehensive search function and entering a company's name, the following screens appears (example Johnson & Johnson):

*Picture 16: This screen appears, after entering Johnson & Johnson*


*Picture 17: After selecting on Johnson & Johnson in the middle of the previous picture, this screen appears*

*Picture 19: After selecting "70 FA Financial Analysis" the screen with financial information highlights about the company shows up. In the upper part of the screen you can see the different taps showing the income statement (I/S), balance sheet (B/S) and cash flow statement (C/F).*

## Summary

For more information about the usage of the Bloomberg® terminals the following two sources can be obtained:

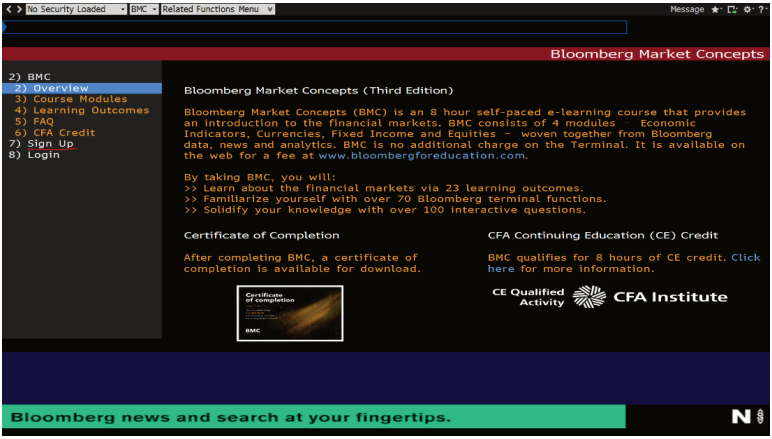
1. Getting Started Guide for Students.The guide is available as physical copy in the DRC and as a digital copy by following this link (Bloomberg – Getting Started)
2. An eight hour tutorial provided by Bloomberg® called Bloomberg® Market Concepts.The Bloomberg® Market Concepts course is an interactive e-learning module you can work on at your own pace to fully understand how to use many functions within the Bloomberg® terminal and how to find business and market specific information for analysis. Once registered your account is active for one full year giving you plenty of time to explore the four modules on economic indicators, currencies, fixed income and equities.

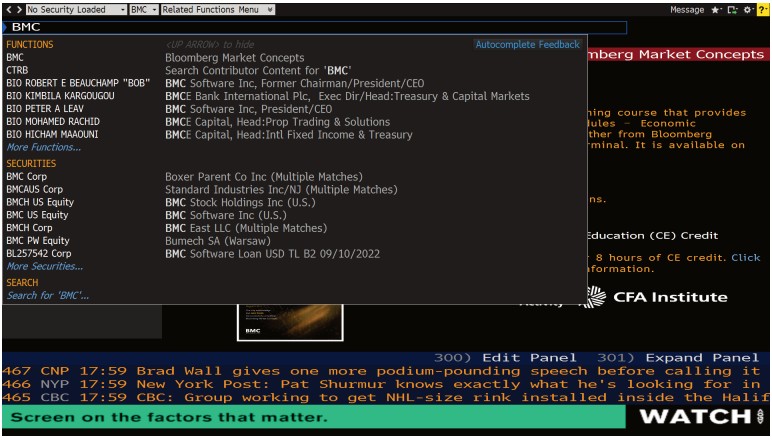
   This tutorial can be found in the Bloomberg® terminal when searching for "BMC" in the command line

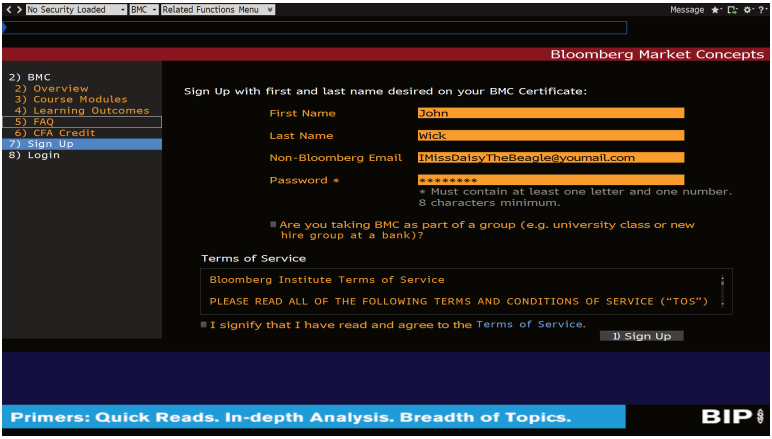
Once on the BMC homepage select the sign up tab located in the top left side of the page. If you receive a professor sign up pop-up message select the "Continue as Learner" option in the lower right.

Fill out the form with your personal info and a valid email address. "Read" the terms and conditions and select the "1)Sign Up" option and you will be redirected to a page asking for an activation code. An e-mail will be sent with a case-sensitive activation code to the email provided.

All that is left is logging in to the Bloomberg® Market Concepts using the e-mail and password you provided in the registration step.






*Picture 20, 21, 22: Screens following step a to d. Getting Started with Bloomberg® Market Concepts*

## Bloomberg® as a Case Creation and Analysis Tool

*Pros*

- Incredible amounts of information on a wide variety of businesses
- Generally provides a good overview of public company information
- Information is sectioned into convenient Company Analysis and Company Overviews
- Information can easily be exported into excel for further analysis or graph creation
- Many great shortcuts/commands to use to navigate easily, and efficiently

- Very convoluted at
  is relevant to your
- Navigation on the B
  first use
- Day Hall can be ver
- There are limited m
  students)
- Many of the Bloomb
  (requires permissio
- Private Company In

## Cons Mitigation

- Helpful tools exist that can help with the stress of accessing and navigating the Bloomberg® terminal including this helpful startup guide.
- Avoiding peak hours in Day Hall or the DRC would allow for a much more peaceful experience at the terminals. Peak Hours 10:00 am – 6:00 pm Monday through Friday. From our experience there are very few terminals in use on weekends and suggest going at that time

# Appendix

## Useful Commands

General Commands

- HL – Comprehensive Search
- MAIN – returns a list of categories encompassing various markets
- N, TOP – Real Time News
- BLAW – Legal Search
- LAST – Returns the last eight pages you've visited

Equity Commands

- DES – Returns descriptions
- CN – Company specific news
- DVD – Dividends
- CF – Corporate Filings
- FA – Financial analysis
- HDS – All large shareholders
- RV – Relative valuation against competition
- ERN – Earnings summary
- HP – Historical pricing and volume

## Useful Keys on the Bloomberg® Keyboard

Help – Opens a list of helpful functions and if pressed twice in quick succession it will contact Bloomberg® support

Menu – Returns to the page previously visited

News – Opens recent news in the current browser

Search – Opens the comprehensive search function

## Important Valuation Terms

The following numbers are key for the valuation of a company and should help to understand the presented data by Bloomberg as well as help to create the business case.

- Profit margin:
  - Divide net income by sales
  - Shows how well a company is able to make revenue from its sales

- Current and Past earnings per share (EPS)
  - Earnings available to common shareholders divided by the number of shares outstanding.
  - Growing EPS often leads to an appreciation in share price. It is a useful indicator of a company's profitability

- Price-to-earnings ratio (P/E)
  - Divide the current stock price by the EPS
  - Critical in valuing investments and useful to visualize the earning potential of companies to potential investors.

- Payout Ratio
    - Dividend per share divided by earnings per share
    - Percentage of earnings is paid out immediately as dividends (McGraw-Hill Education, 2013)

- Debt-to-total-Asset
    - Total Debt divided by Total Asset
    - Shows, how much of the company is financed by debt (McGraw-Hill Education, 2013)

- Market Capitalization
    - Amounts of shares times their value
    - Shows how much a company is worth on the market

## Important Financial Documents

Balance Sheet:

A balance sheet gives information about the company at a specific date. It shows the assets as well as the liabilities and shareholder's equity of a company (McGraw-Hill Education, 2013).

Cash Flow Statement:

The statement of cash flows shows the uses and sources of cash in a company from the start of the financial year to its end (McGraw-Hill Education, 2013).

Income Statement:

The income statement shows the profitability of a company over a certain time (McGraw-Hill Education, 2013).

10-K Form:
The so-called 10-K Form is an annual report of a public company for the United States Securities and Exchange Commission. The form shows a comprehensive financial statement of the company from the last year including and not limited to the income statement, balance sheet, and cash flow statement.

8-K Form:

A form, which provides brief information important for shareholders or United States Securities and Exchange Commission. The form usually has a heading, a short text describing the situation and sometimes additional information related to the heading (e.g. financial statements). The events, when a 8-K occurs could be a change at the top of the company or a bankruptcy.

## *Exercise in Bloomberg® Data Collection*

Using the Bloomberg information discussed in class, complete the following question set using the Bloomberg terminal.

1. In the third quarter of 2017, Apple had a net income (loss) of _____ $.
2. Johnson & Johnson had total assets of _____ $ in 2015.
3. Novartis had a Cash Flow of _____ $ in 2016.
4. What percentage of GlaxoSmithKline PLC's legal disputes fall under the "Patent" category
5. Biotechnology is defined as:

   _____
   _____
   _____
   _____
   _____
6. The largest shareholder of Amazon Inc. is _____
7. What were the total debts of the Trump Organization Inc. in 2015?
8. What is the expected compound annual growth rate of CRISPR in 2018?
9. What is the current stock price of Biogen Inc.?
10. According to a filing January 31st 2018, the board of directors of Orexigen Therapeutics Inc

approved a bonus of _____$ to their President and CEO

_____

11. When did Editas Medicine Inc last file a 10-K _____ and what word does the first letter of each of their values spell out.

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# 6. Porter's Five Forces

AMNA A., MAHAM H., VIOLA H., RASHMI K.

## An Open Educational Resource

Porter's Five Forces is a framework used to analyze the balance of power within a particular industry and therefore, its overall profitability. These outline 5 forces that drive competition and threaten the company's ability to make profits.

Created by Michael E. Porter of Harvard Business School in the 1970s, Porter's Five Forces sets out to answer questions such as: What's going on out there in your industry? What deserves your attention? Of the many things that are happening, which ones matter for competition? It is able to determine how different parts of an industry interact in order to allow for profitability without changing the level of quality of the product or services provided by industry. It is also able to determine how changes within an industry can affect a given sector. Porter's 5 forces are therefore used to predict industry trends and changes in competition, and this information can help a company to make strategic decisions about the industry to gain/ maintain status within it.

The Five Forces consist of Industry Rivalry, threats of potential entrants, threats of substitutes, strength of buyer power and strength of supplier power. As you can see in Figure 1, four of the forces feed into Industry rivalry.

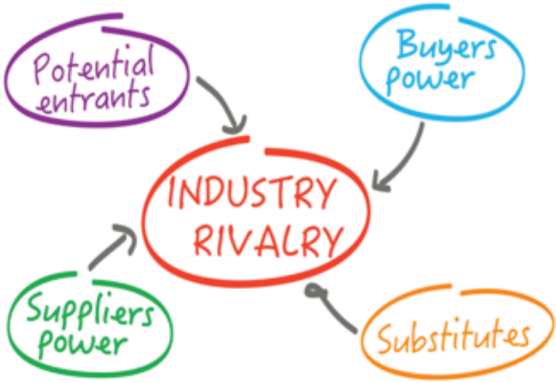


*Figure 1: Porter's Five Forces (Michaux, 2015)*

Buyer's Power

Buyers have the ability to influence the decision-making process of a company. Buyers with a lot of power can force prices down or demand that the company put more value into a service or product. Buyers are able to gain all the value for themselves, consequently decreasing profitability for the industry. If a company has many smaller buyers, the company is able to lose one such customer without any detrimental effects on the business. However, if the company has few larger buyers, this is not the case. Buyers have power if the following occur:

1. A large volume of product is purchased by fewer buyers.
2. Buyers are able to switch companies without incurring costs to themselves. This is due to the undifferentiated and standard nature of the products or services.
3. Buyers have complete information on how the industry is working, including demand, actual market prices, and even supplier costs. This information can place buyers in a better

negotiating position.

Supplier's Power

Similar to buyers, suppliers can also influence industry decision making. Suppliers are able to dictate terms of business such as price, quality, delivery times, etc. A company should not be dependent on one large supplier but have many smaller suppliers in order to decrease supplier power. Suppliers retain their power due to the following:

1. Suppliers are concentrated or have a monopoly on supplies.
2. There are no real substitutes available to compete against.

Potential Entrants

These are individuals looking to enter the industry and create start-ups to compete with the existing companies and gain market share. Barriers to entry are the most critical variables which determine the position of an existing company in the industry. If the factors to start the business-like capital expenditure, technical know-how, regulations, cost advantages, customer's brand loyalty etc. are high, the barriers for new entrants will be higher. The absence of these will allow for easier access for new entrants.

Substitutes

These are alternatives to the existing products or services available that customers can easily switch to. These substitutes have the most power when providing products/services with the same function but at higher quality and lower cost. This concept can restrict industry profitability due to the improvement of price-performance tradeoff, therefore producing higher profits for others.

Industry Rivalry

Firms with the same industry have the tendency to compete in an attempt to dominate the market. Rivalry is dependent on the number of firms within the same market and the extent to which they

collude with each other. Rivalry occurs because there is opportunity or pressure for improvement. Firms compete using a variety of strategies, including price competition, advertising battles, product introductions, customer services changes and extended warranties. Rivalry is able to keep prices down, improve quality and therefore benefits industry customers.

## Porter's Five Forces: Netflix

Netflix is a US-based internet streaming media provider founded by Reed Hastings and Marc Randolph in 1997. It originally started with providing DVD-by-mail service in North America and now provides digital streaming with services available worldwide. Although Netflix is the most popular online subscription service for streaming entertainment in the world, there are some issues which threaten the long-term viability of their business model. Below is an assessment of Netflix using Porter's Five Forces model to determine how market forces may affect the company's business.

Power of Buyers

The bargaining power of buyers is high because:

1. Customer loyalty is weak. Since customers have zero switching cost, they can cancel the subscription anytime and switch to a new or alternate service provider.
2. Customers are highly price-sensitive. They tend to switch to a new or alternate service whenever the cost is increased. For instance, in 2011, Netflix divided their DVD-by-mail service and streaming service into two separate services, which was earlier priced $10 per month for both together. They increased the cost to $7.99 per month for each and in less than 3 months' time, they

lost around 800,000 customers. In 2014, they increased the cost from $7.99 to $8.99 per month and gave 2 years exemption from price increase to the existing subscribers to mitigate this risk.

3. Customer subscription fees are the major stream of revenue since commercials are not included.
4. There is a considerable threat posed by piracy sites which provide free streaming services and customers may compromise quality for this benefit.
5. Mitigation of these concerns can considerably reduce the bargaining power of buyers. Offering original content (for example, original TV series like House of Cards, Orange is the New Black, and Arrested Development) which is available only through Netflix is one of the ways by which they are mitigating this risk.

Power of Suppliers

The bargaining power of suppliers is high because:

1. Suppliers are contracted with Netflix through Licensing Agreements. Once the agreement expires, a supplier may switch to a new/alternate service provider and this will have a significant impact on the business as it reduces the volume of content available for Netflix customers. For instance, in 2013, after the contract with Netflix expired, Viacom contracted with Amazon and Netflix lost access to air their programs.
2. Suppliers are also offering their own digital streaming services. Hulu, a joint venture of 21st Century Fox, NBCUniversal, and The Walt Disney Company, offers high volumes of own content, as well as shows from various other networks. A part of their subscription service supports commercials and hence mitigates the consumer price-sensitivity risk by creating an additional revenue stream that makes them less reliant on subscription volume to remain profitable.

3. Suppliers own a majority of the content and Netflix is highly dependent on them for large volumes of content with high quality, which is a threat to the long-term viability of their business model.
4. Mitigation of these concerns can considerably reduce the bargaining power of suppliers. As a mitigation strategy, Netflix pursued backward integration by making original content, thereby reducing their dependency on suppliers.

Potential Entrants

The threat of new entrants is moderate because:

1. Netflix works on a high economy of scale with high product variety, maintaining low cost and increasing profit. New entrants with low investment capital are less likely to enter this market, but bigger companies like Google and Apple with strong financial and technical capabilities can be a huge threat to Netflix.
2. Competition in online streaming is likely to intensify in the future since the movie and television industry is a well-recognized growth sector.
3. Traditional service providers are entering the market. For instance, Crave TV owned by Bell, one of Canada's leading telecommunication companies, has entered the Canadian market. They provide online streaming service at a much lower cost than Netflix but the service is available only for Bell customers, while Netflix is available for anyone with access to the internet. Likewise, HBO and CBS are new entrants in the US market with a competitive advantage of owning large volumes of content and brand name.

Substitutes

The threat of substitutes is moderate because:

1. Certain customer segments still tend to rely on substitutes like

Satellite and Cable TV, DVDs and Rentals, and Movie Theatres for entertainment. Customers will continue to rely on television to watch live shows which get broadcasted on specific channels and on theatres to watch newly released movies.

2. While there is an increasing trend in the popularity and demand for digital streaming services, rapid technological advancements may result in new and innovative substitutes that could pose a threat in the future.

Industry Rivals

Competitive rivalry is moderate because:

1. Although the competitive environment is high with industry rivals like Amazon, Hulu, YouTube, HBO, and several other networks, a collaborative environment is emerging among the competitors. For instance, products like Amazon Fire TV Stick and Google Chromecast give consumers access to Netflix and other 3rd party services.
2. Consumers are subscribing to two or more services at a time and hence multiple organizations will get the market share.

## Mayhem!

Mayhem is a role-playing activity that will allow students to take part in the framework of Porter's Five Forces for a given company (See Case Summary below). The objectives of the activity are:

- To analyze Porter's Five Forces for a given company by taking on a role in the industry, and to understand the supply chain's effect on industry profitability.

- To assess how an industry changes in response to environmental shifts, and how this affects a given company aiming to grow within the industry.

Rules

1. The students will be divided into five teams of 2-4 people, each representing an industry player outlined in Porter's Five Forces. The presenters will take on the role of the Focal Firm, and the professor will take on the role of "Mayhem". Descriptions of teams are outlined below, as well as relevant information regarding their position in the industry.
2. Each group will be provided with important industry information pertaining to the other teams, for reference throughout the activity.
3. The neutral round of the game will consist of the group members assessing their power or threat standing before any environmental shift or "mayhem" has occurred. This will be used to portray the current "attractiveness" of the industry. Answers will be recorded in in the Industry Outlook Table (see Table 2).

    - For example, the Wannabes will decide whether the threat of new entrants against the focal firm is ↑ (high) or ↓ (low) prior to any environmental shift; the Customers group will decide whether their bargaining power is ↑ (high) or ↓ (low).
    - Industry outlook will be scored by counting the number of ↓ (low) threat/power standings. A total score of 1/5 or 2/5 on the Industry Outlook chart indicates an industry that will not favour the growth of the focal firm. A score of 3/5 indicates a neutral industry, with a "wait and see" approach to be applied by the focal firm. A score of 4/5 or 5/5 indicates an industry that is favourable for growth or entry by the focal firm. See Table 2.

4. For the second round of the game, the Mayhem player will randomly pick and present an environmental shift (see below) that may fluctuate the threat/power standings of the five teams. Groups will discuss how their threat/power standing has been shifted, and revise the “Industry Outlook” table. The class will then decide whether the industry is favourable or unfavourable towards the growth of the focal firm.

    - Note: If a group is unaffected by the environmental shift, they will retain the threat/power standing from the neutral round.

5. Several rounds of Mayhem will be played, depending on the time available.

## Case Summary: Olive and Sinclair Chocolate Company

Olive and Sinclair Chocolate Company is one of the 60 chocolatiers serving the gourmet chocolate niche market. The gourmet chocolate niche market is occupied by artisanal chocolatiers that aim to produce chocolate using fair trade cocoa instead of using cocoa cartels. The main goal of artisanal chocolatiers is to make handmade chocolate with new and unique flavours instead of mass production. As a result, artisanal chocolatiers charge top dollar for their chocolate, averaging at $6.00/2.75 lb. Olive and Sinclair charge $7.00/2.75 lb. As a company, they produce more than 60, 000 pounds of chocolate per year and are planning to expand internationally.

The gourmet chocolate niche is only 10 years old in the US, and it continues to flourish with the addition of new and unique flavours. Therefore, the competition in the industry is high, many opportunities are available for new entrants and the customers have high expectations towards fine tastes. Olive and Sinclair have built their brand around old-fashioned, Southern approach to chocolate making, which adds to their competitiveness.

Environmental Shifts

- There was a crop blight (disease) which impacted the cocoa market globally by causing a decrease in cocoa supply by 40%.
- Nestlé, one of U.S.A's major chocolate confectionaries, went bankrupt and folded.
- A recently published study showed a link between autism and chocolate and has been gaining media attention. The study claimed that chocolate causes autism in children that also take allergy medication.
- OPTIONAL ROUND: Hershey's, one of U.S. A's largest chocolate confectionaries, went bankrupt and folded. Hershey's had previously acquired Scharffen Berger, one of Olive and Sinclair's main competitors.

Note: More details about the case and the activity can be found in the Wilson (2015) paper, as listed in the References.

**Table 1: Key Artisan Chocolate Industry Partners for Olive and Sinclair Case Study**

| Major Players in Case Study | Description |
| --- | --- |
| **Olive and Sinclair Chocolatiers (Focal Firm)** | – Based in Nashville.<br><br>– Specialty: Adding brown-cane sugar to chocolate gives it uniqu<br>Chocolate, Bourbon Nib Brittle, Salt and Pepper Chocolate, and<br>– Branding: old-fashioned, southern, and local. O&S started wi<br>are local.<br>– Has had some success with expansion internationally. Produ<br>Singapore, Japan, and U.K. |
| **Artisan Chocolate Consumers (Customers)** | – High-end artisan chocolate consumers<br><br>– Enjoy artisan chocolate because it is not mass-produced, and r<br>with cocoa-farmers.<br>– These consumers are willing to pay a lot for artisan chocolat<br>farmer-friendly products. The great effort put in by artisanal cho<br>point for customers.<br>– Pay $7 for 2.75-ounce chocolate at Olive and Sinclair<br>– Pay $3.75 per 3-ounce bar at Scharffen Berger (a major comp<br>– Pay $6 for 2.8-ounce bar at Chuao Chocolatier (a major comp |
| **Cocoa Farmers (Suppliers)** | – Farmers that supply cocoa for artisanal chocolatier companies<br>example, 3% of Nestlé's overall cocoa purchase comes from free<br><br>– Most cocoa farming occurs in West Africa, South America, and<br>– Artisanal chocolatiers often visit cocoa farmers in their hom |

| | |
|---|---|
| **Scharffen Berger (Competitor)** | – A San Francisco based artisanal chocolatier company.<br><br>– Carefully sourced cocoa beans produce high-quality cacao.<br>– Add in flavours: pistachios, raspberries, coconuts.<br>– Price is $3.75 per 3-ounce chocolate bars.<br>– Known as the world's best chocolatiers<br>– Recently acquired by Hershey's, but operating under the sam<br>Overall market: niche industry of artisanal chocolatiers is 10 ye competitors. The market is fragmented, with lots of small busine the industry. |
| **Wrigley Confectionary (Substitute)** | – Candy company that mass-produces corn syrup and cane cand<br><br>– Products include Starburst, Skittles, gummies, and various che |
| **Wannabes (New Entrants)** | – External players considering start-up in the industry.<br><br>– They keep an eye on supply, demand, and industry outlook to d the industry and gain profit.<br>Overall market: niche industry of artisanal chocolatiers is 10 ye competitors. The market is fragmented, with lots of small busine the industry. |

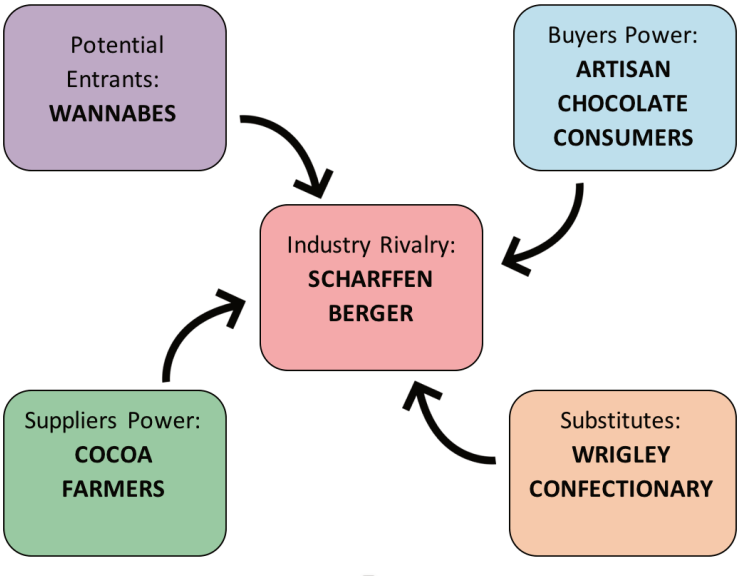


*Figure 2: Placement of Artisan Chocolate Industry Players in Porter's Five Forces Framework*

**Table 2: Industry Outlook Table for "Mayhem" Activity***

| | Threat/Power Standings (↓↑) | | | | |
|---|---|---|---|---|---|
| **ENVIRONMENTAL SHIFTS** | **Artisan Chocolate Consumers (Customer)** | **Cocoa Farmers (Supplier)** | **Scharffen Berger (Competitor)** | **Wrigley (Substitute)** | **Wannabes (Potential Entrants)** |
| **NO Shift** |  |  |  |  |  |
| **Shift:** Crop blight causes worldwide cocoa supply to drop by 40% |  |  |  |  |  |

**Shift:** Nestlé, one of the United States of America's major chocolate confectionary, went bankrupt and folded. 3% of their total cocoa purchase was fair trade.

**Shift:** Highly publicized study released, claiming that chocolate causes autism in children who are taking allergy medication.

**Shift (OPTIONAL):** Hershey's, one of the United States America's largest chocolate confectionary, went bankrupt and folded. Hershey recently acquired Scharffen Berger.

---

*Note: Answers will be filled out in class.

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# Appendix

# Porter’s Five Forces

Amna A., Maham H., Viola H., Rashmi K.

## Definition

Porter’s Five Forces is a framework used to analyze the balance of power within a particular industry and therefore, its overall profitability. These outline 5 forces that drive competition and threaten the ability to make profits.

Created by Michael E. Porter of Harvard Business School

2

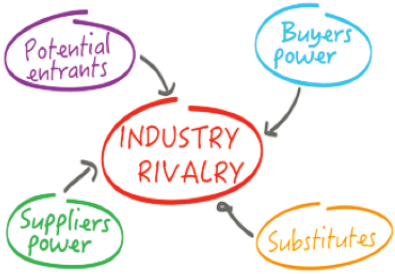
What's going on out
there in your industry?

What deserves your attention?

Of the many things that are
happening, which ones matter for
competition?

3

## The 5 Forces




(Michaux, 2015)

4

## Buyer's Power

- Buyer influences decision making
  - Prices ↓ and value ↑
- Buyer affects profitability of product
- Powerful when:
  - Large volumes go to fewer buyers
  - Buyers can switch companies, without incurring costs
  - Buyers have full information

5

## Porter's 5 Forces for Netflix

Bargaining power of Buyers – **HIGH**

- Weak customer loyalty
- High price-sensitivity
- Customers - major revenue stream
- Threat of piracy sites

NETFLIX

6

## Supplier's Power

- Negotiate leverage
  - Charge higher prices
  - Achieve more favorable terms
- Dictate terms of business
  - Price, quality, delivery times, etc.
- Powerful when:
  - Concentrated/monopoly
  - No substitutes

7

## Porter's 5 Forces for Netflix

Bargaining power of Suppliers – **HIGH**

- Suppliers own majority of the content
- Licensing deals with suppliers
- Supplier's digital streaming services

NETFLIX

8

## Potential Entrants

- Barriers protect from newcomers who:
  - Add new capacity
  - Gain market share
- Raise hurdles to enter into market
  - Cap prices and Increase costs
- Prefer: high investment capital, specialized knowledge/tech, strict regulations

9

## Porter's 5 Forces for Netflix

Threat of New Entrants – **MODERATE**

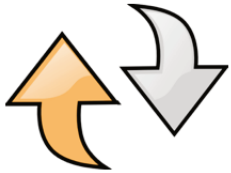
- Barrier for entry is medium
- Weak customer loyalty
- Threat of traditional service providers

NETFLIX

10

## Substitutes

- Alternatives to existing product or service which meets same need
- Restricts industry profitability
  - Low prices
  - Better quality



11

## Porter's 5 Forces for Netflix

Threat of Substitutes – **MODERATE**

- Threat of traditional media
- Popularity of digital streaming
- Rapid change in technology

NETFLIX

12

## Industry Rivals

- Competition dependent on
  - Number of firms existing
  - Level of collusion
- Causes
  - Capped prices
  - Improved quality
  - Happy customers

13

## Porter's 5 Forces for Netflix

Competitive Rivalry – **MODERATE**

- High competition
- Collaborative competitive environment
- Shared market

NETFLIX

14

## Mayhem!

- Class will be divided into 5 teams:
  - Customers, Suppliers, Competitors, Substitutes, Entrants
- Mayhem player will introduce environmental shifts that affect the industry
- Objectives of activity:
  1. Assess industry outlook by evaluating current power/threat of Porter's Five Forces on the Focal Firm
  2. Respond to shifts in the industry, and re-evaluate threat/power standings in the P5F framework

15

## Case Study: Olive and Sinclair

- Artisanal Chocolatiers - offer unique flavours
  - Against mass production
  - Support Fair-Trade cocoa instead of sourcing from cocoa cartels
- Small company with 60 artisanal rivals in US
- Market itself is fragmented and niche
  - Geared towards market that values fine taste over price
    - Artisanal chocolate compared to fine wine
- Produce 60,000 lb of chocolate/year
  - Price = $7.00/2.75 ounces
  - Major competitor's price = $3.75/3 ounces
  - Competitor's average price = $6.00/2.8 ounces


16

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Images

1. Thumbnails were created by presenters
2. Images from slides 5 - 14 are from http://clipart-library.com/
3. Olive and Sinclair image from Wilson, R. C. (2015). Mayhem: A Hands-on Case Playing Activity for Teaching Porter's Five Forces to Undergraduate Business Students. *Small Business Institute Journal; Greenville*, *11*(2), 48–59.

# 7.

*By: Megan Conner, Ben Ferrier, Vasu Patel & Ashley Burton*

Microsoft Office has a lengthy list of helpful applications (apps) to use when working in teams. Each app is designed for specific aspects of a project timeline (ie. Planner is meant to be used at the beginning of a project). However, it is possible to use just one app for an entire project as there is some overlap between the apps. This How-To-Guide will focus on describing the best Microsoft Office apps to use from the start of a project, to presenting it.

## Microsoft Planner

### Purpose

Planner was designed to be used for the initial meeting of team, and as an agenda for due dates and progress-checking (Microsoft Office, n.d.). It is useful for gathering the team members together in a common space where task delegation can be initiated, and deadlines can be agreed upon prior to starting the work.

## Using Planner

To use Planner most effectively, begin by creating a title of the project using the "+" tab. Here you can choose a privacy setting for the team. Next, you will enter a To-Do page where assignments can be listed with one or more team member(s) associated, and a deadline attached to each task (Fig. 1).

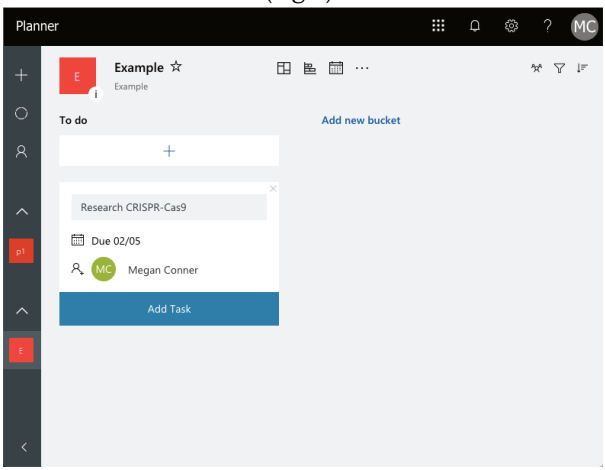



**Figure 1.** The homepage for a new project.

Once tasks are assigned, each team member is emailed a notification of their role in the team. When they enter planner, they can choose the "My Tasks" tab to view their assignments. They can also click each task and select the progress stage they are at, add a detailed description of their task, add relevant attachments, label it based on priority or other filters, and attach comments to the task (Fig. 2).

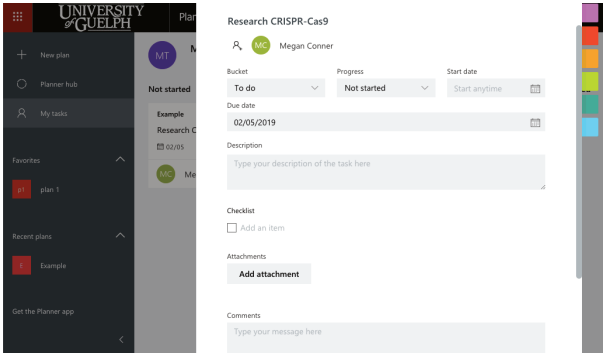



**Figure 2.** Information field for a specific task.

Additionally, if a team requires multiple lists of tasks, they can "Add a new bucket" on the plan's "Board" page to start a new list. The "Board" also allows you to view the Members included. There is a "Group by" tab here as well that lets you change how you want to see your tasks, and the "Filters" tab lets you see the status of progress quickly.

Beside the "Board" there is a "Charts" option. This is a useful page to visualize how many tasks are left to complete, and how each member is progressing through the project. Next to "Charts" there is a "Schedule" option that reveals a calendar of all deadlines. It can also show the date a task was started and shows a list of tasks without deadlines on the right-hand side of the calendar (Fig. 3). By selecting a "Filter" at the top, you can limit the information you see on the calendar to what is important to you.

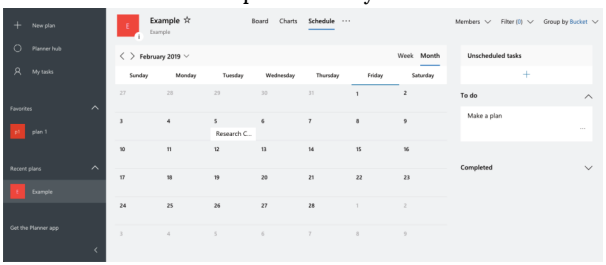



**Figure 3.** "Schedule" of the list of all due dates within a specific

project.
The Three Dots "…" tab beside "Schedule" offers a variety of other options that may be useful for some projects (Fig. 4). For instance, a "Conversation" option is available that is linked to a group email with all members of the team. However, communicating back and forth with a team is recommended to be done through Microsoft Teams. "Files" is also available here as a place to store relevant team documents, although Teams is again a better app to use for group documents due to its group editing feature. A team can also change their settings through "Plan Settings" here, and a plan can be added to members' Outlook Calendars through the "…" tab as well.

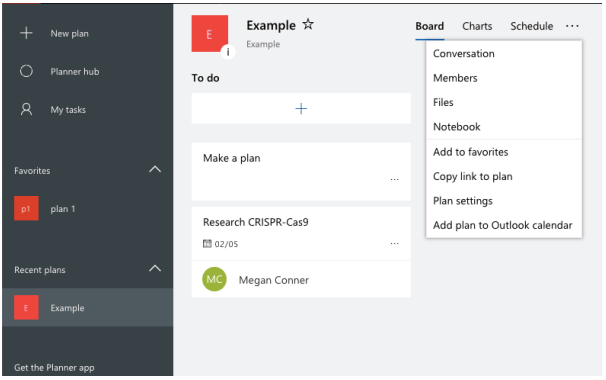



**Figure 4.** Options available within the "…" tab of Planner.
Lastly, as a team member looking to keep track of your specific role, you can select the "My Tasks" tab on the left side bar to quickly view your assignments for the project and update your progress on them here. It is a great way to keep an agenda for each project so that no tasks are left to the last minute. For those that prefer a mobile Planner, that option is also available on the left side bar where team members can enter their phone number and receive a link to download Planner to their smartphones.

## Limitations and Conclusions

It is important to note that Planner is a beneficial app for beginning a project, and to check in on how the team members are doing with their tasks throughout the timeline. It is not, however, designed for working on documents together, sharing ideas, or preparing a presentation. These features are purposely not included in Planner since Microsoft Office has designed other apps for those features (Teams and Stream). Therefore, this app is a vital first step for a successful group project and teams are recommended to continue project preparation with the above-mentioned Office applications (Microsoft Office, n. d.).

# Microsoft Teams

## Purpose

Microsoft Teams was initially launched in 2017, and a stable release of the application occurred in July of 2018. The application is supported on Windows, macOS, iOS, Android and is part of the Office 365 suite of applications. The application is marketed as a cloud-based team collaboration software with business messaging, calling, video meeting, and file sharing capabilities. “Teams” can set up chat logs as well as video messages for easy communication between members. As well, members can set up workspaces using Microsoft Word, Powerpoint and Excel which all members can access and edit at the same time via the cloud-based nature of the program. Files stored on Microsoft Teams are also shared through the cloud with other Microsoft applications such as OneDrive as

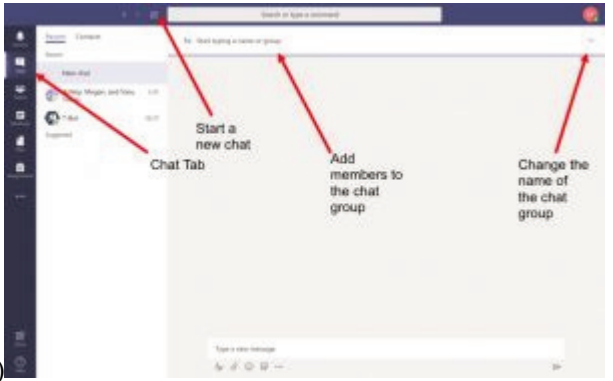
Teams is integrated into the Office 365 platform. Ultimately, this application can help people, organizations and businesses maximize productivity as it allows groups to have access to all the tools they need in one place.

## Using Teams

**1. Setting up a chat group**

To set up a new chat group within teams first select the “Chat” tab on the sidebar to the left of the Teams window as indicated in Figure 5a. Alternatively the Chat feature can be accessed from within any tab by clicking the “pen and paper” icon at the top of the page as seen in figure 5a. From here users can access ongoing chats in the sidebar under the “Recent” tab, as well contacts can be found by clicking the “Contacts” tab. A new chat can be created by typing in the name of contacts in the “To:” search bar as seen in Figure 5a. By clicking the drop-down menu in the “To:” search menu the user can also name the group they are forming as seen in Figure 5b.

A)

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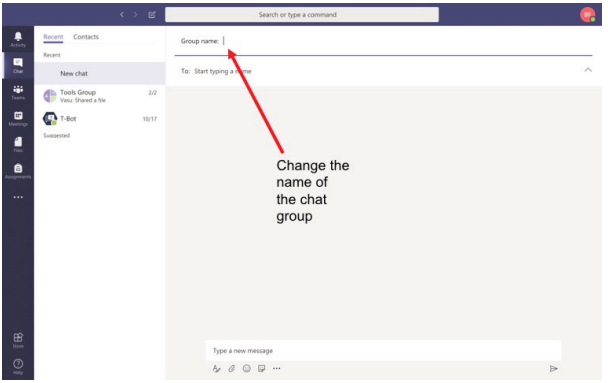
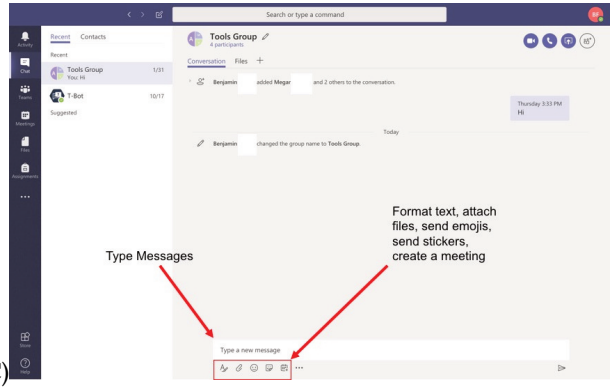



Once a group has been created, users within the group can send text messages, format text, attach files, and attach emojis as well as stickers as indicated in Figure 5c. Users can also schedule a meeting by selecting the calendar option as indicated in Figure 5c. A pop-up window will appear as shown in Figure 5d where users can input information about the meeting such as time, location and any details this function also integrates in with the Microsoft Planner application. Users can also start video calls, audio calls as well as screen share as indicated in Figure 5e.

C)



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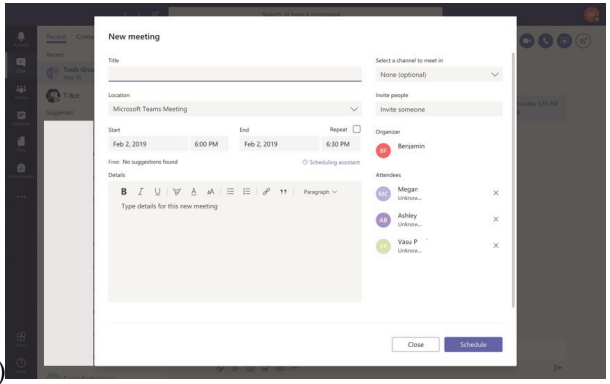


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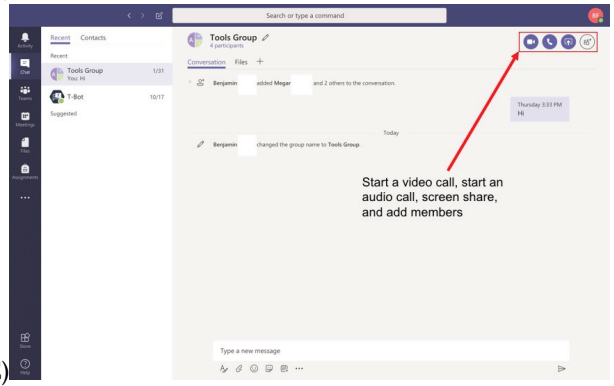
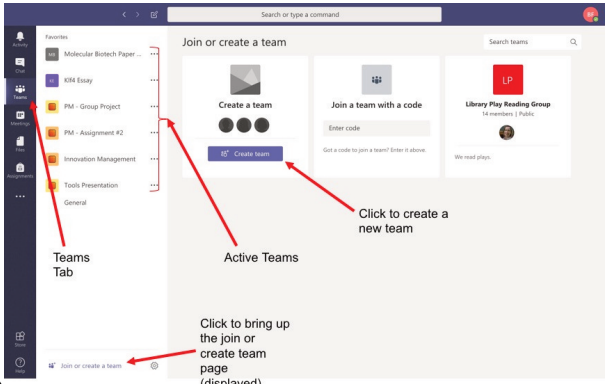



**Figure 5a-e.** A description of the Microsoft teams "Chat" tab.

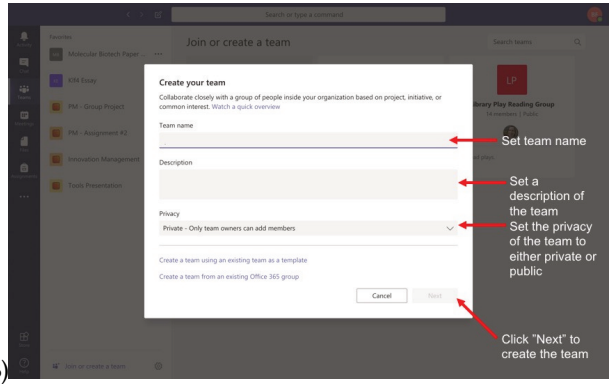
**2. Setting up a new group**

To set up a new group within Teams first select the "Teams" tab on the sidebar to the left of the Teams window as indicated in Figure 6a. Next select the "Join or Create Group" tab in the bottom left corner of the screen this will display the main window as seen in Figure 6a. From here users can decide to create a team, join a team using a team code or join any public groups that are available. To create a new group, select the "create team" option, a popup window will be displayed as seen in Figure 6b. From here users can; name the group, add a description of the group as well as set the privacy of the group to either private (only team members can add members)

or public (anyone in the organization can join).




A)




B)

**Figure 6a and b.** A description of the Microsoft teams "Teams" tab.

**3. Creating/Uploading Files**

Microsoft teams provides a simple platform to share files within team channels. Members of channels are able to edit, view, and collaborate on files shared within teams if they are Visio, Excel, Word, or PowerPoint files. When collaborating on Excel, PowerPoint, and Word documents, changes can be seen in near real time. Each channel has its own "Files" folder (Fig. 7) where files can be shared and accessed.

Once the Files tab is selected, the user has the open to select a file, create a new file (New, Fix. 4, red) upload a file (Upload, Fix. 4, blue),

get a link to share the files with a colleague (Get Link, Fix. 4, green), add additional cloud storage from SharePoint given that the team members have been provided with permissions (Add cloud storage, Fix. 4, purple), and open SharePoint where a SharePoint site is automatically generated to store team channel files (Open in Sharepoint, Fig. 8, black).

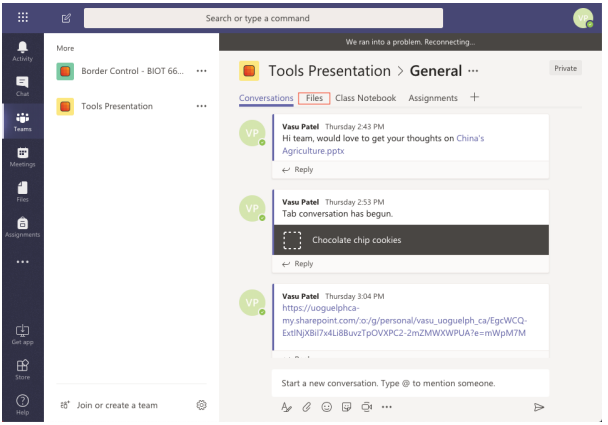



**Figure 7.** Location of the "Files" tab in any Microsoft Teams.

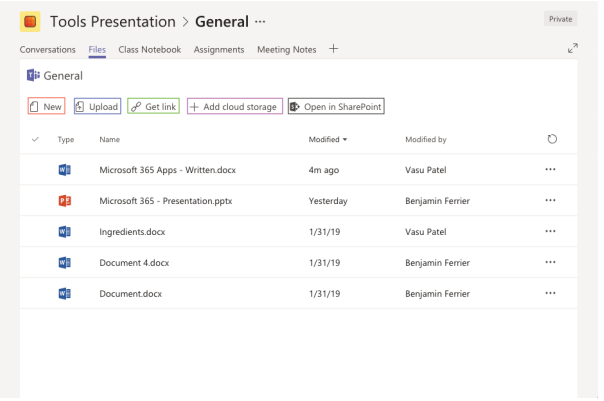



**Figure 8.** "Files" tab options.

When a file is selected, the file can be opened (Open) , a link can be

generated to share the file (Get Link), a tab can be created to highlight the file by placing it next to the general channel tabs (Make this a tab), the file can be downloaded (Download) and opened in SharePoint (Open in SharePoint). The file can be opened and edited in Teams, online, and on the desktop if the file being opened belongs to Word, Excel, PowerPoint. Opening a Microsoft App based file in Teams provides a unique option to start a conversation about the file while editing (Fig. 9). Once the user finishes editing a file, the conversation is posted in the team channel conversation to update members.

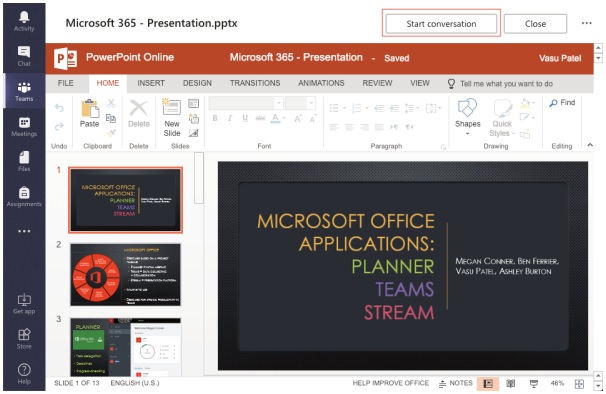



**Figure 9.** "Start Conversation" option when opening file in Teams

**4. Video Conferences**

The "Conversations" tab provides various chat options including chat formatting, attachments, emojis, gifs, and video chatting. The video chatting option is indicated by the video camera symbol and titled "Meet Now". Once selected, the video chat is given a title, a specific meeting time can be set, or the meeting can be held immediately indicated by the "Meet now" button. Starting a video chat presents several features including: video camera toggle (Fig. 10, white), microphone toggle (Fig. 10, light blue), desktop/app sharing (Fig. 10, green), recording (Fig. 10, pink), meeting notes (Fig. 10, black), and inviting members using the search bar in the upper

right corner. If recording is initiated, the meeting is uploaded to Microsoft Stream and shared to the channel conversation (Bisson, 2017).

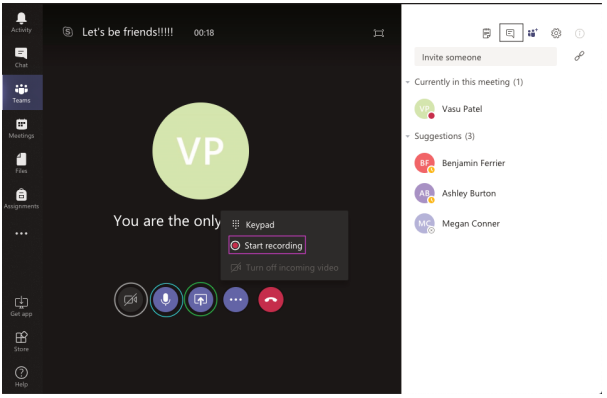



**Figure 10.** "Meet Now" options: video camera toggle (white), microphone toggle (light blue), desktop/application sharing (green), recording (pink), meeting notes (black).

## Limitations and Conclusions

Despite the several unique collaboration and communication capabilities featured on teams, some cons are present. Teams features a plethora of tools which causes confusion amongst users if they aren't familiar with them. In addition to this, it is difficult to keep track of where conversations are being held between Teams and Yammer which is also a communication app by Microsoft. Notifications in teams are not sent when a duplicate team name is created, which could result in confusion. Microsoft Teams also uses a large quantity of storage which can reduce free memory shared by the whole organization. Finally, the number of channels is limited to 100 per team. Although 100 channels may be more than enough for

most teams, large organizations may need more. The cons associated with Teams can be circumvented by investing in employee training, unlimited memory, and smaller functional teams. Overall, Microsoft Teams provides essential collaboration and communication capabilities that outweigh any associated cons (Bisson, 2017).

# Microsoft Stream

## Purpose

Stream, a Microsoft application launched in 2017, is a video service available that makes it easy to create, securely share, and interact with a video (Microsoft, n.d.). This application can be utilized within a team, or across an entire organization. Companies can upload training videos and other work-related content that can be viewed on any time on any device using the Stream application. Unique features of the application include: auto-generated closed captions, face detection features, and an interactive comment section (Foley MJ, 2018). Videos that are uploaded onto the application are done securely, and are only loaded into the desired team/organization group unless the worker wants to upload it to the company's database of video files (Microsoft, n.d.). Stream has increased the collaboration within an organization by bringing together training videos, team meeting recordings and more.

## Using Stream

When first working with Stream, first create a group or channel (+ Create) in order to create a central location for the videos being uploaded and viewed. The main difference between a channel and a group when using Microsoft Stream is its accessibility. A channel can be viewed by anyone who has access to the company's Stream, while the visibility of a group can be restricted to only the group members. A channel can also be created from within groups. After deciding to create a group or channel, fill in the required information (i.e. title, members, access and restrictions), before the group/channel is available to its members (Fig. 11).

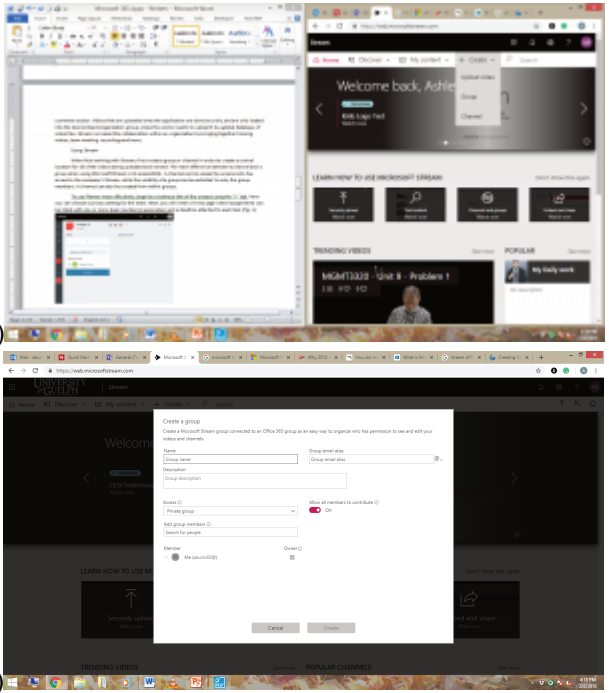



**Figure 11.** Screenshots of Microsoft Stream. A) "+Create" function, B) Information field to be filled out during creation of a group.

Once the group or channel has been created, click “My Content” for a pull down menu to view the different content that you have access to. Under this menu the employee can see the videos uploaded by them, groups and channels they are a member of, videos that are within their watchlist, as well as channels that they follow (Fig. 12A). Once in the group or channel the employee is a part of, the team member can view the videos that are within that group/channel according to their sorting criteria. Additionally, at a glance you can see the number of views, likes, and comments each video has (Fig. 12B).

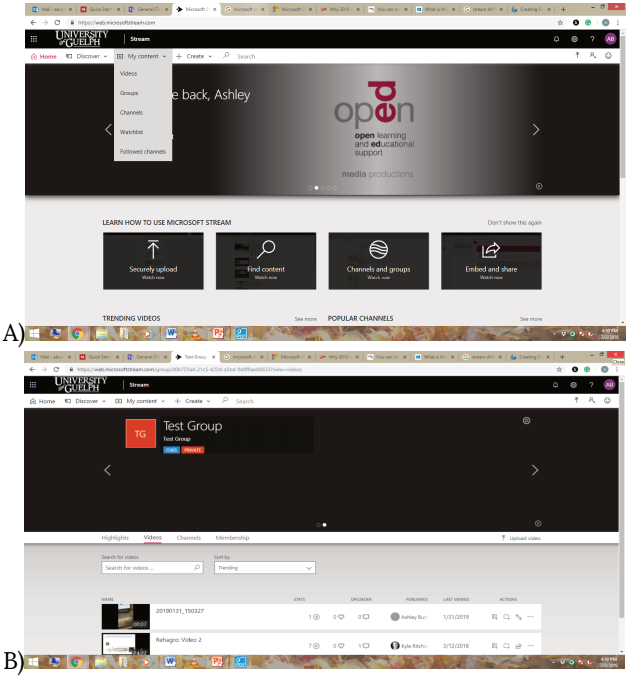



**Figure 12.** Screenshots of Microsoft Stream. A) “My Content” feature, B) Display field of a group team member is a part of.

Team members can search for videos or channels/groups using the “Search” or “Discover” tab at the top of the Steam menu. Once the individual views the video the employee can leave a comment, like

the video, add the video to a watchlist, or even add the video to a group/channel for others within their organization to view (Fig. 13). When viewing a video, the team members can also see the transcript of the entire video to the right of the video. Employees can search the transcript for key words to then jump forward within the video for the section of interest to them.

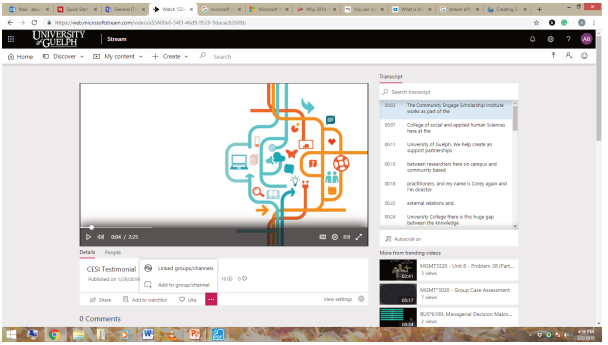



**Figure 13.** Screenshot of Microsoft Stream showing display of an example video being viewed.

The team member can then upload a video to the group/channel that they are a part of (if the administrator of the group/channel has given such access to its members). To upload a video to the group/channel they are a part of, they must just click the file the want to upload ("+ Create –> Video), and fill in the required information prior to sharing. This required information includes the name and description of the video, permissions of who can view it, as well as if the originator wants to upload a subtitle file, or use auto captions. Stream accepts a variety of file formats for upload, including but not limited to: .mkv, .flv, .mp4, .avi, etc (Microsoft, 2017).

There are also a number of additional features of interest within Microsoft Stream. Live meeting capabilities are a recent addition that extends upon Skype's Meeting Broadcast, allowing interaction and engagement between attendees before, during, and after meetings. Once the administrator has allowed live event capabilities, a live event can be initiated (four hour maximum meeting length)

when the producer can monitor audience engagement in real time (Microsoft, 2018). Additionally, on the home page of Microsoft Stream is there a trending video section as well as popular channels that can be followed. These features allow videos within the company that are most popular to be easily found, as well as promote additional relevant content that has been generated by the company and/or its employees.

## Limitations and Conclusions

There are a few limitations within the existing Microsoft Stream Application. As this is a relatively new application to the Microsoft frame work there are some technical issues that are still being ironed out. As the premise of a video sharing site is not new for most people, many employees with basic technical expertise are able to easily use the application. Since this is a video sharing platform based out of a company, it is significantly dependent upon the users of the application, and the company must promote its use in order to ensure its continuous successful use. Overall, Microsoft Stream allows for an easy to manage video sharing platform for companies to use both at work and when on location or at home. Companies can keep training videos in one location for easy reference, provide video reference of set-up procedures to employees, and even conduct live meetings that are recorded allowing for easy minute keeping.

# Conclusion

In conclusion, Microsoft Office and its variety of business based

applications are useful tools that can and should be utilized within organizations of any size in order to encourage and facilitate organization, team-work, and cohesion within an organization.

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# 8. SWOT analysis

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## S.W.O.T. Analysis

February 27 2018

SWOT analyses are performed by organizations allowing for identification of a company's strengths and weaknesses, as well as external opportunities and threats. This tool is meant to identify the goals of an intended business and to highlight possible advantages and disadvantages to the business by analyzing internal and external factors. This is why SWOT analysis is sometimes referred to as Internal-External Matrix. This kind of strategic formulation is often key to the development of a business.

SWOT analysis is a relatively simple way to discover major advantages and obstacles that a company or project has to face. This information is very valuable to determine if the project is worth moving forward or not. With too many obstacles and disadvantages, it may be more beneficial to terminate. This is why SWOT is often completed in the idea stage of a business plan or project.

**How to conduct a SWOT analysis**

The best way to conduct a SWOT analysis is with a group brainstorming different ideas and perspectives in relation to the company. Group members from different parts of a company can all contribute to the development of a SWOT analysis.

Factors in the plan should be prioritized by relative significance to the overall development of a business/project. This can be done by meticulous analysis of every possible factor that could have an impact, whether positive or negative on business development.


SWOT
ANALYSIS
Find Opportunities,
Eliminate Threats
SWOT Analysis helps you to identify your Strengths and Weaknesses, possible Opportunities, and potential Threats.
You can use it to find and exploit a sustainable market niche.

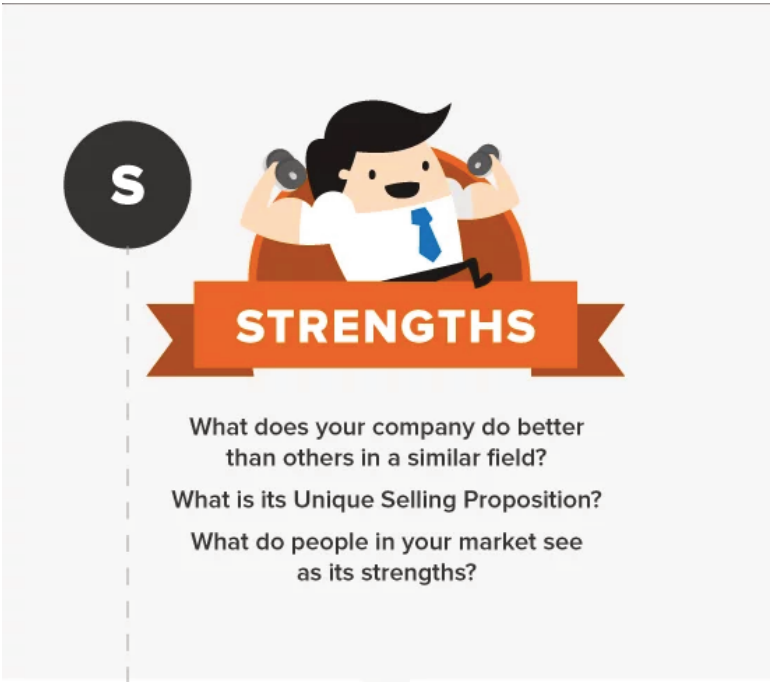

You can distinguish yourself from your competitors and gain a competitive advantage over them by assessing your company's strengths and market position.
And, by understanding its weaknesses, you can manage and eliminate threats that would otherwise catch you by surprise.
Now let's looks at some of the questions to ask when you carry out a SWOT Analysis.

**Strengths**

The ability to identify strengths of a company, business or idea, is key in building a foundation for success. This tool is an internal positive, the strengths of the company do not rely on external factors. The identification of advantages over the competition and what the particular business/company is able to do better than others is of utter importance. The strengths identified will increase the internal confidence within, that the business will be successful.

When identifying ones strengths, there is no need for modesty. These factors are those that will make the company successful. Many of the strengths that can be identified, can lead to further opportunities, as well as future gains. The strengths listed by any business or company can be in terms of their production line, group of employees, any particular sets of skills and the ability to be competitive & profitable within the defined market.

All strengths will be identifiable on the basis that they will play a role in success. The success of companies is typically related to the profit margin. Profits can be based on either direct factors or indirect factors. Identification of all strengths, is important in internal confidence and awareness as to what is brought to the table in every aspect by the company, business or even individual.




**Weaknesses**

Identifying key weaknesses is vital to establishing a business strategy. These are often direct internal factors that are detrimental to the overall plan, but can also be underlying external elements. The negative impact these factors have is usually seen as a general decrease in overall sales. However these weaknesses do not have to be existing problems with the company. They can also be hypotheticals or factors that can be avoided, as well as situations the company or project can improve upon.

An important aspect in this section is perspective. You need to see how your company and factors affecting it are perceived by other companies as well as the general market. Very often something

that doesn't seem like a weakness to a company is overlooked when to other competitors or consumers it is. This is why before even analyzing a company's own weaknesses it must first take a step back and perceive itself from the viewpoint of the market.

Another key detail in weakness analysis is that it must be rigorous and realistic. You must be thorough in highlighting every potential problem even if some seem unlikely or minor. No matter how small a weakness seems, it is important to identify it and determine its severity.

Some examples of weaknesses within a company could be:

- Limited access to resources
- Little recognition within the market
- Unknown brand name
- Insufficient staff or staff with a narrow skillset

**Opportunities**

Opportunities usually refers to external attractive factors that represent reasons why you or your business may flourish. These are factors that a business or an individual can capitalize or use to their advantage. When looking at opportunities for a business, its is best to look at strengths and ask whether these open up any opportunities. This can also be applied to weaknesses; you can look at a company's weaknesses and ask whether opportunities could be opened up by eliminating these weaknesses.

When looking at opportunities, a business or individual must consider what kinds of opportunities exist in their market or environment that they can benefit from? For example, if an individual is trying to promote their personal training business, they may exploit social media platforms such as instagram and facebook pages to promote themselves especially because a majority of their client base uses these platforms. Local events also pose a potential for opportunities; this allows for possible partnership opportunities as well

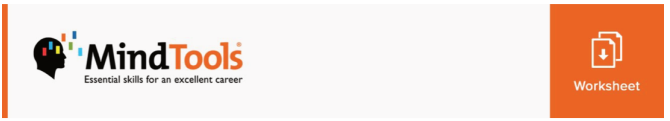

**Threats**

Determining the threats is one of the most important aspects of the SWOT analysis. The weaknesses that were previously determined are used to see if they are viable threats. Along with looking at the internal weaknesses of the company or project, it is also important to determine the external threats of competitors.

Other threats can come from the obstacles the company faces. For example, are there laws in place that you need to be aware of? Are there patents that you need to avoid? These are just some of the many obstacles a project could face that the company has to be aware of.

Some threats may involve technology. This can include if

technology is changing and improving. It is often very important to stay technologically relevant because most technology changes can threaten a business or project. Once all threats have been determined it is necessary to take action to prevent said threats. If there are too many threats and not enough solutions, termination of the project may be necessary.




## SWOT Analysis Worksheet

- For instructions on using SWOT Analysis, visit www.mindtools.com/rs/SWOT.

| **Strengths** | **Weaknesses** |
|---|---|
| What do you do well?<br>What unique resources can you draw on?<br>What do others see as your strengths? | What could you improve?<br>Where do you have fewer resources than others?<br>What are others likely to see as weaknesses? |
| | |
| **Opportunities** | **Threats** |
| What opportunities are open to you?<br>What trends could you take advantage of?<br>How can you turn your strengths into opportunities? | What threats could harm you?<br>What is your competition doing?<br>What threats do your weaknesses expose you to? |
| | |



SWOTAnalysisWorksheet

**SWOT Analysis Video Explanation**


*A YouTube element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/bio16610w18/?p=177*

**Example Using PepsiCo**

PepsiCo is a very well established company that was formed as a result of a merger between two food industry giants, the Pepsi-Cola Company and Frito-Lay, Inc. However, the organization has also since then acquired various other food companies such as Tropicana Products, and the Gatorade brand. It is the world's leading producer of convenient snacks, foods and beverages with over 63 billion in annual sales and 263, 000 employees in 200 countries. Since the company started their SWOT analysis has definitely changed drastically, however here is an analysis of PepsiCo today.

**Strengths**

No company can become as widely renowned and successful as PepsiCo without multiple strengths in the business. The two most

prominent strengths PepsiCo has going for them right now would be current sponsorship deals and their diversified product line.

Sponsorship deals have been made with professional sports leagues in North America, including the NHL, NBA, MLB and NFL. The NHL and NHLPA has recently (Jan 2018) inked a five year deal with PepsiCo, which is the largest partnership agreement in league history. This is a resigning to a previous agreement, which saw PepsiCo have full rights to the non-alcoholic beverage, sports nutrition and snacks categories. These partnerships lead to strong marketing abilities as professional sports venues and events can be utilized to unveil new products.

A diversified product line brings an advantage to PepsiCo over its main competitors as they are not just a one trick pony. The long and arduous battle with Coca-Cola over soft drink supremacy had been ongoing for decades. However, the overall success of PepsiCo does not rely solely on outcomes in the Cola Wars. Non-carbonated beverages are crucial to the success of PepsiCo, these products include Gatorade and Lipton Teas. Straying away from beverages, Lay's chips have a strangle-hold atop their respective savory snacks market and show no signs of slowing.

A third strength of PepsiCo is that they have a clearly defined target audience; youth. Unlike competitors, all advertisements for company products are created and directed towards younger crowds. Finally, the world-wide distribution of products from this company is astronomical in nature. Over 200 countries benefit from the product line that is PepsiCo, allowing for a strong distribution network.

**Weaknesses**

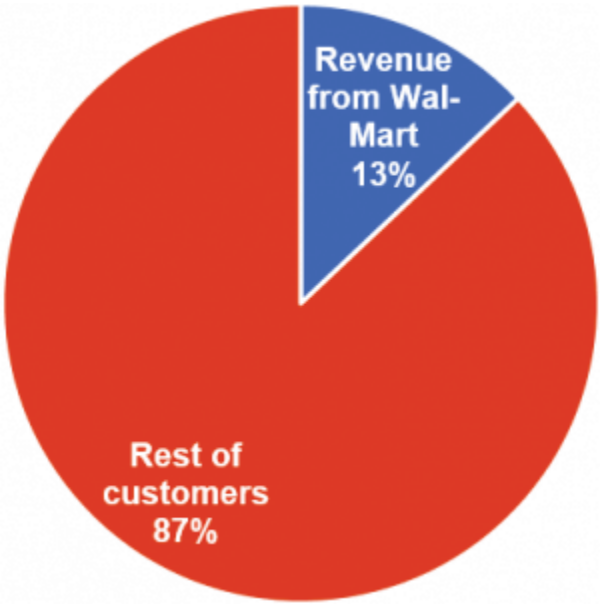
Surprisingly, even as a world-renowned food company Pepsi still has several areas that could use improvement as well as weaknesses to the overall brand. Some of these are even as a direct results of the companies recognition. As a major company PepsiCo is constantly under the spotlight and under criticism. An example from the past several years was that the company experienced media backlash for

claiming their products were make using pure spring water, when in reality they used tap water as well as overusing water in areas where water is not readily available.

Also, similar to other snack food and beverage companies, PepsiCo is under continuous scrutiny due to health concerns over their products. The soda lines in the company are among its weakest revenue generators. This is due to the fact that less people are buying soda and looking for healthier alternatives. This will force PepsiCo to develop or explore non-carbonated lines of drinks.

Another weakness that Pepsi has is its over reliance on one major customer in the form of Wal-Mart. This customer represents approximately 13% of the total annual revenue of PepsiCo. Any decline in sales to Wal-Mart could result in a drastic reduction in total sales. This can be even more potent considering that Wal-Mart is a massive company in itself that PepsiCo has little power over. PepsiCo also has an overdependence on developed markets which account for 69% of sales. The company in the future should focus on the markets in underdeveloped countries like several of its other competitors.

PepsiCo also has a smaller net profit margin in comparison to competitors. This is the total profit relative to total revenue generated. PepsiCos profit margin of 8.6% is almost half of The Coca Cola Companies 16.6%. The company should devote resources into lowering the costs of manufacturing and selling their various products.




**Opportunities**

People are starting to become more health conscious; therefore, there in an increased demand for healthy snacks, food and beverages worldwide. Additionally, obesity is a growing concern for many developed nations and there have been many attempts to try and fight this growing pandemic with the use of laws to decrease consumption of fats, salts, and sugars. PepsiCo is aware of this growing concern and has therefore introduced 'Good for You' brands which includes nutritious products such as fruits, seeds, whole grains, and low-fat dairy with limits on sodium, sugar, and saturated fats.

In 2015, ready to drink teas and coffees is a booming industry and are some of the fastest growing beverage segments in the U.S market. As a result, PepsiCo has partnered up with Starbucks and Lipton in

RTD coffee and tea segments. However, the company has no brands of its own; if they were to create its own RTD brand, it could possibly generate more revenues and higher profits.

Bottled water is one of the largest beverage segments and is one of PepsiCo's key products. The beverage marketing corporation reveals that bottled water consumption grew from 7.3% in 2014 to 7.9% in 2015. PepsiCo sells Aquafina and LifeWTR brands successfully to its consumers. The company should strengthen its portfolio by adding more brands.

**Threats**

Although PepsiCo has many products, the one they are most known for is Pepsi. One of the main threats of Pepsi is Coca-cola. Coca-cola uses large scale marketing and is the clear soda giant. This limits the pricing of Pepsi since they have to compete with Coca-cola.

On a larger scale, a major threat for PepsiCo is the amount of water needed to produce all of their beverages. Water is a limiting resource in many countries and many places have water shortages. In the future it may be difficult to access clean inexpensive water.

The U.S dollar exchange rate will continue to increase against other currencies. This will become a threat to PepsiCo since a large portion of their revenue is generated outside of the states (about 44%). Due to the rise in the USD, the profits made outside of the U.S. will lose value when converted back into USD.

Another threat to PepsiCo is that a lot of their products contain large amounts of sugar. Excess amounts of sugar consumed in diet is a leading cause of diabetes and also may contribute to cancer. The U.S. government may be passing legislation that product labels must disclose such information. This puts PepsiCo at risk for losing customers and a threat to their business.

**Conclusion**

The SWOT analysis is best performed at the beginning of a new project or business venture to create a marketing action plan. By looking at the strengths, weaknesses, opportunities, and threats, it

outlines a course of action to follow. However, this analysis can be performed later on and can be useful to help change, point the project or company in the right direction, and take the greatest possible advantage of opportunities available. The use of SWOT is important to gain an understanding of a company or individual's competitors as well as their future endeavours.

**Appendix**

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# 9. How Graph Misrepresents Data

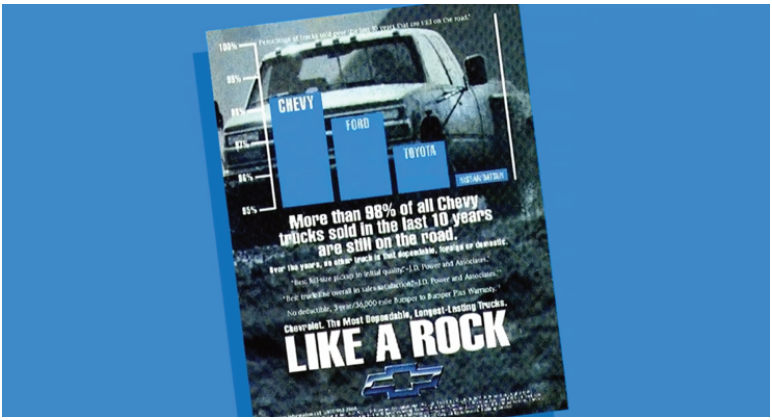
1. **Truncated graph:**

This is the most common way of data manipulation. A truncated graph usually involves manipulation of the axis to make something not significant at all look like a huge difference.

Let's look at a real-world example.

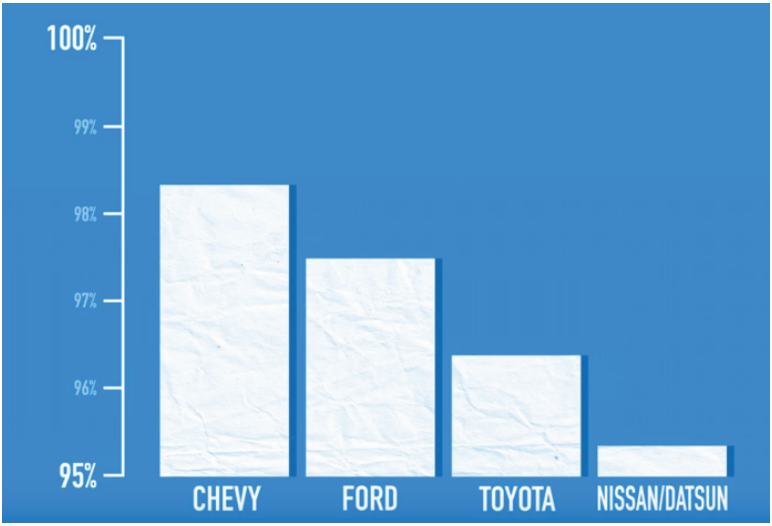
This is an advertisement from the Chevrolet;

They claim that "more than 98% of all Chevy trucks sold in the last 10 years are still on the road".

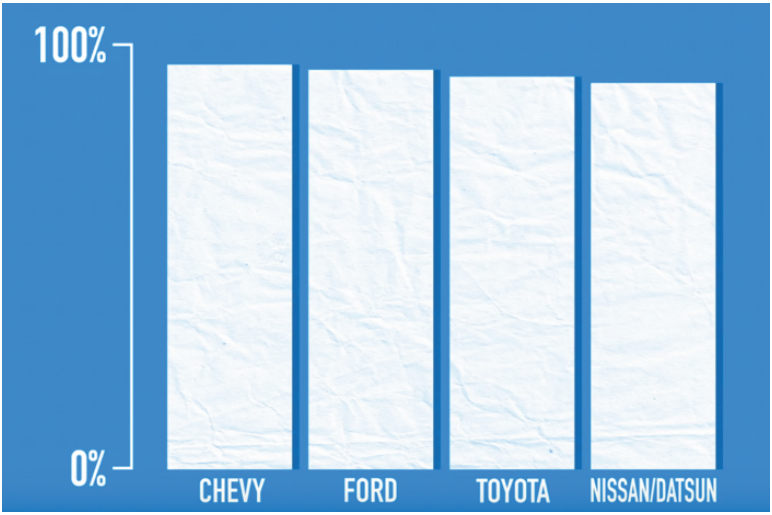



And this is how they presented this data; From this graph, it seems like Chevy trucks are almost two times more reliable than Toyota and ten times more reliable than Nisssan/Datsun. However, when we

look at the y-axis, we realize the scale range is from 95% to 100%; so a seemingly big difference is actually nothing at all.




And it actually looks like this if we use normal 0%-100% scale; By using this type of data manipulation, Chevy has "successfully" manipulated customers to think they are way better than everything else out there.



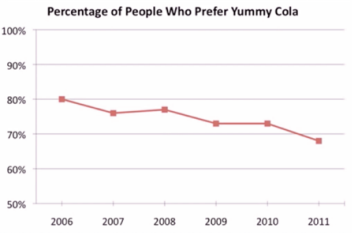

This is one of the most common way graphs misrepresent data: by distorting the scale.

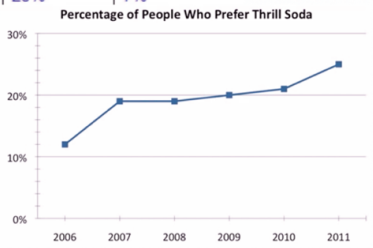
Zooming in a small portion of the y-axis exaggerate a barely detectable difference, and it is especially misleading in bar graphs, since we assume the difference in the size of the bars is proportional to the values.

Here is another example:

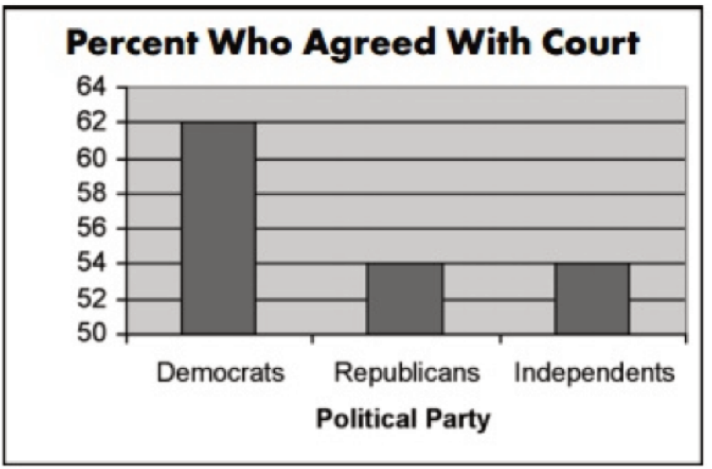
The two graph below plotted the percentage of people who prefer Yummy Cola and percentage of people who prefer Thrill Cola. After the first glance, we might think the percentage of people who prefer either Cola is similar, and the percentage of people who prefer Thrill Soda is increasing. But after we notice the scale used on y-axis, we see the little trick they used:50%-100% vs. 0% 30%.

| Year | % of respondents who prefer Yummy Cola | % of respondents who prefer Thrill Soda | % of respondents who have no preference |
|---|---|---|---|
| 2006 | 80% | 12% | 8% |
| 2007 | 76% | 19% | 5% |
| 2008 | 77% | 19% | 4% |
| 2009 | 73% | 20% | 7% |
| 2010 | 73% | 21% | 6% |
| 2011 | 68% | 25% | 7% |



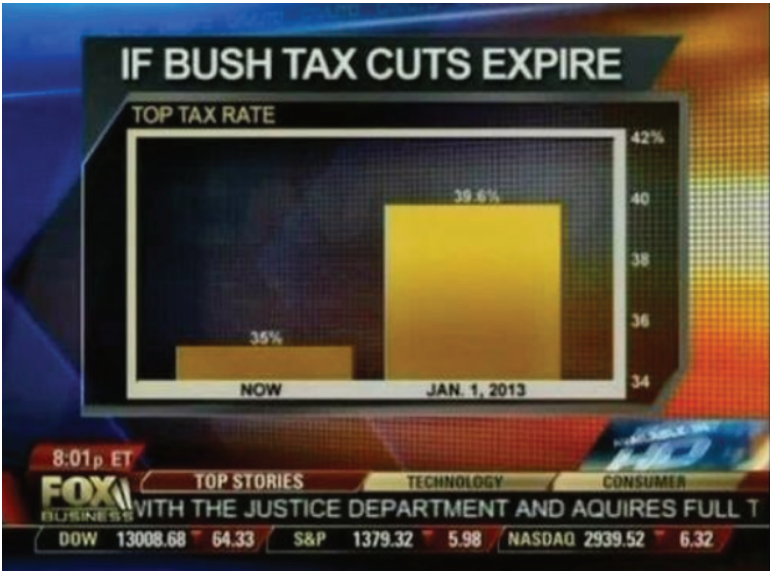

We not only see this in the business world, but also in politics;



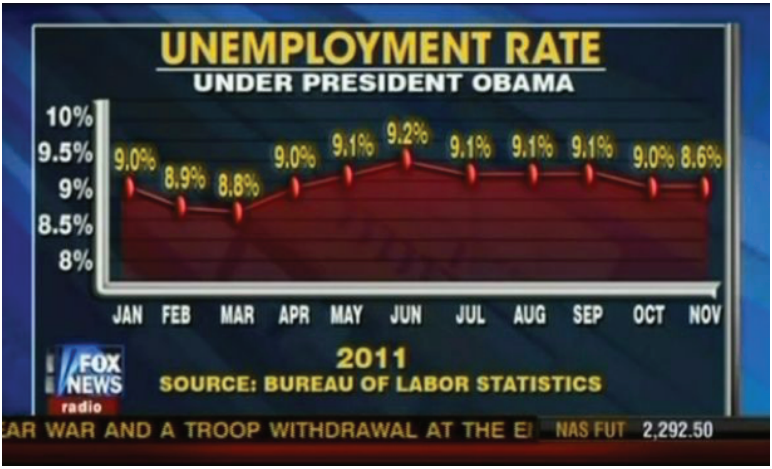
At the first glance, you would probably think that Democrats agreed almost three times more than Republicans and Independents. However, after taking a closer look, we can see the difference is much less prominent (14%). It is obvious that this graph is trying to manipulate us so we hold incorrect opinions against certain group.

Now let's look at an example from Fox News.

In this graph, they are trying to do the same thing as the previous example. If you take a closer look, you'll realize the margin is only 4%. However, the graph that Fox published makes one tax rate seems 4x larger than the other. It is very obvious what they are trying to do here: manipulate their audience.




Here's another example from Fox News:

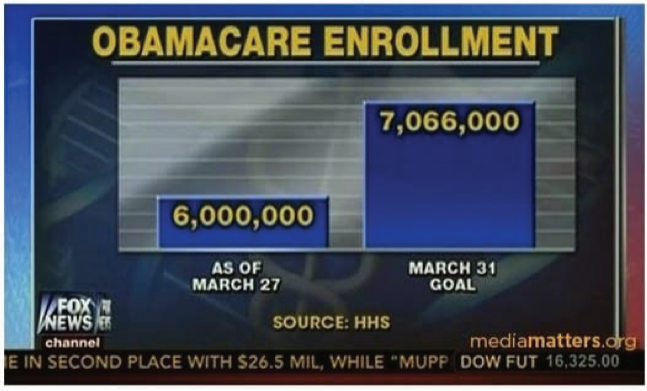



There are two mistakes in this graph:

1. The value for November (8.6%) was plotted incorrectly. It should be much lower.
2. It has been plotted as it looks like there is a steep increase (From March to June), but in fact, the unemployment rate is almost stable at around 9%.

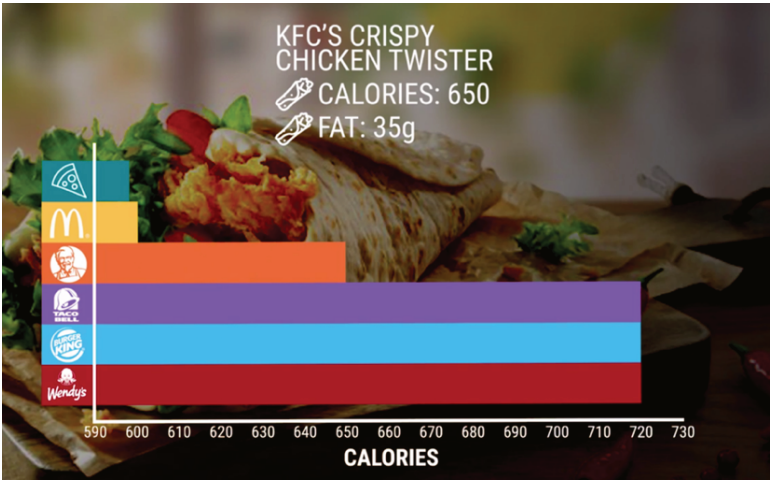
The time when 7 million was five times more than 6 million.

Obamacare Signups, According to Fox News




Source: Media Matters of America

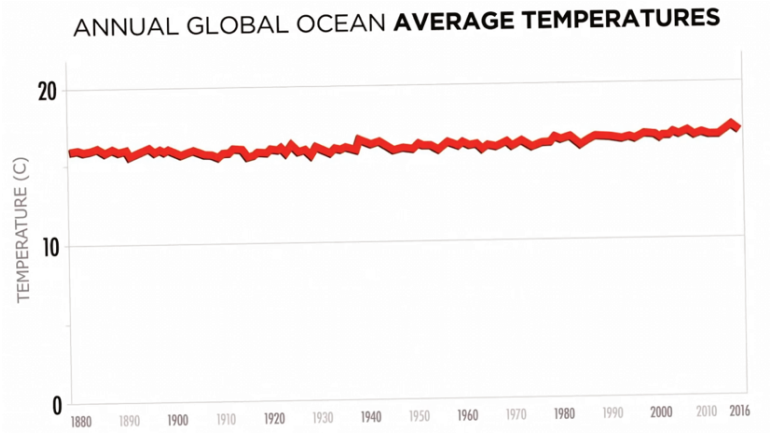
We see the same thing in nutritional information; this time the scale is distorted on the x-axis:



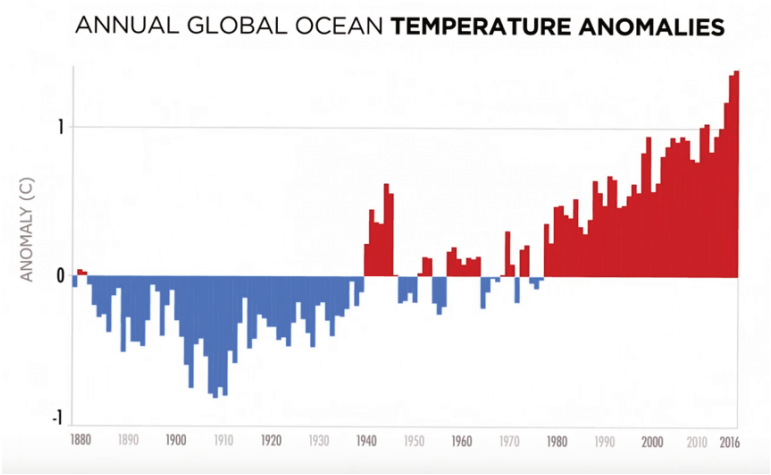

Axis alteration is a very powerful tool and can be used to push a false narrative.

For example, take a look at this graph of global warming data from the National Review:

They intentionally used the scale from 0 to 20 degrees, making the change in ocean temperature seem insignificant, supporting their claim that: global warming is not happening.

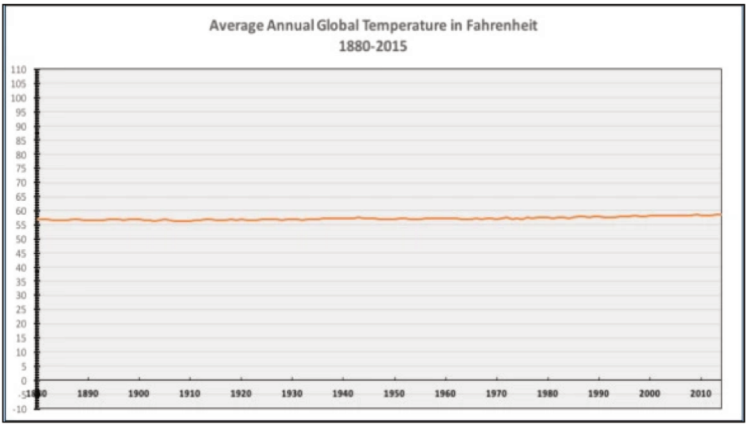


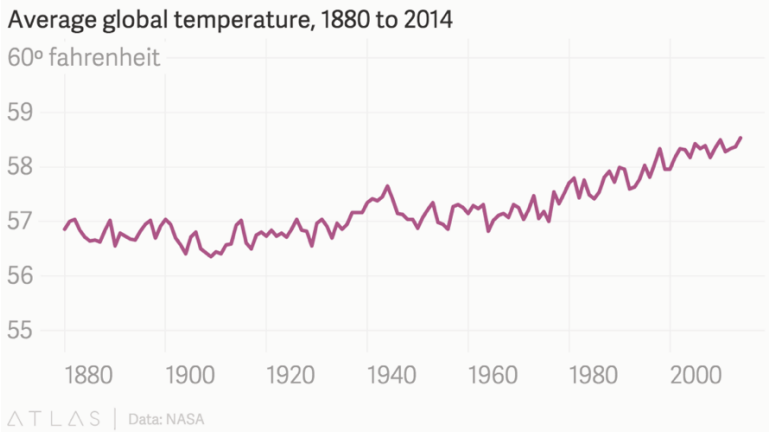

Now let's plot it a different way. Now we can tell that the ocean temperature is definitely changing.



Also, a graph can't tell you much if you don't know the full significance of what's being presented. Although the ocean temperature has only been changing 1-2 degree Celsius, the fact is, a rise in even half a degree Celsius can cause massive ecological disruption.

Same thing happened here:

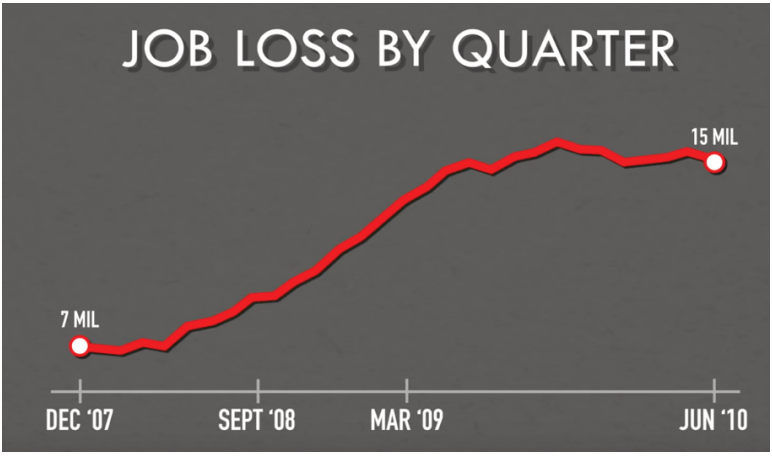


The following is another example of axis manipulation:

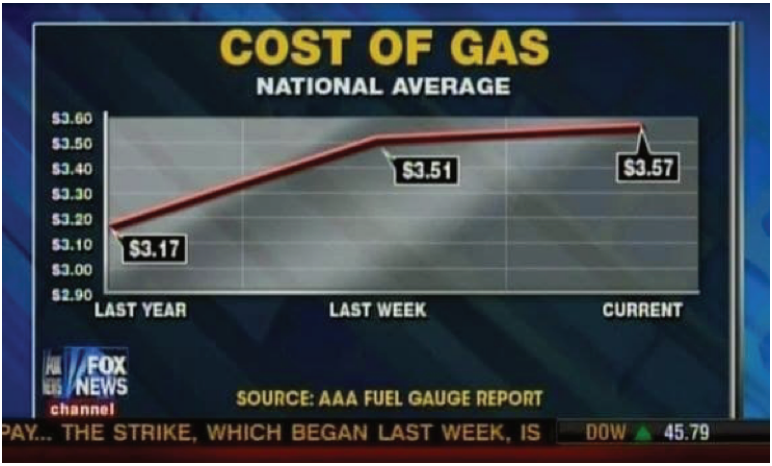
Here Fox News is trying to give the impression that the number of job loss kept increasing from December 2007 to June 2010. If we take a look at the x-axis, the interval between March 2009 and June 2010 isn't the same as the others.


Using more consistent data point, let's replot the graph;




Now it is obvious that the job loss actually started to plateau since March 2009. And if you are wondering there were increasing in the first place, the timeline starts immediately after the US biggest final recession since the Great Depression.

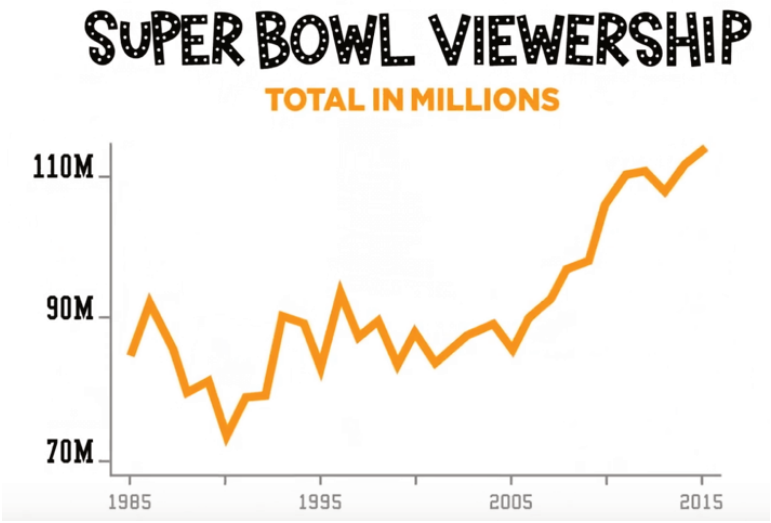
The graph where last year, last week, and today are equally far apart.



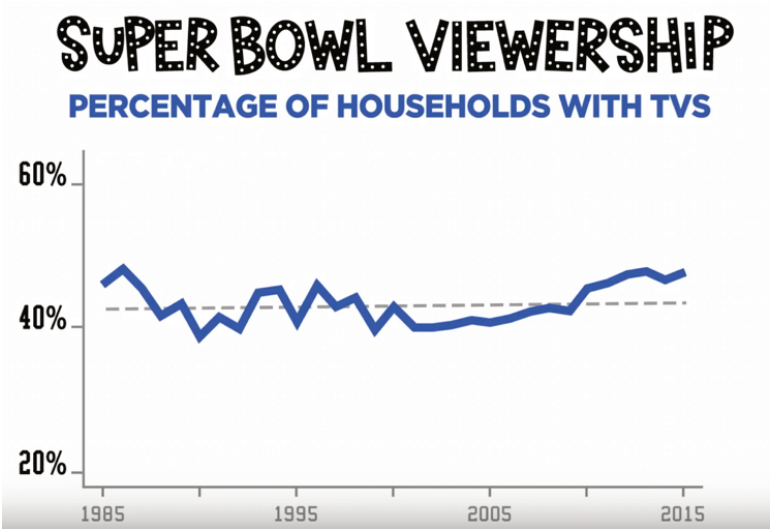

2. **Incomplete data**

Cherry picking data is another way to mislead the audience. By including only certain parts of the data, it could skew our viewpoint in a certain way. This technique is also called improper extraction, as only a certain proportion of the data is included. Such technique is very often used when there is time as one of the axis. A time range can be carefully chosen to exclude the impact of the major event right outside it. And picking specific data points can hide important changes in between. Even if there is nothing wrong with the graph itself, leaving off data can give a misleading impression.

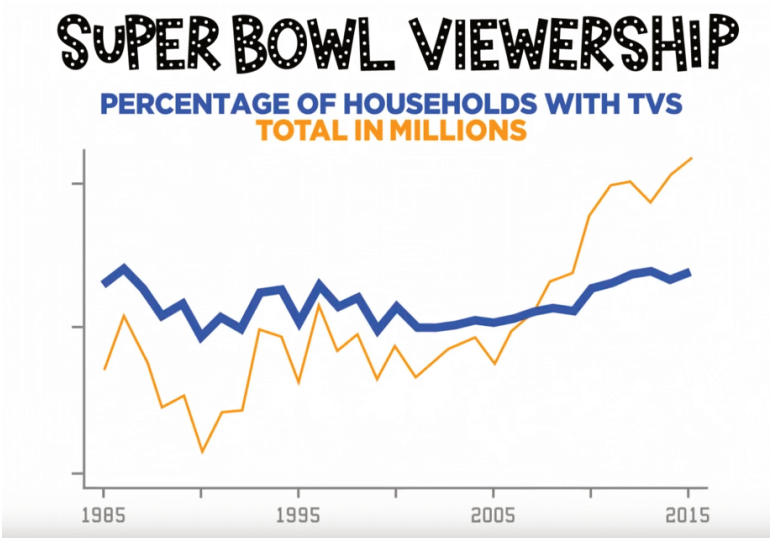
The following graph charted how many people watch the Super Bowl each year, making it look like the popularity is exploding.



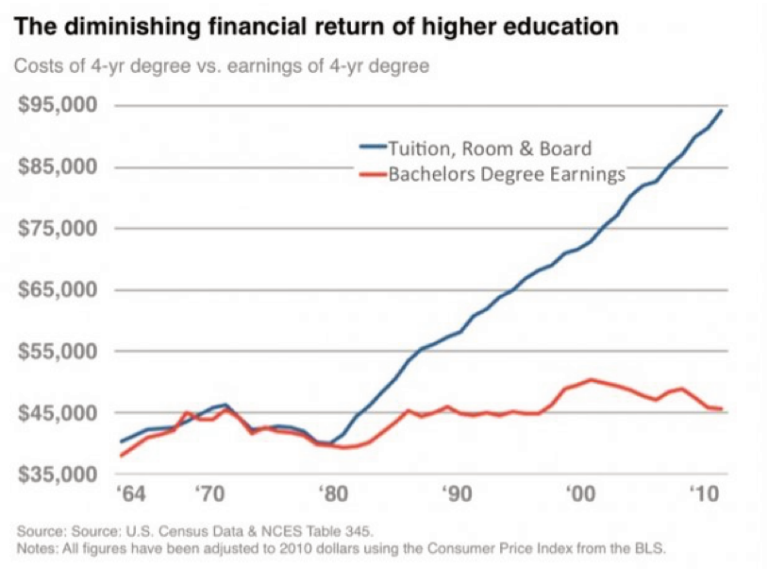

However, it did not account for the population growth.



The ratings have actually held steady. Because while the number of football fans has increased, their share of overall viewership has not.




How about this graph: can it prove that college education is not worth the money (This is what Business Insider deduced from this chart):

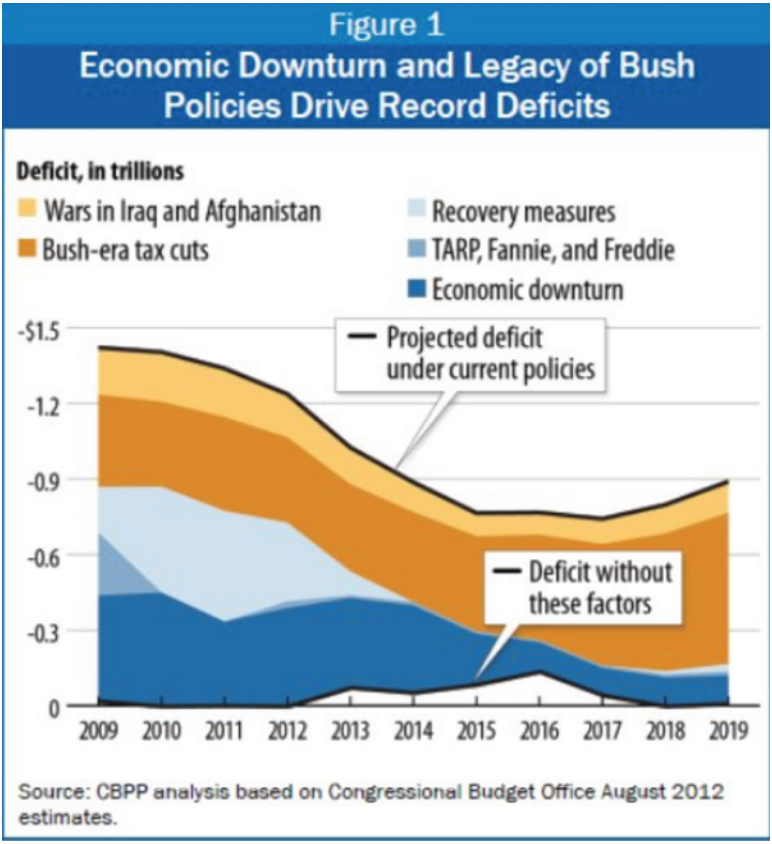



No. Because $45,000 is the average yearly income of a college grad in 2010. It's per year. Not the net income over their lifetime. Also, the fact is, the cost of not going to college is even higher.

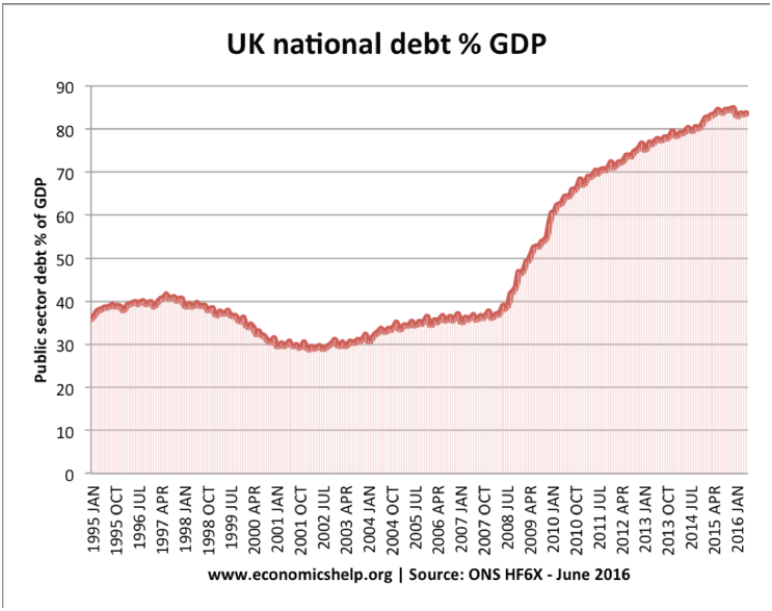
Let's look at another example;

This graph shows the economic downturn and legacy of Bush policies drive record deficits.

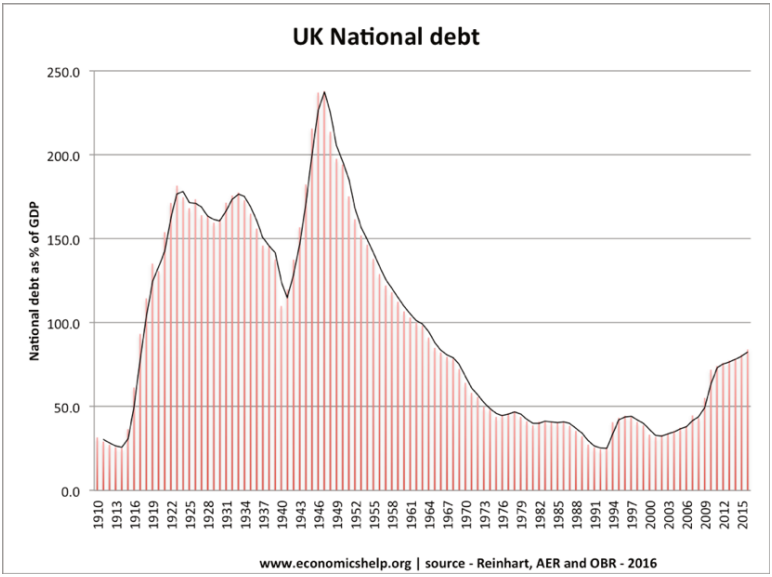
This graph makes it look like the deficit has always been high, because the graph starts in 2009. This might make you to think that the deficit has been an ongoing problem. the truth is: The deficit was just 1.2 percent of GDP in 2007, when the housing market collapsed. When you want to show an economic downturn and record deficit, you should go back in time as far as possible to draw the whole picture.




Here's another one:




After seeing this graph, everybody would think that the UK national debt has been increasing recently and has reached the highest point in history. However, if we looked at the time previously, we can see the whole picture: the debt is actually much lower compare the 1940s.




3. **It's just wrong**

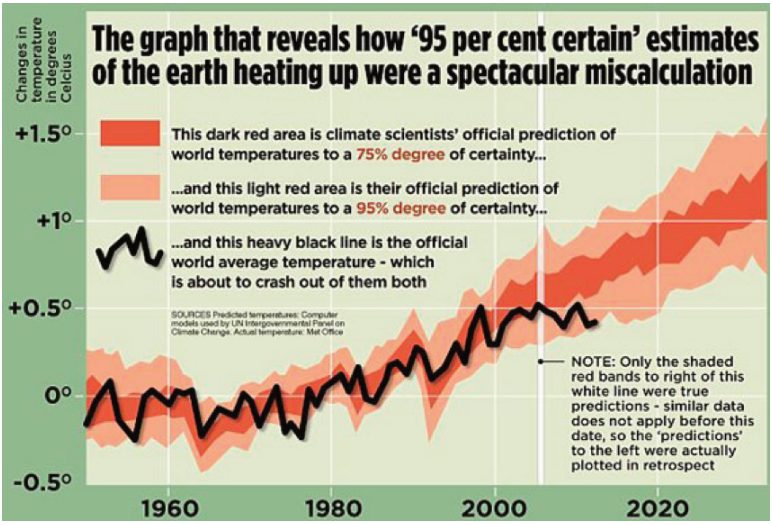
Here's another global warming picture, from the British tabloid the Mail on Sunday. The newspaper used it to claim that *global warming had stopped.*

When we read newspapers, we often think the people writing the articles are experts. In fact, the journalist who wrote the article to go with this picture just didn't understand what the graph was telling him. He made two errors:

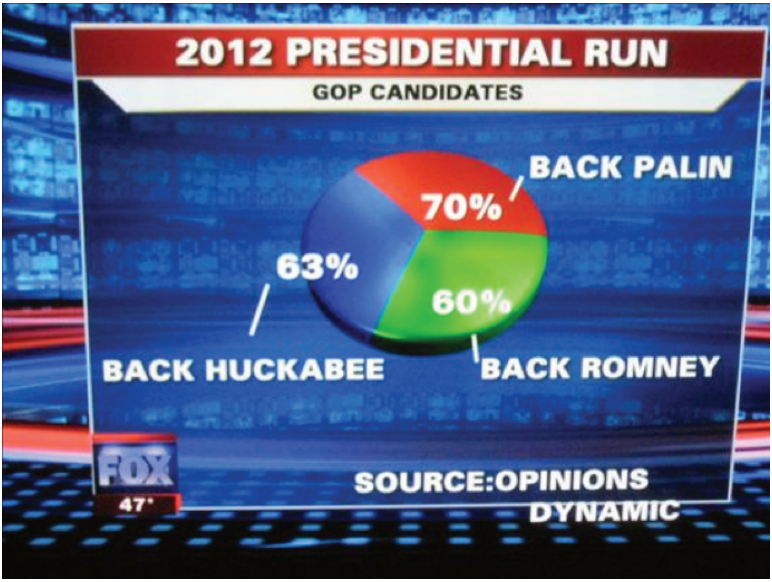
There are two mistakes in this graph:

1. The graph is showing air temperatures. In fact, air temperature is a very poor measure of global warming. Ocean temperature is a much more accurate measurement since most of the heat ends up trapped in the ocean.

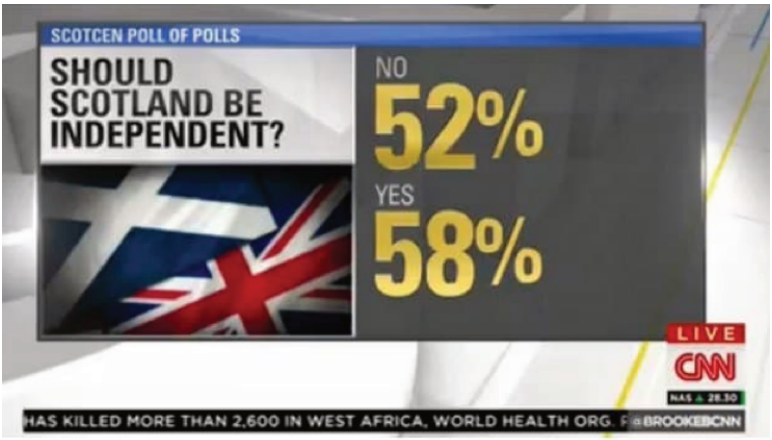
2. This is a very short-term graph. we need more data to see the whole picture.



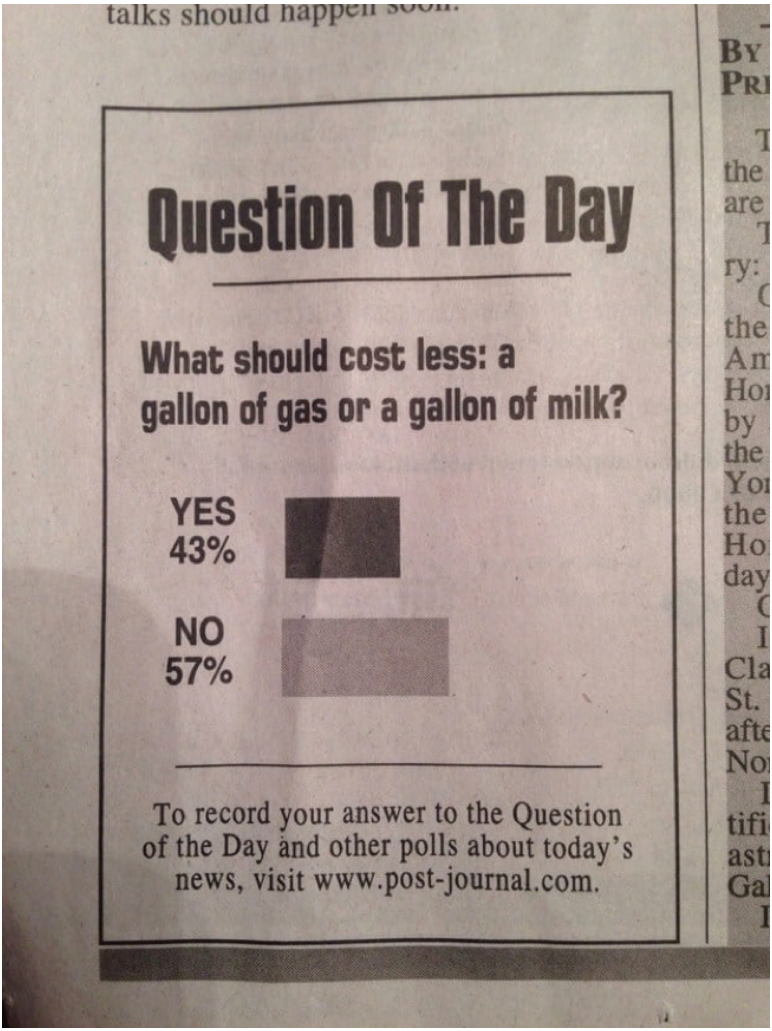

This one is just wrong: we all know each component of the pie chart should add up to 100%.




Same thing happened here:

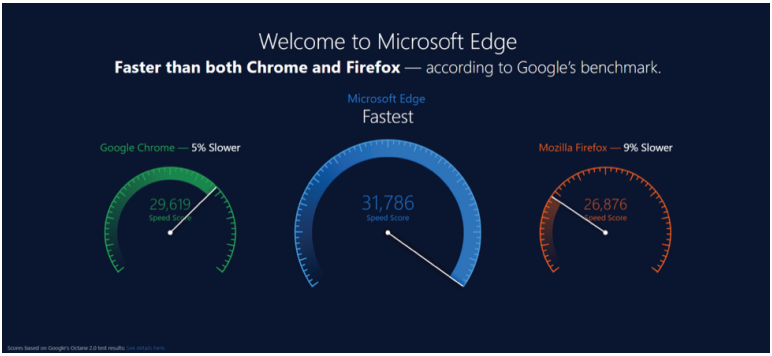


It just doesn't make any sense:

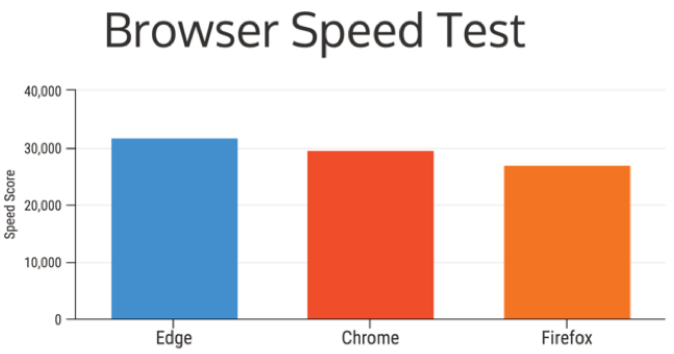



This is an advertisement from Microsoft.

Obviously, it is trying to convince the viewer that Microsoft edge is faster than Chrome and Firefox. Although that is true, it is only faster by a slight margin. From the graph it looks like Edge is 25% more faster than Chrome and 50% more faster than Firefox.

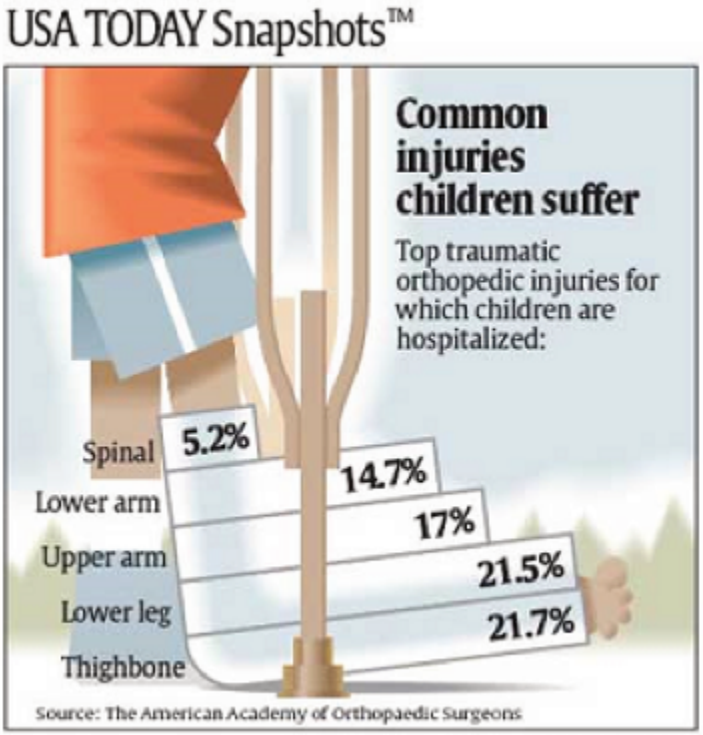



If we plot it differently, it looks something like this:



Let's look at this graph:

You might think there's nothing wrong with it, until you take a look at the heading: 5.2% of the common injuries children suffer are spinal injuries. That is a very scary number. The truth is: only 5.2% of traumatic orthopedic injuries are spinal injuries. And the number of spinal injuries is only about 2000 injuries per year, out of a population of 74,000,000 injuries. So the real figure is only around 0.000003%.



# 10. PESTLE Analysis

LOUIS GASPARINI, JOHN BRITTO, ALLAN HUMPHREY, NAHEEN IMTIAZ

## PESTLE – An External Environment Analysis Tool –

When a business wants to enter into a new market, launch a new product or both (often both when a business is starting out) there are several different factors that must be considered in order to be successful. Many of these factors are external to the actual business itself, and often completely out of the control of those running the company; however, they may have profound effects on the growth of the business or sale of a product. Often, trying to consider all of these outside topics can seem overwhelming; however, this is where analysis tools such as PESTLE become useful. PESTLE, and acronym

for Political, Economic, Social, Technological, Legal, Environmental (or Ethical), allows for the user to compartmentalize these topics, and to review the implications in more focused areas first before looking at the larger picture. Using PESTLE type analysis tools usually isn't to purpose solutions right away, but rather to consider what external factors the company has little control over, which category they exist in, and how they may impact the growth of your business or product.

The PESTLE system is flexible, with the user free to add or remove letter as needed or as necessary. For example, PEST (Political, Economic, Social, Technological) may be used if Legal or Environmental do not need to be considered. Or there is PESTLIED which adds International and Demographic to the analysis.

For this project, we will outline what factors a PESTLE user should consider when using the system. Each letter will be looked at individually and examples are considered in each case.

## Political Factors

Political factors have substantial influence on the way firms conduct their operations. Governments are responsible for implementing laws and codes that can directly or indirectly affect every aspect of a business. Political factors are therefore innately intertwined with legal factors. The main difference being that political factors are trends in attitude toward certain things, while legal factors are defined and must be complied with. A few examples of political factors that should be considered when conducting a PESTLE analysis are:

- Taxes;
    - How much does a government deem fair to tax?
    - What tax incentives and benefits exist based on the vision

of a political regime?

- Trade Agreements and Regulations;
    - Does the government have free trade deals with other countries (such as NAFTA)?
- Consumer Protection;
    - What standards must your products and services meet?
- Competition Regulation;
    - Does the government impose regulations to promote competition and restrict monopoly?
- Government Stability;
    - Is there civil unrest under a certain regime, or a potential conflict forming between two countries? How does this affect the level of risk for a firm?

For a list of more political factors to consider in a PESTLE analysis See table 1.

The effects that governmental regulations have on a business are extensive, and cause direct or indirect consequences. An example of an indirect effect would be emissions reductions incentives causing an increase in demand for electric vehicles. These incentives are set forth in order to reduce pollution but can indirectly influence market demand for certain products. An example of a direct effect would be the abolishing of trade deals, causing an increase in the cost of importing and exporting materials, and subsequently a firm's budget.

The amount of influence that certain political factors have on business operations will be unique to a firm. Analysing positive and negative effects caused by governance can aid in determining potential risks and rewards for a business and should be taken into consideration when examining the external environment.

## Economic Factors

The economic environment that a business operates in is arguably the most significant source of opportunities to capitalize on, as well as challenges and risks that must be addressed. Economic factors encompass everything to do with growth rates, trade, supply and demand, market trends, competition, currency fluctuations. Economic forecasting can be used to predict the direction and scope of economic trends and can be a valuable tool in decision making. Major Economic factors that should always be taken into consideration are:

- Growth rates and projections;
    - Is growth expected in your industry?
- Stock market and investment trends;
    - Is your industry hot for investing, or stagnant?
    - Are stocks expected to increase or decrease in value?
- Currency fluctuations;
    - Are your holdings in the currency of a particular country? Will their value hold?
- Customer preferences;
    - Are consumer trends changing? How will this affect demand for your product or service?
- Interest rates;
    - Significantly affect the growth of capital.

The set of economic factors that a company might face will vary significantly between industries. It is the responsibility of a particular company to take into account the economic environment they are operating in. The performance of the economy has direct effects on the success of a business, and can have long lasting consequences.

Companies, for example, must operate carefully during economic downturns, so as not to burn through all the resources they possess.

## Socio-cultural Factors

This segment of a PESTLE analysis focuses on the socio-cultural factors of a region that can affect an organization. The influence these factors have can be overt or subtle, but they play an important role in shaping the way an organization operates. Socio-cultural factors include, but are not limited to:

- Population demographics
- Cultural values & traditions
- Social taboos
- Buying trends
- Popularity of forms of media
- Prevalence of technology
- Education
- Spending & saving attitudes

These factors can provide crucial information about the local populace that an organization can use to when deciding how to operate. Socio-cultural factors can have some obvious impacts on organizations such as influencing what products and services they develop, how they advertise and their overall revenue. These are some of the more overt impacts of socio-cultural factors, however there are more subtle impacts that they can have. For example, if the area of operation is saturated with an aging/retired population more resources may need to be allocated to employee operations to provide employment incentives.

The way an organization responds to, and works with, the sociocultural factors in the area they operate can have a large impact on their overall success

## Technological Factors

There are a few different technological factors that need to be considered during a PESTLE analysis. These topics fall into a few different categories. The first is manufacturing technology. These look at the technology used by a company to manufacture a product. These considerations are applicable from small scale to large automated production lines. Some questions that need to be answered are:

- What technology is available to aid in manufacture the product?
- What new technology exists that would make manufacturing better?
    - Automation
    - Higher quality materials
    - Better quality control technology
- Is upgrading affordable? Will it save money or increase profit?
- What technology does the competition use to manufacture its products?
    - Does this give them a competitive advantage?

Examples of manufacturing technology are easy to find. There are countless large-scale manufacturing operations today, with an obvious example being the automotive industry whose advancements in automation has allowed them to increase production . In the biotech industry there are also many examples of increased efficiency of manufacturing technology. Looking at alcohol

production or bio-pharmaceuticals, better molecular biology understanding and techniques, improved bioreactors, and downstream process equipment has allowed for these industries to gain increased production through these technological advantages. PESTLE analysis of these manufacturing technologies gives the user an overview of what type of tech is out there and what is the proper fit for their business model or product development.

The technological analysis must also consider the technology of the product itself and the trends of innovation surrounding the tech. Things that need to be considered are:

- What do consumers use the product for?
    - Can this application be improved?
    - Consider additional applications using the same product
- How rapidly does technology change in your sector?
    - What is the life cycle of the technology?
    - Does it change every year? Or is it stable over decades?
- How is your product distributed or sold?
    - Will advancement in other technology change the distribution?

An example of changing technology trends that had a large impact is in the film industry. Technological advancements have changed the landscape of how this product is distributed. The development of television and home video technologies would give rise to the home video market, and eventually the video rental market, which was a huge deviation from the traditional theater model. However, advancement of the internet and digital content technologies lead to digital downloads and streaming services and which caused huge problems for the home video and rental market. A PESTLE analysis considering these factors may allow for a user to keep ahead of these trends and adapt the product or company accordingly.

Finally, there are also technological considerations that overlap with social, political and economic factors. Biotechnologies like GMOs have a negative status in many markets, and politically they are banned in Europe (for GMO crops.) An example of technological/economic factor, is when the the government increases of decreases spending in a technological sector, health or agricultural research for example, which will impact the funding available to develop technology in those areas.

## Legal Factors

This segment of the PESTLE focuses on the legal factors that an organization can operate within, these can range from federal to local and includes all laws, rules, regulations and policies. It also includes all the internal rules, policies and regulations that an organization might have.

- Employment Laws
    - Minimum wage rate
- Tax laws
- Laws specific to certain products
    - Biologicals for example

These factors are very important as they make up a strict framework that an organization must operate within, failure to meet legal requirements can lead to severe penalties. These can include fines, suspension of operations and loss of reputation. Larger organization that operate on a global level must deal with the multiple legal frameworks that exist over the multiple countries they operate it.

## Ecologic/Environmental Factors

Environmental awareness is of increasing importance to businesses operating in modern society. We are living in a world which faces changes in climate and where there are increased frequency environmental disturbances caused by human activity. Environmental impacts can include issues such as natural resources limitation, waste management and recycling procedures. There are lots of factors that are changing in the environment and therefore gathering information about them is a priority step in PESTLE analysis.

Environmental factors take into consideration ecological and environmental aspects. Ecological factors consist of all forms of natural resource conservation and its management which includes water, oil and land. They can also affect the workforce's health and moral and can cause uncertainty and risk if it is ignored.

The factors in this tool are determined and influenced by the surrounding environment. For example, in tourism, farming and agriculture business, environmental aspect holds a crucial value.

Factors of environmental (ecological) analysis could include but are not limited to the following:

- Geographical location of the company or organization
- Changes in climate
- Weather offsets
- Concerns in causing pollution;
    - Is there a more sustainable alternative to current operations?
- Recycling
- Waste disposal and sustainability;
    - What opportunities exist to reduce pollution?

- Whether the company/organization is affecting any endangered species or not
- Whether the organization is open towards the use of renewable energy, ecological or "green" products.
- Carbon emissions

These factors have become important recently over the years due to the scarcity of raw materials, increased burning of fossil fuels, pollution level, carbon emissions targets set by the government, etc as way of doing business as sustainable company. Nowadays consumers are demanding that the products they are using are sourced out ethically and sustainably. It is necessary that these elements be analyzed as the importance of corporate sustainability and responsibility (CSR) is growing. Climate change is a hot topic these days. Discussions are taking place on how to reduce the global warming effect and thus the operation of businesses needs to be reconstructed so that more space can be given to innovation and can also lead to development of green business. Ecological and environmental factors not only engage the organizational behavior and culture but also involve engagement of the employee.

A firm's decision regarding doing their business must be impacted by environmental factors as the business in question needs to be environmentally and socially acceptable. In this way, they will also gain a positive image in the consumer's eyes.

## Ethical Factors

Ethics is another factor that needs to be taken into consideration. It is one of the new factors that have recently came into the forefront when conducting a PESTLE analysis. PESTLE analysis underwent some changes as ethical concerns can be utilized in the framework

of PESTLE while researching about the market. Ethics can be defined as a "set of moral principles and values that govern the actions and decisions of an individual or group" (Oxford Learning Labs). Ethical analysis can provide guidelines for an organization on how to act rightly and in a just manner so that the organization does not have to face dilemmas regarding ethics, such as public backlash.

The factors of concern in ethics can include the following:

- Whether the practices in sales and advertising are ethical or not;
    - Is everyone getting a fair end of the deal?
- Standards with accounting, management, and marketing are acceptable or not
- The attitude of the organization towards counterfeiting and breaking patents
- The recruitment process and the standards of employment are ethical or not (for example hiring children to do the work is not acceptable).
- Affiliation between corporations and charities

Ethical factors are important as they address responsibilities regarding the corporate and social actions.

These PESTLE factors can be weakness or opportunity for an organization or company depending upon the situation. Therefore it is crucial that the above factors are identified and analyzed so that any alterations in the business climate change arises, appropriate actions could be taken so to respond to factors that could impact the product or service offering in an ever changing business environment.

**Conclusion**

Using the above PESTLE analysis will allow a business to consider many external factors before launching a new product or entering a new market. While PESTLE is extensive, there are more factors

that can be considered if needed. The analysis should not feel limited and those performing it can freely add or remove sections that are applicable. The one thing to keep in mind is that this is not meant to provide immediate solutions. It is a tool to neatly identify all factors that a company may not have any control over, see the connections between them and gain insight that should give an edge in the market and over competition.

**References**

# 11. Visualizing Your Data with Tableau

You can view this tutorial in PDF format here

## INTRODUCTION

Tableau is a user-friendly platform for visualizing, analyzing, and sharing data. Its aim is to make easy-to-understand solutions based on raw data.

The platform can be easily used by individual analysts or scaled across a large organization. Tableau makes it simple for data from different individuals or departments to be combined or shared in one place.

There are multiple paid products produced by Tableau, each with unique services and customer segments:

**Tableau Prep** allows users to combine, shape, and clean their data from a variety of sources.

**Tableau Desktop** is the main platform for visualizing and analyzing data and turning them into interactive dashboards and reports.

**Tableau Online** allows you to publish your work online and share it with anyone you give access to.

**Tableau Server** gives you more control over who can see your work, and it is usually used to share data within an organization.

**Tableau Public** is a free service that allows you to create data visualizations from limited sources that must be published to the public server.

Tableau's paid products enable users to collect data from a variety

of sources, including Microsoft Excel spreadsheets, PDF files, and web-based data providers. Your work can even be updated live as your source data is updated. Tableau is also able to combine your data from multiple sources into one document.

Tableau can be used on desktop, tablet, or mobile, making it very convenient for sharing data with many users on a variety of platforms. Dashboards and other work can be shared with anyone you'd like to give access to it, whether by sharing links to your Tableau profile through social media or emails, or by embedding Tableau dashboards into your own website.

If you are interested in learning more about using Tableau beyond this introduction, there are hundreds of eLearning and live training opportunities available on the Tableau website. A variety of tableau certifications can also be identified through the website. More video tutorials can be found on YouTube, Lynda, or Udemy.

For an example of the power of Tableau in action, check out Western Carolina University's profile on Tableau Public to see some of their interactive dashboards at this link

## Tableau Public Tutorial

Use the following dataset to complete this tutorial!

Tableau Sample Data

## FORMATTING AND UPLOADING DATA

It is important to ensure that data that is obtained from external sources is of good quality. If you choose to select data from online sources, choose websites that are reputable. Sites such as Statistics

Canada or the World Health Organization are great resources. In the example throughout this tutorial we selected data from The Canadian Institute for Health Information.

You are able to select from various file types when working with tableau.

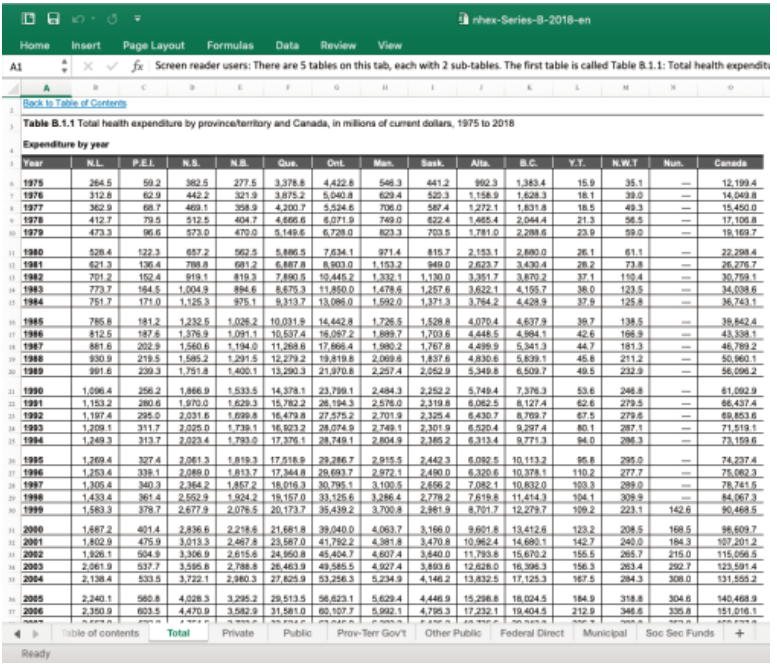
Examples of acceptable data files include Excel files, PDF, or text files. Data can also be uploaded from servers such as Google Sheets.

The data needs to be in the correct format before uploading to Tableau

The data you want to use in Tableau should follow these guidelines.

1. The data should be granular as possible. This means that your data is detailed rather than just average values.
2. Ensure that there are no aggregated data (no total values)
3. All extra titles and notes should be removed. This excludes data headers.
4. Ensure that there are no blank cells or rows
5. The data should follow database format where it is row-oriented rather than column oriented. Tableau is optimized to work with row-oriented tables. This can be done either in Tableau or before you upload your data.

Here's an example of how to reformat the data:



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Home Insert Page Layout Formulas Data Review View

A1 Screen reader users: There are 5 tables on this tab, each with 2 sub-tables. The first table is called Table 8.1.1: Total health expenditu

Back to Table of Contents

**Table B.1.1** Total health expenditure by province/territory and Canada, in millions of current dollars, 1975 to 2018

**Expenditure by year**

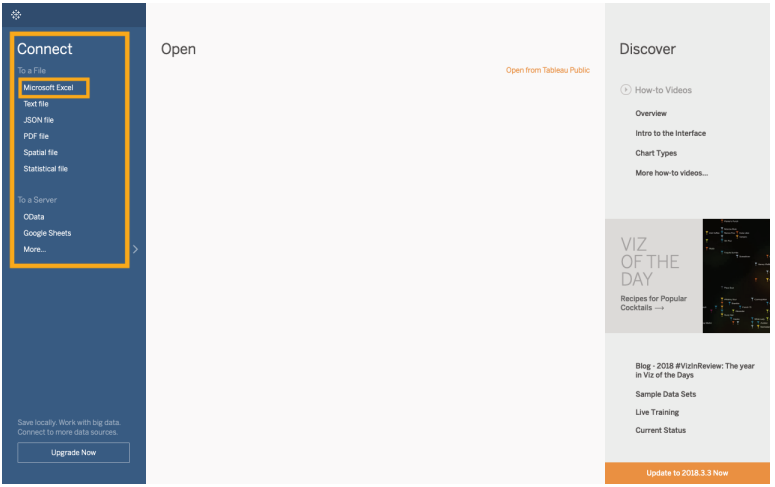
| Year | N.L. | P.E.I. | N.S. | N.B. | Que. | Ont. | Man. | Sask. | Alta. | B.C. | Y.T. | N.W.T | Nun. | Canada |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1975** | 264.5 | 59.2 | 382.5 | 277.5 | 3,378.8 | 4,422.8 | 546.3 | 441.2 | 992.3 | 1,383.4 | 15.9 | 35.1 | — | 12,199.4 |
| **1976** | 312.8 | 62.9 | 442.2 | 321.9 | 3,875.2 | 5,040.8 | 629.4 | 520.3 | 1,158.9 | 1,628.3 | 18.1 | 39.0 | — | 14,049.8 |
| **1977** | 362.9 | 68.7 | 469.1 | 358.9 | 4,200.7 | 5,524.6 | 706.0 | 587.4 | 1,272.1 | 1,831.8 | 18.5 | 49.3 | — | 15,450.0 |
| **1978** | 412.7 | 79.5 | 512.5 | 404.7 | 4,666.6 | 6,071.9 | 749.0 | 622.4 | 1,465.4 | 2,044.4 | 21.3 | 56.5 | — | 17,106.8 |
| **1979** | 473.3 | 96.6 | 573.0 | 470.0 | 5,149.6 | 6,728.0 | 823.3 | 703.5 | 1,781.0 | 2,288.6 | 23.9 | 59.0 | — | 19,169.7 |
| **1980** | 528.4 | 122.3 | 657.2 | 562.5 | 5,886.5 | 7,634.1 | 971.4 | 815.7 | 2,153.1 | 2,680.0 | 26.1 | 61.1 | — | 22,298.4 |
| **1981** | 621.3 | 136.4 | 788.8 | 681.2 | 6,887.8 | 8,903.0 | 1,153.2 | 949.0 | 2,623.7 | 3,430.4 | 28.2 | 73.8 | — | 26,276.7 |
| **1982** | 701.2 | 152.4 | 919.1 | 819.3 | 7,890.5 | 10,445.2 | 1,332.1 | 1,130.0 | 3,351.7 | 3,870.2 | 37.1 | 110.4 | — | 30,759.1 |
| **1983** | 773.7 | 164.5 | 1,004.9 | 894.6 | 8,675.3 | 11,850.0 | 1,478.6 | 1,257.6 | 3,622.1 | 4,155.7 | 36.0 | 123.5 | — | 34,038.6 |
| **1984** | 751.7 | 171.0 | 1,125.3 | 975.1 | 9,313.7 | 13,086.0 | 1,592.0 | 1,371.3 | 3,764.2 | 4,428.9 | 37.9 | 125.8 | — | 36,743.1 |
| **1985** | 785.8 | 181.2 | 1,232.5 | 1,026.2 | 10,031.9 | 14,442.8 | 1,726.5 | 1,528.8 | 4,070.4 | 4,637.9 | 39.7 | 138.5 | — | 39,842.4 |
| **1986** | 812.5 | 187.6 | 1,376.9 | 1,091.1 | 10,537.4 | 16,097.2 | 1,889.7 | 1,703.6 | 4,448.5 | 4,984.1 | 42.6 | 166.9 | — | 43,338.1 |
| **1987** | 881.6 | 202.9 | 1,560.6 | 1,194.0 | 11,268.6 | 17,866.4 | 1,980.2 | 1,767.8 | 4,499.9 | 5,341.3 | 44.7 | 181.3 | — | 46,789.2 |
| **1988** | 930.9 | 219.5 | 1,585.2 | 1,291.5 | 12,279.2 | 19,819.8 | 2,069.6 | 1,837.6 | 4,830.6 | 5,839.1 | 45.8 | 211.2 | — | 50,960.1 |
| **1989** | 991.6 | 239.3 | 1,751.8 | 1,400.1 | 13,290.3 | 21,970.8 | 2,257.4 | 2,052.9 | 5,349.8 | 6,509.7 | 49.5 | 232.9 | — | 56,096.2 |
| **1990** | 1,096.4 | 256.2 | 1,866.9 | 1,533.5 | 14,378.1 | 23,799.1 | 2,484.3 | 2,252.2 | 5,749.4 | 7,376.3 | 53.6 | 246.8 | — | 61,092.9 |
| **1991** | 1,153.2 | 280.6 | 1,970.0 | 1,629.3 | 15,782.2 | 26,194.3 | 2,576.0 | 2,319.8 | 6,062.5 | 8,127.4 | 62.6 | 279.5 | — | 66,437.4 |
| **1992** | 1,197.4 | 295.0 | 2,031.6 | 1,699.8 | 16,479.8 | 27,575.2 | 2,701.9 | 2,325.4 | 6,430.7 | 8,769.7 | 67.5 | 279.6 | — | 69,853.6 |
| **1993** | 1,209.1 | 311.7 | 2,025.0 | 1,739.1 | 16,923.2 | 28,074.9 | 2,749.1 | 2,301.9 | 6,520.4 | 9,297.4 | 80.1 | 287.1 | — | 71,519.1 |
| **1994** | 1,249.3 | 313.7 | 2,023.4 | 1,793.0 | 17,376.1 | 28,749.1 | 2,804.9 | 2,385.2 | 6,313.4 | 9,771.3 | 94.0 | 286.3 | — | 73,159.6 |
| **1995** | 1,269.4 | 327.4 | 2,061.3 | 1,819.3 | 17,518.9 | 29,286.7 | 2,915.5 | 2,442.3 | 6,092.5 | 10,113.2 | 95.8 | 295.0 | — | 74,237.4 |
| **1996** | 1,253.4 | 339.1 | 2,089.0 | 1,813.7 | 17,344.8 | 29,693.7 | 2,972.1 | 2,490.0 | 6,320.6 | 10,378.1 | 110.2 | 277.7 | — | 75,082.3 |
| **1997** | 1,305.4 | 340.3 | 2,364.2 | 1,857.2 | 18,016.3 | 30,795.1 | 3,100.5 | 2,656.2 | 7,082.1 | 10,832.0 | 103.3 | 289.0 | — | 78,741.5 |
| **1998** | 1,433.4 | 361.4 | 2,552.9 | 1,924.2 | 19,157.0 | 33,125.6 | 3,286.4 | 2,778.2 | 7,619.8 | 11,414.3 | 104.1 | 309.9 | — | 84,067.3 |
| **1999** | 1,583.3 | 378.7 | 2,677.9 | 2,076.5 | 20,173.7 | 35,439.2 | 3,700.8 | 2,981.9 | 8,701.7 | 12,279.7 | 109.2 | 223.1 | 142.6 | 90,468.5 |
| **2000** | 1,687.2 | 401.4 | 2,836.6 | 2,218.6 | 21,681.8 | 39,040.0 | 4,063.7 | 3,166.0 | 9,601.8 | 13,412.6 | 123.2 | 208.5 | 168.5 | 98,609.7 |
| **2001** | 1,802.9 | 475.9 | 3,013.3 | 2,467.8 | 23,587.0 | 41,792.2 | 4,381.8 | 3,470.8 | 10,962.4 | 14,680.1 | 142.7 | 240.0 | 184.3 | 107,201.2 |
| **2002** | 1,926.1 | 504.9 | 3,306.9 | 2,615.6 | 24,950.8 | 45,404.7 | 4,607.4 | 3,640.0 | 11,793.8 | 15,670.2 | 155.5 | 265.7 | 215.0 | 115,056.5 |
| **2003** | 2,061.9 | 537.7 | 3,595.8 | 2,788.8 | 26,463.9 | 49,585.5 | 4,927.4 | 3,893.6 | 12,628.0 | 16,396.3 | 156.3 | 263.4 | 292.7 | 123,591.4 |
| **2004** | 2,138.4 | 533.5 | 3,722.1 | 2,980.3 | 27,825.9 | 53,256.3 | 5,234.9 | 4,146.2 | 13,832.5 | 17,125.3 | 167.5 | 284.3 | 308.0 | 131,555.2 |
| **2005** | 2,240.1 | 560.8 | 4,028.3 | 3,295.2 | 29,513.5 | 56,623.1 | 5,629.4 | 4,446.9 | 15,298.8 | 18,024.5 | 184.9 | 318.8 | 304.6 | 140,468.9 |
| **2006** | 2,350.9 | 603.5 | 4,470.9 | 3,582.9 | 31,581.0 | 60,107.7 | 5,992.1 | 4,795.3 | 17,232.1 | 19,404.5 | 212.9 | 346.6 | 335.8 | 151,016.1 |

Table of contents | Total | Private | Public | Prov-Terr Gov't | Other Public | Federal Direct | Municipal | Soc Sec Funds | +

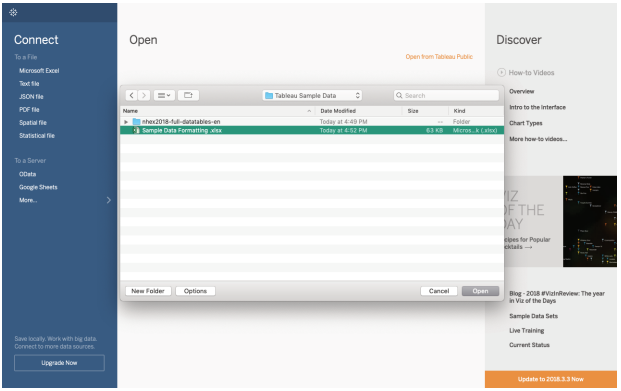
Ready

*Original Data*

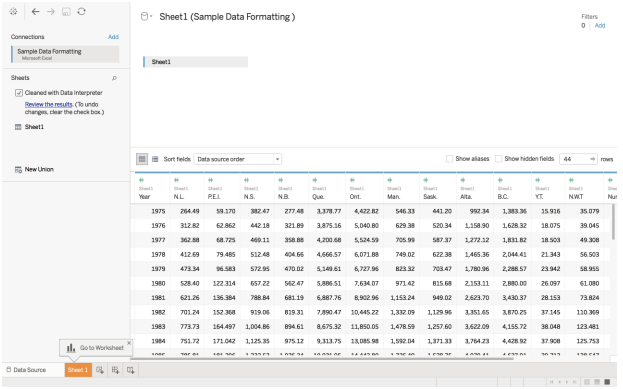
In order to optimize the data for tableau, the null data cells needs to be replaced with zeros. The extra notes at the top must also be deleted.




*Once all the data is in the correct format, you can upload the file to Tableau. From the home screen, click on the corresponding file format in the blue payne highlighted in the orange box.*




*Select the data file you need.*




*Once the data has loaded your screen will look like this.*

From here, you can reformat the table so that it is row-oriented. While holding the shift key, select the data that you want to be grouped together. In this example we want three columns, the year, province, and the expenditure. To achieve this, we need to group together all the province columns. After highlighting all columns we want to be grouped, click on the dropdown menu that appears in the heading of any province columns, and select pivot table. After pivoting the table you can rename your columns and being to work with your data set.

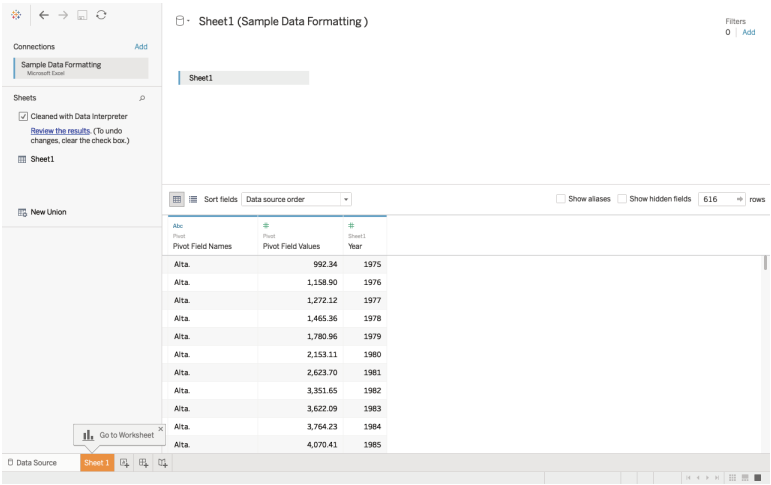
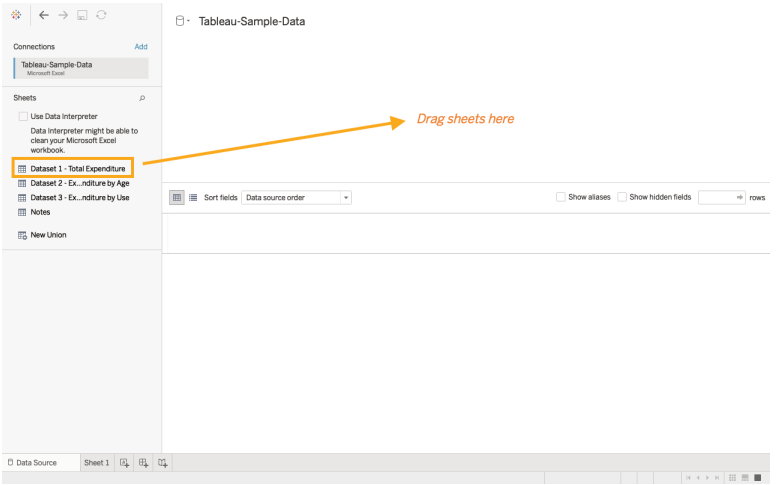
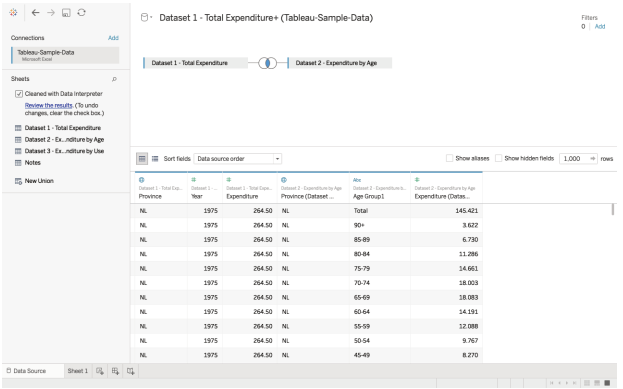



Tableau will allow you to select which sheet from the file you want to work with if you have more then one sheet in your excel file. To select a sheet, click and drag the file into the open space on the top half of the screen. During this stage you also have the option to clean up your data by checking the box on the left hand side of the screen.




To combine a data set from two seperate sheets, click and drag the two sheets you want to the center space on the top half of the screen.



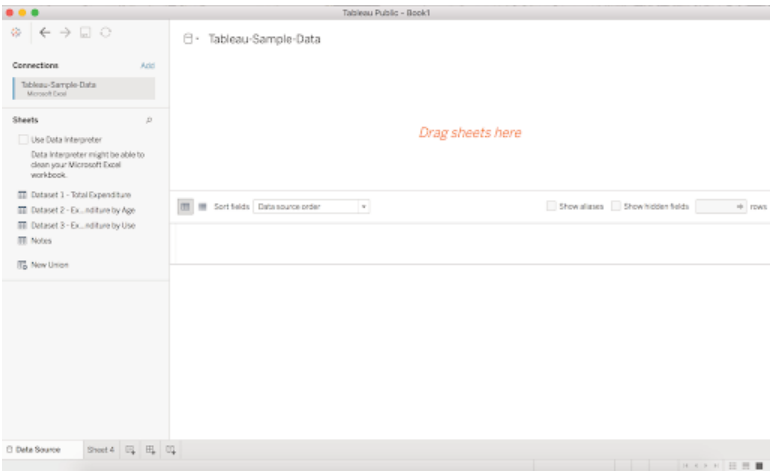

*ex) Combined data sets from different sheets on one excel file*

To begin manipulating and working with the data, select a sheet at the bottom left of the screen.

# CREATING DATA VISUALIZATIONS

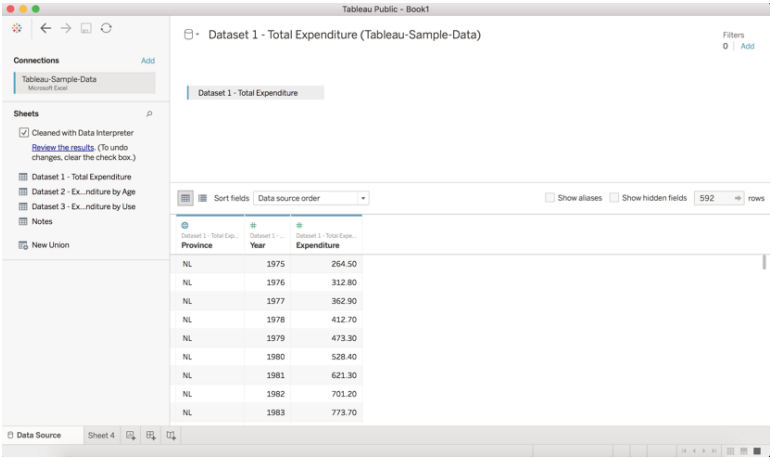
## I. CREATING A MAP OF CANADIAN HEALTH EXPENDITURE BY PROVINCE IN 2016

Once you have uploaded your properly formatted geographic data your screen will look like this:

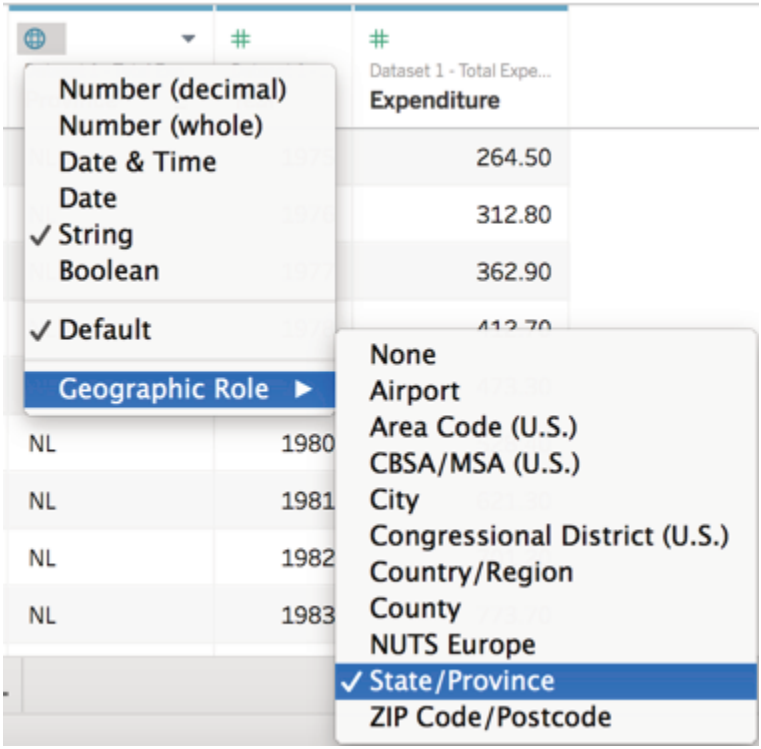



*This is your Data Source page, where you can organize your data. On the left panel, you can see the sheets that were in the Excel file that was uploaded. If these sheets have common fields, you can join them by dragging them to the center together. For our purposes, we just need Dataset 1 – Total Expenditure, so drag that sheet to the centre. But before doing this, check off the box Use Data Interpreter so that Tableau can clean up the workbook and make it suitable for use.*

After cleaning the data and dragging the sheet to the centre, your screen should look like this:

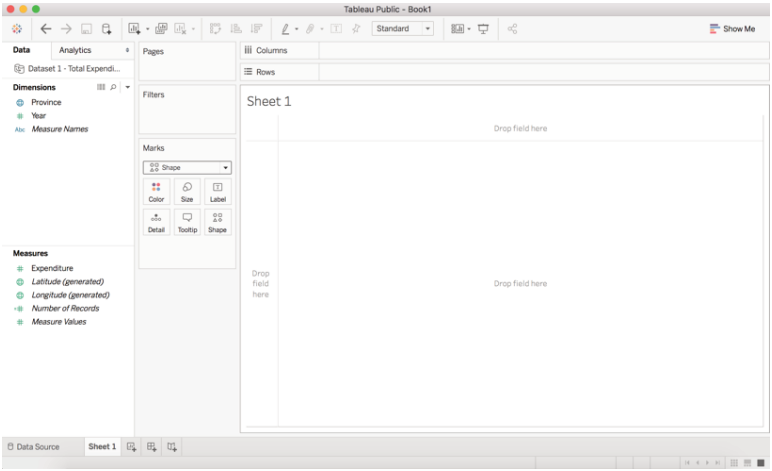



Your data is now connected, and Tableau has assigned a Data type to each column. Click the symbols in the header of each column to make sure it's the type you want. In our case, we want to make sure the Province column is assigned a geographic role. When we click this icon, we see that Tableau recognized the Province codes and did it for us!



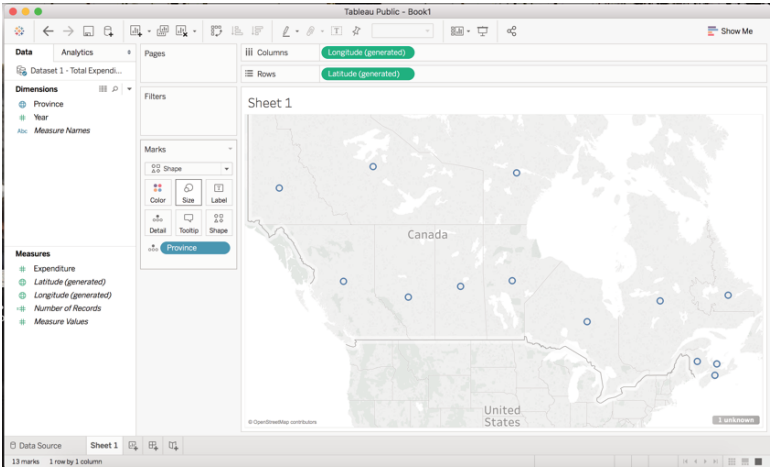

We can also see that Expenditure and Year have been assigned as Numbers which is also what we want. It's important to know about this feature for future uses.

Now, on the bottom of your screen, you should see a tab labelled Sheet 1, click this. Your screen should now look like this:



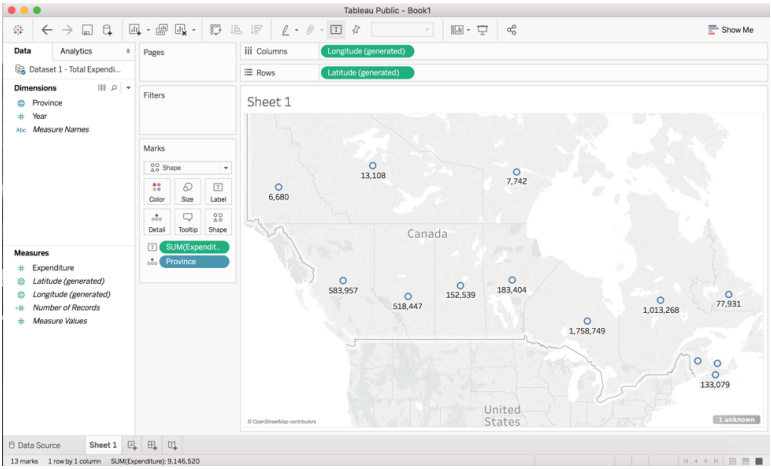

So now you're in the worksheet and this is where you will build your map. On the left side of your screen is the Data pane. The columns of your data are listed as fields and assigned as Measures or Dimensions. Dimensions are usually qualitative data and Measures are quantitative, you can drag and drop fields into either of these categories to change their assignment if needed. You can see that Tableau automatically generated Latitude and Longitude Measures because we're using geographic data.

Now, to begin creating the map, drag and drop Province into the centre of your sheet. Your screen should now look like this:



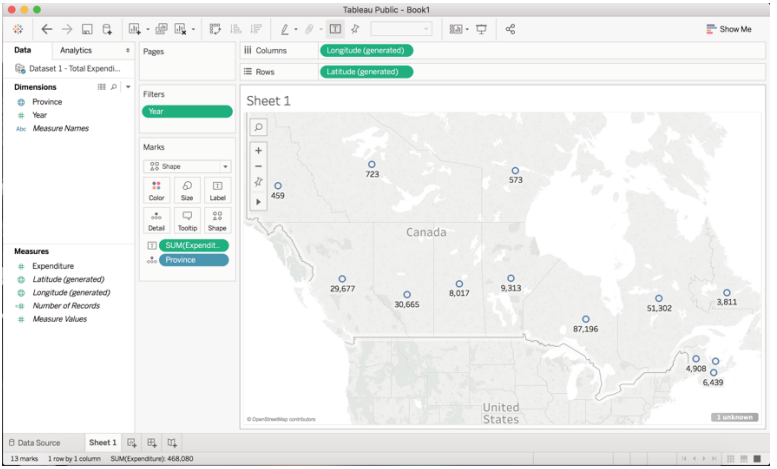

You will see that longitude and latitude have automatically been placed into the Columns and Rows shelves. You now have a basic map view that can be edited as you like by dragging and dropping other fields into the marks.

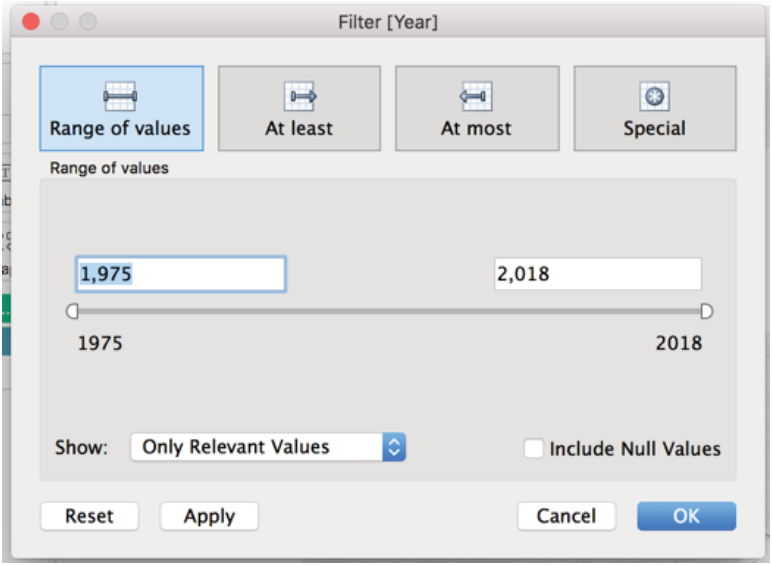
We are now going to drag Expenditure into Label:



Now, each province has the sum of their health expenditures since 1975 labelled on the map. But, we only want the expenditure for the year 2016, so we have to place a filter on the map. To do this, we will drag Year from Dimensions into the Filters box. This box should appear.

Change the Range of values from 1975-2018 to 2016-2016 to just get expenditure data from the year 2016.

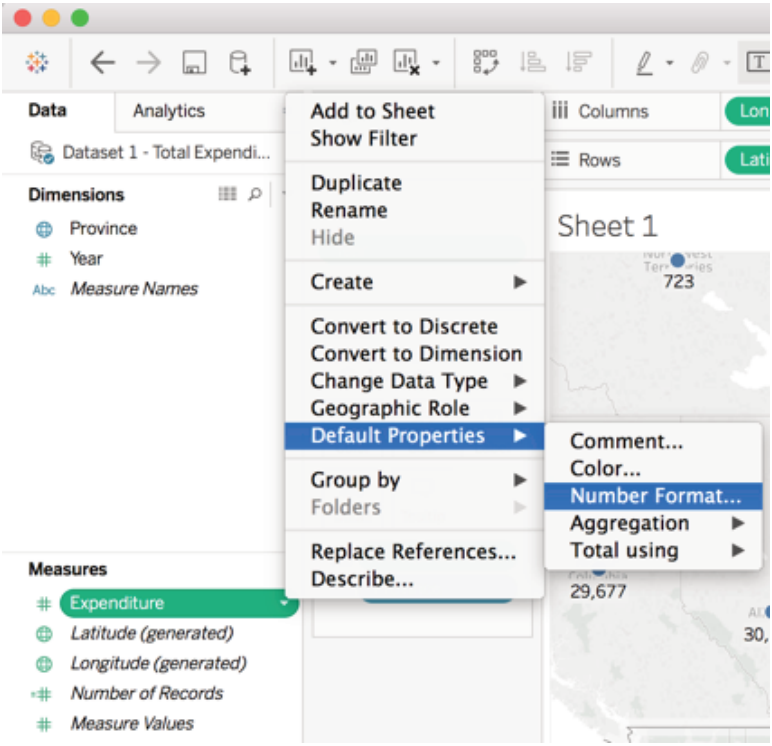




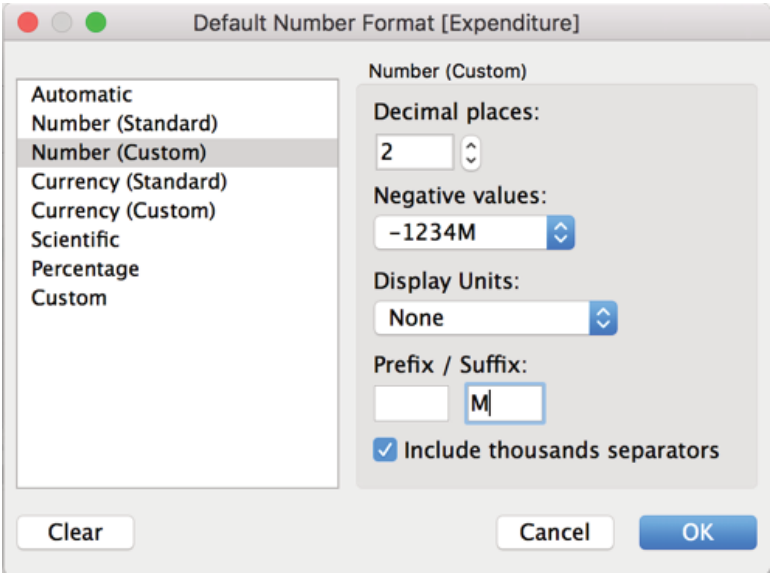

The expenditure labels should now change to look like the above image.

Now, we want to edit the label properties because we know expenditure is in millions of dollars. To do this, we click Expenditure in the Measures tab and the drop down menu should appear. Click on Default Properties and Number format.

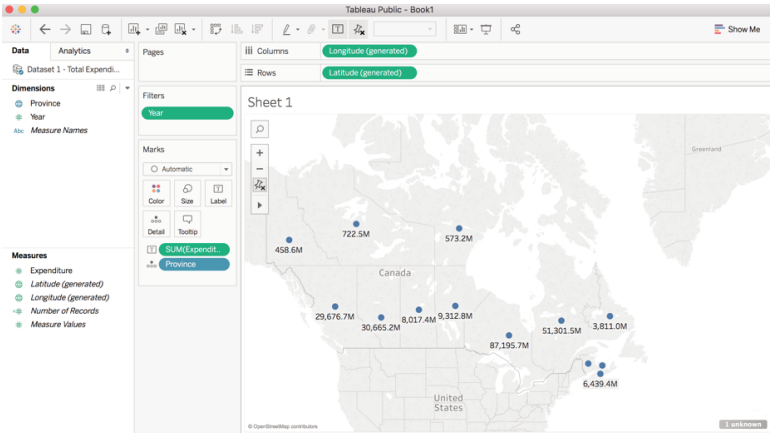
(1)


Data
Analytics
Dataset 1 - Total Expendi...
Dimensions
Province
Year
Abc Measure Names
Measures
Expenditure
Latitude (generated)
Longitude (generated)
Number of Records
Measure Values
Add to Sheet
Show Filter
Duplicate
Rename
Hide
Create
Convert to Discrete
Convert to Dimension
Change Data Type
Geographic Role
Default Properties
Group by
Folders
Replace References...
Describe...
Comment...
Color...
Number Format...
Aggregation
Total using
Columns
Rows
Sheet 1
723
29,677

(2)

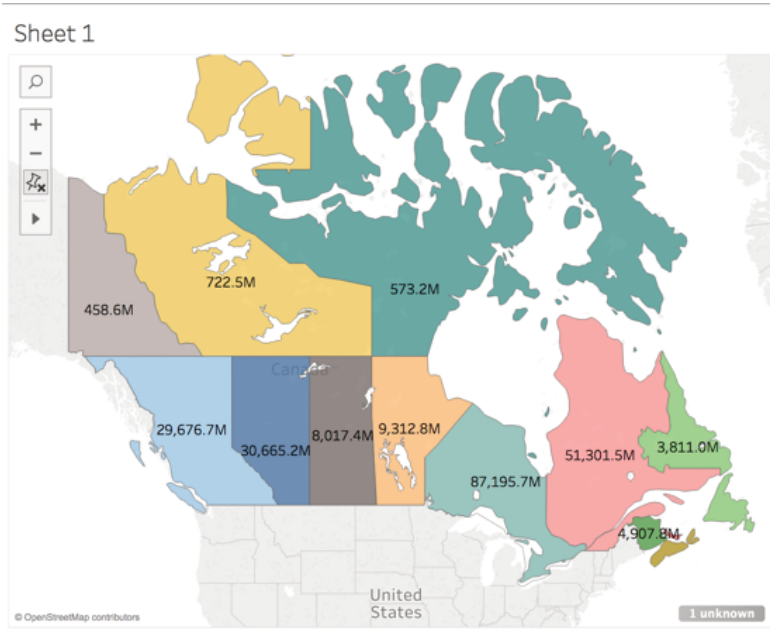



This allows us to change the properties of how Expenditures appear on our map. In the box that appears, (2), change the Suffix to "M", so all the expenditure values will carry an M as in millions at the end. We won't use the Display Units option because our units from our data are displayed in millions and it will not translate to the right amount with this set of data. In other cases, you can use this option. Also, set the Decimal places to 1. Your screen should now look like this:

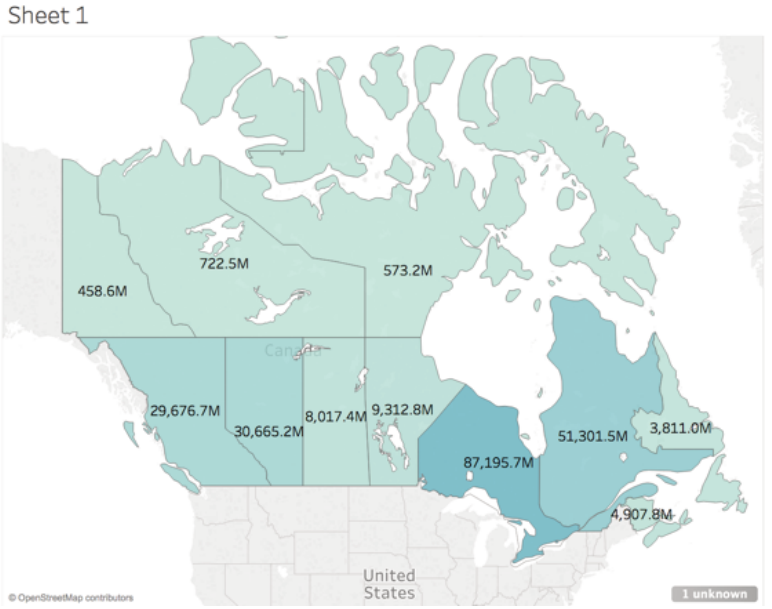



Next, we are going to colour our map based on the provinces. To do this, drag and drop Province from Dimensions to Colour in the Marks card. Make sure to change the marks tab to Map at this point from Automatic in the drop down menu. Each province is now coloured by region (see Image 1 below). You could also colour the map based on Expenditure if you chose to drag Expenditure to colour (see Image 2 below).

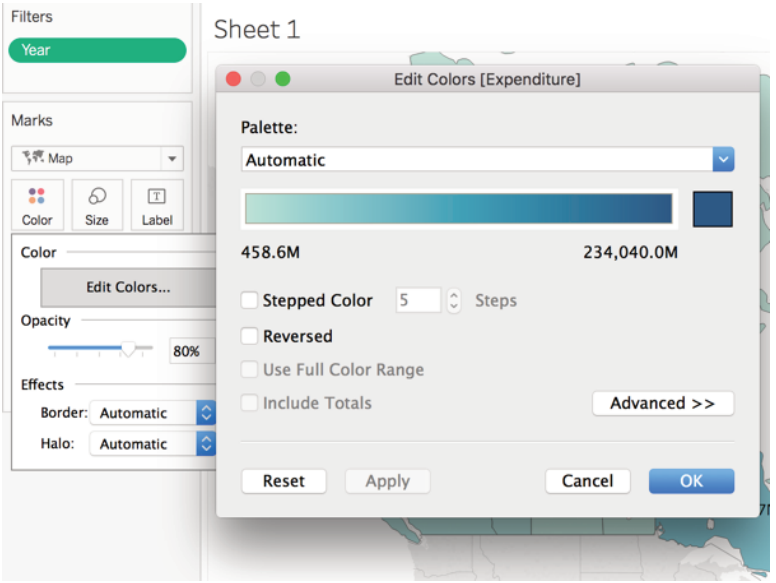
(1)


Sheet 1
458.6M
722.5M
573.2M
29,676.7M
30,665.2M
8,017.4M
9,312.8M
87,195.7M
51,301.5M
3,811.0M
4,907.8M
United States
© OpenStreetMap contributors
1 unknown

(2)

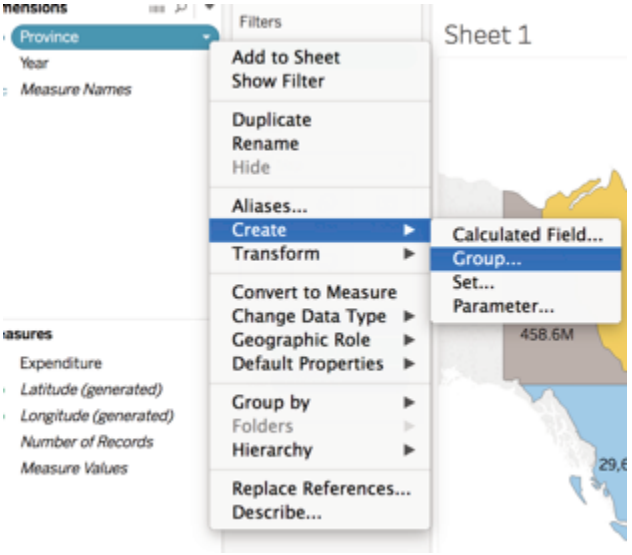



You can also click on Colours in the Marks card to edit and choose other colour schemes. Just click on Edit Colours after clicking on Colours, then click the drop-down menu underneath Palette, and choose the one you like.

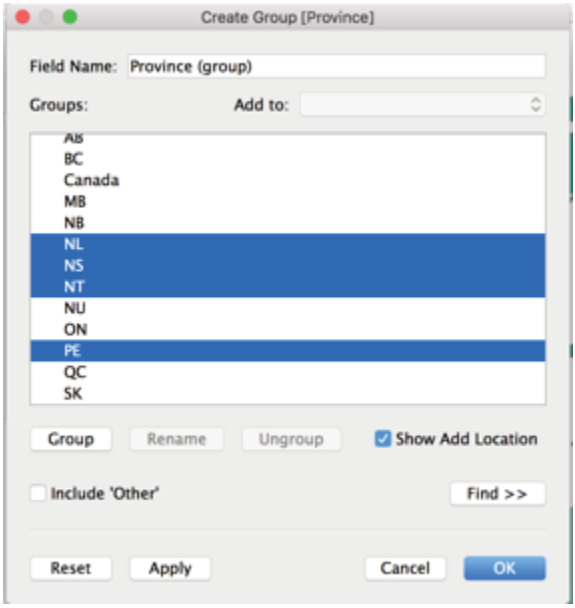



Next, we're going to create custom territories in our map. This may be useful to look at trends in certain geographic areas on the map. To do this, click on Province in Dimension. From the drop-down menu, choose Create, then Group (Image 1). In the box that opens (Image 2), you can group provinces together based on custom sub-groups.

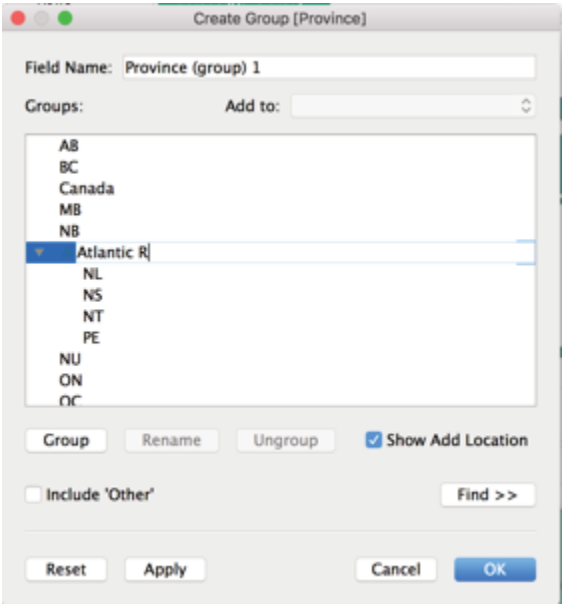
(1)


Province
Year
Measure Names
Expenditure
Latitude (generated)
Longitude (generated)
Number of Records
Measure Values
Filters
Sheet 1
Add to Sheet
Show Filter
Duplicate
Rename
Hide
Aliases...
Create
Transform
Convert to Measure
Change Data Type
Geographic Role
Default Properties
Group by
Folders
Hierarchy
Replace References...
Describe...
Calculated Field...
Group...
Set...
Parameter...
458.6M

(2)


Create Group [Province]
Field Name: Province (group)
Groups:
Add to:
AB
BC
Canada
MB
NB
NL
NS
NT
NU
ON
PE
QC
SK
Group
Rename
Ungroup
Show Add Location
Include 'Other'
Find >>
Reset
Apply
Cancel
OK

(3)

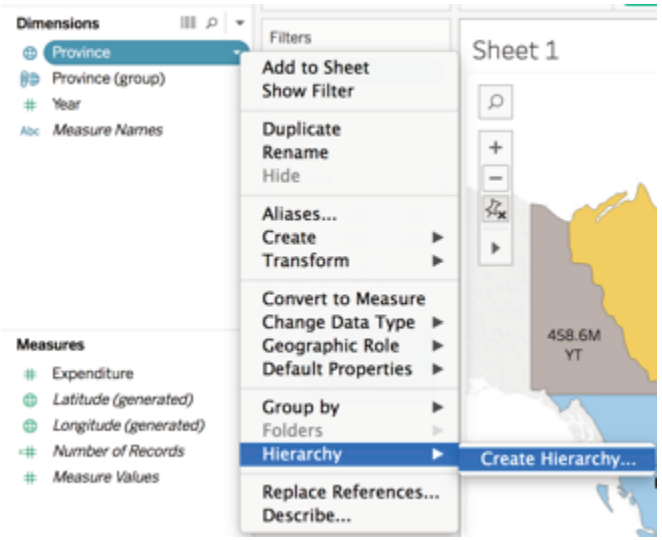



We are going to group ours based on regions in Canada. I am first going to select using the command key NL, NS, NT, PE to create a sub-group for Atlantic Canada (Image 2), click Group, then name it Atlantic Region (Image 3). I can repeat this for all regions in Canada. Click OK when finished to create all the groups and return to the main page.

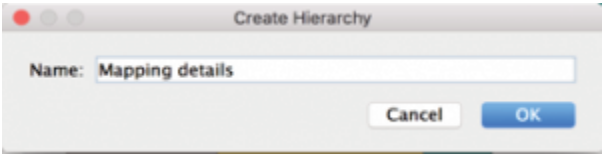
Now returning to the main page, I should see under Dimension a field called Province (group). If I drag this new field to the Marks section, it can be applied in a variety of ways to the map. But, I want to apply it in a way to create a map that groups expenditures based on these regions. So, I need to create a hierarchy of my geographic region fields. To do this, I will click on Province in Dimensions and select

Hierarchy from the drop-down menu and then create Hierarchy (Image 1). From the Hierarchy dialogue box that appears, name the Hierarchy something, such as Mapping details (Image 2), then click OK. Province will now appear under Mapping details in Dimensions. Drag Province Group under this Hierarchy as well. Dimensions should now look something like Image 3.

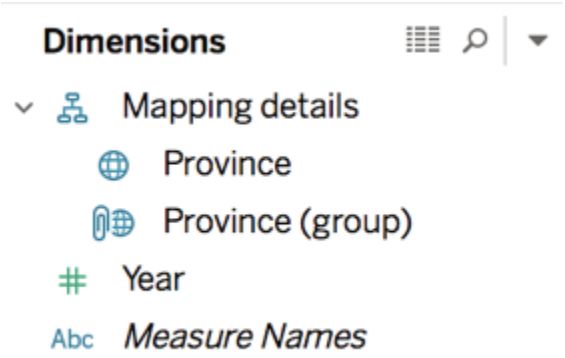
(1)




(2)



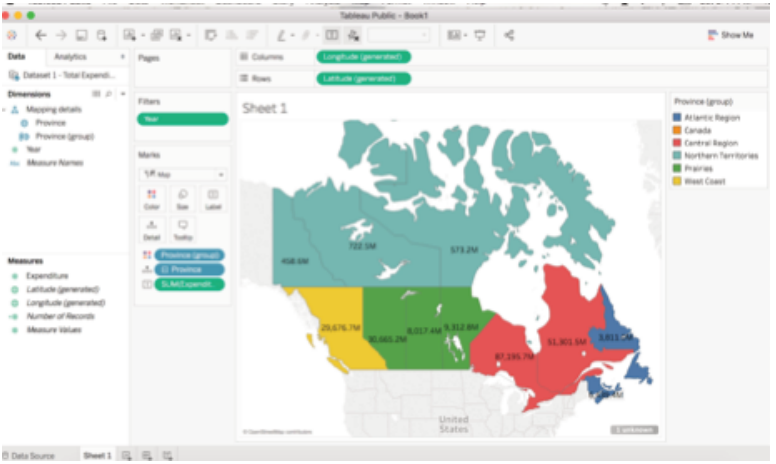
(3)



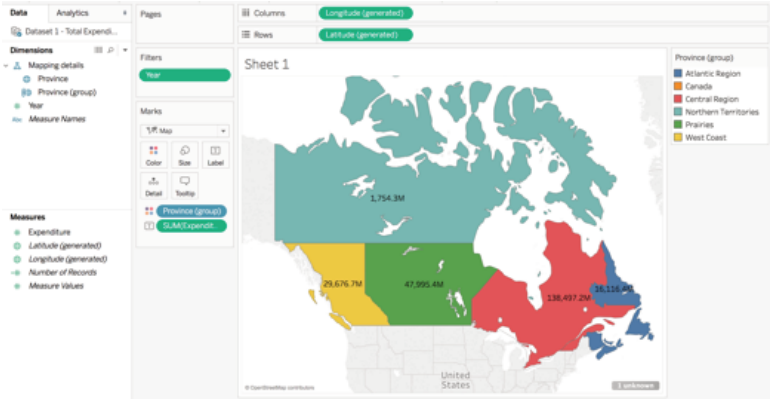

Having this Hierarchy made will now allow us to visualize expenditures based on the geographic regions we created.

To do this, I will drag Province (group) to Colour in the Marks box. You will see the map will change and be coloured by the geographic regions (Image 1). Then, I will remove Province from the Marks box, and the expenditures for each province will sum to the region (Image 2):

(1)

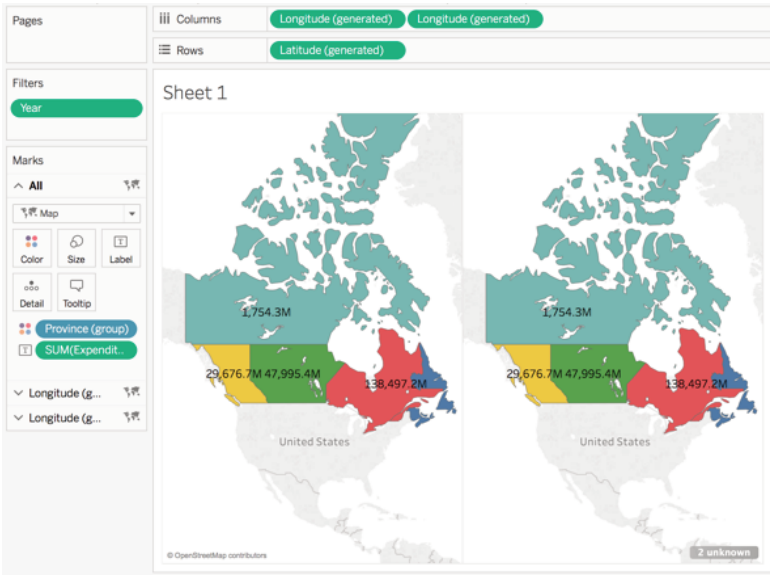



(2)

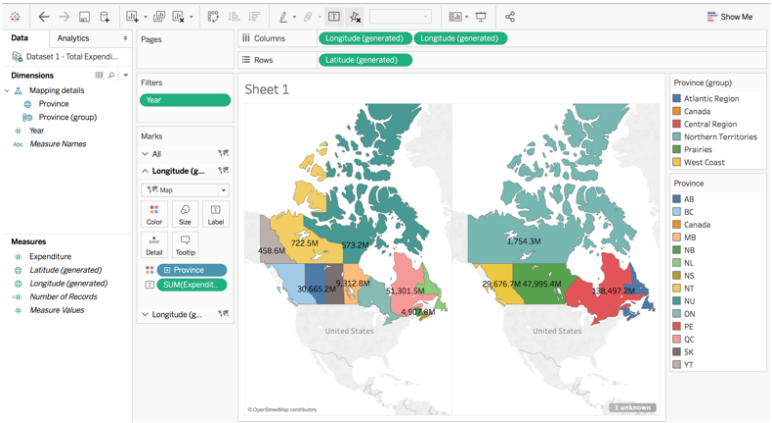



Now I want to compare expenditures by region and province, so I want to create a dual axis map. So, I will drag Longitude or Latitude to the Columns or Rows shelf, respectively, depending on what axis

I want my second map to appear (Longitude → Columns for besides one another, Latitude → Rows for on top of one another). For this example, I want the maps beside one another like so:



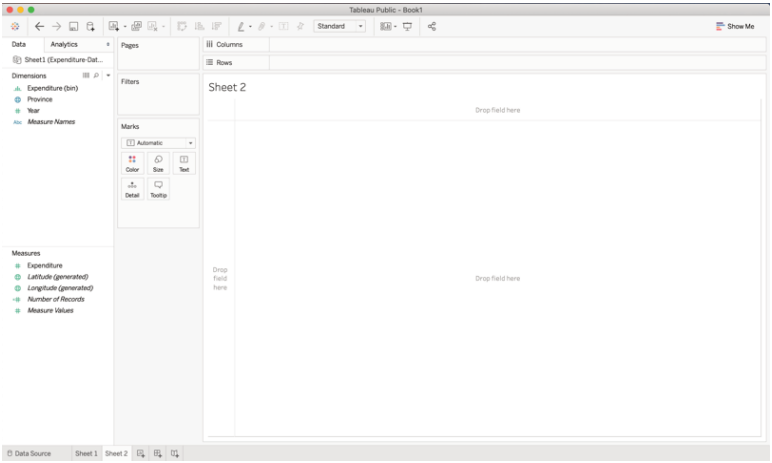

Now to change the map on the left to display expenditure by province, I will click on Longitude Generated tab to open up a Marks for just the left province. Here, I will drag Province from Dimensions to Colour. The map on the left should change to show expenditure by province, while the right map remains the same. Your screen should look like this:



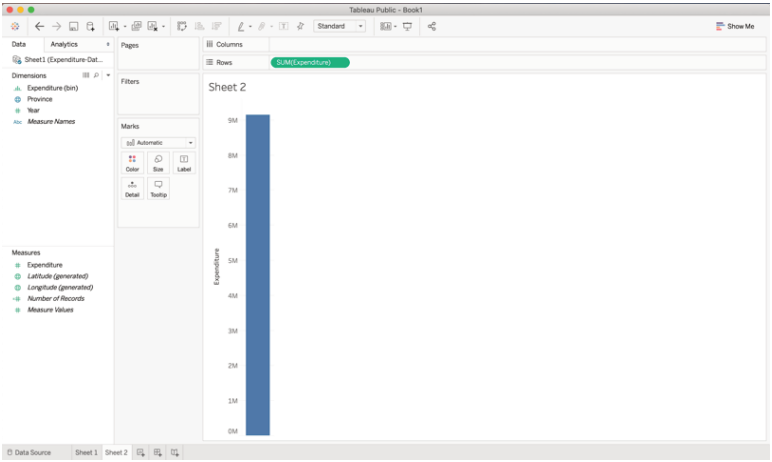

Congrats! You now have a Dual Axis Map to compare between provinces and regions the healthcare expenditures of each.

## II. CREATING A LINE GRAPH OF CANADIAN HEALTH EXPENDITURE BY PROVINCE IN 1975-2018

Next, we are going to create a line graph of each province's health expenditure from 1975-2018. We are going to continue to use the same data as in the previous example, so we do not have to return to the data source tab. Click on "New Worksheet" located at the bottom right of your screen next to Sheet 1 to add a new sheet. Your screen should now look like this:

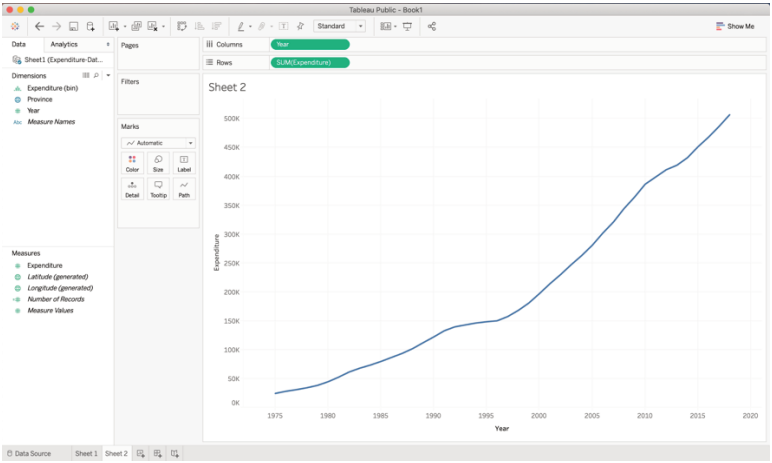



To begin building your line graph, double click on “Expenditures” in the Measures field. Your screen should now look like this:

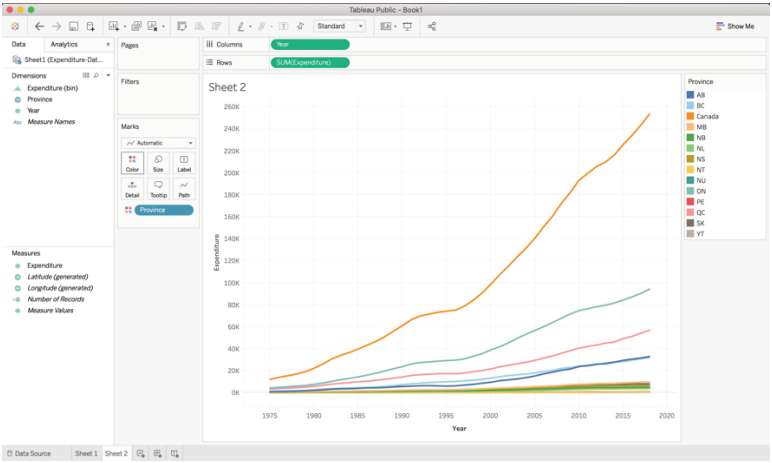


You will see that Tableau has summed the health expenditures from the years 1975 to 2018 and has placed this value in the Row shelves.

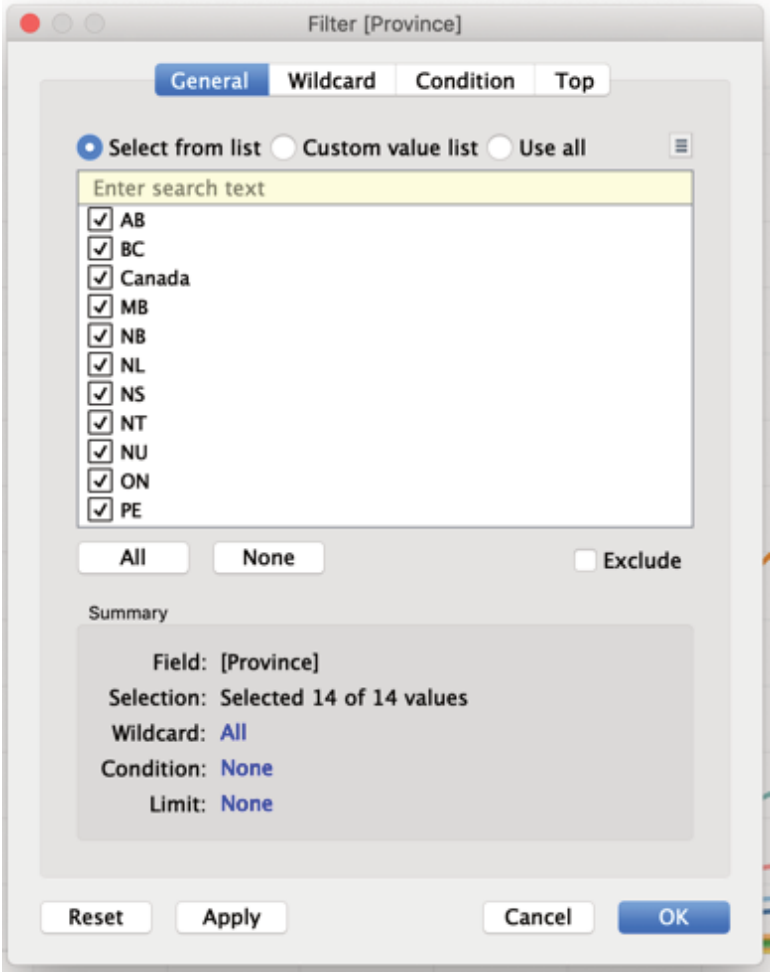
We are now going to double click on “Year” in the Dimensions field.



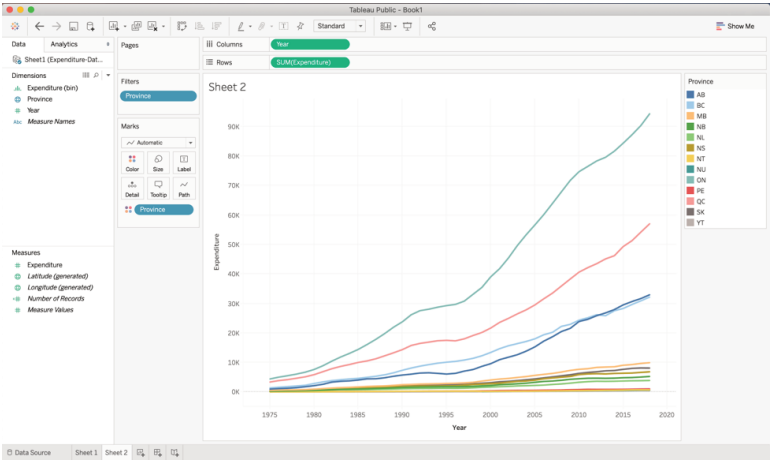

This line graph is showing the summed health expenditures across all provinces on the x-axis and year on the y-axis. We can continue to edit this graph to compare health expenditure by each individual province. To do this, double click on “Province” in the Dimensions field.




You will see that the summed health expenditure for all of Canada is still be represented on the map, which is denoted by the orange line. We can edit this by dragging “Provinces“ from the Dimensions field into the Filters box. This box should appear:



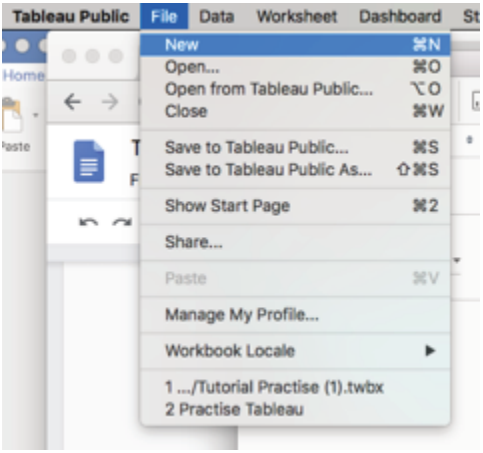

De-select “Canada” and then press “OK”. Your graph should now look like this:




You can change the colour schemes of the line graph similar to how we changed the colour on the map in the previous example. Just click on “Color” and then “Edit Colors” and select the palette of your choice from the drop-down menu.

## III. VISUALIZING THE PROPORTIONAL DISTRIBUTION OF HEALTH CARE EXPENDITURE AMONG AGE GROUPS IN CANADA

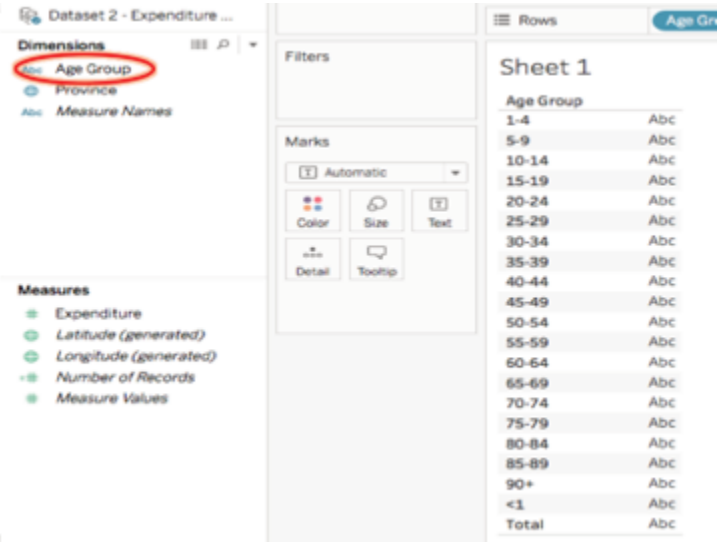
This section uses a new set of data. To create a new Tableau Public workbook with the new data, click the “New” button under the “File” tab.



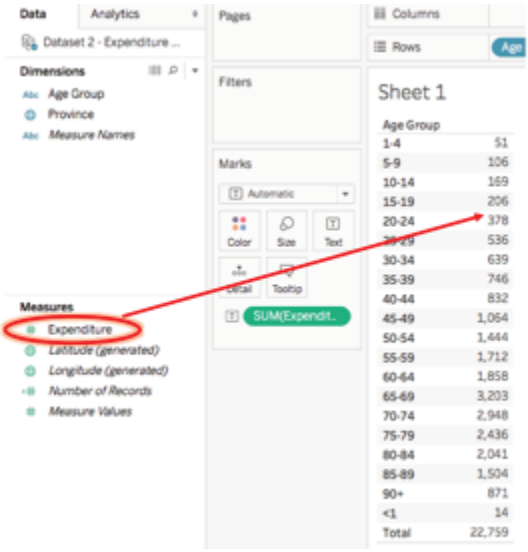

Using the same data uploading method as earlier, select "Dataset 2 – Expenditure by Age" from the sample data and open a new sheet.

There are several methods of visualizing the proportional distribution of data in Tableau Public. On the first sheet, you will be creating a stacked bar graph comparing health care expenditures between provinces while also visualizing the distribution amongst age groups. On the second sheet, you will create a pie chart that visualizes the distribution of Canada's total expenditure among age groups.

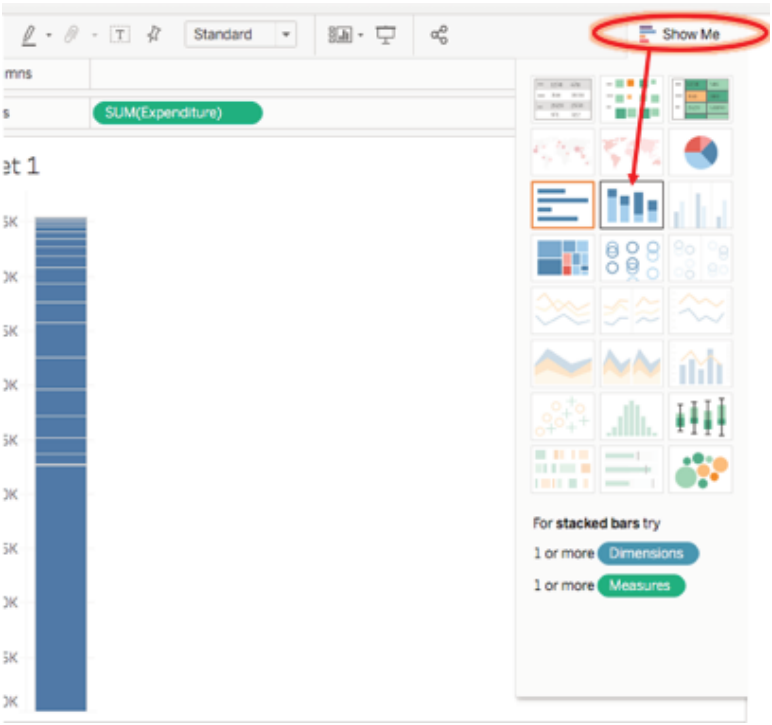
On the first sheet, start off by double-clicking on the dimension "Age Group." A chart should appear showing the age groups.



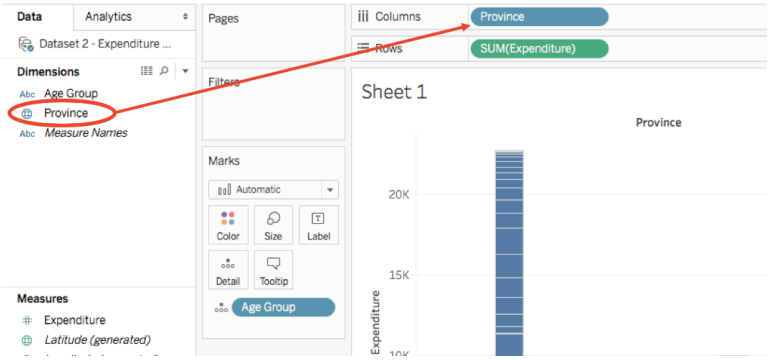

Next, drag the "Expenditure" measure onto the undefined data column (Containing "Abc") on the chart. The chart then lists the total Canadian expenditure for each age group.



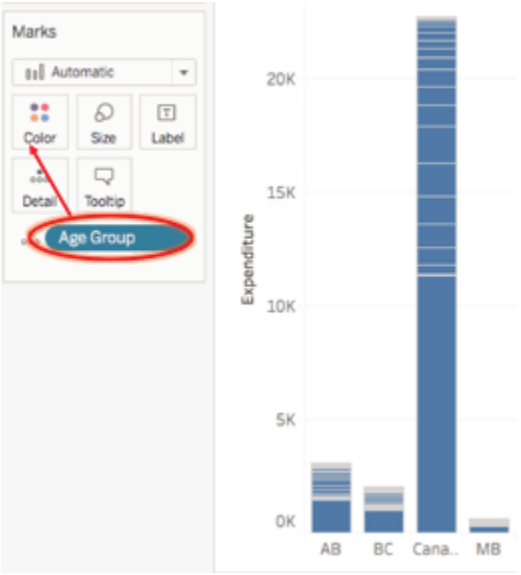

Click on the “Show Me” tab at the top right of the page to display a variety of data visualization techniques. If you already see the bar open, do not click on it. Then, select the “stacked bars” option to transform your data chart into a stacked bar graph.



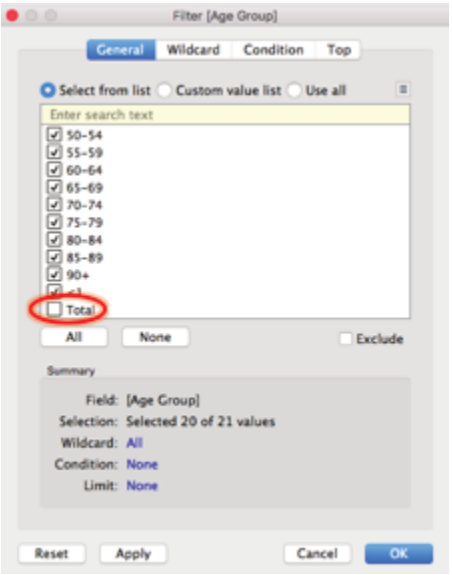

Now, divide the expenditure data into its provincial distributions. Do this by dragging the "Province" dimension into the "Columns" bar near the top of the page.



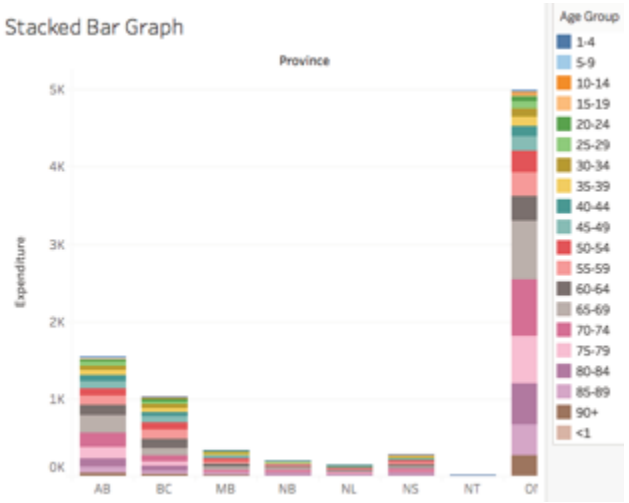

Now to add some colour to the graph to visualize the proportions better. Drag the blue “Age Group” mark to the “Color” square.



You may notice that half of each bar is one colour. This is because the "Total" value for each province is still being included. To remove this measure, drag the "Age Group" dimension to "Filters" and de-select "Total" in the "General" tab. If you wish to also remove the large bar that represents Canada's total expenditure from the graph, repeat this step with the "Province" dimension and de-select "Canada" from the list.

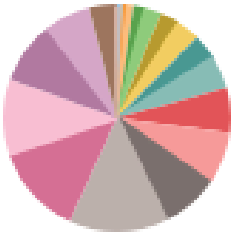



Your stacked bar graph is now complete! If you wish to make the graph larger or smaller, press shift+command+B or command+B, respectively. Or you can go to the "Cell size" option in the "Format" tab.



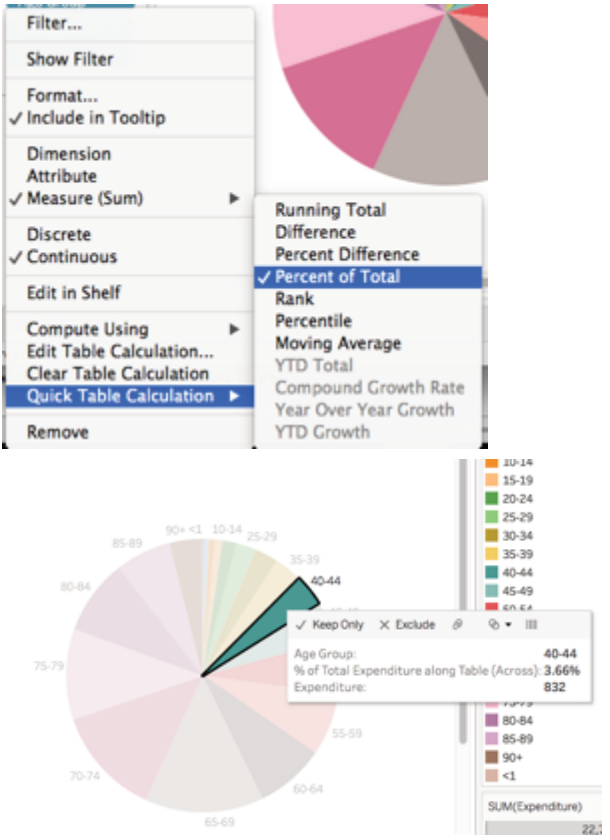

Open a new sheet again to get started on your pie chart. To begin, double-click "Age Group" and drag in "Expenditure" the same way you did to start your stacked bar graph. You should again end up with a chart displaying age groups in the left column and their respective expenditures in the right column. This time select the "pie charts" option from the "Show Me" menu.


Just as you did so when making the stacked bars, add filters to remove data from the “Total” age group. You should now have a pie chart with a slice & colour representing each age group.



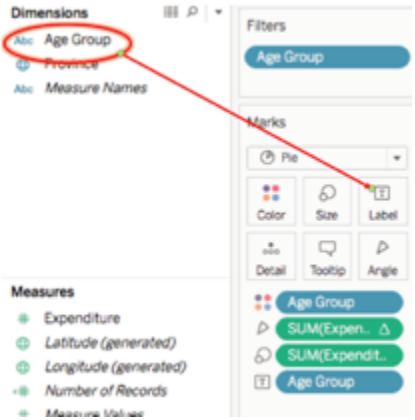
When hovering over each slice, the respective age group and expenditure value should be displayed. Another helpful piece of information is the percent of the total expenditure allocated to that

age group. To add this info, click the arrow on the right of one of the green "SUM(Expenditure)" buttons in the "Marks" box. Then hover to "Quick Table Calculation" and select "Percent of Total." This both ensures that the slices of the pie are proportionate to their respective percent of total expenditure, and will also display this information when you click on a slice of the pie chart.

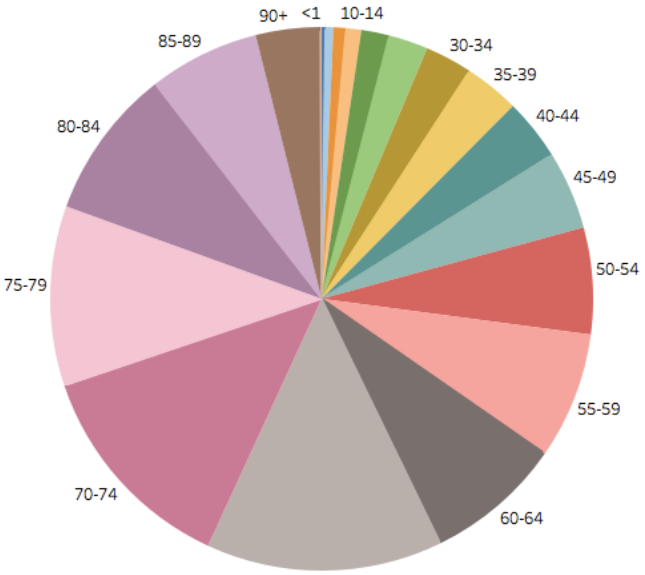



To add labels to the pie chart, drag the information that you want

labelled onto the “Label” box. For example, you can label the slices according to age group.




Your pie chart should now be complete! Again, if you wish to make the chart larger or smaller, press shift+command+B or command+B, respectively. Or you can go to the “Cell size” option in the “Format” tab.



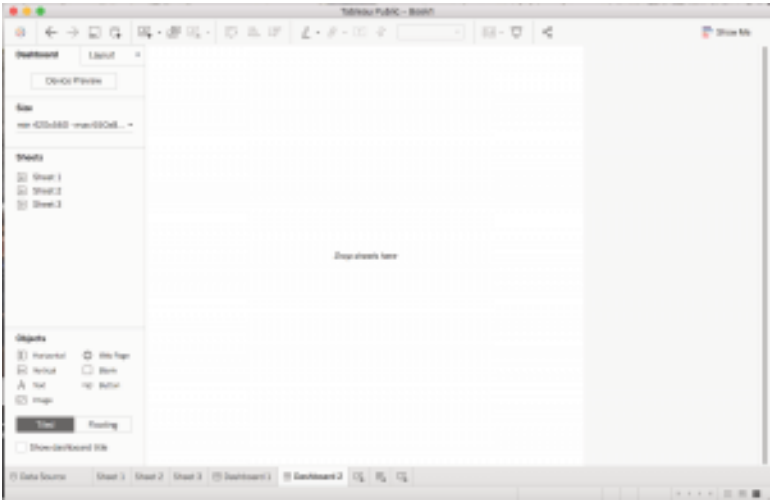

Congrats! You can now visualize the proportional distribution of your own data! You're also ready to add that data to an interactive dashboard!

## *CREATING A DASHBOARD WITH TABLEAU PUBLIC*

Dashboards are a great way to combine your data visualizations and have them interact with one another. A lot of businesses use dashboards to keep up-to-date in real time about key performance indicators at a glance. In this example, we will combine just two of our data visualizations, the map and the line graph from the first section of the tutorial, but in reality, it can be used to combine many visualizations at once.

The first step in creating your dashboard is to open up the Dashboard tab at the bottom of the screen:

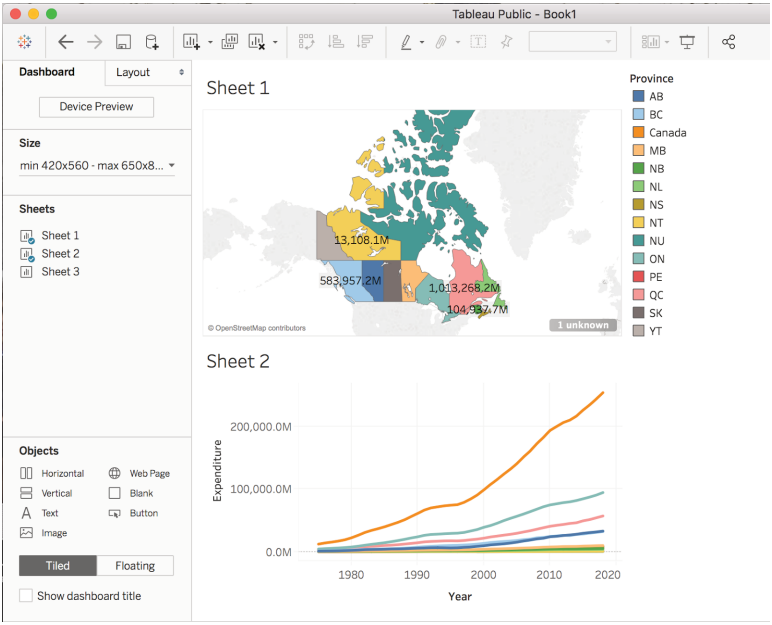
After clicking this icon, your screen should open to this:



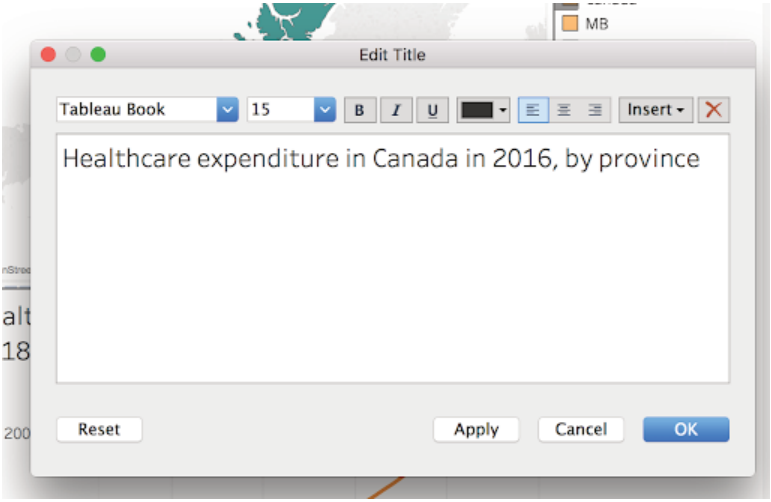
This is your Dashboard Sheet. On the left side you can see that there is a list of the sheets you have made from your current data source.

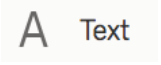
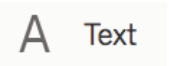
To build your dashboard, drag the sheet you want in to the centre where it says Drop sheets here. For our purposes, we will need to drag Sheet 1 and Sheet 2 where the map and line graph are saved. When you drag, you will notice an area of your screen will shade over

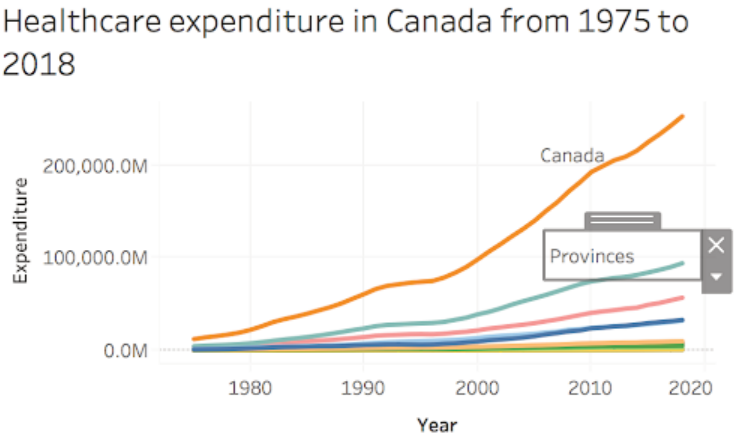
where your graph will drop when you put it down. Organize your dashboard to look like the following:



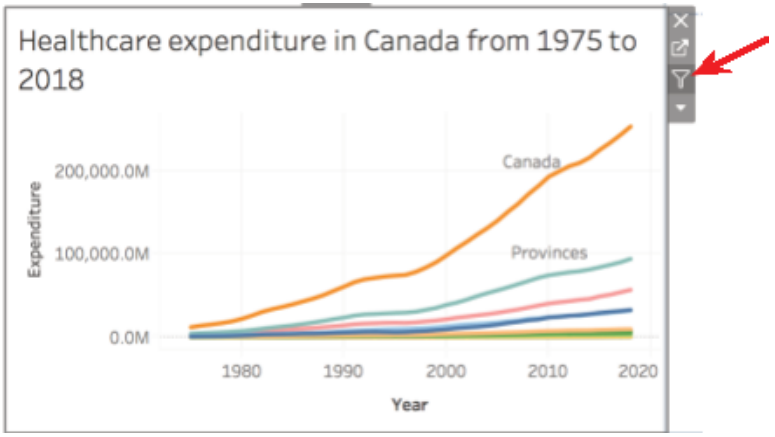

Now to add titles to the graphs that were chosen, double click on the automatic titles generated based on the sheet name, and a new window should appear, type in a title that describes the graph like so:




We can also add additional titles and objects to the dashboard by choosing an object from the Objects side panel and dragging it to the dashboard. We are going to add titles to the bottom line graph to differentiate between the Canada line and the provinces. To do this, drag  to the area near the orange line that corresponds to the sum of all provinces expenditure throughout the years. Type in "Canada". Drag  once more to label the remaining provinces. Your bottom graph should look like this:




Now, to add an interactive layer between the graphs, we can choose a graph that can act as a filter to the other. We will choose the line graph to act as a filter to the map. To do this, click on the line graph and a grey sidebar should appear. From this bar, click the filter icon to use this graph as a filter:

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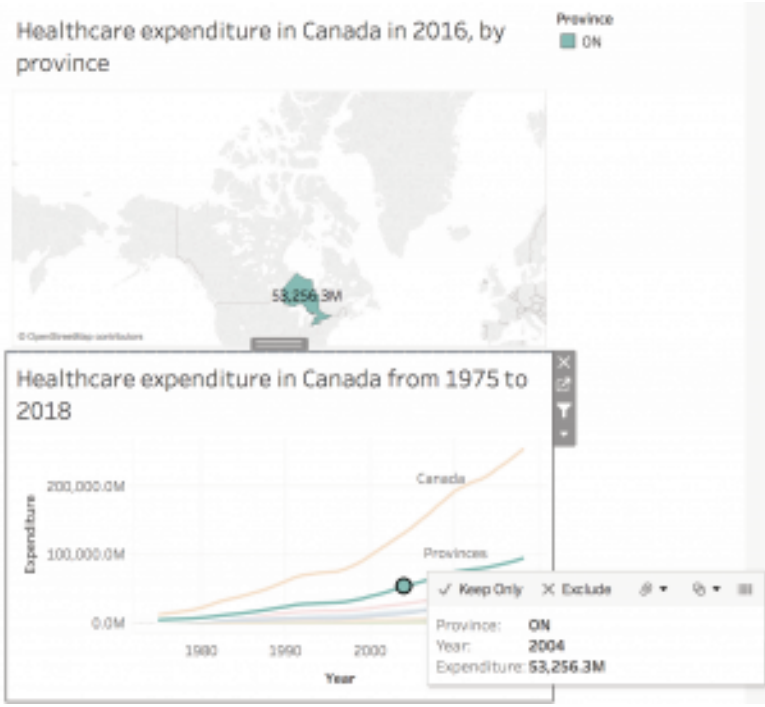
Now, when you click a given line, it will be highlighted on the above map:




Congrats, now you have an interactive dashboard that is ready to be published or saved!

## *CREATING A STORY WITH TABLEAU PUBLIC*

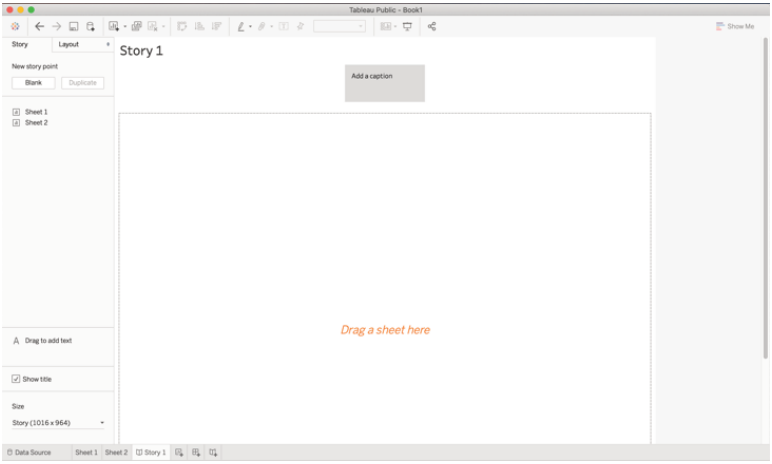
With Tableau public, you are able to organize your data in order to tell a meaningful story. This is beneficial when you are doing a

presentation, creating an article, or uploading to a website, as it helps your audience understand your data.

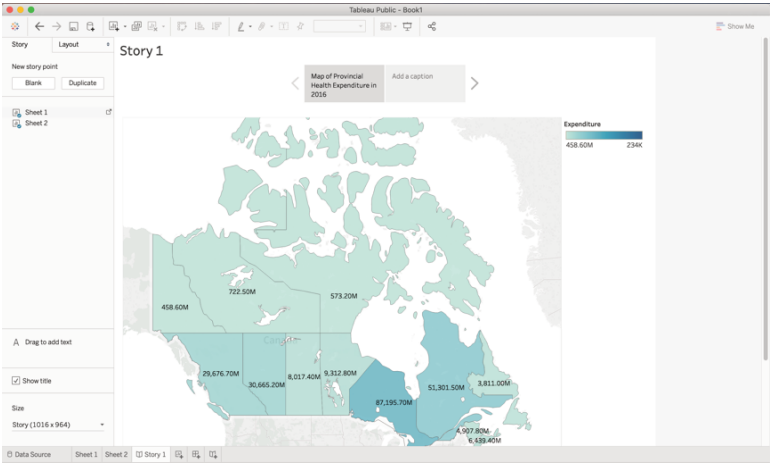
Stories are created through assembling the different worksheets and dashboards. We can highlight important data points, add text box and pictures to help convey our story. However, there are many different ways to tell a story. For example, one technique is called "tailoring in" where the story starts with a big picture view and zooms in on a specific detail. In contrast, a story can also be told by starting with a case and zooming out to that big picture view.

We are going to return to our health expenditure worksheets to create a tailoring in story and illustrate the changes in Canada's spending in a meaningful way.

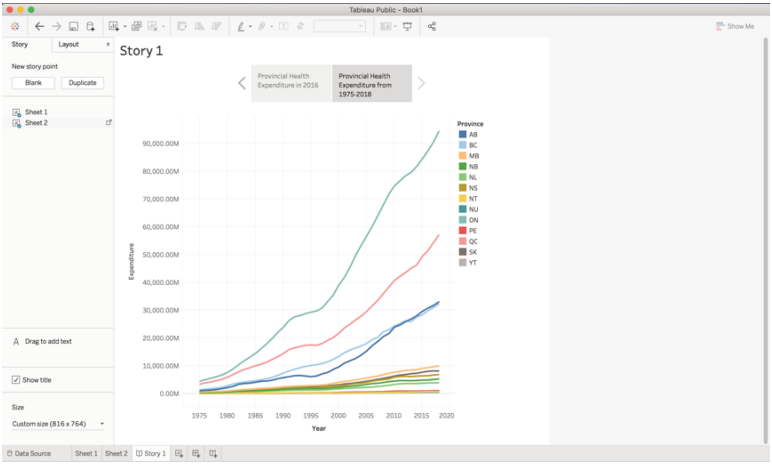
To begin, select "New Story" at the bottom right of your screen.



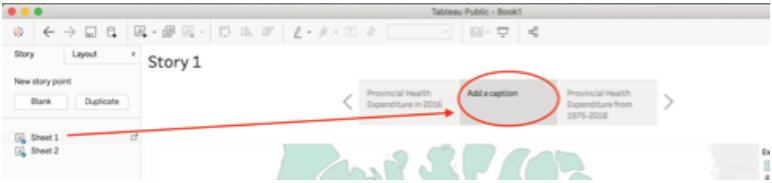

Drag "Sheet 1" and "Sheet 2" on to "Drag a sheet here". We can rename each storyboard by clicking "Add a caption". Rename Sheet 1 to "Provincial Health Expenditure in 2016".

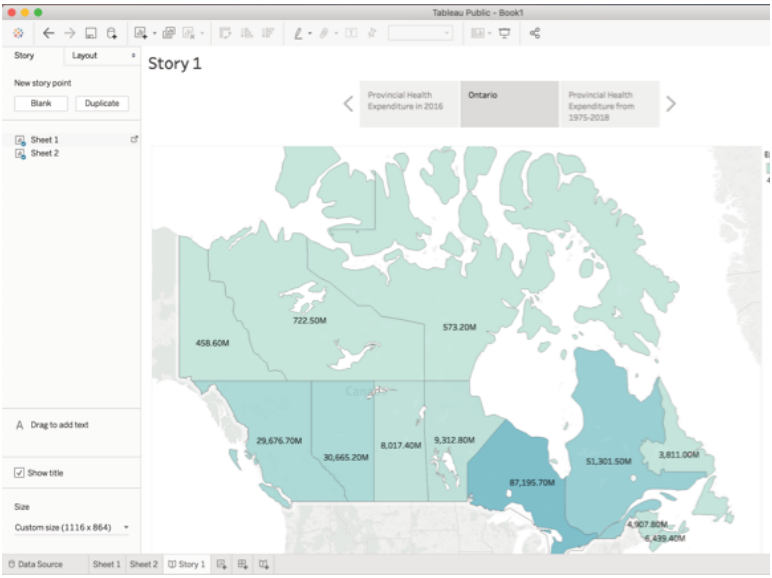



Use the arrows located on the side of the caption field to navigate to Sheet 2. Click on “Add a caption” and rename Sheet 2 to “Provincial Health Expenditure from 1975–2018”.

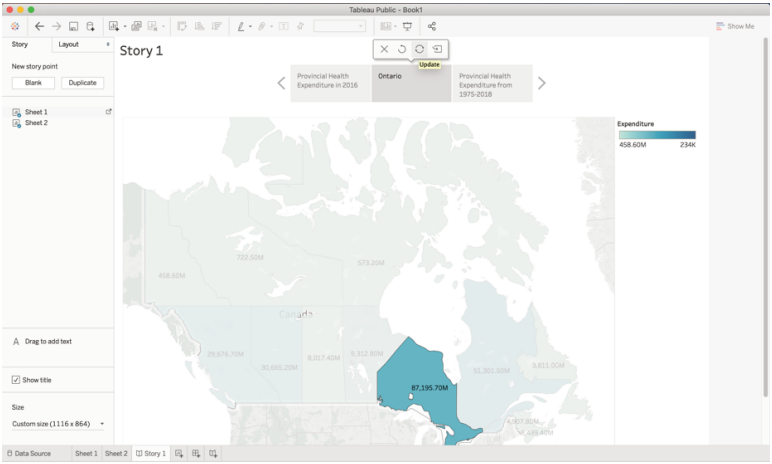


In this story, we are going to narrow in and draw attention to the province or territory that is spending the most amount of money on health. Drag an additional copy of “Sheet 1” and drop it between the two existing sheets. Select “Add a caption” and rename it to “Ontario”.

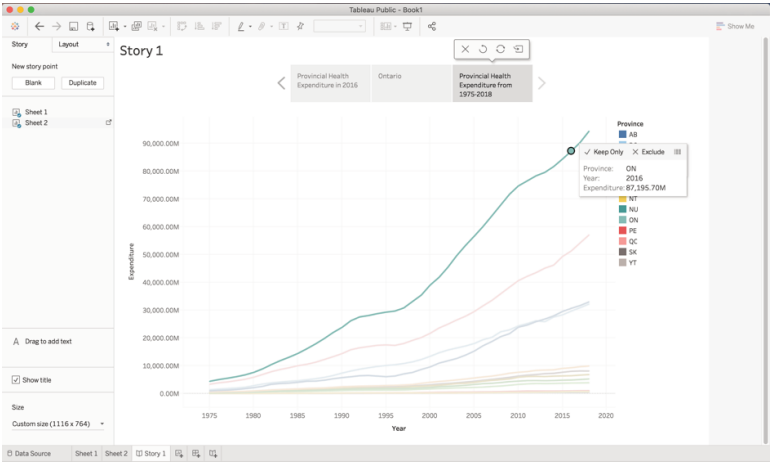


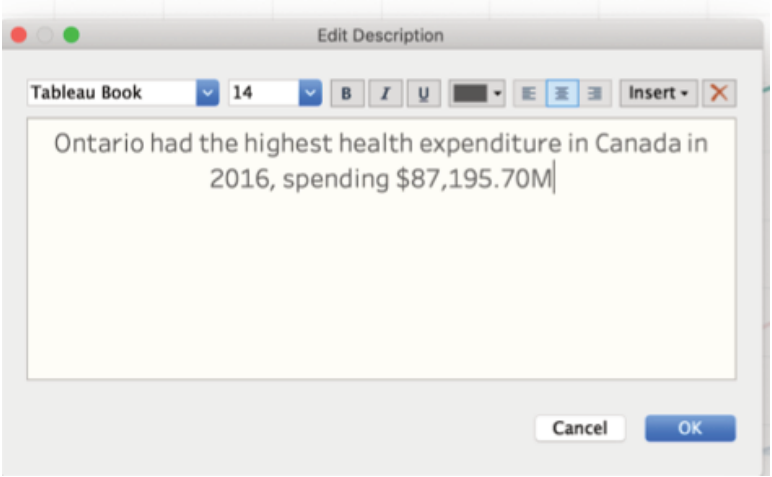

On the map, click on the province Ontario and then navigate to the caption field and select “Update”. Your screen will show Ontario highlighted from the rest of Canada.



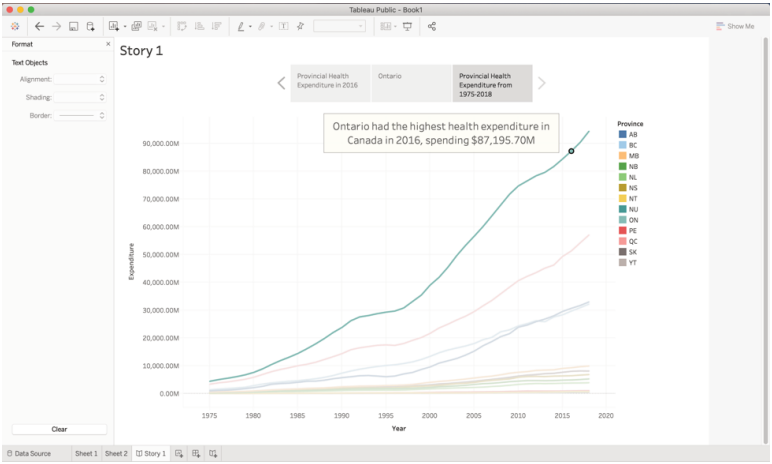

Select the right arrow to navigate to "Provincial Health Expenditure from 1975-2018". Hover over the line representing Ontario and select the data point representing health expenditure during the year 2016. Then click "Update". Your screen should look like this:



We can add a textbox to label the highlighted pointed by dragging "Drag to add text" on to the line graph. Write a key message in the textbox, such as "Ontario had the highest health expenditure in Canada in 2016, spending $87,195.70M". Select "OK".




You can the edit the text box by selecting "More options" which will open a drop-down menu. Expand the text box by dragging the borders in order to show the full message.




We have now created a story with three sheets of how Ontario had the highest health expenditure in the year 2016. If you choose to add a dashboard, it will allow your audience to play with data. You can navigate between the story as shown below:


Tableau Public - Book1
Story 1
Provincial Health Expenditure in 2016
Ontario
Provincial Health Expenditure from 1975-2018
Ontario had the highest health expenditure in Canada in 2016, spending $87,195.70M
Province
AB
BC
MB
NB
NL
NS
NT
NU
ON
PE
QC
SK
YT
Expenditure
Year

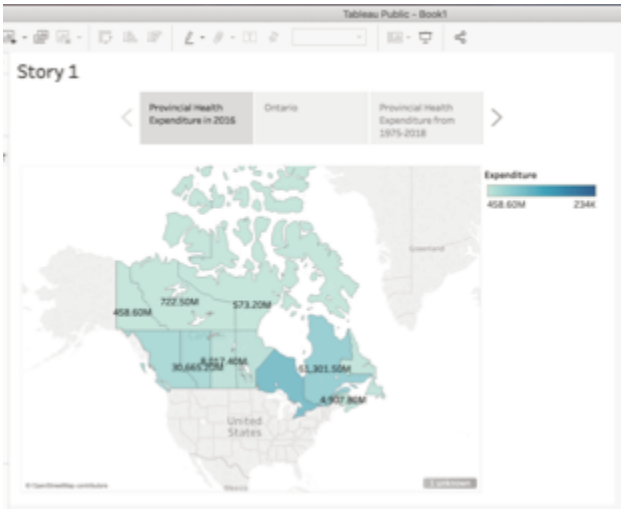
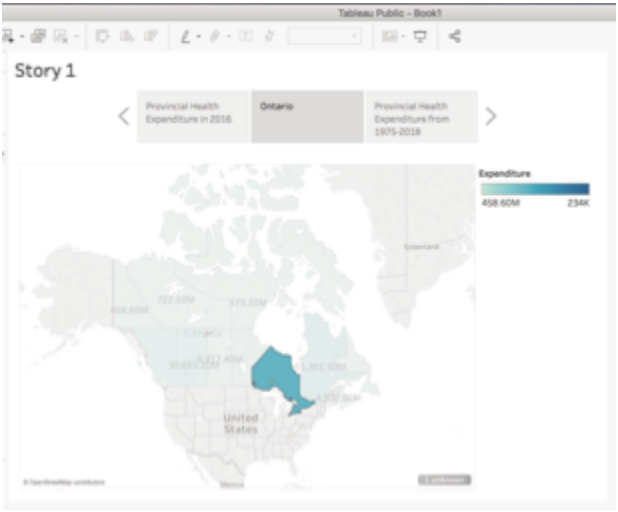


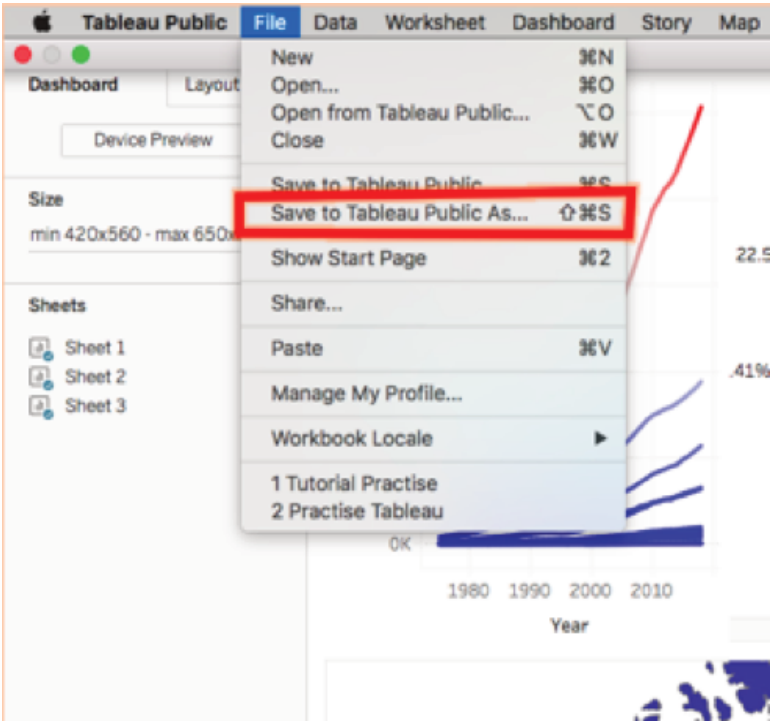
Tableau Public - Book1
Story 1
Provincial Health Expenditure in 2016
Ontario
Provincial Health Expenditure from 1975-2018
Expenditure
458.60M
234K
722.50M
573.20M
458.60M
8,917.40M
30,665.95M
11,301.50M
4,937.80M
United States




## *SAVING AND PUBLISHING YOUR TABLEAU PUBLIC WORKBOOK*

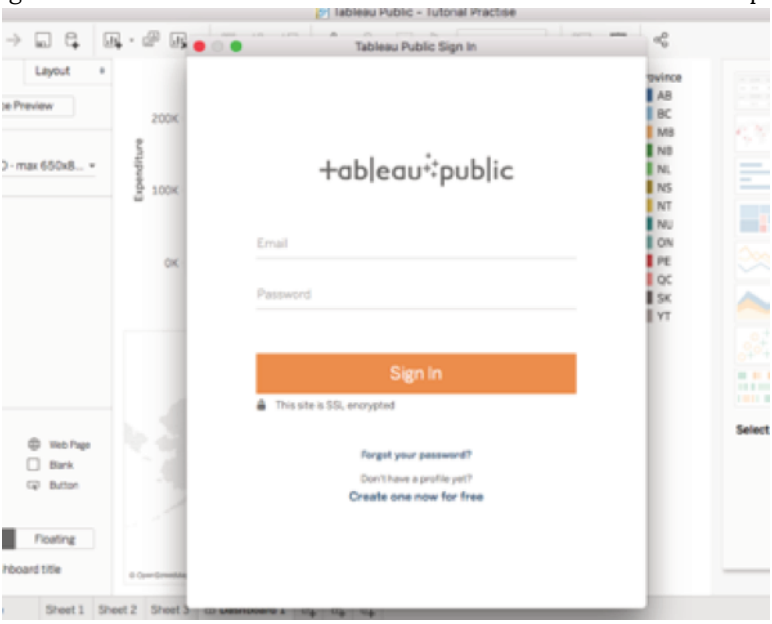
Once satisfied with your workbook, which includes sheets, dashboards, and stories, you can publish it to the Tableau Public website. This is the only way to save your work when using Tableau Public, so make sure to do it if you wish to return to the workbook in the future.

Once ready to publish, select the "Save to Tableau Public As..." option under the "File" tab.

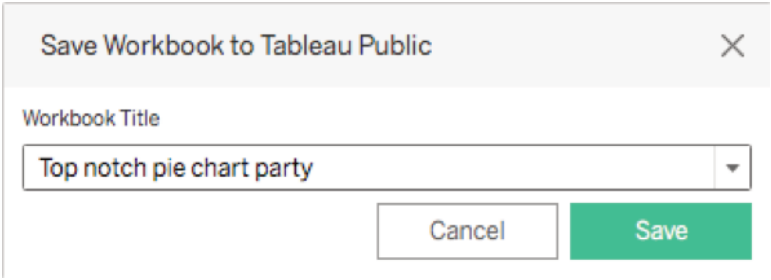



From here, you will likely be prompted to log in to the Tableau Public website. You can create an account for free if you have not already. If you are not prompted, you are already logged in and can

ignore this step.

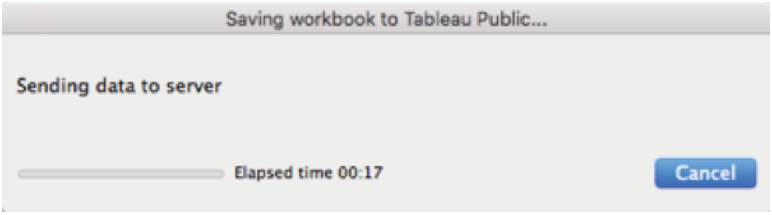



Then, create a title for your workbook.




Your workbook will then be uploaded to the Tableau Public server.

This may take a couple minutes.




You will then be directed to the webpage on which your workbook is publicly available for download. Your workbook has now been published and saved! This page includes information on you, including a link to your Tableau Public profile, as well as additional information on the workbook. There are several options for making use of your work data visualizations that can be found at the bottom right of the workbook image.

By clicking Share (A), you can get the code for embedding the workbook into a website or the link to find the workbook on tableau public. The Share button also gives you the option to share your work over email, Facebook, or Twitter. By clicking Download (B), you or any other Tableau Public users can download your workbook and make use of the data themselves.


On Tableau Public, all saved data visualizations are uploaded and available to all other users. This means you can use other users' work

for your website, presentations, or research as well. To search for interesting data, there is a search function (D) at the top right corner of the webpage, along with highlighted visualizations (A), authors (B), and blogs (C).


When you wish to access your published workbook, or any public workbooks you've downloaded, in the future, simply open the Tableau Public application and your workbooks will be there waiting for you!

# 12. Staying one step ahead of the competition with Porter's Value Chain Analysis

*By: Saji N, Hoffman N, Kaiser F and Abraham N.*

> ***Strategy is about making choices, trade-offs; it's about deliberately choosing to be different.***"

– Michael Porter

## *About Porter's Value Chain*

The concept of the value chain was first presented by Michael Porter

in the book 'Competitive advantage: Creating and Sustaining Superior Performance' published in 1985 (Kumar & Rajeev, 2016).

The value chain consists of different stages that are needed to bring a conceptual product from **raw materials** to end **customers** (Kumar & Rajeev, 2016).

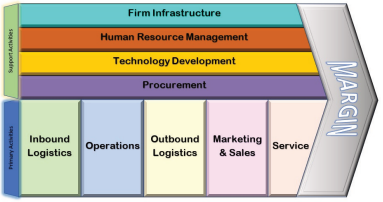



***Figure 1. The Value Model.***

The value chain model analyses what value can be added to each phase in order to **maximize profit** without compromising the quality of the product and the customer service (Kumar & Rajeev, 2016). This can either be by decreasing the manufacturing cost or by increasing the price of the product or service when they are of high-value (Free-management-ebooks, n.d).

The model consists of **nine activities** which are divided into two categories: Primary activities and Support activities. (Kumar & Rajeev, 2016)

## *Primary Activities*

Primary activities include inbound logistics, operations, outbound logistics, marketing & sales, and service (Kumar & Rajeev, 2016).

The primary activities are directly involved in the **production** and **distribution** of products and service. The support activities are indirectly involved across the primary activities to **synchronize all the primary activities** (Kumar & Rajeev, 2016).

1. ***Inbound Logistics***: include transport, receiving, storage, redistribution of goods coming into the business like raw materials (Harrison, 2018).
2. ***Operations***: involves processes that turn the raw materials into finished products (Harrison, 2018).
3. ***Outbound Logistics***: include packing, shipping, transporting, and delivering the final product to customers (Harrison, 2018).
4. ***Marketing & Sales***: activities involved in the promoting and selling of products to customers like distribution channels, advertisements, and competitive pricing (Harrison, 2018).
5. ***Service***: comprise activities that ensure that the end product meets the expectations of the customers like product installation, warranty, repairing, customer training, or replacement of product when necessary (Harrison, 2018).

*Key Concept*

Each step in primary activities **adds value** to the end product. When more value is created for a product, the greater the success of selling a product!

## *Support Activities*

These activities are not directly involved with product manufacturing but **support** the primary activities. Without support activities, the primary activities are not able to create valuable products.

*Key Concept*

Support activities are **interlinked** with primary activities. Hence, improving even one support activity has a direct influence on a primary activity in the

1. ***Procurement***: activities involved with purchasing all the resources to operate and create products. It is directly linked to all primary activities. Bargaining power, or getting the best possible prices from vendors is what affects the total cost of the product later on.
2. ***Human resource management***: is one of the most important parts to run a company successfully. To recruit and hire promising personal and train and motivate them can be an advantageous part.
3. ***Technology Development***: is related to the use of modern technology (operation, outbound logistics), the management of gained information (marketing & sales, service) and state of the art procedures in manufacturing. It is very important to maintain the costs within a certain range.
4. ***Firm infrastructure***: is needed to support and maintain the daily operations of a company. It includes accounting, legal, general management, and the company's infrastructure to run the daily business.

## *Value Chain Analysis*

Michael Porter initially based the concept of the value chain on the manufacturing industry. However, the tool is not just limited to this industry! With a little bit of tweaking, it can be

applied to other businesses as we will see in the latter sections.

value chain!

Understanding the **competitive advantage** of a company against its competitors is key to measuring the potential value in each activity, involved from accessing raw materials to service delivery (Ensign, 2001). Successful coordination between different sections of the company is important as this is important to improve the company's competitiveness.

"The value chain analysis tool can be used to generate cost advantage and differentiation advantage"

Such integration between activities is very important in today's world where raw materials produced from different p arts of the world are shipped to a different country for assembly and then sold in a different market (Ensign, 2001). Well-coordinated companies can rapidly change their working strategies to match changing consumer demands, which makes them successful in their field (Ensign, 2001).

## *Steps behind value chain analysis*

In order to carry out a value chain analysis, it is key to identify activities that provide more value to the company. This analysis is what helps a business weigh its advantages and disadvantages in comparison to a competing business.

There are three main steps to conducting a value chain analysis.

## *Step 1 – Activity Analysis*

*Linkages*

All of the value activities in the value chain are interdependent.

In order to represent these inter-dependencies, a 'link' is drawn to indicate the

This step involves **identifying** and **listing** all the client facing and non-client facing **activities** that add value to the finished product or service. The activities identified can range from supply chain management, production processes, advertisement, customer relation management, recruiting & training of employees, etc. (Value Chain Analysis, n.d.)

## *Step 2 – Value Analysis*

This step determines the level of importance that each activity contributes towards the value, as seen by consumers, of business outputs (Value Chain Analysis, n.d.)

## *Step 3 – Evaluation and Planning*

Following the value analysis, a list of suggestions that can be implemented to improve customer satisfaction is generated. The list is then narrowed down to highlight changes that add value to the customer (Value Chain Analysis, n.d.). Finally, it is important to conduct a cost-gain analysis to decide which changes are worth implementing and prioritize them for sequential implementation. Enacting all changes at once can

disrupt the proper working of the company as the people and the infrastructure may not be prepared to absorb the changes (Value Chain Analysis, n.d.).

direct relationship between two activities.

## *What does a value chain analysis achieve?*

The value chain analysis tool helps companies develop strategies to either generate a cost advantage or a differentiation advantage (Jurevicius, 2013).

1. Cost Advantage: used by a company whose primary objective is to bring the product to market for a **competitive price** (Jurevicius, 2013).
2. Differentiation Advantage: used by company's whose primary objective is delivering **premium products** to the market rather than focus on reducing the price. Here, the development of unique features to differentiate a particular product from a competitors product is key! (Jurevicius, 2013).

*Example 1. To buy or not to buy... that is the question!*

Companies use different strategies to thrive in competitive landscapes. So, one company may offer the same product, but at a fraction of the cost compared to its rival.

***Who do you think wins? Huawei with its affordability or Apple with its novel, albeit expensive features?***

However, other companies may choose instead to create superior products they know customers are willing to pay for.

## On to the Case Study!

### *Applying Porter's Value Chain Model*

### *Company Profile – Wellington Brewery*

**W**ellington Brewery is one of Ontario's oldest known microbreweries based in Guelph. The brewery was founded in 1985 by Phil Gosling.

The company produces craft beers and is famous for their original products including Special Pale Ale (which won a medal at Ontario's 2018 Brewing Awards), County Brown Ale and Arkell Best Bitter. The company also features other innovative blends such as Chocolate Milk Stout in addition to seasonal products like Helle's Lager and recently, for Valentine's Day 2019 a Baltic porter lager – Dissolved Splendor.


The brewery prides itself on being the first in North America to produce real English Style Ales –an un-adulterated beer which has been left to mature in wooden casks. Paramount to Phil Gosling's vision, the production

process and serving style is highly reminiscent of the 1900s pub culture in Britain.

Two years following the company's establishment, Wellington Breweries began packaging their beers in 1 litre PET bottles. Since then, the company has witnessed steady growth through the nineties and leading to the early 2000s when the company ownership transitioned to Doug Dawkins and Michael Stirrup. Business expansion continued under the helm of these two co-owners whose primary focus was to introduce their craft beers to restaurants and bars.

Upon the sudden passing away of Doug Dawkins and retirement of Michael Stirrup, the brewery is now solely owned by Brent Davies.

Currently, Wellington breweries products are distributed through the brewery itself, LCBO and Beer Stores and beer is available in cans, bottles, and growlers. Additionally, the company also set up an online store carrying some of their iconic craft beers and store merchandise.

The company is actively involved with the community and hosts events where individuals can learn more about the beer-making process and even gain hands-on experience creating their own brews.

## *Value Chain Analysis for Wellington Breweries*

The primary activities of the company are listed below.

- ***Inbound Logistics***

| ***Raw Material*** | ***Supplier*** |
|---|---|
| Yeast | Possibly White Labs (US)<br>Escarpment Laboratories (Canada) |
| Barley or often times, malt | Canadian 2-Row (Canada)<br>Specialty Malts (UK, Germany) |
| Hops | Primarily US-based<br>Clear Valley Hops (Canada)<br>Hayhoe Hops (Canada) |
| Other Ingredients: Fair Trade Cocoa, Oats, berries | Variety of suppliers |

Wellington Breweries also maintains their own warehouse located within a 10-minute distance from the brewery where they store their key ingredients and finished product.

- ***Operations***

| *Location* | *Operations* | *Equipment* |
|---|---|---|
| Wellington Breweries (Taproom and retail store) is located at:<br>950 Woodlawn Road West<br>Guelph, ON N1K 1G2 | Beer brewing | Brew Kettle<br>Fermentation Vessels<br>Beer Aging tanks<br>Brite tanks<br>Cartridge filters<br>Canning line* |
| Wellington Breweries (Warehouse)<br>510 Governor's Road<br>Guelph, ON N1K 1E3 | Packaging | KRONE's packaging line |
| Partnership with a farmer who obtains the 'spent' or used up grain as cattle field. The manure produced via this process ultimately is used as fertilizer. | Waste Management | N/A |

*In 2007, the company was also packaging their product into 473 ml beer cans using Cask Brewing Systems Inc which produced 24 cans a minute and relied on manual labor to stack the cans onto the machines conveyor belt.

- ***Outbound Logistics***

| *Type of Outbound Logistic* | *Mode of achievement* |
|---|---|
| Product distribution | Retailers: LCBO, Beer Store, Wellington Brewery retail store<br>E-commerce |
| Delivery | Wellington Brewery vans and trucks<br>Canada post for online orders |
| Product inventory | Warehouse at Governor's road location*<br>Cold storage |

*The company in 2015 expanded its warehouse space to include 12,000 sq feet of floor space to allow for more inventory to be stored.

- ***Marketing and Sales***

The company hired an experienced sales team with representatives for parts of Toronto as well as South Western Ontario. The team also has an Event Coordinator as Wellington Brewery sponsors charitable events as well as workshops where beer lovers and the general public alike get hands-on experience brewing beer. In terms of sales, the company offers discounts (online store) when customers buy in bulk. Beer is available in various quantities and packaging to cater to individual tastes and needs. You can buy cans and bottles for personal consumption, or growlers that are ideal for sharing with friends or even a whole keg for large parties or to have in your Kegerator at home. Wellington Brewery products, from beer cans to apparel, typically contain their trusted and iconic rubber boot logo sometimes accompanied by the phrase "Try A Welly On". It is visible on all Wellington Brewery tap handles to let customers at licensed restaurants know that Wellington beer is available on tap. The

company also has an Instagram page, Facebook and Twitter page where new and upcoming products are highlighted and marketed directly to consumers.

- ***Service***

The company is very active in the community and sponsors charity events. In this way, the company gives back to the community as well. Wellington Breweries also organizes tours of its facilities along with beer samplings to reinforce its brand. The breweries also offer warehouse space to host events and as an example, the company also hosted a contemporary art exhibition in September 2018 as a positive move forward to support local artists. The company also offers customers the option to sign up for a Newsletter and learn of new and upcoming products in the pipeline. Wellington Brewery is also a member of the Guelph.Beer association consisting of all Guelph Breweries which includes Sleeman, Royal City, Brothers Brewing and Fixed Gear Brewing. This association was created to foster cooperation, responsibility, conservation, and quality in the industry as well as enhancing the Guelph community.

The support activities of the company are listed below.

- ***Firm Infrastructure***

Wellington Breweries currently has an Administrative and Production team. This team includes the current president and owner of the brewery – Brent Davies. The company also has a purchasing manager to communicate with suppliers as well as logistics and distribution manager. In terms of overseeing production, the company has a lead brewmaster. The company also has a marketing and sales team whose tasks entail event coordination, managing sales across the GTA and so forth.

- ***Human Resource Management***

The company does not have a human resources department or a team, rather it consists of one person – a human resources representative. Important human capital consists of the Brewmaster Marvin Byck and other brew staff, Taproom staff with good beer knowledge as well as motivated sales staff to acquire licensing sales. Of course, Logistics and Purchasing managers, as well as good general managers critical to ensure day to day operations, run smoothly and seamlessly.

- ***Procurement***

Wellington Breweries has partnerships with certain hops farmers in Ontario to create certain craft beers. Additionally, they also have collaborations with Escarpment Laboratories and have recently begun purchasing liquid yeast cultures that have been harvested from regions in Ontario. Other items to that are procured include equipment for brewing and for the taproom operations, glassware and merchandise, bottles/cans/growlers for packaging (if not made on-site).In 2016, the company received a $184,000 in federal and provincial grants which were invested towards a completely automated, state of the art KRONE's packaging line.

- ***Technological Development***

Due to increasing demand for their craft beer, the company switched to state of the art Krone system bottle and can packaging systems for improved efficiency. The company also increased tank capacity; all-in-one fermentors to enable faster turn-around time. Now the company is able to brew beer 24/7 at their facility. Increased warehouse space for inventory to around 12,000 sq feet. Research and development is another big aspect in terms of product development as the company follows craft beer trends and is vital to product differentiation.

## *On to the Class Activity!*

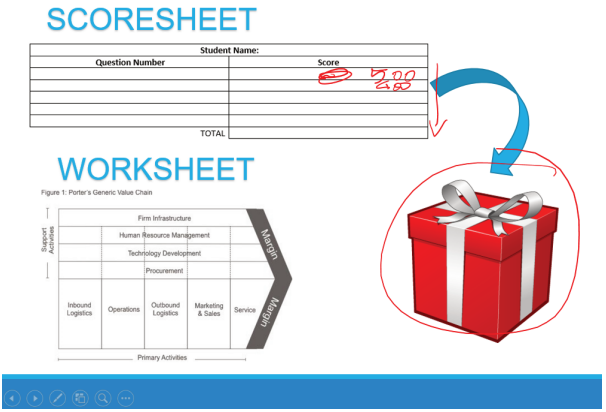
The class activity has two parts – an interactive case study and a worksheet to be completed at the end of the class.

### *Interactive Case Study segment*

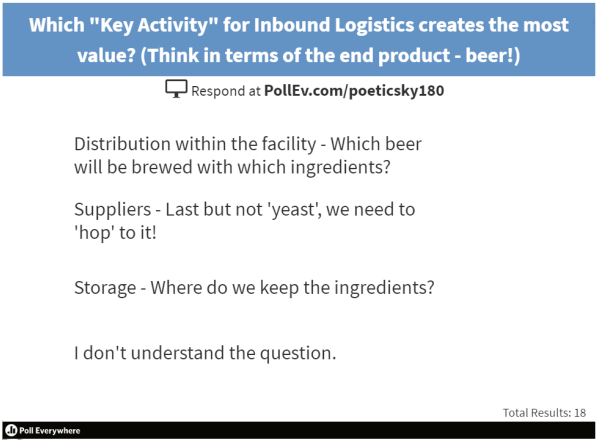
An interrupted format case study was designed centered on the Wellington Brewery. This activity was executed the following way:

The ***Activity Analysis*** portion was already completed for the class. This information was presented to the class on Powerpoint slides 'interrupted' with questions based on the information presented.

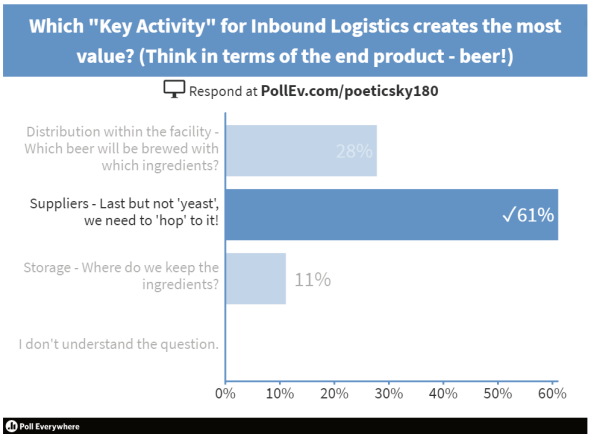

*Step 1. Instructions to join the polling session provided by Poll Everywhere.*




*Step 2. The incentive to join the polling session.*

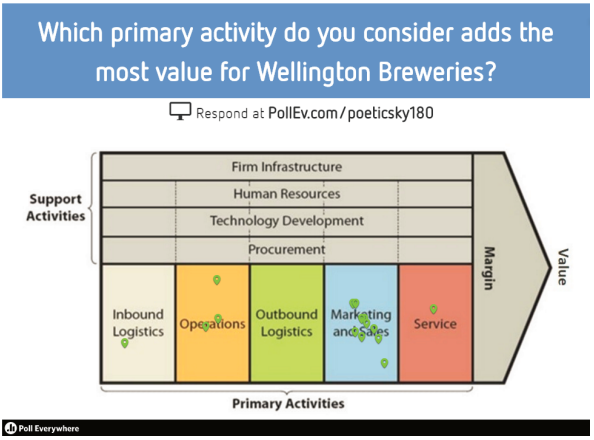



*Step 3. The first question of the presentation.*

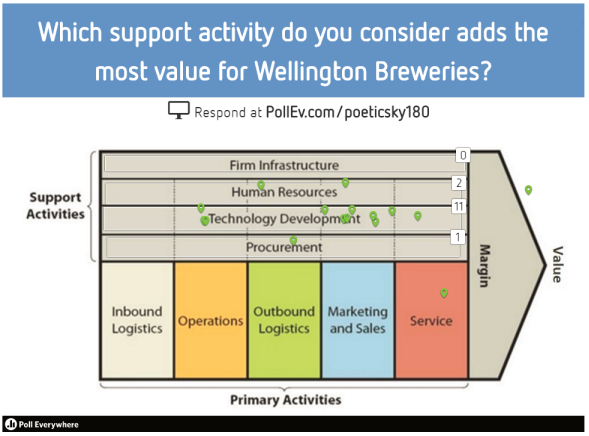



*Step 4. The results from the first question. The results are highlighted in bold with the proportion of students who scored correctly and incorrectly displayed.*


*Step 5. The scoreboard with the top winners. Note, student names have been omitted for privacy reasons.*




*Step 6. A touch-screen based question for students to vote on which primary activity holds the most value.*



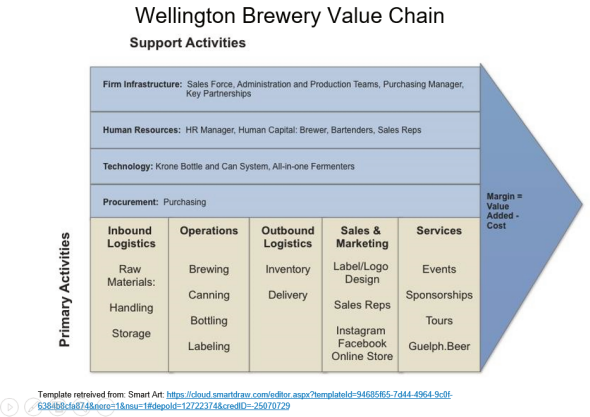

*Step 7. A touch-screen based question for students to vote on which support activity holds the most value.*

### *Hands-on worksheet segment*

This class activity demonstrated how to construct a value chain map for Wellington Brewery and then apply competitive advantage by differentiation in order to identify the value producing steps to make a cannabis-infused beer.

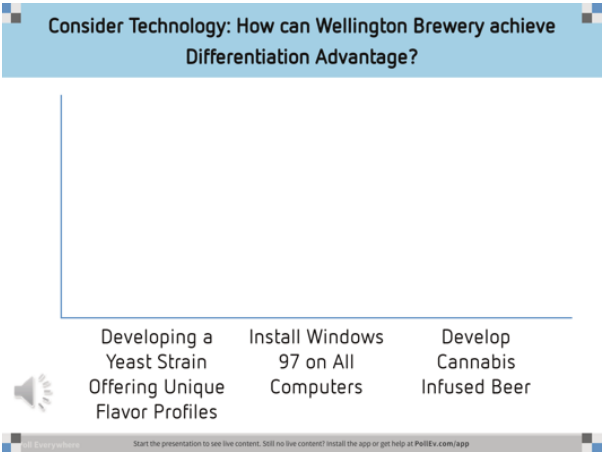
Steps for execution:

1. Hand out Blank Value Chain Maps to students prior to the Wellington Brewery Case study.
2. Have the students follow along and fill out the Value Chain Map as the case study proceeds.
3. The completed Value Chain Map may look similar to what is presented below:




*Step 1. What the completed value chain map may look like.*

4. Inform the class we will be looking at a way to achieve differentiation advantage.




*Step 2. A question on competitive advantage – specifically product differentiation.*

5. Steer the class through the identification of the related linkages as observed below.


*Step 3. The completed value chain map with linkage analysis conducted in tandem with the class.*

## *Conclusion:*

The porter's value chain is a useful tool in understanding the strengths and weakness of the company relative to its competitors. This information can be used to increase the value of a company's product or service. This model can be tailored to meet the needs of different types of business using value chain analysis. Overall, the model can be used to reduce the cost, and improve profit by bringing competitive products to the market.

*Key Takeaways*

- Wellington Brewery's competitive advantage is **product differentiation**.
- Further improvements to **operations** and **marketing and sales** could boost value within primary activities.
- Further improvements to **technology and development** could boost operations.

*References:*


1. Ensign, P. C. (2001). Value Chain Analysis and Competitive Advantage. Journal of General Management, 27(1), 18-42. doi:10.1177/030630700102700102
2. Harrison, K. (2018, September 18). What Is a Value Chain Analysis? Business News Daily. Retrieved February 25, 2019, from https://www.businessnewsdaily.com/5678-value-chain-analysis.html
3. Jurevicius, O. (2013, April 25). Looking at your Value Chain will make you Smarter. Retrieved from https://www.strategicmanagementinsight.com/tools/value-chain-analysis.html
4. Kumar, Dilip & P.V. Rajeev, Prof. (2016). Value Chain: A Conceptual Framework.

5. http://www.free-management-ebooks.com/news/porters-value-chain-analysis/ Accessed: 02/19/2019
6. Our vision. (n.d.). Retrieved from https://www.wellingtonbrewery.ca/about

# 13. Using Statistics Canada and Interpreting Data to Generating Graphs

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Feb 6, 2018


## Introduction to StatCan:

Statistics Canada is a Canadian organization that collects and analyzes information on population demographics, resources, the economy, society, and culture.

Their mission: "Serving Canada with high-quality statistical information that matters."

A few notes on how they collect information:

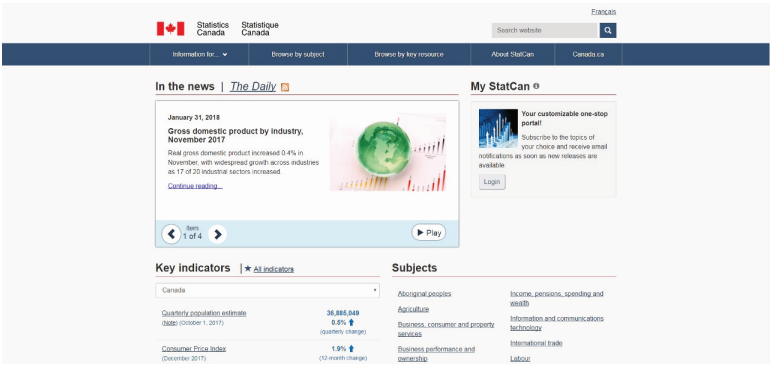
- There are hundreds of active surveys on all sorts of topics at any given time.
- Census data is collected every five years with the latest being in 2016, so it is fairly up-to-date. There are a lot of intricacies to combing through census information, as with any database, so here is a link with search help tips: *http://www.bac-lac.gc.ca/eng/census/Pages/census.aspx.*

# Homepage:

*https://www.statcan.gc.ca/eng/start*

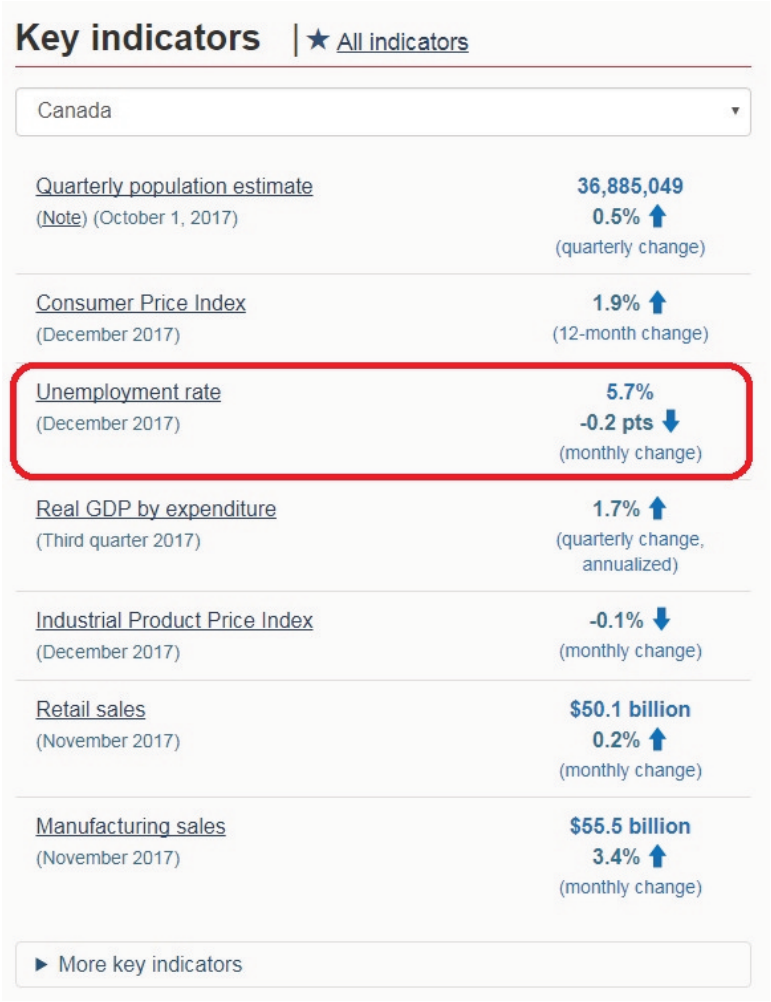
The homepage has quick links to important economic information like the quarterly population estimate, consumer price index, unemployment rate, etc. (Fig 1).

**(Fig 1)**




For example, under Key indicators, one can select Unemployment rate (Fig 2). This will open the page containing information on the labour force as of the date listed at the top of the page. Here, there will be a written report detailing the un/employment rates by region, different age groups, and some details on different industries. There are also line graphs displaying the employment and unemployment rates for the country for the past (approx.) five years (Fig 3 and 4).

**(Fig 2)**


Key indicators
★ All indicators
Canada
Quarterly population estimate
(Note) (October 1, 2017)
36,885,049
0.5%
(quarterly change)
Consumer Price Index
(December 2017)
1.9%
(12-month change)
Unemployment rate
(December 2017)
5.7%
-0.2 pts
(monthly change)
Real GDP by expenditure
(Third quarter 2017)
1.7%
(quarterly change, annualized)
Industrial Product Price Index
(December 2017)
-0.1%
(monthly change)
Retail sales
(November 2017)
$50.1 billion
0.2%
(monthly change)
Manufacturing sales
(November 2017)
$55.5 billion
3.4%
(monthly change)
More key indicators

**(Fig 3)**

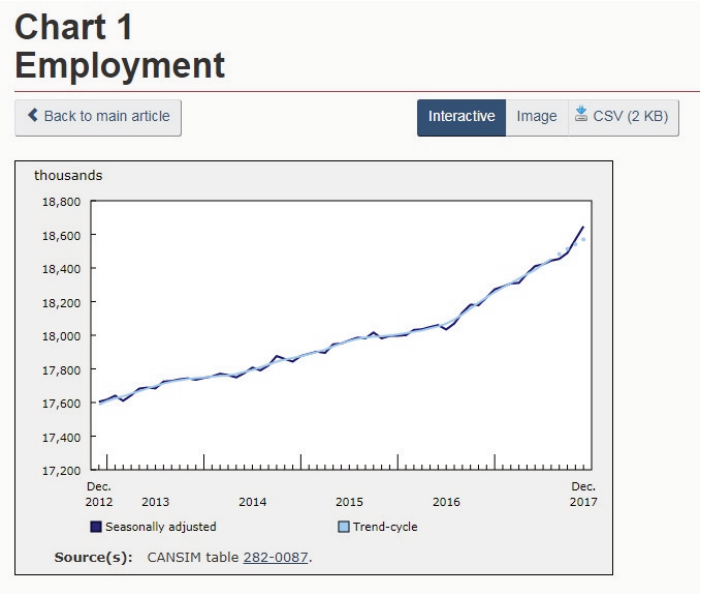
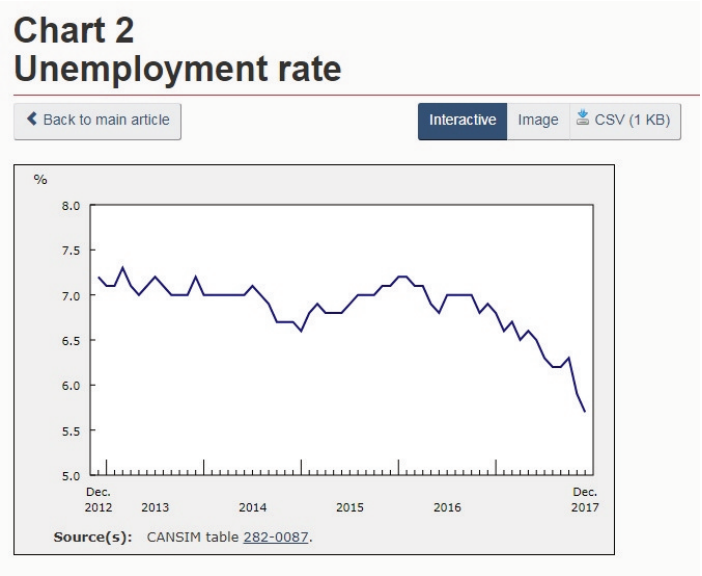


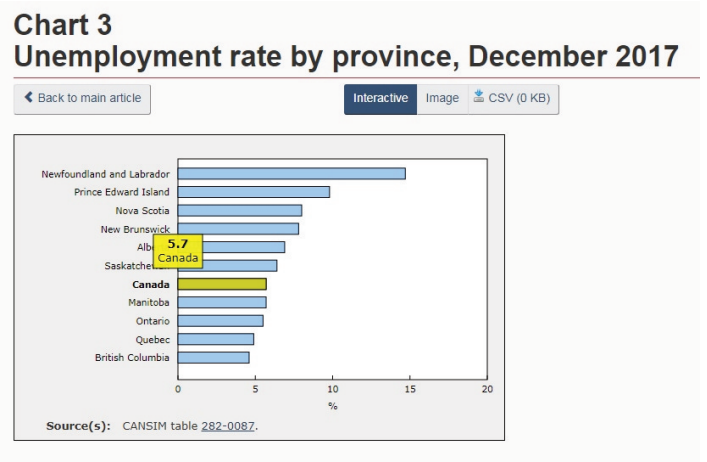
Chart 1
Employment
Back to main article
Interactive
Image
CSV (2 KB)
thousands
18,800
18,600
18,400
18,200
18,000
17,800
17,600
17,400
17,200
Dec. 2012
2013
2014
2015
2016
Dec. 2017
Seasonally adjusted
Trend-cycle
Source(s): CANSIM table 282-0087.

**(Fig 4)**




Also on this page is a breakdown of the unemployment rate by province in bar graph format (Fig 5).

**(Fig 5)**



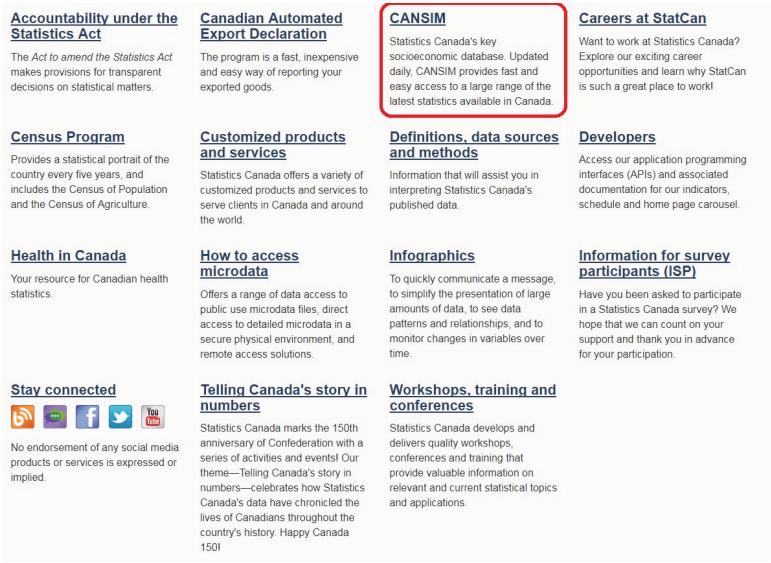

Clicking on the images will show an interactive graph as well as the raw data (below the graph) from which it was made. An image of the graph can be saved by clicking the button above the graph and saving the resulting image or the data can be saved in .csv format (button also above the graph) to be manipulated using other software.

## CANSIM and searching for data:

Back on the homepage, there are many links to browse by subjects: Aboriginal peoples, agriculture, etc. as well as additional links further below that lead to other important resources for data.

CANSIM (CANadian Socioeconomic Information Management system) is a database of socioeconomic information that has been generated from numerous surveys and is updated daily (Fig 6 and 7).

**(Fig 6)**

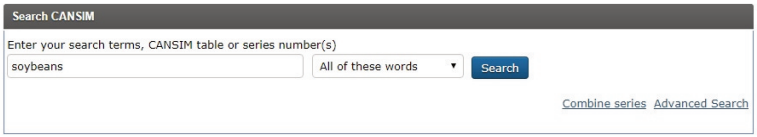

Accountability under the Statistics Act
The Act to amend the Statistics Act makes provisions for transparent decisions on statistical matters.
Canadian Automated Export Declaration
The program is a fast, inexpensive and easy way of reporting your exported goods.
CANSIM
Statistics Canada's key socioeconomic database. Updated daily, CANSIM provides fast and easy access to a large range of the latest statistics available in Canada.
Careers at StatCan
Want to work at Statistics Canada? Explore our exciting career opportunities and learn why StatCan is such a great place to work!
Census Program
Provides a statistical portrait of the country every five years, and includes the Census of Population and the Census of Agriculture.
Customized products and services
Statistics Canada offers a variety of customized products and services to serve clients in Canada and around the world.
Definitions, data sources and methods
Information that will assist you in interpreting Statistics Canada's published data.
Developers
Access our application programming interfaces (APIs) and associated documentation for our indicators, schedule and home page carousel.
Health in Canada
Your resource for Canadian health statistics.
How to access microdata
Offers a range of data access to public use microdata files, direct access to detailed microdata in a secure physical environment, and remote access solutions.
Infographics
To quickly communicate a message, to simplify the presentation of large amounts of data, to see data patterns and relationships, and to monitor changes in variables over time.
Information for survey participants (ISP)
Have you been asked to participate in a Statistics Canada survey? We hope that we can count on your support and thank you in advance for your participation.
Stay connected
No endorsement of any social media products or services is expressed or implied.
Telling Canada's story in numbers
Statistics Canada marks the 150th anniversary of Confederation with a series of activities and events! Our theme—Telling Canada's story in numbers—celebrates how Statistics Canada's data have chronicled the lives of Canadians throughout the country's history. Happy Canada 150!
Workshops, training and conferences
Statistics Canada develops and delivers quality workshops, conferences and training that provide valuable information on relevant and current statistical topics and applications.

**(Fig 7)**

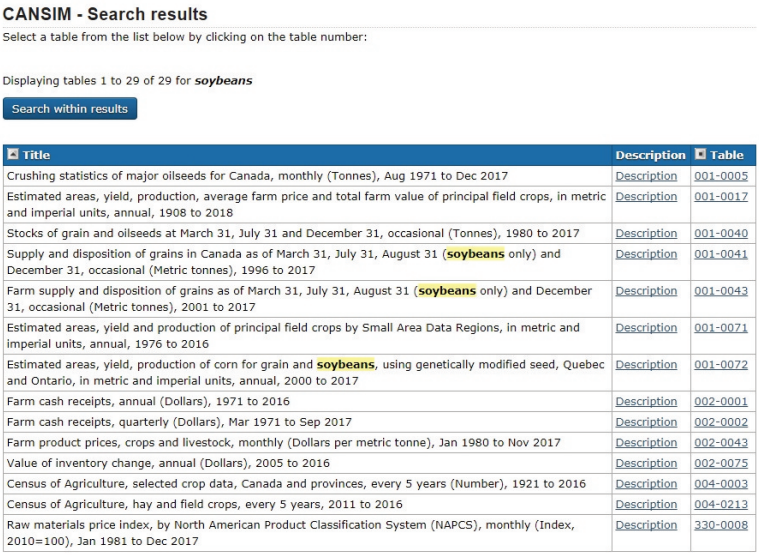

Let's imagine that a person has a new biotechnological application that makes use of soybeans and is looking to build a new facility in Canada in a convenient location where there are a lot of soybeans. How would one go about determining what a good location would be?

Searching *soybeans* in CANSIM will bring up a list of tables that contain information on soybeans (Fig 8 and 9). Take a look at the titles. Clicking on the Description link will give more information on that specific table while clicking on the Table code link will open up the table containing the data.

**(Fig 8)**



**(Fig 9)**



**CANSIM - Search results**

Select a table from the list below by clicking on the table number:

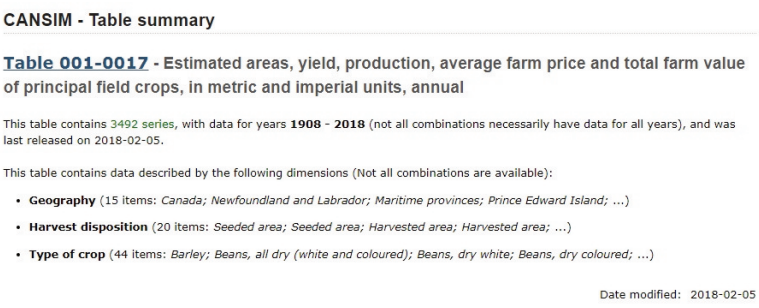
Displaying tables 1 to 29 of 29 for ***soybeans***

Search within results

| Title | Description | Table |
|---|---|---|
| Crushing statistics of major oilseeds for Canada, monthly (Tonnes), Aug 1971 to Dec 2017 | Description | 001-0005 |
| Estimated areas, yield, production, average farm price and total farm value of principal field crops, in metric and imperial units, annual, 1908 to 2018 | Description | 001-0017 |
| Stocks of grain and oilseeds at March 31, July 31 and December 31, occasional (Tonnes), 1980 to 2017 | Description | 001-0040 |
| Supply and disposition of grains in Canada as of March 31, July 31, August 31 (**soybeans** only) and December 31, occasional (Metric tonnes), 1996 to 2017 | Description | 001-0041 |
| Farm supply and disposition of grains as of March 31, July 31, August 31 (**soybeans** only) and December 31, occasional (Metric tonnes), 2001 to 2017 | Description | 001-0043 |
| Estimated areas, yield and production of principal field crops by Small Area Data Regions, in metric and imperial units, annual, 1976 to 2016 | Description | 001-0071 |
| Estimated areas, yield, production of corn for grain and **soybeans**, using genetically modified seed, Quebec and Ontario, in metric and imperial units, annual, 2000 to 2017 | Description | 001-0072 |
| Farm cash receipts, annual (Dollars), 1971 to 2016 | Description | 002-0001 |
| Farm cash receipts, quarterly (Dollars), Mar 1971 to Sep 2017 | Description | 002-0002 |
| Farm product prices, crops and livestock, monthly (Dollars per metric tonne), Jan 1980 to Nov 2017 | Description | 002-0043 |
| Value of inventory change, annual (Dollars), 2005 to 2016 | Description | 002-0075 |
| Census of Agriculture, selected crop data, Canada and provinces, every 5 years (Number), 1921 to 2016 | Description | 004-0003 |
| Census of Agriculture, hay and field crops, every 5 years, 2011 to 2016 | Description | 004-0213 |
| Raw materials price index, by North American Product Classification System (NAPCS), monthly (Index, 2010=100), Jan 1981 to Dec 2017 | Description | 330-0008 |

Based on the title and description, the second table looks like a good place to start (Fig 10). But after opening up the table, we see there is way too much irrelevant information (Fig 11). Let's change that by selecting the "Add/Remove data" tab or link (Fig 12).

**(Fig 10)**



**CANSIM - Table summary**

**Table 001-0017 - Estimated areas, yield, production, average farm price and total farm value of principal field crops, in metric and imperial units, annual**

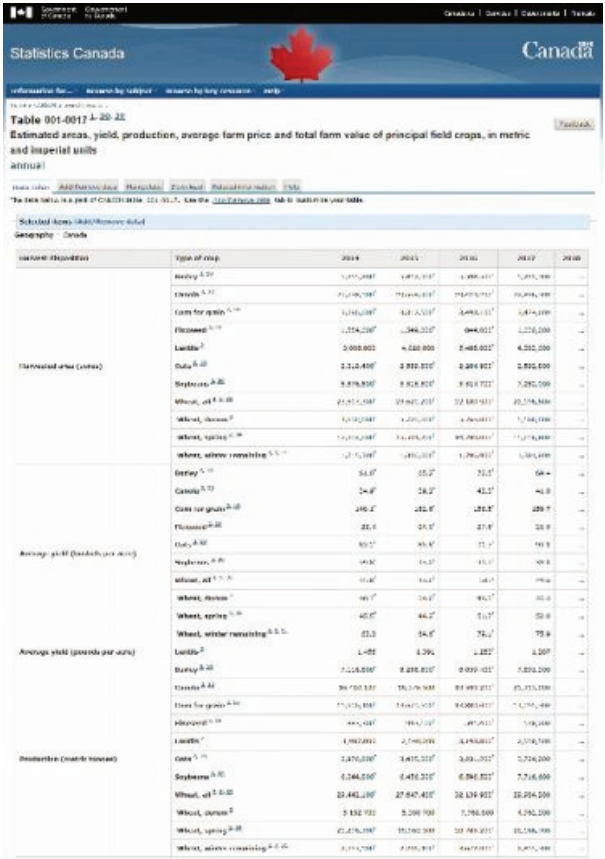
This table contains 3492 series, with data for years **1908** - **2018** (not all combinations necessarily have data for all years), and was last released on 2018-02-05.

This table contains data described by the following dimensions (Not all combinations are available):

- **Geography** (15 items: *Canada; Newfoundland and Labrador; Maritime provinces; Prince Edward Island;* ...)
- **Harvest disposition** (20 items: *Seeded area; Seeded area; Harvested area; Harvested area;* ...)
- **Type of crop** (44 items: *Barley; Beans, all dry (white and coloured); Beans, dry white; Beans, dry coloured;* ...)

Date modified: 2018-02-05

**(Fig 11)**


Statistics Canada

Canada

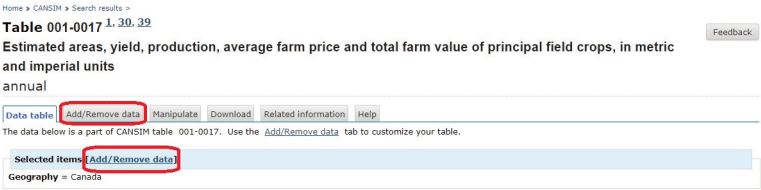
Table 001-0017

Estimated areas, yield, production, average farm price and total farm value of principal field crops, in metric and imperial units

annual

Using Statistics Canada and Interpreting Data to Generating Graphs | 245

**(Fig 12)**




Here we can modify what data we are looking at by selecting the boxes that contain relevant information. For this example we will look at: each province (Geography); *Harvested area* (acres) and Production (metric tonnes) (Harvest disposition); Soybeans (Type of crop); select a reasonable time frame like the 2010 to 2018 (Select the time frame), and HTML table, time as rows (Select the Screen output format) (Fig 13).

**(Fig 13)**

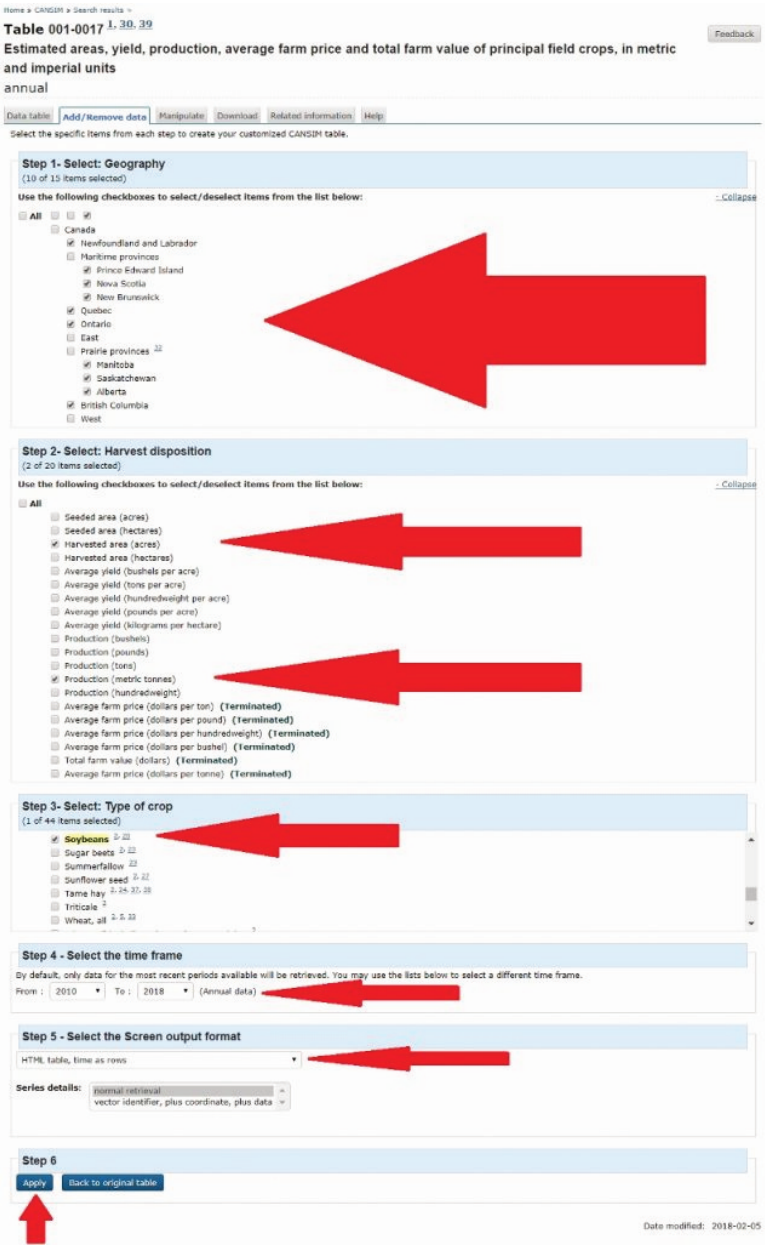


Table 001-0017
Estimated areas, yield, production, average farm price and total farm value of principal field crops, in metric and imperial units
annual
Feedback
Data table
Add/Remove data
Manipulate
Download
Related information
Help
Select the specific items from each step to create your customized CANSIM table.
Step 1- Select: Geography
(10 of 15 items selected)
Use the following checkboxes to select/deselect items from the list below:
Collapse
All
Canada
Newfoundland and Labrador
Maritime provinces
Prince Edward Island
Nova Scotia
New Brunswick
Quebec
Ontario
East
Prairie provinces
Manitoba
Saskatchewan
Alberta
British Columbia
West
Step 2- Select: Harvest disposition
(2 of 20 items selected)
Use the following checkboxes to select/deselect items from the list below:
Collapse
All
Seeded area (acres)
Seeded area (hectares)
Harvested area (acres)
Harvested area (hectares)
Average yield (bushels per acre)
Average yield (tons per acre)
Average yield (hundredweight per acre)
Average yield (pounds per acre)
Average yield (kilograms per hectare)
Production (bushels)
Production (pounds)
Production (tons)
Production (metric tonnes)
Production (hundredweight)
Average farm price (dollars per ton) (Terminated)
Average farm price (dollars per pound) (Terminated)
Average farm price (dollars per hundredweight) (Terminated)
Average farm price (dollars per bushel) (Terminated)
Total farm value (dollars) (Terminated)
Average farm price (dollars per tonne) (Terminated)
Step 3- Select: Type of crop
(1 of 44 items selected)
Soybeans
Sugar beets
Summerfallow
Sunflower seed
Tame hay
Triticale
Wheat, all
Step 4 - Select the time frame
By default, only data for the most recent periods available will be retrieved. You may use the lists below to select a different time frame.
From : 2010
To : 2018
(Annual data)
Step 5 - Select the Screen output format
HTML table, time as rows
Series details:
normal retrieval
vector identifier, plus coordinate, plus data
Step 6
Apply
Back to original table
Date modified: 2018-02-05

Applying this will result in a table containing the data we selected (Fig 14). From there, a person can look at the trends in soybean farming for the listed provinces and decide where a good location to build would be.

**(Fig 14)**

| Geography | Canada | | Prince Edward Island | | Nova Scotia | | New Brunswick | | Quebec | | Ontario | | Manitoba | | Saskatchewan | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Harvest disposition | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) | Harvested area (acres) | Production (metric tonnes) |
| 2010 | 3,721,300 | 4,444,600 | 44,000 | 40,700 | 5,500 | 6,600 | 9,500 | 9,100 | 657,300 | 823,000 | 2,495,000 | 3,129,800 | 510,000 | 435,400 | .. | .. |
| 2011 | 3,840,800 | 4,466,500 | 50,500 | 45,400 | 8,500 | 9,300 | 10,000 | 8,400 | 738,800 | 800,000 | 2,463,000 | 3,189,700 | 570,000 | 413,700 | .. | .. |
| 2012 | 4,188,500[1] | 5,086,400 | 51,000 | 51,400 | 9,500 | 10,600 | 10,000 | 9,300 | 706,000[1] | 843,000 | 2,587,000 | 3,401,900 | 825,000[1] | 770,200 | .. | .. |
| 2013 | 4,608,700[1] | 5,355,900[1] | 57,000[1] | 58,500[1] | 10,000 | 12,000 | 16,000 | 13,200 | 725,700[1] | 847,000 | 2,595,000 | 3,238,600 | 1,045,000 | 1,068,200 | 160,000 | 118,400 |
| 2014 | 5,576,500[1] | 6,044,800[1] | 62,000[1] | 58,200[1] | 12,000 | 14,800 | 12,500[1] | 11,700[1] | 880,000[1] | 898,000 | 3,060,000 | 3,791,100 | 1,290,000[1] | 1,107,700 | 260,000 | 163,300 |
| 2015 | 5,516,500[1] | 6,456,300[1] | 49,500[1] | 45,700[1] | 11,000 | 12,800 | 11,000[1] | 10,900[1] | 845,000[1] | 1,088,100 | 2,930,000 | 3,728,500 | 1,405,000[1] | 1,390,700 | 265,000 | 179,600 |
| 2016 | 5,514,700[1] | 6,596,500[1] | 44,000[1] | 40,800[1] | 11,000 | 12,800 | 13,000[1] | 12,800[1] | 861,700[1] | 1,129,400 | 2,770,000[1] | 3,429,200[1] | 1,585,000[1] | 1,769,000 | 230,000 | 202,500 |
| 2017 | 7,252,000 | 7,716,600 | 50,000 | 49,000 | 12,500 | 15,500 | 21,000 | 16,200 | 978,500 | 1,115,000 | 3,060,000 | 3,796,600 | 2,285,000 | 2,245,300 | 845,000 | 479,000 |
| 2018 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |

It is important to look at the footnotes to be able to properly interpret the data that has been generated.

## Conclusion:

Statistics Canada is a useful, free, credible, and up-to-date source for information about Canada, socioeconomics, and many other topics. Please make use of everyone's tax dollars and use it.

## How to Interpret Data and Generate Appropriate Graphs

After obtaining your data from StatsCan or from another source, you must now be able to convey this data in the most appropriate way possible to get your point across.

What should be done first is determining what kind of data and how much you have

- If your findings are in structured numeric format with more than 4 numbers, **using a table** would be the best option
- If your findings have to do with relationships between numbers, such as comparing or showing trends, **a graph** will be a better option

Determining the type of graph would be the next step.

- **Bar Graphs** are best used to compare values when these values are important and the users will compare these between columns
- **Pie Charts** are best used when you want to visualize something as a whole
- **Line Graphs** are best used for continuous sets of data where a trend is to be shown

Lets use the following data as an example and see how it would best be incorporated:

Types of Apples consumed in Guelph on a monthly basis:
Granny Smith: 30
Honeycrisp: 53
Golden delicious: 81
Gala: 75
Red delicious: 162

Since we are trying to compare these values with each other the most appropriate graph to use would then be the bar graph.

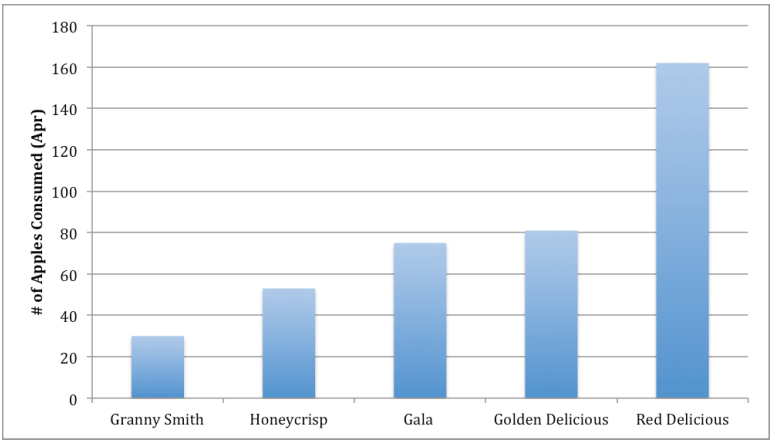



**Figure 1:** Types of apples consumed during the month of April in the City of Guelph

If this data was given slightly differently or if you are trying to represent the entire apple consumption in Guelph, we would be able to use a pie chart as we are visualizing the data as a whole:

Total Apples consumed in Guelph: 404
Granny Smith: 8%

Honeycrisp: 13%
Golden Delicious: 20%
Gala: 19%
Red Delicious: 40%

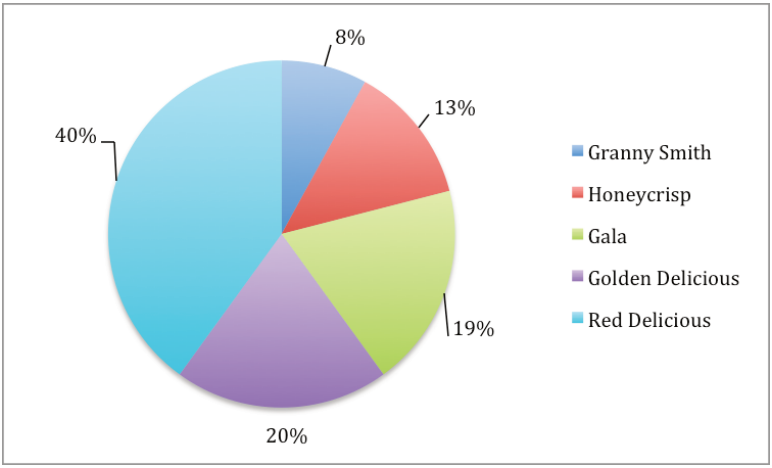



**Figure 2:** Types of apples eaten in the City of Guelph shown in percentages with a total of 404 apples consumed

If the data given was in the time frame of several months, for example, the most efficient way of displaying the information would be to use a line graph.

Total Apples consumed in Apr, May, Jun, Jul:
Granny Smith: 30, 37, 52, 59
Honeycrisp: 53, 60, 65, 57
Golden delicious: 81, 69, 89, 72
Gala: 75, 81, 89, 83
Red delicious: 162, 150, 161, 183

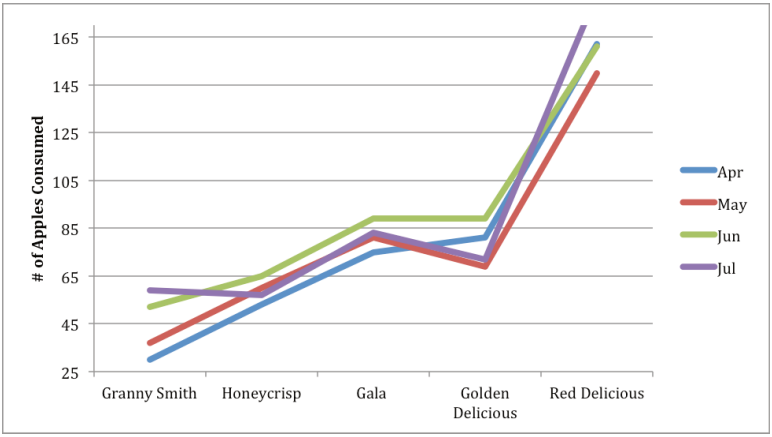



**Figure 3:** Various types of apples consumed in the City of Guelph over the time span of April to July

When you have a data set similar to the one above with 4 or more series of information, it may be more efficient to place said data into a table instead of to crowd a graph. A table would also be useful here to spotlight when each type of apple was consumed most during the time span.

Total Apples consumed in Apr, May, Jun, Jul, Aug, Sep:
Granny Smith: 30, 37, 52, 59, 55, 61
Honeycrisp: 53, 60, 65, 57, 67, 61
Golden delicious: 81, 69, 89, 72, 75, 76
Gala: 75, 81, 89, 83, 72, 82
Red delicious: 162, 150, 161, 183, 149, 159

**Table 1:** Consumption of various types of apples through the months of April to September in the City of Guelph

| | Apr | May | June | July | Aug | Sep |
|---|---|---|---|---|---|---|
| **Granny Smith** | 30 | 37 | 52 | 59 | 55 | **61** |
| **Honeycrisp** | 53 | 60 | 65 | 57 | **67** | 61 |
| **Golden Delicious** | 81 | 69 | **89** | 72 | 75 | 76 |
| **Gala** | 75 | 81 | **89** | 83 | 72 | 82 |
| **Red Delicious** | 162 | 150 | 161 | **183** | 149 | 159 |

With all of this in mind, it is important to remember that both graphs and tables must have titles and descriptions in order for the reader to understand what the figure represents.

# 14. McKinsey 7s Framework

McKinsey 7s Framework

# 15. Balanced Scorecard

## Strategic Management: Balanced Scorecard

**"What you measure is what you get"**
**(Kaplan and Norton, 1992: 71)**

## Introduction

The balanced scorecard (BSC) is a strategic management and planning tool used by many organizations. It focuses on aligning daily work with the organization's strategy while putting in place specific measures that allow management to progress towards strategic targets.

The BSC concept was first suggested by Kaplan and Norton in 1992 to evaluate financial and non-financial performance measurements. They were able to conceive the idea after examining the top corporations in the world and how they were run. The scorecard provides managers with a comprehensive framework to assess both tangible and intangible assets in the corporation (Kaplan and Norton, 2001a). While focusing on four perspectives (financial goals, customer satisfaction, internal processes, and learning and growth), companies are able to effectively evaluate their overall performance.

The BSC helps individual organizations evaluate their performance

based on their own strategy and internal environment. It can set the stage for developing performance measures on the basis of two specific characteristics: transparency and strategy orientation.

What makes the BSC effective is its capability to convert the organization's strategy to practical measures (Kaplan and Norton, 2001a). The BSC also suggests that intangible assets play a significant role in creating an organization's value (Nolan Norton Institute, 1991). Intangible assets are objects the company owns that are not physically available. This includes intellectual property (i.e. patents and trademark), human capital (i.e. employees' talent) and customer loyalty (Kaplan and Norton, 2009). On the other hand, tangible assets are of the physical form and include machinery, buildings, and lands.

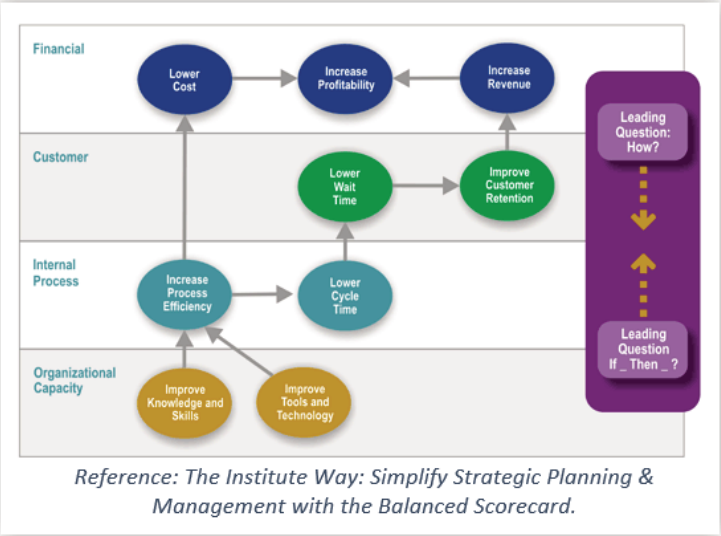
According to Norton and Kaplan, in order to improve the management of their intangible assets, corporations are required to incorporate the non-financial measures to their management systems. It should be noted that intangible assets rarely make value by themselves, instead they should be integrated into other intangible and tangible assets to generate value. For example, with the implementation of a new growth-oriented sales strategy in the organization, different aspects should be aligned. This includes knowledge about customers, databases, organization structure, and incentive compensation program.

Management systems contain many interrelated parts which need concurrent coordination among different line and staff units in the corporation. Independent functions such as budgeting, human resources, and process management should be coordinated to make the strategic alignment. Indeed, they should act as an integrated system rather than a set of independent sub-systems. To align different units and personnel to the strategy, the BSC suggests three efficient tools: strategy map, dashboard, and scorecards.

## Strategy Map:

The concept of the strategy map, (Kaplan & Norton 2000, 2001, 2004), illustrates causal relationships between project objectives. For instance, training personnel can boost service quality which in turn leads to higher customer satisfaction, increased customer loyalty and eventually higher revenues and margins.

All the objectives are connected to each other through cause and effect relationships. These interactions begin from employees, pass through processes and customers, and end with financial outcomes.




*Reference: The Institute Way: Simplify Strategic Planning & Management with the Balanced Scorecard.*

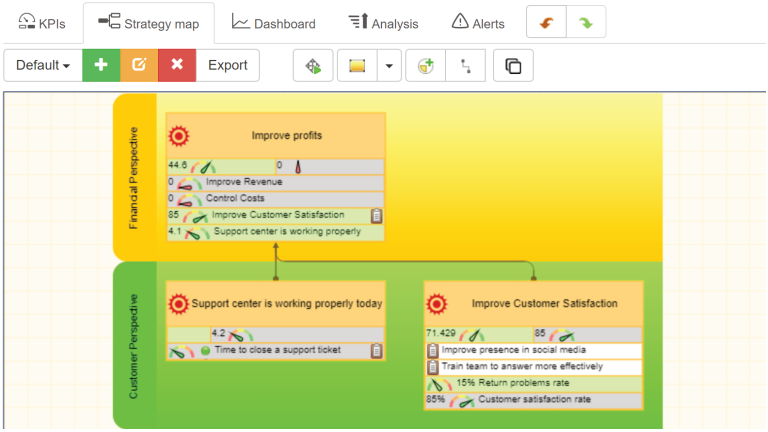
Retrieved from: https://www.balancedscorecard.org/BSC-Basics/Abo

## Dashboard:

The dashboard is a set of measures that provide managers with information regarding various operations and processes within the organization. It demonstrates current progress on an operational level and therefore allows managers to get an idea of the current state of the company.

## Scorecards:

While the dashboard is used as a way of measuring performance, the scorecard is used to manage performance. Scorecards use key performance indicators (KPIs; critical indicators of progress toward an intended result) as a tool to measure progress in order to plan and execute the company's strategy. Kaplan and Norton compare scorecards to an "airplane cockpit providing the pilot with detailed information about several aspects of the flight" (Kaplan and Norton, 1992) which ultimately allow future planning.




Retrieved from: https://bscdesigner.com/dashboard-vs-balanced-sc

## The four perspectives

As mentioned earlier, in order to be well-rounded and successful, the BSC suggests that the company views itself from four perspectives and consequently develop objectives, measures (KPIs), targets and initiatives that are in relation to these points of view. Generally speaking, companies can follow the proposed hierarchy of perspectives (from top to bottom: Financial → Customer → internal processes → learning and growth), yet it's important to note that it is encouraged to tailor the BSC to the company's strategy and needs, consequently arranging the perspectives as required.

- **Financial perspective:**

When an organization begins creating a BSC, how they will want to improve financially will come as an initial concern. For example, the financial perspective for start-ups is about survival as they need the cash flow to help them stay afloat. However for more established companies, their financial perspective should look to keep their shareholders happy and keep them invested in their company.

This is where a business will develop their goal as it will give an organization more specificity with their project. For example, tech companies may look for revenue growth on a new product. Accounting, consulting and law firms may focus on increasing profit margins. A company is then able to track their goals with key performance indicators (KPI's). KPI's are measurements that are

linked to the goal that is the best way to follow the success of a project. These can include cash flow, total asset holding, market price per share, total expenses and revenue per employee. More can be seen from this website here https://bscdesigner.com/sample-kpis.htm.

The financial objective is also a consequence of the other three objectives so they will have to be connected and balanced. Even though a lot of companies are aimed at being financially successful, the top companies in the world have shown that a balance of all four perspectives is their key to success (De Wet, Johannes & Jager, Phillip, 2007).

- **Customer perspective:**

The Customer perspective addresses how a company creates value for its customers (Atkinson et al. 2012). For this perspective, the objectives are to fulfill their consumers' value propositions and to create win-win partnerships in order to strengthen dealer and distributor relationships. If the organization is able to meet these objectives, it should see a positive effect on its financials because happy consumers continue to buy from organizations that treat them well. If the organization is unable to meet these objectives, their financials will suffer.

However, the outcome of the Customer perspective, "Delight the consumer" is not explicitly linked to the Financial perspective. It is a general belief that if consumers are delighted, they should buy more products. The first step in developing this perspective is to define its customer/market segments (Figge, Hahn, Schaltegger and Wagner 2002). Once a company has identified its market segment, it was suggested that the company selects two sets of measures: generic

measures (market share, customer retention, customer acquisition, customer satisfaction, and customer profitability) and performance drivers (product/service attributes, customer relationship, and company image and reputation) (Kaplan and Norton 1996a). Second, the company must determine what customers value and define how they differentiate (performance drivers) themselves from other companies to retain, attract, and satisfy (generic measures) their target customers (Kaplan and Norton 2001). In sum, the Customer perspective uses a value proposition to describe the product, price, and image that a company offers.

- **Internal processes perspective:**

This perspective focuses on the objectives necessary to satisfy both customer and financial needs. That being, the company must develop "internal processes" which are the core/critical business processes where the company creates value (Kaplan and Norton, 2001). To do so, a corporation can either improve existing business systems or develop new business systems.

This perspective is best understood when presented with examples. For instance, when a company's mission is to be a leader in product development, established objectives revolve around the creation and development of products. Therefore, in relation to the customer perspective, the internal perspective could in return develop products that satisfy those needs. Looking at Apple, it has developed its camera in order to satisfy the customer's need to capture moments with their phone. On the other hand, when a company focuses on operational excellence, the internal perspective will aim to satisfy objectives such as decreasing running costs, increasing product quality or optimizing the supply chain.

Similar to the rest, this perspective is interdependent with all other perspectives. Although it serves a specific subgroup of the balanced scorecard, it ultimately serves the overarching mission of the company. Another important thing to note when developing the internal perspective is to not use binary indicators when assigning KPI's to the objectives. Binary indicators are those that have two possible values/states (i.e. complete/incomplete). The issue with such indicators is that they don't grant us control over the progress of the company. The team's knowledge is limited to whether the objective is completed or not, and therefore nothing is known about how far along we are from completion. Moreover, having a binary indicator could reduce the team's ambition since there is no set target that will push the team's performance (instead of hitting a quantified target, the team only aims to complete the task). In order to avoid binary indicators, objectives must be correctly formulated/worded.

- **Learning and growth perspective:**

"Learning and Growth" is the extent to which a company should learn and develop its vision. According to Kaplan and Norton, 'learning' is more important than 'training' which contains mentoring and coaching in the corporation. This perspective also evaluates the flow of information among employees. That is how easy the communication between workers is that let them resolve the problems efficiently.

Furthermore, this perspective determines the extent to which a company must learn in order to fulfill the customer's expectations, improve internal processes, and obtain financial objectives.

Through the measurement of "Learning and Growth" perspective managers can develop the following capabilities:

1. Employee capabilities: Managers can provide employees with the necessary skills aligned with the strategy. Moreover, they give personnel the opportunity to obtain a better understanding of different functions of the company such as marketing, sales, etc.
2. Information system capabilities: They can figure out what information systems such as CRM, ERP, BMP that organization may require to implement the strategy effectively.
3. Strategy awareness and motivation: Managers can motivate and align employees by holding specific programs about the understanding and implementation of the strategy.

learning and growth constitute the essential foundation for the success of any knowledge-worker organization. In a knowledge-worker organization that the employees are the core resource and due to the rapid technological change, it is vital for the organization to provide workers with continuous learning. BSCs help managers focus on learning programs where they can have the biggest contribution in the execution of strategy.

## BSC's advantages:

Kaplan and Norton (1996a), suggest several benefits to applying the BSC in companies:

1. Clarify and reach consensus about strategy.
2. Communicate strategy across the company.
3. Align sectors and employees' goals to the strategy.

4. Make a connection between strategic objectives and long-term goals and annual budgets.
5. Determine strategic initiatives.
6. Conduct periodic evaluation and systematic reviews based on strategy.
7. Receive feedback for improving strategy.

## BSC's disadvantages:

Disadvantages of having a focus: Excessive focus on one strategy could ruin the business. Although It is important to have a specific focus on a trademark area of expertise for the company, there is a need to take care of other aspects of the company and keep a "balanced" focus.

## How to implement a Balanced Scorecard.

1. Establish company strategy/vision/mission.

This is what will determine the direction of the company and build the framework for the perspectives that will be put in place. Although they are superficial and can be tailored to best suit the company, there are 3 generic strategies that a company can adopt (Kaplan and Norton, 2001):

1. Product Leadership Strategy (creating new products and services; build the franchise).If it is heavily reliant on tech, the company can focus on this strategy. The objectives are mainly focused on:
    1. Developing new products.
    2. Innovating existing products.
    3. Improving speed to market.
2. Customer Intimacy Strategy (improving existing products or customer service; increase customer value).Here, the company prioritizes customer experience. Therefore objectives could be related to:
    1. Implementing customer relationship management systems (i.e. the company's activity in social media).
    2. Establishing customer support service (i.e. call center responsible for customer concerns)
    3. Improving customer interaction (the process by which the company integrates customer feedback in R&D phase)
3. Operational Excellence Strategy (cutting operational costs; achieving operational excellence).This could be implemented by a manufacturing company whose objectives focus on optimizing operational functioning. Specific objectives could draw inspiration from these themes:
    1. Decreasing operating costs and cycle time.
    2. Ensuring high standards of quality and delivery time.
    3. Optimizing supply chain.

2. Choose specific objectives for the different perspectives based on the strategy determined initially (i.e. product leadership, customer intimacy, operational excellence). Note that objectives in different perspectives are interrelated. The completion of an

objective in one perspective could help complete an objective in another perspective. Here, we will give examples of how to choose the objectives in the different perspectives based on the three mentioned generic strategies

1. Financial perspective: As mentioned earlier, the typical financial goals for a company revolve around improving profits and revenue while cutting on costs. When looking at the three generic strategies, objectives can focus on:
    1. Developing new revenue streams via new products and services (product leadership strategy).
    2. Ameliorating profitability by improving customer value proposition (customer value strategy).
    3. Optimizing resources via cost reduction, scaling production or sharing resources between departments (operational excellence strategy).
2. Customer perspective: In this perspective, goals are implemented to satisfy the customer by mapping what the customer wants from the company (and not the other way around). Therefore, based on the three generic strategies, objectives could include:
    1. Improving product quality (product leadership strategy).
    2. Optimizing customer experience (customer intimacy strategy).
    3. Improving pricing and timing (operational excellence strategy).
3. Internal processes perspective: This perspective aims to improve the business' inner systems in order to satisfy both customer needs and financial goals. Examples of such objectives include:
    1. Simplifying product initiation (product leadership strategy).

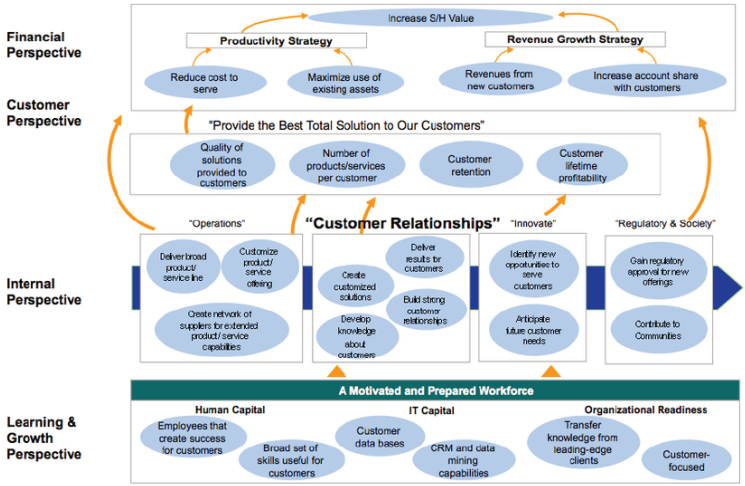
2. Improving customer service and relationship management (customer intimacy strategy).
3. Optimizing process flow by re-sequencing tasks (operational excellence strategy).

4. Learning and growth perspective: Given the continuous evolution of the business world, there is a constant need for organizations to develop accordingly. Interestingly, this perspective adopts a different strategic framework when developing its objectives. There are three themes that this perspective focuses on, within which different objectives can be developed:
    1. Team capabilities theme (do the employees possess the skills required to achieve the internal perspective objectives?).
        1. Assess employee skills.
        2. Train employees.
    2. Strategy awareness and motivation theme (to ensure employees are motivated and understand the company strategy).
        1. Implement strategy awareness program.
        2. Improve leadership and motivation.
        3. Develop organizational culture.
    3. Information system capabilities theme (the information systems necessary to execute the company's vision).
        1. Improve information system capabilities.

Below are examples of BSCs within the different generic strategies. For now, focus only on the main objectives within each perspective (the corresponding measures will be explained in the following sections of this manual). In the examples below, the companies have a main focus but it is key to observe that they show a proper execution

of a balance between the different perspectives but also between different strategies. This is because it is crucial for a company to satisfy diverse needs in order to succeed in the industry. Moreover, these examples represent the concept of key measures which will be discussed in the following sections of this OER.

**Customer intimacy strategy example:**

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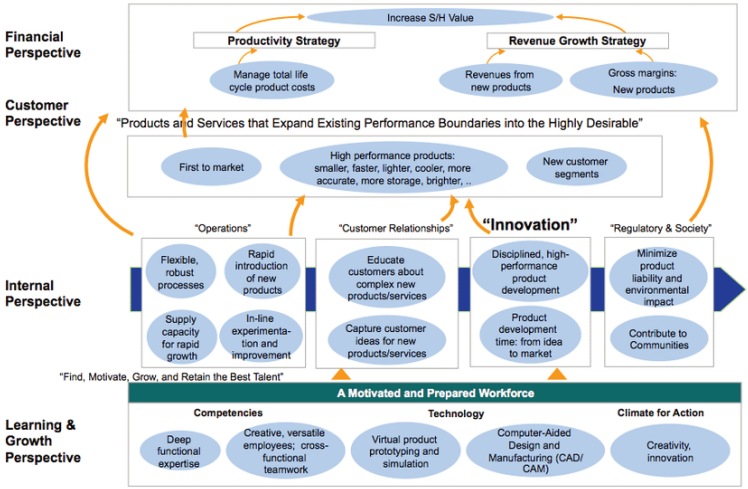
**Product leadership strategy example:**

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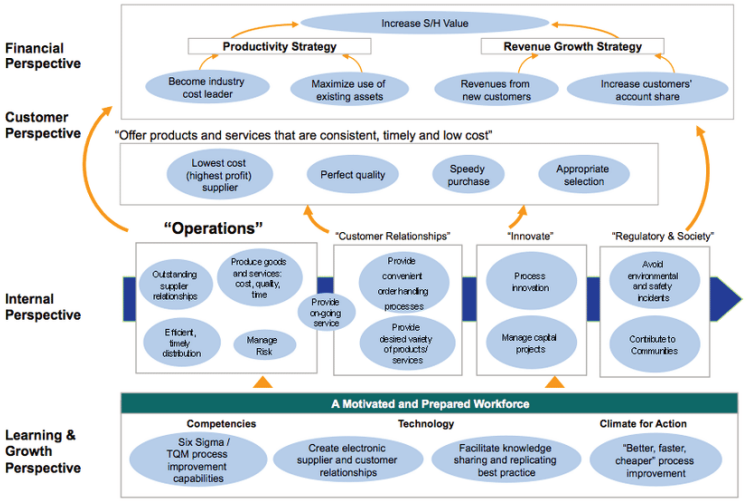
**Operational excellence strategy example:**

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3. After we have specified the objectives required, we must complement them with appropriate indicators.Also known as Key Performance Indicators, KPIs are a metric that allow a company to set a standard of measurement. Consequently, this gives the ability to compare with past results or different companies, as well as plan ahead. These indicators will allow the company to measure progress based on specific criteria that best suit the strategic objectives. This is best explained by defining and giving examples of the types of indicators used.There are two types of indicators used:

Leading: Indicators that will positively influence/drive towards the desired outcome. This is considered to be a predictive measurement.

I.e. The percentage of people wearing hard hats on a building site is a leading safety indicator.

Lagging: this indicator is an output measurement and can only be used as a record to what has already happened.
I.e. the number of accidents on a building site is a lagging safety indicator.

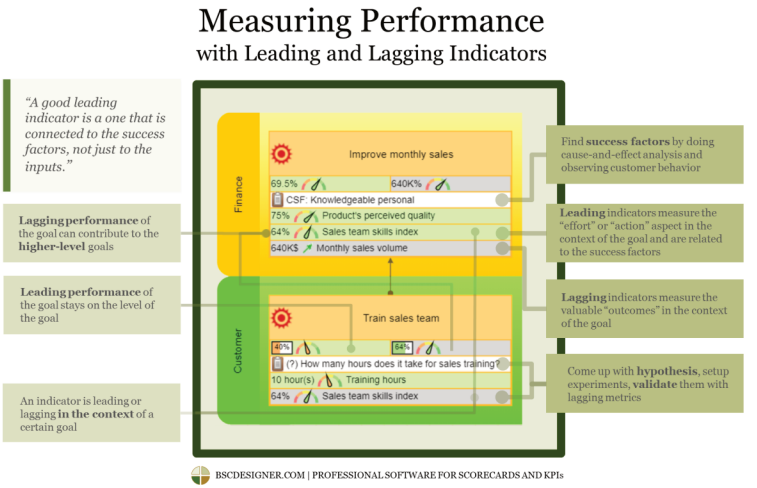
Note: Lagging indicators can be considered reactive measurements while leading indicators can be considered proactive measurements.

Examples:

- Customer Service KPIs:
    - Average speed of answer.
    - Cost per inbound contact.
- Innovation KPIs:
    - R&D budget.
    - Revenue from new projects.
- Operational excellence KPIs:
    - Time of product production.
    - Cost per unit.

For a more detailed guide to KPIs: https://bscdesigner.com/kpis-guide.htm

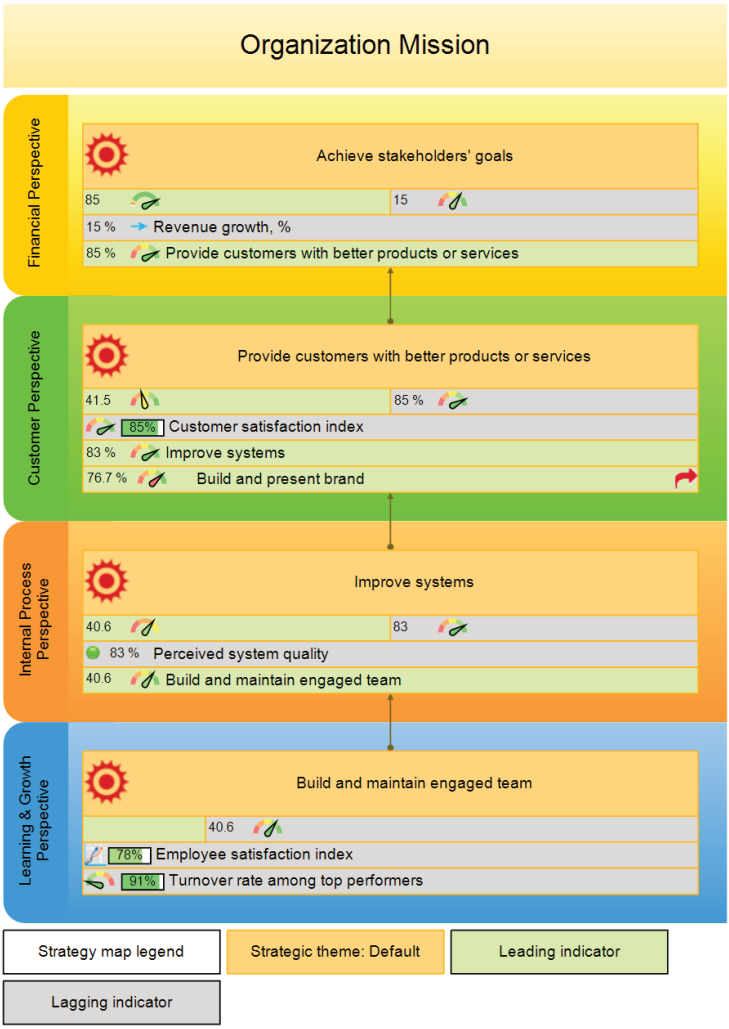
Below is an infographic explaining the implementation of performance indicators (for more detailed information about this section, visit the origin of this infographic: https://bscdesigner.com/leading-vs-lagging.htm ).

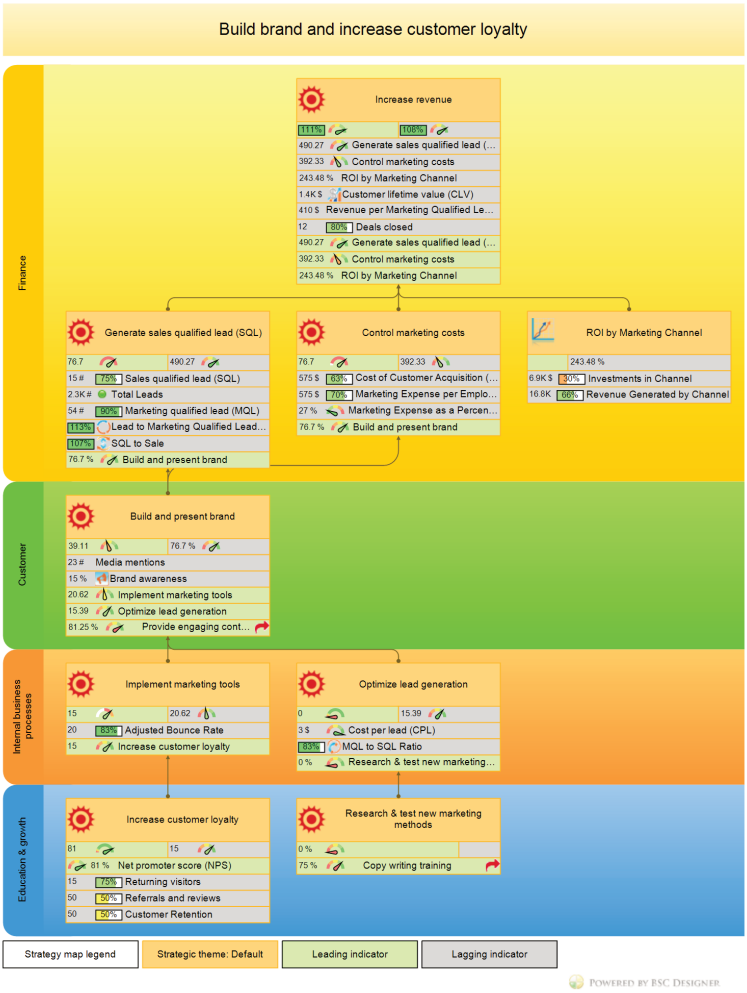



4. Finally, we need to cascade internal objectives.Also known as "alignment", cascading is applicable to all perspectives. This step involves translating the corporate-wide objectives (Tier 1) down to smaller subunits of the company such as departments (Tier 2) and teams/individuals (Tier 3). This allows the entire organization to maintain a clear understanding of the overarching strategy and vision. Moreover, this allows the corporate level to precisely pinpoint areas of strength and weakness and therefore allow improve the company's productivity. As the management system is cascaded, objectives become more operational and strategic.

The process of cascading objectives basically revolves around finding the specific tasks required to complete the objective (objectives within objectives). This is exemplified in the example below: the company wishes to "provide customers with better product or service" (Tier 1), which requires building and presenting brand by the marketing team (Tier 2). Accordingly, the website team

(Tier 3) within the marketing team will need to “provide engaging content” in order to “build and present brand”.


Organization Mission
Financial Perspective
Achieve stakeholders' goals
85
15
15 %
Revenue growth, %
85 %
Provide customers with better products or services
Customer Perspective
Provide customers with better products or services
41.5
85 %
85%
Customer satisfaction index
83 %
Improve systems
76.7 %
Build and present brand
Internal Process Perspective
Improve systems
40.6
83
83 %
Perceived system quality
40.6
Build and maintain engaged team
Learning & Growth Perspective
Build and maintain engaged team
40.6
78%
Employee satisfaction index
91%
Turnover rate among top performers
Strategy map legend
Strategic theme: Default
Leading indicator
Lagging indicator

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Note how among the different tiers of the company, there is a constant alignment of strategy and objectives within different perspectives.

## A case study with BSC in Toyota.

Toyota is one of the leading car companies in the world, originating from Japan but eventually manufacturing cars all over the world. In America, their mission statement is to be the most successful and respected car brand in America. To gain this success in 2003, Toyota management implemented a BSC. They began by creating a strategy to complement their mission statement like expand sales to youth buyers, expand shares of the SUV market and have the tops sales in passenger cars. Throughout this process, the executives maintained contact with their employees for feedback and updated them about their progress. This was done in order to align the company and ensure that the whole system understood the process and objectives of each goal. Through the employees' feedback, Toyota was able to assess where they needed to improve on and create objectives to work on these weaknesses(Delta Publishing 2014).

After creating their overall strategies and listening to the feedback from their employees Toyota's management started devising a way to incorporate these goals into a BSC. This meant having a balance between the four goals with some of the objectives overlapping with

each other. For increasing financial goals they had tasks like control the growth of general expenses, manage workforce costs and also sustain a high level of profitability given a challenging market. While looking at the internal business process they had focused on expanding sales and service capability and focus on completing major technology process. Toyota also wanted to maintain its high level of customer loyalty, sustain a high level of dealership satisfaction and also improve customer and sales satisfaction. Lastly to improve their learning and growth they wanted a successful model launch, achieve #1 in passenger sales and maintain luxury SUV leadership(Delta Publishing 2014)..

*Financial BSC*

| **Business priorities** | **Measure** | **2003 results** | **2003 target** | **Signal** |
|---|---|---|---|---|
| **Sustain high level of profitability given a challenging market** | Operating Income | On Track | $650M | |
| **Control the growth of general expenses** | % Reduction | On Track | 0.6% | |
| **Manage workforce cost to support the achievement of business priorities.** | % of sales | On Track | 1.4% | |

## *Learning and growth BSC*

| Business priority | Measure | 2003 Results | 2003 Target | Signal |
|---|---|---|---|---|
| **Support successful launch of Scion** | Buyer % under the age of 35 | 49% | 45% | |
| **Achieve # 1 in passenger car position for Toyota sales** | Passenger Car segment | #1 | #1 | |

## *Internal Process BSC*

| Business priority | Measure | 2003 Results | 2003 Target | Signal |
|---|---|---|---|---|
| **TOMS(Toyota ordered management system)** | Release 1 | Launch complete by Nov 17, 2003 | Launch complete by Nov 17, 2003 | |
| **Service capacity** | Lexus (Increase # of technicians) | Increase by 13.6% | Increase by 13% | |
| **Sales Capacity** | Lexus # out outlets | 206 | 207 | |

*Customer Segment BSC*

| Business priority | Measure | 2003 Results | 2003 Target | Signal |
|---|---|---|---|---|
| **Maintain high level of customer loyalty** | Replacement Loyalty | 54% | 56% | |
| **Sustain high level of dealer satisfaction** | Toyota NADA | #1 | #1 | |
| **Improve customer and sales satisfaction overall** | JD power Sales satisfaction index (SSI) | Toyota ranked 34th lexus ranked 6th | Improve target | |

With Toyotas implementation of the BSC we can see their strategy succeed in many areas of their vision. The BSC shown above provides an excellent example of creating an understandable project for the employees and management to understand. With each objective to improve the company, they also included KPI's to evaluate the progress of each of their goal. We can also see the crossing over of each of the four BSC perspectives, for example in learning and growth the successful launch of a new car will impact the financial goals of the company. The dashboard is also seen on the side of each BSC which shows the managerial team where the company is at with the targets. The BSC was able to benefit the employees, customers, and management in a different way. Employees saw more contribution from their work, managers saw increased profit and sales while improving customers loyalty. From Toyota, other companies can learn success and follow the BSC with a strategy

of their own. It shows that financial success is not always the only measure of success and that other non-financial options can lead a company to be just as successful. The only thing Toyota could have improved on was a strategy map that would include the causal relationships between each goal(Delta Publishing 2014).

Conclusion:

The BSC is a strategic management tool helping to measure, monitor, and communicate strategic goals throughout the organization through an understandable way and get everybody on the same page working towards the same goals (Lawson et al. 2008). The BSC is a set of coherent performance measures providing executives with a comprehensive framework for an organization's vision and strategy (Kaplan and Norton 1996a). Organizations are using the BSC to provide a quick look at whether or not they are achieving their goals and strategy. The BSC is considered as a mean of communication, informing, and learning system and should not be used as a controlling system (Kaplan and Norton 1996b). Top management of an organization can use the BSC to translate its strategy into performance measures that employees can easily understand. The BSC is organized into four perspectives: Learning and Growth perspective, Internal Process perspective, Customer perspective, and Financial perspective (Atkinson, Kaplan, Matsumura, and Young 2012).

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6 examples of balanced scorecards: https://www.clearpointstrategy.com/full-exhaustive-balanced-scorecard-example/

Demonstration of how to build BSC on website.

https://bscdesigner.com/try-bscdesigner

https://bscdesigner.com/internal-processes.htm

PART III

# PASSPORT,A GLOBAL MARKET INFORMATION DATABASE BY EUROMONITOR

BY: ALINA MARIA EINETTER, SAJIDA NOOR, LUANYS VILLATE & ANDREA CAMPOS

## INTRODUCTION

Euromonitor International has been recognized as the world's leading independent source of strategic market research that creates data and analysis on thousands of the products and services in the world. Passport, which is delivered by Euromonitor, is a database for insight on industries, economies, and consumers worldwide. Euromonitor is also known as GMID, Global Information database.

Passport is a global research database providing shared access to internationally comparable market research quickly and cost-effectively (Euromonitor International., 2019). It covers 210 markets and 207 countries to help clients analyze market context and to identify future trends.

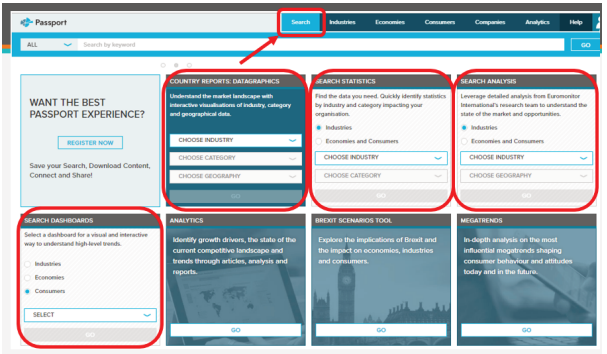
The world's top academic institutions use Passport for teaching and research across a wide range of disciplines. It helps the faculty to design teaching materials and projects with real-world relevance, such as strategic planning, economic analysis, industry benchmarking, competitive threats and market entry studies.

Passport provides data set in a range of formats such as Excel tables, charts, graphs, visual figures known as dashboards to provide quick access to information about selected areas.

Retail market sizes can be determined by passport which further provides a breakdown of expenditure the population of a country has. Consumer lifestyles such as a full-text country report with specific lifestyle factors such as eating, shopping, family, travel, work, leisure and shopping habits in each country can also be obtained by it. Brands and companies, cities report, and statistical database of economic, demographic and marketing parameters of countries are also provided to the users. Passport has broad applications and utility for the users to understand the thousands of data points analytically by shifting the focus from 'what is happening' to 'why is this happening.' Experts clarify published data support if need be.

**Students from the University of Guelph can access it at the university website:**
*https://guides.lib.uoguelph.ca/az.php?q=passport*

## NAVEGATING THE "PASSPORT" WEBSITE

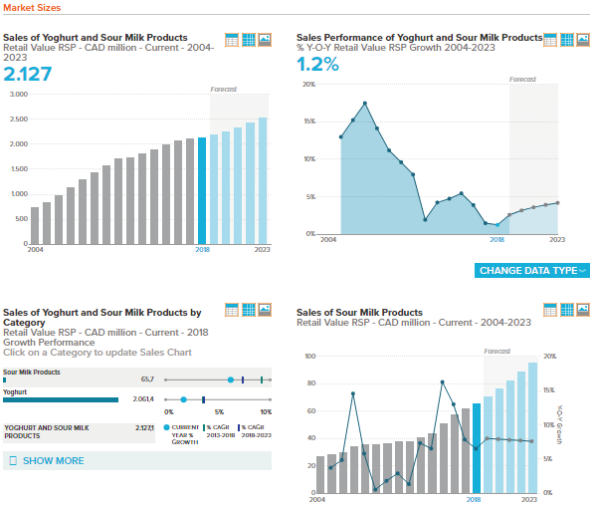



### SEARCHING TOOLS

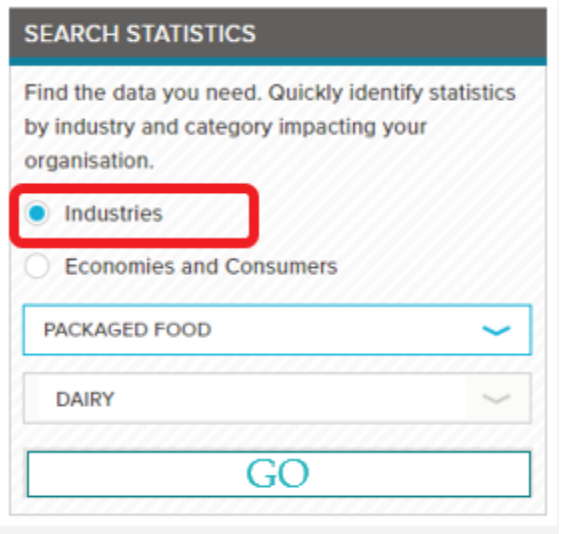
The website of passport offers a lot of searching tools to obtain the desired information. Each button can be used to retrieve different types of information.

* First, there is the tool called DATAGRAPHICS which can be used to get various graphics showing the information. For the example of Yoghurt in Canada, the following parameters were chosen. One example of the output is found in the figure on the right.

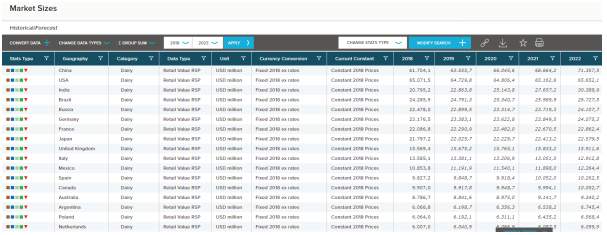

COUNTRY REPORTS: DATAGRAPHICS
Understand the market landscape with interactive visualisations of industry, category and geographical data.
PACKAGED FOOD
YOGHURT AND SOUR MILK PRODUCTS
CANADA
GO


Market Sizes
Sales of Yoghurt and Sour Milk Products
Retail Value RSP - CAD million - Current - 2004-2023
2.127
Sales Performance of Yoghurt and Sour Milk Products
% Y-O-Y Retail Value RSP Growth 2004-2023
1.2%
CHANGE DATA TYPE
Sales of Yoghurt and Sour Milk Products by Category
Retail Value RSP - CAD million - Current - 2018
Growth Performance
Click on a Category to update Sales Chart
Sour Milk Products
Yoghurt
YOGHURT AND SOUR MILK PRODUCTS
SHOW MORE
Sales of Sour Milk Products
Retail Value RSP - CAD million - Current - 2004-2023

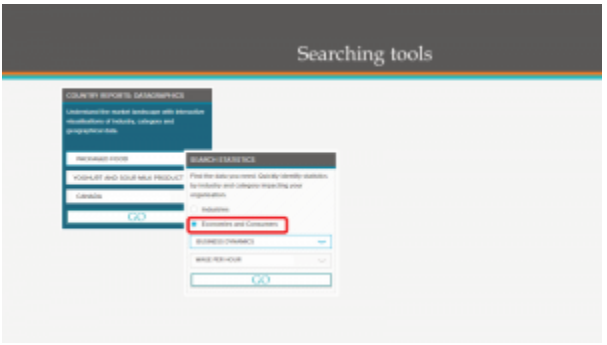
* The second searching box is called SEARCH STATISTICS which can be utilized to find statistics over the past few years and a forecast of the next years with an overview of countries related to industries.



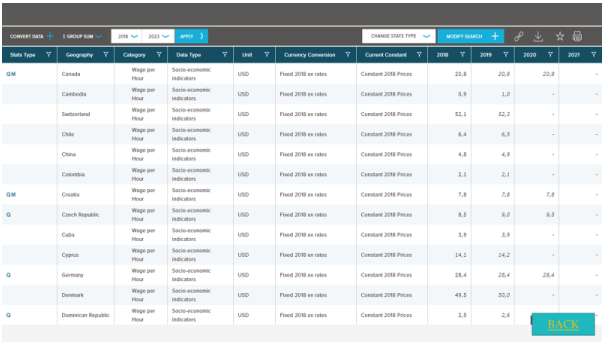

* For example, one can look for the comparison of the market size for dairy products of the whole world. Then the results would look like the following:



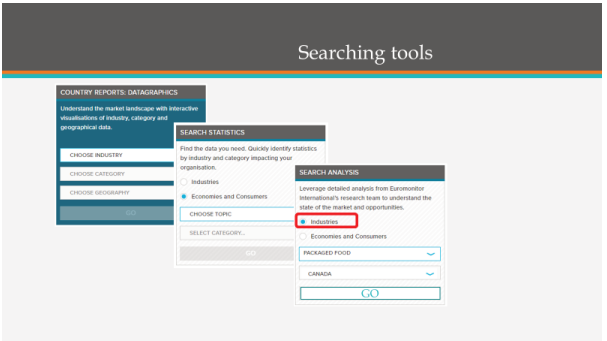
* As an example of Search Statistics for Economies and Consumers -a search f Hourly wages under the Business Dynamics category can be obtained for the category of “Packaged Foods/ Yoghurt and Sour Milk Products/Canada – Select and chose from the drop- down then hit “GO”



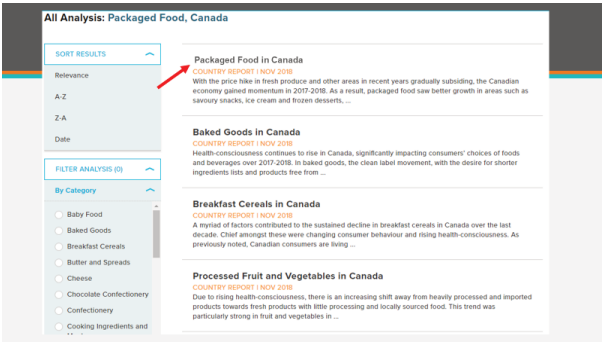

* The results are shown below. Information on hourly wages for the industry and category for Canada will be presented and compared to other country information.



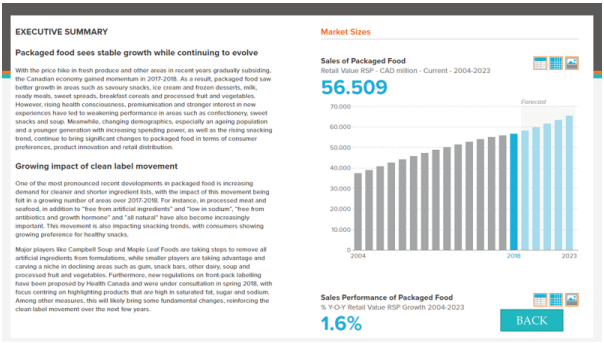
* Selecting Search Statistics for Industries and the drop-down category “Packaged Foods” in Canada and hit “GO” :



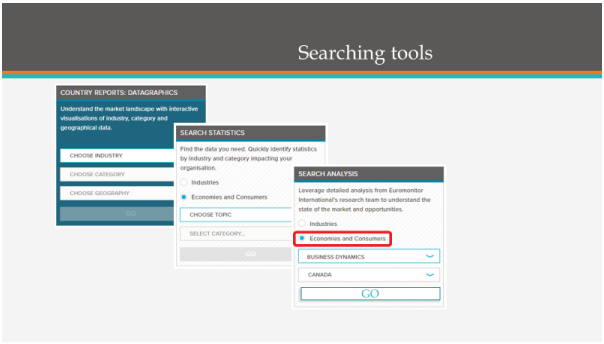

* Presents a list of reports for the Packaged Food industry in Canada. To view details, click on any of the sub-categories.



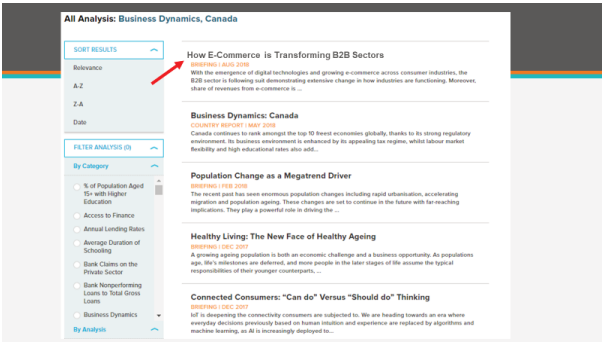

* Complete display of the Package Foods Country Report. The top right allows a view in different buttons formats




* A Search Analysis for Economies and Consumers for the category of Business Dynamics in Canada can be done by choosing from the drop down and hitting “GO”




* The resulting is a screen with information on Business Dynamics in Canada and each category can be expanded for further detail by clicking on it

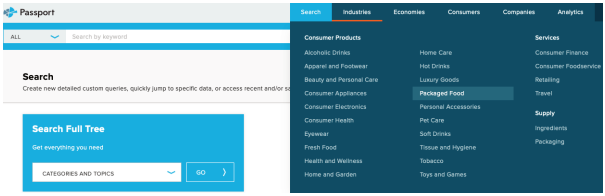



## OTHER TABS

If you don't know exactly what kind of information you are looking for, or you just want to see what they have about a broad topic, you can use the tabs next to "SEARCH":


## "INDUSTRIES" TAB

Here you will find statistics and analysis reports organized by trade. Select the product category where the article you are interested in falls in




The opening screen will offer the following options, divided in to major areas:

**"STATISTICS":**

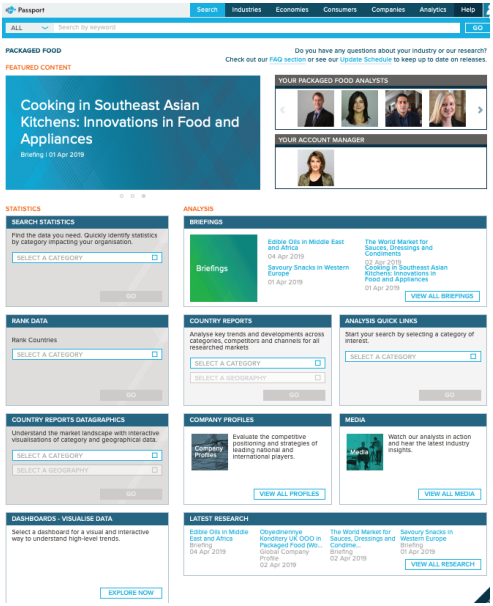
- **"SEARCH STATISTICS"**: General search by sub-category within the chosen product category (which will give you additional options that are discussed below)
- **"RANK DATA"**: Top rank of countries for the selected sub-category within the chosen product category
- **"COUNTRY REPORTS DATAGRAPHICS"**: Analytical report by country for the selected sub-category within the chosen product category
- **"DASHBOARDS – VISUALISE DATA"**: A global dashboard for the chosen product category

**"ANALYSIS":**

- **"BRIEFINGS"**: Available reports for areas related to the chosen product category
- **"COUNTRY REPORTS"**: Same as above, Analytical report by country for the selected sub-category within the chosen product category
- **"ANALYSIS QUICK LINKS"**: Listing of all types of analysis reports available (including Country reports, Briefings, Company

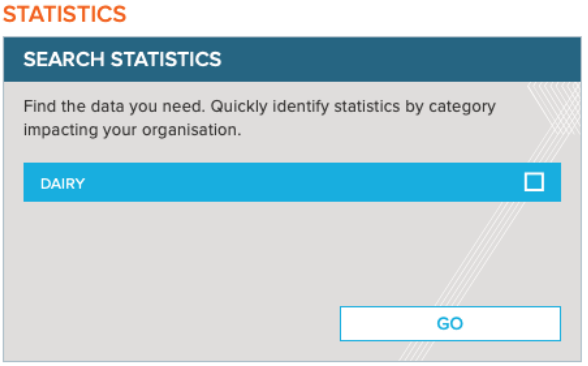
Profiles, etc.), related to the selected sub-category within the chosen product category

- **“COMPANY PROFILES”**: Profile on a limited number of companies, usually the ones recognized internationally
- **”MEDIA”**: List of podcasts and videos produced by Euromonitor and associated to the chosen product category, usually related to market trends or industry movements
- **“LATEST RESEARCH”**: Lists the most recent publications, no matter what type, related to the selected sub-category within the chosen product category, produced by Euromonitor.

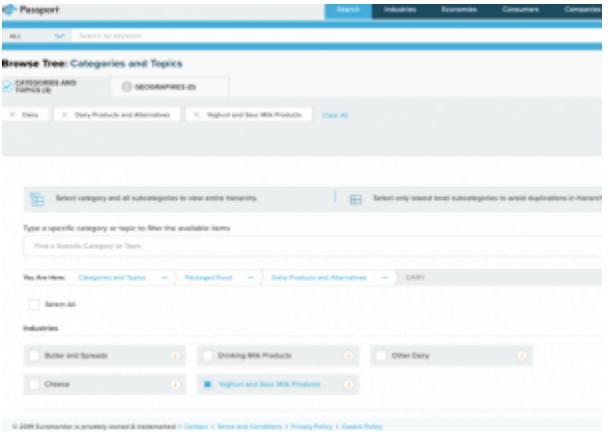


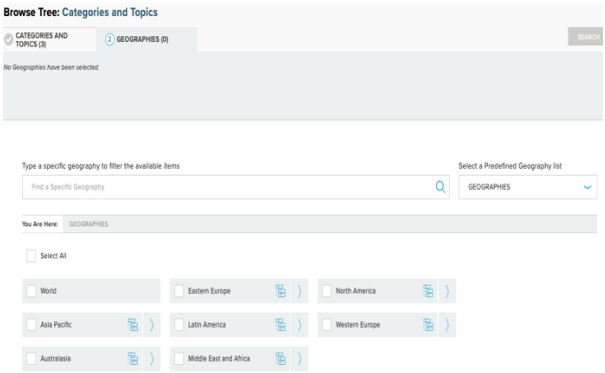
## "INDUSTRIES" TAB > "STATISTICS" > "SEARCH STATISTICS":

Once you have selected a product sub-category:

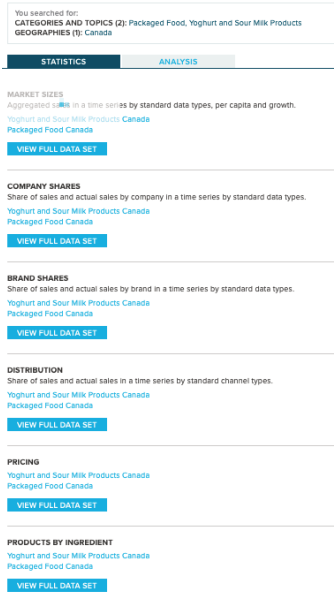



you will find some further options to narrow your search by "Categories and Topics" and "Geographies":






Then, you will get results for both "**STATISTICS**" and "**ANALYSIS**" areas:



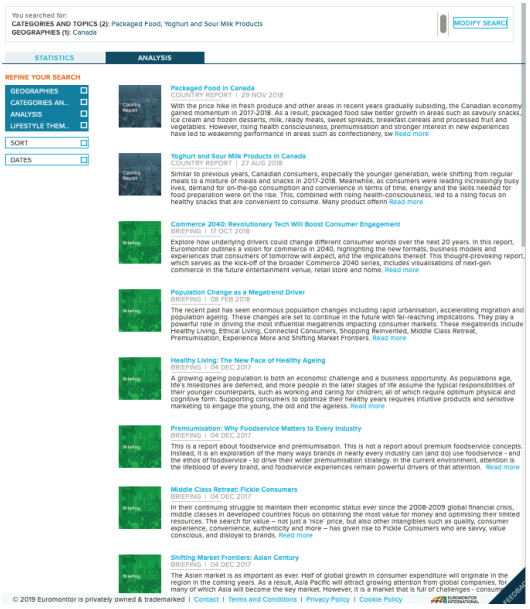
In the "***STATISTICS***" area you will get some of the options reviewed earlier, like:

- "MARKET SIZES"
- " COMPANY SHARES"
- "BRAND SHARES"
- "DISTRIBUTION"
- "PRICING"
- "PRODUCT BY INGREDIENT"

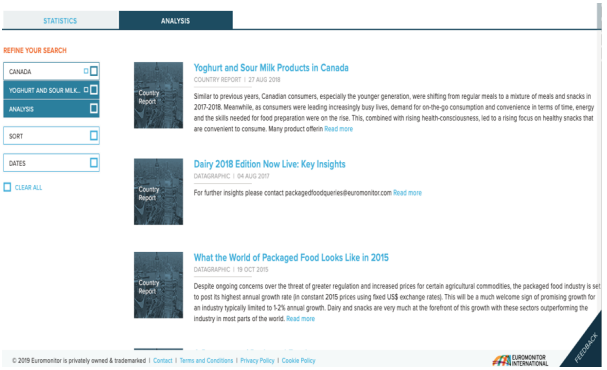
when clicking on any of them, the corresponding full data set will be displayed.

In the "***ANALYSIS***" area, you will be given the option to narrow down your search by:

- "***GEOGRAPHY***":



- “**CATEGORY AND TOPICS**”:


limiting the region and product sub-category for the results.

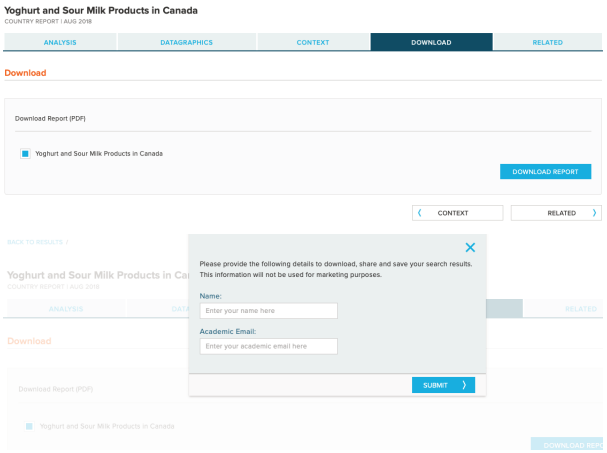
Following the format previously explained, requested report will be then displayed, :


Yoghurt and Sour Milk Products in Canada
COUNTRY REPORT | AUG 2018
ANALYSIS DATAGRAPHICS CONTEXT DOWNLOAD RELATED
Save to my content Change language
HEADLINES
• Yoghurt and sour milk products increases by 1% in both retail volume terms and current value terms in 2018, to reach 417,400 tonnes and CAD2.1 billion
• The snacking trend and growing demand for healthier and more natural offerings significantly impact yoghurt and sour milk products
• Sour milk products sees the fastest growth in 2018, with 7% retail current value growth to reach CAD66 million
• The average unit price increases in current terms in 2018, due to premiumisation and the continued rising popularity of Greek yoghurt
• Groupe Danone, General Mills and Agropur Co-operative Agro-Alimentaire lead in GBO terms in 2018, with value shares of 33%, 24% and 19% respectively
• Yoghurt and sour milk products will record a retail value CAGR of 1% at constant 2018 prices over the forecast period, to reach CAD2.3 billion in 2023
PROSPECTS
Snackification develops further in yoghurt
Similar to previous years, Canadian consumers, especially the younger generation, were shifting from regular meals to a mixture of meals and snacks in 2017-2018. Meanwhile, as consumers were leading increasingly busy lives, demand for on-the-go consumption and
Market Sizes
Sales of Yoghurt and Sour Milk Products
Retail Value RSP - CAD million - Current - 2004-2023
2,127
Forecast
3,000
2,500
2,000
1,500
1,000
500
0
2004
2018
2023

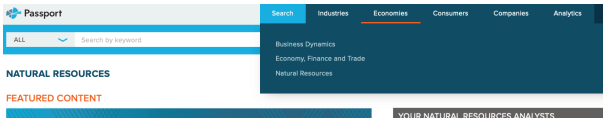
These reports often include information like:

- Industry headlines, prospects & Competitive Landscape analysis
- Market sizes, Sales Retail values, and Year over year sales performance statistics
- Company and brand shares, distribution and Competition analysis
- Economic indicators and trends for the industry

Last but not least, keep in mind you will be able to download the generated report:




# "ECONOMIES" TAB




Here you will find general info about:

- Business Dynamics
  - Access to finance
  - Advertising & Media access
  - Communications
  - Corruption
  - Crime

    - Facilitation for business
    - Economic freedom
    - Education & skills
    - Competitiveness
    - Government stability and safety risks
    - Health Care services
    - Socio-economic development
    - New businesses
    - Infrastructure
- Economy, Finance & Trade
    - Payment & confidence indicators
    - Exchange & Interest rates
    - External debt
    - GDP, GNI & FDI indicators
    - Productivity, Industrial production, price and inflation indicators
- Natural resources
    - Agriculture
    - Biodiversity & Climate
    - Metals & Minerals mining
    - Natural disasters
    - Energy and water resources
    - Pollution and waste

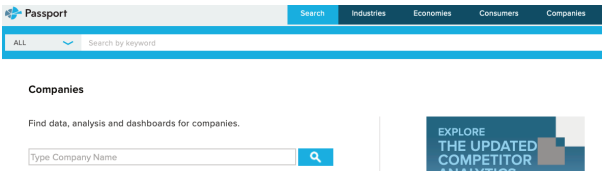
As previously seen in other tabs, here you will be able to filter results by country and by the subcategory options, pre-set by Euromonitor.

## “CONSUMER” TAB


Includes the following options (among others not included in this report):

- Digital Consumer: Digital landscape & Commerce, e.g., Internet access, cellphone use, Electronics possession rates
- Households: Average size, price, composition, types, members info, buildings
- Income & Expenditure: By type, gender and age, consumer indicators savings, poverty, saving practices, tax contribution, social-economic segmentation
- Lifestyles: Dietary preferences, exercise, ethics, leisure
- Population: Marital status, fertility, migrations, density

## “COMPANIES” TAB



This option provides a complete report on a limited selection of companies. Most likely only the ones recognized as global players. Some of the aspects included are:

- Strategic Direction
- Key facts
- Competitive positioning
- Related Statistic & analysis reports
- Related Industry reports & company profiles

# 16. Business Case 1 • Funky Genetics Co.

The CEO of Funky Genetics Co. kicked back in her chair and thought about the days events. “There is a meeting with the Board Finance Committee tomorrow; whatever shall I do?”...

# 17. 23andMe - Insights into Direct to Consumer Genetic Testing

## 23andMe – Insights into Direct to Consumer Genetic Testing

### By: Louis Gasparini

It was a usual sunny day in California when Anne Wojcicki heard about companies that were sequencing human genomes at an affordable price for consumers. This sparked an idea in her, to deal with a problem she had been observing for years. It was 2006, society was in the age of the internet and information, online movements such as YouTube enabled anyone to broadcast video. Internet giants like Google, Microsoft, and Apple were opening new possibilities with computing, and rendering information increasingly accessible at an ever growing scale. However, the problem Wojcicki saw was that the healthcare industry was not hopping onto these technological revolutions, if only there was some way to change that.

The idea of improving the healthcare industry, and moving it into the age of the internet is what spurred the founding of 23andMe in 2006 by Anne Wojcicki, Linda Avey, and Paul Cusenza (Seife, 2013). Over the past 12 years through aggressive strategies and significant capital investments, 23andMe has grown to a company now valued at over $1 billion. The name 23andMe refers to the 23 pairs of

chromosomes that make up a person's genome (the sum of all their genes). 23andMe offers what is called Direct to Consumer Genetic Testing (DTCGT), a process where an individual sends in a sample of their DNA and 23andMe performs DNA sequencing and reports back on the results. 23andMe's personal genetic testing service has garnered notoriety around the world, it was awarded the title of "Invention of the Year" in 2008 by TIME magazine and the company has gained attention for establishing efforts in researching several genetic diseases (23andMe Inc., 2008). There is a myriad of information to be gleaned from an individual genome. Genome sequencing reveals everything about someone, from their sense of smell, to where in the world their distant ancestors came from. In recent years genetic tests that report health related traits have been put on the market. 23andMe markets health tests that report on predispositions to certain diseases and carrier status of recessive disease genes, which can be inherited by a person's children. 23andMe built a business on marketing this information to consumers, however they stirred up significant consumer controversy while doing so.

## Context: Direct to Consumer Genetic Testing

The DTCGT industry is growing rapidly and is expected to be a market worth over $340 million USD by 2022 (Philips, 2016). It is a rapidly growing market full of many companies looking to claim market share (Philips, 2016). These companies operate outside of the traditional health care industry in which genetic testing is used as a clinical tool (Agurs-Collins *et al.*, 2015). DTCGT enabled anyone to access health related genetic information without a prescription from a medical professional. DTCGT flourished over the past decade due to several factors: improvements in the cost of DNA sequencing

technology, increasing awareness of genetic science in the population, and movements in the medical industry toward personalized medicine. 23andMe capitalized on these opportunities and constructed a simple yet effective business model.

## *The declining cost of DNA Sequencing*

Substantial improvements in DNA sequencing technology is what made conducting DTCGT possible. The first complete human genome was sequenced in 2003 by the National Human Genome Research Institute (NHGRI). This first whole genome sequence took 12 years and over $3 billion USD to complete (NHGRI, 2010). However DNA sequencing technology improved significantly to the point where a human genome could be sequenced in a matter of days for about $1000 USD (NHGRI, 2016). Additionally there was no longer a need to sequence entire genomes to learn important things about a person's DNA. Genetic and medical research determined the exact locations of important regions in the human genome, allowing scientists to pinpoint small regions for testing (Farr, 2018). By sequencing many small regions, as opposed to an entire genome, the cost of determining a set of specific traits dropped to less than $50 USD (NHGRI, 2016). Indeed, these improvements made 23andMe's entire business model possible by attracting consumers through offering genetic testing services at a cut rate price.

## *Consumer Trend: Increasing Awareness of the Importance of Genetics*

Modern North American consumers have become increasingly aware

of the importance of genetics over the last decade. According to the data from the 2013 U.S. Health Information National Trends Survey, over 35% of participants were aware of DTCGT, up 8.5% from 3 years previous (Agurs-Collins *et al.* 2015). Additional independent surveys showed that 81% of participants knew that "their genetics influence their risk for developing certain diseases" and that over 74% were "interested in exploring their DNA" (23ndMe Inc., 2017). These various survey results were backed up by market trends, that showed increased demands for DTCGT, especially for ancestry services. Additionally over 70% of respondents indicated that they would prefer to know what genetic health risks they possessed even for diseases without a cure (23ndMe Inc., 2017).

## *Personalized Medicine – An Emerging Field*

Personalized medicine is a field in which medical practices and decisions are based on an individual's particular risks for disease or predicted response to treatments (McMullan, 2014). The aim of personalized medicine is to prevent disease and also to treat it properly if it develops (Chen, 2015). Treating patients based on their unique medical history and genetics is a procedure being adopted over traditional methods. These traditional methods involve treating anyone with the same condition the same way, without looking at specific factors that may be unique to an individual (McMullan, 2014). The power of personalized medicine is increasing as more targeted therapies to diseases are developed. Genetics plays a major role in personalized medicine, especially for genetic diseases and cancer (McMullan, 2014). For example, someone who carries genes that increase their risk of developing breast cancer will be prescribed an annual mammogram to monitor for tumors. Consumers armed with knowledge of their genetics obtained from DTCGT would be able to

make better informed decisions about their healthcare by speaking with medical professionals about the results.

## *23andMe: Business Model*

DTCGT became a frictionless process that can be completed by any consumer with ease. In the case of 23andMe consumers need only order a saliva collection kit online, which is mailed to them, they then provide a non-invasive saliva sample, and send it back to 23andMe for sequencing. An online report is then sent to consumers with the results when DNA testing is complete. These results can be viewed and shared without any training. DTCGT results are obtained without the need for a prescription from a doctor. 23andMe offers 2 genetic testing services:

1. Ancestry Service: Informs on what geographic regions of the world a person's DNA came from, as well as trivial traits like eye colour and finger lengths (for full report details see Exhibit 1).
2. Health + Ancestry Service: Includes everything from the ancestry service as well as reports on health related traits, genetic disease risk factors, and carrier status of disease traits (for full report details see Exhibit 1).

23andMe developed a simple yet effective business model to generate revenue from these 2 products. Initial revenue comes from the purchase of the test kits, but this is far from their most lucrative source. The price of the test kits dropped significantly over a few years, from $299 to $99 for the ancestry service (Farr, 2018). The real power of 23andMe's business model came from the data generated from customers DNA. For every DNA sample they receive from a consumer, 23andMe added and stored a new genetic profile in their

database, which passed 5 million records in 2017 (Farr, 2018). This massive amount of data was 23andMe's most valuable resource. Using this data, 23andMe established 2 major branches of the company, Research Services, and Therapeutics (R&P Research, n.d).

The research services department of 23andMe focused on collaborating with other research companies such as biotechnology and pharmaceutical firms for the purposes of identifying new genetic associations with diseases (R&P Research, n.d). Essentially 23andMe would sell access to their vast genetic database if a company paid the right price. Pfizer and Genentech are two companies that have paid for access to 23andMe's database for their own research purposes (Chen, 2015). Storing and selling user's data prompted public privacy concerns. However consumers agreed to these terms when signing up for the service. Additionally, 23andMe ensured that the genetic data is anonymous when accessed in this way, with no personal information linked to the records. As time went on, controversy over user privacy did not abate.

23andMe also established a therapeutics division which in their own words "is committed to discovering and developing novel therapies that can offer significant benefits for patients" – 23andMe Inc. (23andMe Inc. 2018b).

23andMe aimed to use their genetic database as a starting point to identify potential drug target candidates for treating several types of disease, from cancer therapies to respiratory disorders (23andMe Inc., 2018b). These therapies would work in symphony with personalized medicine. The financial value of creating new drugs or therapies is that they may have constituted a blockbuster patent, and lead to substantially increased revenue for the company.

This model of using consumer's genetic data prompted controversy over privacy concerns and led many medical professionals to question the ethics with which 23andMe operated.

## Navigating the Controversy

### *Concerns over Direct to Consumer Health Testing*

DTCGT was a young industry and the regulations pertaining to different aspects such as kits, health testing, and the storage and usage of genetic data were lagging (Niemiec & Howard 2016). Medical professionals throughout the healthcare community voiced their concerns over several aspects related to health testing for consumers as well as the genetic data generated from personal genetic services. Significant controversy arose with the inclusion of health reports in DTCGT services. 23andMe introduced their health testing service after a messy regulatory run-in with the United States Food and Drug Administration (FDA) (Seife, 2013).

In early 2013 the FDA notified 23andMe that its test kits were classified as "medical devices" which the agency is responsible for regulating, and as such 23andMe was responsible for passing federal approval if it was to market them (Woods 2013). 23andMe started working with the FDA on obtaining regulatory approval of their kits, but for unknown reasons the company cut communications with the FDA for 6 months and failed to meet their regulatory deadlines (Seife, 2013). In another unconventional move, 23andMe started marketing their health service soon after, without obtaining any approval for this additional service (Seife, 2013). This resulted in the FDA banning the sale of 23andMe's kits on November 22, 2013. An excerpt from the warning letter states:

"your company has failed to address the issues described during previous interactions with the Agency or provide the additional information … Therefore, 23andMe must immediately discontinue marketing the [personal genome service] until such time as it receives FDA marketing authorization for the device."

- James L. Woods (Woods 2013).

23andMe did not comply however and continued selling their kits for ancestry services, but did discontinue their health related testing on December 5, 2013. The company then started working with the FDA on gaining approval for their products. CEO Anne Wojcicki said in a press release:

""Our goal is to work cooperatively with the FDA to provide that opportunity in a way that clearly demonstrates the benefit to people and the validity of the science that underlies the test."

- Anne Wojicki (23andMe Inc, 2013).

23andMe was granted full approval of its ancestry service and partial approval of its health services in early 2015, with which they could market DTCGT for carrier status of genes for certain diseases including Blooms Syndrome (23andMe Inc., 2015). Since receiving this partial approval in 2015 23andMe has expanded their health services to encompass 8 diseases including Parkinson's disease and late onset Alzheimer's (23andMe Inc. 2018a). The service also included reports on carrier status of over 40 recessive conditions including cystic fibrosis (see Exhibit 1). Most recently 23andMe was granted approval for the first ever direct to consumer cancer risk test, where they offered testing of 2 mutations that may bring increased risk of developing breast cancer (Stallings, 2018).

However as 23andMe's efforts to expand their health testing continued so did the controversy around the usefulness of the data and the ethics involved in the process. Doctors and genetic experts questioned the validity of the data generated as most genetic diseases are not cause by the presence of a gene alone but are multifactorial (Stallings, 2018). The chances of developing a certain condition can depend on a person's lifestyle and environment in addition to their genetics (Niemiec & Howard, 2016). Medical

professionals therefore question just how relevant and applicable the data is to a person's health. Concerns were also raised over the ethics behind telling someone they may develop a disease with no cure (Masunaga, 2017). This process may spur fits of undue anxiety over complex processes that non-experts don't fully understand (Masunaga, 2017). Surveys showed that most DTCGT customers don't fully understand that health reports are based on likelihood statistics (Stallings 2018). Experts worried that results would be misinterpreted and that this placed undue stress on people and their families.

## *Concerns over Consumer Privacy and Data Usage*

Major controversy was raised over DTCGT companies taking advantage of consumers through harvesting genetic data from unknowing people and using it for their own purposes (Seife, 2013). Public concerns pertaining to user data privacy proved to cause major public relations crises for companies such as Facebook, which was the subject of a major scandal after news of its data collection practices broke, resulting in a severe multibillion dollar devaluation (Smythe, 2018). 23andMe has been the subject of much scrutiny for the way it handles and monetizes user data. Awareness initiatives were promoted by consumer rights activists to inform consumers exactly what they are handing over when giving 23andMe access to their DNA (Seife, 2013). For every sample of consumer DNA 23andMe created a permanent genetic record, which under the right circumstances may be given to parties which a person did not want to have access (Madan, 2017). 23andMe as well as other DTCGT companies are required to hand over an individual's genetic records if a warrant is issued by law enforcement (Madan, 2017). Additional concerns over genetic discrimination by health insurance companies were brought up (Madan, 2017). These concerns spurred the

formation of laws such as the Genetic Non-Discrimination Act in Canada put in place by the Canadian Human Rights Commission (CHRC) (CHRC, 2017). This set of laws prevents insurance agencies and any other institution from discriminating against Canadians based on their genetics. However threats of uncontrolled data leaks and hacking remained, which could cause dissemination of users data to any number of third parties, a risk consumers might not be aware of.

23andMe aimed to alleviate these concerns, outlining in their privacy policy that they would not share personal data with any third party without the consent of an individual. Vocal critics cited the afore-mentioned abilities of law enforcement that contradict this claim though. 23andMe's efforts did little to quell the onslaught of controversy as 23andMe itself was cited saying that its scientific research "does not constitute research on human subjects" and is therefore not bound by regulations relating to consumers privacy and welfare (Seife 2013). This is a grey area that would cause accusations of bad business against 23andMe.

## Future Considerations

While constantly under the microscope of regulatory and public scrutiny 23andMe maintain their objectives of giving people access to their genetics, and furthering personalized medicine through medical and therapeutic research (23andMe Inc., 2018c). They have not yet met a regulatory hurdle they could not overcome, or a controversy they could not wade through, however there were questions facing 23andMe about how they would navigate future obstacles. 23andMe expanded into international markets in the UK, Canada, and Australia. If its past troubles in the United States were

any indication, they would face further controversy in these new markets.

"We believe it's important for consumers to have direct and affordable access to this potentially life-saving information. We will continue pioneering a path for greater access to health information, and promoting a more consumer-driven, preventative approach to health care."

- Anne Wojcicki (23andMe Inc., 2018c).

23andMe had several considerations to make going forward. What is the best way to market their health service so as not to cause controversy or create potential public relations setbacks? How will they deal with potential scenarios, such as handing personal information to law enforcement? What is the best way to use consumer's genetic data, without stirring up concerns over privacy? Will their current business model be their downfall if they continue in the same direction they are headed now? These considerations were of increasing importance as 23andMe expanded into international markets.

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## Exhibit 1: Elements of 23andMe Ancestry and Health Reports

**Source:** 23andMe Inc. (2018). List of Reports Included in Each Service. Retrieved from: https://www.23andme.com/dna-reports-list/

### Ancestry Service Report:

- Ancestry Composition
- Maternal & Paternal Haplogroups
- Neanderthal Ancestry
- Your DNA Family
- Opt-in DNA Relative Finder Service

## Health + Ancestry Service

*Includes all services available in Ancestry Service plus:*

**Genetic Health Risk reports**

- Age-Related Macular Degeneration
- Alpha-1 Antitrypsin Deficiency
- Celiac Disease
- Hereditary Hemochromatosis (HFE-Related)
- Hereditary Thrombophilia
- Late-Onset Alzheimer's Disease
- Parkinson's Disease

**Wellness reports**

- Alcohol Flush Reaction
- Caffeine Consumption
- Deep Sleep
- Genetic Weight
- Lactose Intolerance
- Muscle Composition
- Saturated Fat and Weight
- Sleep Movement

**Traits reports**

- Asparagus Odor Detection
- Back Hair (available for men only)
- Bald Spot (available for men only)
- Bitter Taste
- Cheek Dimples
- Cleft Chin
- Earlobe Type

- Earwax Type
- Eye Color
- Finger Length Ratio
- Freckles
- Hair Texture
- Light or Dark Hair
- Early Hair Loss (available for men only)
- Newborn Hair
- Photic Sneeze Reflex
- Red Hair
- Skin Pigmentation
- Sweet vs. Salty
- Toe Length Ratio
- Unibrow
- Widow's Peak

**Carrier Status Reports**

- ARSACS
- Agenesis of the Corpus Callosum with Peripheral Neuropathy
- Autosomal Recessive Polycystic Kidney Disease
- Beta Thalassemia and Related Hemoglobinopathies
- Bloom Syndrome
- Canavan Disease
- Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)
- Cystic Fibrosis
- D-Bifunctional Protein Deficiency
- Dihydrolipoamide Dehydrogenase Deficiency
- Familial Dysautonomia
- Familial Hyperinsulinism (ABCC8-Related)
- Fanconi Anemia Group C
- GRACILE Syndrome
- Gaucher Disease Type 1

- Glycogen Storage Disease Type Ia
- Glycogen Storage Disease Type Ib
- Hereditary Fructose Intolerance
- Herlitz Junctional Epidermolysis Bullosa (LAMB3-Related)
- Leigh Syndrome, French Canadian Type
- Limb-Girdle Muscular Dystrophy Type 2D
- Limb-Girdle Muscular Dystrophy Type 2E
- Limb-Girdle Muscular Dystrophy Type 2I
- MCAD Deficiency
- Maple Syrup Urine Disease Type 1B
- Mucolipidosis Type IV
- Neuronal Ceroid Lipofuscinosis (CLN5-Related)
- Neuronal Ceroid Lipofuscinosis (PPT1-Related)

# 18. Pond Technologies Inc. - Target Markets

**by Amna Alam**

It was a 2008 article in the Washington post that first fueled Steve Martin's inspiration behind Pond Technologies Inc. in Markham, Ontario. The article indicated that algae was a promising alternative to fossil fuel derived biofuels, and that it could pave the way for greener and more renewable energy [1]. A mere twelve hours later, Martin started growing algae in a coffee cup, taking the first stock from the film growing on his swimming pool. Humble beginnings propelled Martin into the biofuels industry, through numerous programs funded by the government and private investors. Aptly named Pond Biofuels at the time, it wasn't until 2016 that the company reached a crossroads – one that would prompt them to adopt a new name: Pond Technologies Inc.

A few years after starting the original company, it became clear to Martin that algal biofuels were not as close to being adopted on a large scale as he had hoped. While the government and large energy companies were interested in investing in research into the creation of renewable transportation fuel, the high capital costs associated with the resources required for producing biofuels left little room for profit. Mainly, Martin found that while they had proprietary technology that would allow for efficient and rapid algal growth, this new industry that they were trying to tackle was not ready to leave fossil fuels entirely behind. Therefore, Martin wanted to expand the scope of the company and shift it from simply producing biofuels to creating other algal technologies, as demonstrated by the change in company name. The question that then remained was: Which algal products industry would be best to aim towards, such that it could

provide sources of revenue but also remain in line with the original vision of the company for cleaner products from algae?

**Industry (Algae Products)**

Algae has been known to have applications across several industries. Globally, the algae products market was projected to reach approximately $3 billion USD by 2022 with a compound annual growth rate of 6.7% from 2017-2022 [2]. The largest share of the market was claimed by biofuels, but overall, nutraceuticals were growing at the fastest rate. These were followed by other applications such as cosmetics and bioplastics.

*Key Trends*

Growing demand for renewable and sustainable energy: By 2024, the largest sector of the algal products industries was projected to be biofuels, primarily in response to the awareness of the harmful effects caused by burning fossil fuels [3]. The Canadian government launched the Clean Air Agenda in 2007, looking towards fostering innovations that reduced greenhouse gas emissions and reduction of fossil fuel use in favor of renewable energy sources [4]. Included alongside solar, wind and hydropower were energy products derived form plant biomass.

The Asian Pacific Partnership (APP), had also implemented climate programs to foster innovations that would mitigate or possibly reverse the harmful effects of fossil fuel use. Altogether, the APP was made up of countries such as the United States, Korea, Japan, and more, which produced 62% of the world's cement, 65% of the world's smoke, and 60 % of the world's steel [5] In 2009, Pond Technologies received funding by the APP to create a pre-commercial pilot algal photobioreactor that would be powered by carbon dioxide emissions released by the St. Mary's Cement facility in Ontario [6].

Growing demand for natural products: Data from a 2015 Statistics Canada survey indicated that 45.6% of Canadians had used a form of

nutritional supplement in the past year [7]. The most common types of these supplements included vitamins, omega-3 fatty acids, fibers and antioxidants. A 2011 survey projected that the largest increase in the natural health products industry was to be whey protein, omega-3 fatty acids, glucosamines, probiotics and sterol esters [8]. The major trend in the market was the shift in buyer power from baby boomers to millennials, who were more likely to expect nutritional information on the foods they were consuming, as well as becoming generally more health conscious [9]. With this, the nutraceuticals and functional foods industry saw an increase in the global market, and is projected to be almost $600 billion by 2025 [10].

**Company History and Algal Technology**

Pond Technologies Inc. was founded in 2008, when it was initially named Pond Biofuels. It was created by Steve Martin, who served as Senior Scientist at EXFO Photonics Solutions, a company that specialized in developing optics systems. His background made him an expert at helping to identify the ideal light conditions required for growth of algae strains under study [11]. Together with a gradually growing staff of project managers, sustainability experts and engineers, Pond Biofuels was able to receive numerous funds from the Canadian government and private investors [6]. They created a proprietary photobioreactor that caused algae to grow at a rapid rate due to novel light technology, as well as other relevant patents that offered the company strong IP protection [11]. With the large biomass of algae, they could extract fuels such as biodiesel (from the fats), and bioethanol (from the carbohydrates) [12]. Exhibit #1 shows the company's patented photobioreactor.

The breakthrough for the company came when it received funding from the APP (Asia-Pacific Partnership) to create a pre-commercial pilot algal photobioreactor that was powered by carbon dioxide emissions released by the smokestack at St. Mary's Cement facility in Ontario [6]. Smokestack emissions from the plant fed directly into

the photobioreactor, where carbon dioxide supply was used for the growth of algae strains that were known to produce high saturated fat content. Initially aimed at creating biofuels on a large scale, it was this project that indicated to Martin and his colleagues that algae's applications can be applied to different industries. And so, in 2014, Pond Technologies Inc. emerged, ready to target new sales channels.

**The Technology**

Algae consisted of a group of single-celled aquatic microorganisms that relied on light energy, water, and carbon dioxide in order to growth through photosynthesis [12]. These organisms were found to produce oils and carbohydrates in larger quantities in comparison to other land plants, making them a promising source for biofuels (See Exhibit #2 for yield data) [12. 13]. Once refined, the oils or carbohydrates could be converted into sustainable forms of diesel and ethanol, which were shown to produce fewer harmful emissions of carbon dioxide and nitric oxides in the atmosphere compared to their fossil fuel derived counterparts [12]. The oil, protein, and carbohydrate content per overall biomass varied across species, and depending on the desired end-product, an algal species that produces the largest quantity of the unrefined molecule could be chosen. For example, for the production of biodiesel, which is created from unsaturated fats, scientists would cultivate *Neochloris oleoabundans* and *Schizochytrium sp.*, two species known to produce large quantities of unsaturated fats per overall biomass [12]. See Exhibit #3 for oil content of various algal species.

Closed vessel systems called photobioreactors were used to facilitate the rapid growth of algae, by providing control over factors such as light, temperature, water supply, and carbon dioxide content [12]. Bioreactors also decreased the overall risk of contamination that was associated with open cultivation systems, such as outdoor ponds [12]. This strict control made large-scale production of algae economically feasible. Pond Technologies had a patented algae

platform that could grow algae at a fast rate by taking advantage of its response to light [14]. As an expert in optics, Martin and fellow engineers constructed an artificial LED system that exposed algae to strobing light [14]. The constant flickering of the lights indicated to algal cells that days are shorter, leading to an increase in the organism's biomass and oil production, the latter of which could be dried, filtered and refined for use as transportation fuel [14].

The ability of algae to sequester carbon dioxide from the air and use it as a nutrient for its own growth has significant implications in the clean energy industry. It could not only mitigate the greenhouse gas emissions that were released by industrial facilities with smokestack, it could also use this to create oils which can be used as a cleaner oil that itself emits fewer green house gasses. The remaining biomass also had relevant uses: aside from fats, algae also produce protein and antioxidants that held importance in the nutraceutical and health supplement market [12]. One large disadvantage that algal biomass production faced was the high capital and operational expenditure that was associated with algal cultivation in photobioreactors [12].

**The Opportunities**

Up until 2013, Pond Biofuels had focused on cultivating carefully chosen algal species and extracting unsaturated fats (only single bonds in their chemical structure) for biodiesel production and carbohydrates for bioethanol production [15]. However, the company soon realized that the amount of nutrient resources required to get algal biofuels on the commercial level was far higher than they could supply with their own funds. With Martin's background in optics, they were able to create patented technology that would increase the rate at which algae grew; however, they had no immediate solutions for the amount of carbon dioxide that was needed. Initially, they had been able to chemically alter dissolved glucose to release ethanol and carbon dioxide, the latter being used as a nutrient for algal growth

(see Exhibit #4 for the chemical reaction) [16]. This resource was needed in great quantity and led to a high running cost for overall cultivation of the algae, which increased further when considering the manufacturing and operational costs of the photobioreactor itself. Martin decided that the company needed to tap into revenue streams that would allow it to mitigate some of the capital cost associated with the algae cultivation, and they had to look no further than algae's other benefits outside of biofuel production.

Martin intended on delving deeper into the algal products market, specifically that of natural algal health products and pollution control in the energy industry. The biology of the species they had structured their technology on prevented them from initially being able to approach both industries. The first was an issue they were already familiar with based on their experience at the St. Mary's cement facility: in order to grow algae on a commercial scale, large amounts of carbon dioxide were required [17]. Secondly, depending on the type of species of algae they chose, different valuable products could be derived [12]. The market they would choose to attempt to establish themselves in depended on these two factors.

The main decision that the company had to make was to decide whether they should go towards the fast-growing nutraceuticals industry, or to remain in the energy industry and capitalize carbon sequestering? Both of these came with their own benefits and limitation, making it a difficult decision for Pond Technologies Inc.

**Potential Sales Channels and Strategies**

1. Nutraceuticals Industry

As the company had not delved into the nutraceuticals market in their research initiatives, the outreach from nutraceutical companies was not as large as that in the energy industry. The angle taken

at the start of the company, when it was still called Pond Biofuels, was to produce renewable energy. However, Martin knew that the value of algal biomass was too great not to consider entering the nutraceutical market. Specifically, in their novel photobioreactor's ability to produce algae on a rapid scale in comparison to outdoor systems, the company could provide the raw materials required for the production of supplements for nutraceutical manufacturers [11].

To start, algae species that produced high quantities of the desired molecules for supplement production were preferred. *Chlorella* and *Spirulina* species-derived nutraceuticals were already on the market in Canada, and Pond Technologies had the potential to follow suit [19]. These algal species produced unsaturated fatty acids, which are preferred forms of omega-3 on the market. Most importantly, an antioxidant called Astaxanthin which is derived from algal species such as *Haematococcus sp.*, saw a surge in public interest and was readily incorporated in carotenoid supplements [19].

Pond Technologies Inc.'s strategy for this market was to produce the desired molecules in their in-house facility in Markham, and to sell the products to manufacturers [11]. In doing so, they were responsible for supplying their own resources, including large quantities of carbon dioxide. It would become the company's responsibility to use carbon dioxide derived from dissolved glucose. Therefore, capital expenditure associated with algae's production was not likely to be mitigated.

Additionally, the algal strains that Pond Technologies had used up to this point were aimed towards biofuels production. The company had conducted extensive research on algal species that produced unsaturated fatty acids, as well as large quantities of carbohydrates [20]. However, the nutraceuticals industry placed more importance on protein, fiber, and unsaturated fatty acids that made up omega-3 [8]. Overall, the demand for the molecules that particular algal species could produce were high, but came with limitations

associated with large resource costs, and the company having to work with new algal species.

With these limitations taken into account, Pond Technologies Inc.'s calculations suggest that despite an estimated capital expenditure of $1.6 million per bioreactor and an additional $600,000 of operating costs per year, the cashflow would be positive in 18 months, if targeting customers that required biomass from *Chlorella* and *Spirulina* species, as well as raw Astaxanthin [8]. With the nutraceutical market projected to be worth over 500 million in the coming years, this was not an opportunity that Pond Technologies wanted to dismiss [10]. These market estimations are presented in Exhibit #5.

*Company*: *Neptune Wellness Solutions* [11, 21]

A Quebec based company specializing in manufacturing customized formulations of natural health products using healthy extracts from marine species and terrestrial seeds. The unsaturated fatty acids used in omega-3 oils (different from saturated fatty acids used in biofuel production) was a product of algae that served as an important ingredient in the gel-capsule formulations for this company. The red-pigmented antioxidant, Astaxanthin, was also valuable in preserving the quality of capsules by protecting them from light and heat, as well as providing health benefits of fighting off harmful effects on the body due to ultraviolet rays and converting harmful UVB rays into vitamin D. Production of these valuable compounds in Pond's facility had the potential to create revenue by selling to this company, which itself sold raw materials to other manufacturers.

2. Pollution Abatement in the Energy Industry

As growing concerns for greenhouse gas emissions take place around

the world, Pond Technologies discovered a niche market that would not only take advantage of their breakthroughs in algal research, but also feed back into the company for the production of value products that the company could sell for profit.

Steve Martin was aware that algae could sequester carbon dioxide from the environment and use it as a nutrient for its own growth. In fact, in 2014, the company had done just that by installing their photobioreactor adjacent to St. Mary's Cement [6]. However, after the successful implementation of Pond's photobioreactor at the facility, Martin understood that carbon capture could serve as a sales channel on its own. By licensing their technology and selling their proprietary equipment to industrial facilities across North America, they could not only create a revenue stream, they could also cut back on cost of resources such as carbon dioxide, as well as use the produced algae into bioethanol, biodiesel, and other valuable products. In this way, the company would not lose sight of its original pursuit for renewable energy.

This sales channel did not work on a small scale, such as providing energy for a single house or furnace, as the net energy consumed would be far greater than the net energy produced. However, on a larger scale, and by targeting industrial emitters that produced over 25,000 tons of carbon dioxide per year, Pond Technologies had a way of settling into the niche market. There were over 10,000 large industrial emitters across North America, providing a large potential customer base [22].

The main reason value products could not overlap with the nutraceuticals market (omega-3 unsaturated fatty acids and protein) were because the algal strains that Pond had been working with in the industrial settings produced molecules more suitable for production of biodiesel and bioethanol. These included saturated fatty and carbohydrates. Without the limitation of using "clean" carbon dioxide, Pond Technologies had the potential to not only sequester air pollution, but also to continue creating an alternative

energy source. On the other hand, this entailed that Pond was restricted by producing only forms of biofuels, which Martin had already discovered was not currently as established as the nutraceuticals industry. In targeting this industry, Martin found that even though fossil fuels were not ready to be discarded for other alternative biofuels, he could mitigate their harm and continue to collaborate with the government and private investors to create innovations that would make algal biofuels economically feasible [22].

*Company: Markham District Energy* [23]

By late 2016, the city of Markham had also shown an interest in collaborating with Pond Technologies. The proof-of-concept project at St. Mary's Cement had shown enough promise that Markham District Energy was eager to work with the company on potential energy systems. MDE was involved in providing heating and electricity to city-wide infrastructure, and wanted to use the company's photobioreactors to sequester carbon dioxide emissions form industrial facilities and produce algal biomass that could be burnt as a heating source.

The CEO of MDE, Bruce Ander, was a former chair of the International District Energy Association, and also wanted to further Pond's network globally by introducing the company's breakthrough technology to other members of the group, which spanned across 26 countries.

This was a significant advantage as it promised an increase in the company's profit potential.

*Company: Stelco Canada* [24]

This Ontario based steel company provided products for transportation and infrastructure construction across North America, and was looking for a way to continue to reduce their carbon footprint without significantly decreasing their production value. Sujit Sanyal, Chief Operating Officer at Stelco Canada knew

that Pond Technologies Inc. had become a leader in the carbon abatement sector. He said that a partnership with Pond Technologies Inc. could "demonstrate the potential for the steel industry to utilize science and innovation to make significant reductions in greenhouse gas emissions.... Our intention is to divert thousands of tonnes carbon from our operations while making Stelco more competitive and environmentally sustainable" [24]. This view was seconded by Steve Martin, who foresaw partnerships with heavyweight emitters like Stelco Canada leading to "transforming their GHGs into significant revenue streams" for Pond Technologies [24]. Stelco Canada hoped to start a project with Pond Technologies Inc. in creating the first ever commercially sized carbon-abatement system.

**Future Challenges and Questions**

Martin knew that regardless of which industry his company chose to focus on in the coming future, algae products would contribute not only to the financial wellbeing of the company, but also add value to the environment by fostering the production of green products. In 2008, when he had first read the article in the Washington Post, the goal had been to create green energy to replace fossil fuels. As the company grew, he found that perhaps conquering it was still further down in the pipeline, but that algal products could mitigate several of the harms that came with using fossil fuels, or even create green products in an entirely different sector. Despite finding himself in a place he hadn't anticipated with his company, he felt that expanding the applications of algae, and fostering research into its many benefits was certainly the best way to go.

Having always been the idea man, he thought about how he could take algae further. Was there was a way to introduce genetic modification into the equation? Could he find a way to alter an algal cell's genome such that it could not only increase the production of molecules required for the nutraceuticals industry, but enhance the production of those required for the energy industry? Would that

prove to be the ultimate solution in establishing Pond Technologies Inc. in both markets, or would the public opinion on large scale production of transgenic organisms prove to be a setback?

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**Exhibits**

**Exhibit #1**: Pond Technologies Inc.'s 25,000L Photobioreactor


Source: Votorantim Cementos News [25].

**Exhibit #2:** Oil and Ethanol Yield Comparison Between Microalgae and Land Crops

a) Comparison of some source of biodiesel:

Comparison of some sources of biodiesel

| Crop | Oil yield (L/ha) | Land area needed (M ha)[a] | Percent of existing US cropping area[a] |
|---|---|---|---|
| Corn | 172 | 1540 | 846 |
| Soybean | 446 | 594 | 326 |
| Canola | 1190 | 223 | 122 |
| Jatropha | 1892 | 140 | 77 |
| Coconut | 2689 | 99 | 54 |
| Oil palm | 5950 | 45 | 24 |
| Microalgae[b] | 136,900 | 2 | 1.1 |
| Microalgae[c] | 58,700 | 4.5 | 2.5 |

[a] For meeting 50% of all transport fuel needs of the United States.
[b] 70% oil (by wt) in biomass.
[c] 30% oil (by wt) in biomass.

b) Ethanol production capacities by various feedstock, (L/Ha)

| **Feedstock** | **Ethanol Yield** |
|---|---|
| Switch grass | 10,760 |
| Sugar beet | 5,010–6,680 |
| Corn | 3,460–4,020 |
| Sweet sorghum | 3,050–4,070 |
| Cassava | 1,050–1,400 |
| Wheat | 2,590 |
| Corn stover | 1,050–1,400 |
| Algae | 46,760–140,290 |

Sources: a) Chisti, 2007 [12]; b) Grandview Research [13].

**Exhibit #3:** Oil Content of Some Microalgae

Oil content of some microalgae

| Microalga | Oil content (% dry wt) |
|---|---|
| *Botryococcus braunii* | 25–75 |
| *Chlorella* sp. | 28–32 |
| *Crypthecodinium cohnii* | 20 |
| *Cylindrotheca* sp. | 16–37 |
| *Dunaliella primolecta* | 23 |
| *Isochrysis* sp. | 25–33 |
| *Monallanthus salina* | >20 |
| *Nannochloris* sp. | 20–35 |
| *Nannochloropsis* sp. | 31–68 |
| *Neochloris oleoabundans* | 35–54 |
| *Nitzschia* sp. | 45–47 |
| *Phaeodactylum tricornutum* | 20–30 |
| *Schizochytrium* sp. | 50–77 |
| *Tetraselmis sueica* | 15–23 |

Source: Chisti, 2007 [12].

**Exhibit #4:** Chemical reaction for the conversion of glucose into ethanol and carbon dioxide


Source: Essential Chemical Industry website [16].

**Exhibit #5:** Pond Technologies Inc.'s Nutraceutical Revenue Model

## Nutraceutical Revenue Model

| 5 YEAR REVENUE TARGET | GROSS MARGIN | CASH FLOW POSITIVE |
|---|---|---|
| $99MM | 80% | 18 months |

| BIOREACTOR SIZE | CAPEX/UNIT | OPERATING COSTS/YEAR/UNIT |
|---|---|---|
| 65,000L (approx. 1 Shipping container) | $1.6MM | $600K |

| | Astaxanthin | Chlorella | Spirulina |
|---|---|---|---|
| Price per tonne | $160,000 | $25,000 | $15,000 |
| Revenue per bioreactor | $3.8 MM | $1.2 MM | $0.9 MM |
| # of bioreactors | 18 | 14 | 14 |
| Target revenue in 5 years | $69.1 MM | $16.8 MM | $12.6 MM |

Source: Pond Technologies Inc – Corporate Presentation [11].

# 19. TAXA Biotechnologies Inc.: A Genetic Engineering Start-up

**Case Study: Challenges faced by a synthetic biology start-up firm**

By Rashmi Kurup

While watching *Avatar*, a 2009 American film, it seemed that glowing plants were yet another visual effect added to an epic science fiction film; but the truth is that it is not a fiction [2, 3, 23]. In 1986, scientists added Luciferase, a gene encoding the firefly enzyme, to a Tobacco plant and when a chemical substrate named Luciferin was sprayed on the plant, it glowed temporarily [2, 24]. In 2010, Krichevsky and colleagues from State University of New York used bacterial genes to genetically engineer a Tobacco plant and made it dimly glow [3, 14]. In the same year, scientists from the University of Cambridge used the genes involved in the bioluminescence pathways found in fireflies to create light-generating BioBricks which made bacteria produce both luciferase and luciferin and also glow continuously [3, 22]. Inspired by these researches on bioluminescence, a budding entrepreneur from San Francisco, California decided to manipulate these bacterial genes, insert them into plants, and make it glow [3].

In 2012, Antony Evans, CEO and founder of TAXA Biotechnologies Inc., abandoned his corporate career to become a technology entrepreneur as he strongly believed that Biology is the ultimate sustainable technology [23]. Evans started the Company with a vision to make new products using synthetic biology that would delight and inspire his customers [13]. He and his colleagues – Omri Amirav-Drory, founder of Genome Compiler in Berkeley, California, and Kyle

Taylor, a graduate from Stanford University in California – conducted an experiment on Arabidopsis and successfully made it glow [3]. Excited by the outcome of their lab experiments, Evans decided to generate the initial funding for the Glowing Plant project using crowdfunding campaigns. In April 2013, Evans officially launched his 8 months old project at the NASA Ames Research Park in San Francisco Bay Area and this drew the attention of media and investors alike [3]. Evans and team organized their first Kickstarter campaign and gave away stickers and T-shirts depicting glowing plants and vases to keep his soon-to-be product, The Glowing Plant [3]. Although Evans' initial fund-raising goal was only $65,0000, with support from 8,433 backers, he successfully raised $484,013 in pre-orders [9].

On 25th April 2013, Evans and team shared this good news with all his supporters, expressed his deepest gratitude, and celebrated the National DNA Day like never before [4, 28]. He informed his backers that the fund raised from Kickstarter campaign will be used for research and development activities and also to develop an open policy framework for DIY-Biowork involving recombinant DNA which would support their work [8, 9, 10]. Evans believed that this framework would provide guidelines to navigate the regulatory and social challenges, some recommendations to other DIY Bio enthusiasts, and also create an awareness about what kinds of projects were safe and what processes should be put in place for similar synthetic biology projects [8, 9, 10]. In 2013, along with the research and development of glowing plants, TAXA started working on another product, Fragment Moss in a Terrarium, which was named *Orbella* [13, 17, 20] [Refer Exhibit 1, 2]. The value propositions of *Orbella* were Natural Fragrance, Safe/Non-toxic, Zero Waste/ Compostable Packaging, and Educational as it can inspire kids about science [17]. By the end of 2016, TAXA raised $752,807 from more than 500 investors through crowdfunding campaigns including Kickstarter, WeFunder, Y-Combinator, and SAFE agreements (Simple Agreement for Future Equity) with third parties [12, 18, 47, 61].

**PUBLIC SAFETY AND REGULATORY COMPLIANCE**

Evans announced that his backers will receive the seeds to grow a glowing plant at home and within no time, as expected in any GMO (Genetically Modified Organism) initiative, questions about public safety and regulatory compliance arose from various stakeholders [8, 9, 10, 42, 43]. According to George Church, the head of Genetics at Harvard Medical School, who works extensively on engineering biosafety, the glowing plant itself and their DIY Maker Kit [Refer Exhibit 3] were safe for public use [8, 9, 10, 42, 43]. Evans added that they will use non-pathogenic, non-toxic, and well-categorized genes and that their lab will comply with all NIH guidelines on recombinant DNA research; their work was graded at Biosafety Level 1, which was the lowest level of risk [8, 9, 10, 42, 43].

The glowing plant being a GMO product, TAXA needed to obtain a nod from three Regulatory Agencies in the United States before releasing their product to market. First, the USDA (United States Department of Agriculture), the U.S. federal executive department responsible for developing and executing federal laws related to farming, agriculture, forestry, and food and APHIS (Animal and Plant Health Inspection Service), the lead agency of USDA for collaboration with other agencies to protect U.S. agriculture from invasive pests and diseases [1, 25]. APHIS had established a strict set of guidelines on testing Genetically Engineered crops before releasing them to the environment [1, 7, 9]. APHIS had raised some concerns which were mainly related to the introduction of potential plant pests through TAXA's products and they issued a mandatory instruction to use the gene-gun technique to transform their plants, instead of Agrobacterium; TAXA promised to comply with all the guidelines set by APHIS in order to safely release their glowing plants [8, 9, 10]. Second, the EPA (Environmental Protection Agency), the federal agency that regulates new uses of pesticides – many GMOs introduce pesticide and/or herbicide resistance to their plants (either as a selection agent or as an intended outcome) [8, 25, 26]. Evans

informed his stakeholders that TAXA had opted not to introduce such resistance in their glowing plants and moreover since the glowing effect itself was a natural marker for this plant's selection procedure, they do not need to go through EPA's specific testing procedures [8, 9, 10]. Third, the FDA (Food and Drug Administration), the federal agency that regulates food and feedstock implications [6]. Since the glowing plant was an ornamental plant and not meant for consumption by humans or animals, TAXA was exempted from FDA's regulatory compliance also [6, 8]. Hence, TAXA gave assurance to its stakeholders that they had to comply only with the USDA's regulations before releasing their glowing plants to the market [8, 25].

**FUNDING AND REVENUE**

**The TAXA Infrastructure**

In 2015, Evans announced the launch of the TAXA *Platform* – a platform as a paid service that enabled other synthetic biology start-up firms to develop new consumer applications without having to invest in a sophisticated lab [19]. TAXA's value proposition was to provide a platform with low cost and automated technologies and systems, access to expertise, cost-effective agile development, reusable DNA parts, multi-gene constructs, and biolistic methods to make unregulated products which can be sold and distributed in the United States without requiring regulatory review [16, 19, 20, 21]. The TAXA *Platform* was a technology stack with four components – Protein Engineering System, Automated DNA Assembly System, Transient Experiments, and Stable Transformation – from which the companies could pick and choose based on the specific experiments they needed to run in order to develop their specific applications [16, 19, 20, 21].

**Collaborative Research Agreements**

TAXA earned revenue from two streams: First, from Collaborative Research Agreements (CRA) wherein TAXA offered platform as a paid service to other companies for product development [13, 20]. Depending on the nature of the research goals these revenues were

either milestone based or monthly recurring payments [13, 20]. By 2016, TAXA had signed three such CRAs and partnered with other companies for the development of some new products wherein TAXA took part in the research and development of new products [13, 20]. TAXA earned recurring revenues from the sale of products developed under Collaborative Research Agreement which included monthly recurring payments. This monthly recurring payment facilitated a steady cash flow for TAXA's in-house product development and operations [13, 20]. For instance, the product Blue Rose for which TAXA had such a collaborative partnership with a spin-out from the University of Southern Illinois. Researchers from the University of Southern Illinois had found a novel pathway for producing blue cells in E.coli. The patent for the innovation was owned by the university and it was licensed to a small start-up firm which in turn paid TAXA to express that blue pathway in plants and confirm its feasibility in higher plants. Second, from the sale of in-house genetically engineered plants which were sold directly to consumers [13, 20]. Products that were developed in-house like the Glowing Plant typically had high gross margins (>90%) [13, 20]. In some instances where another party had a patent claim on part of their product, TAXA also paid out royalties to third parties [13, 20]. The sale of final products which were developed under a CRA helped to earn royalties of between 7.5% and 92% of revenues depending on the risk incurred by TAXA on those projects; however, TAXA had reduced costs and risks associated with such products as the partner handled the manufacturing of products as per the agreement [13, 20].

**MARKET**

In an interview, when asked about how big the market is, Evans responded that their growth strategy was to enter and lead a small market to start with and later to leverage that market power in order to expand in multiple segments [as cited in reference 12]. He added that, in the United States, consumers spend around $5 BN on home fragrances and $28 BN at florists [as cited in reference 12]. TAXA's

consumer products like Fragrant Moss and Blue Rose had a good market and they had planned for more such consumer products in their pipeline like the Ever Blooming Flowers [12].

As for Agricultural Sector, he added that plants contribute trillions of dollars to the global economy but only less than 14% of those have been engineered, leaving room for countless opportunities and improvements [as cited in reference 12]. The crop production has a market of $210 BN in the US and a global market of $2+ TN of which only 12% has a GMO presence [as cited in reference 12]. Evans strongly believed that with TAXA's future products like Fast Growing Lettuce, Caffeinated Apples, Vitamin D Enhanced Greens etc. he can target the remaining market for engineered crops [12, 13, 20].

As for Energy and Industrial Chemical Markets, Evans said that "the fossil fuels are stored photosynthetic energy buried in the ground and it should be possible to use plants to make fuels and chemicals directly from sunlight, enabling a carbon-neutral economy" [as cited in reference 12]. Evans dreamt of using synthetic biology to make useful products like Lab Grown Meats, Self-Fertilizing Plants, and even Trees as Streetlights [13, 15, 20].

**REGULATORY AND TECHNICAL CHALLENGES**

In August 2013, Kickstarter changed its project guidelines to specifically exclude the offering of Genetically Modified Organisms [7, 42]. TAXA, along with their supporters, signed a petition requesting Kickstarter to reconsider their decision, however, that went in vain [42]. Kickstarter responded that the glowing plant project sparked a debate in the scientific community and triggered concerns from some scientists and anti-GMO advocates [42]. They decided to abstain from supporting GMO products since the scientific community was unsettled on the ethics and best practices for releasing genetically modified organisms into the world [7, 42]. Kickstarter, a funding platform for artistic and creative projects, continued to appreciate and verbally support TAXA and its "cool ideas", however, they stood firm on their decision until the scientific

community came to a consensus on GMOs [7, 42]. This was a huge hindrance to TAXA's current and future business as they were largely dependent on external funding, however, TAXA continued to work on their existing in-house projects – the Glowing Plant and the Fragrant Moss.

In April 2014, the traditional software accelerator – Y-Combinator, expressed interest to invest in TAXA and by August 2014, TAXA raised around $120,000 [12, 18, 47, 61]. Considering the financial instability of the firm, funding from Y-Combinator was truly the need of the hour. TAXA geared up their work to make the glowing plant ready for shipment by December that year [48]. They faced some technical challenges in the development of plants which significantly delayed the shipment [49, 50]. By the end of the year, TAXA hired experienced resources to resolve the issues and expedite the development and shipment of finished products, but their attempts were not successful [50,51]. In April 2015, after realizing that making the glowing plant was not possible with the chosen plant species, TAXA reached out to its backers and stakeholders to understand their views on changing the plant species [52]. TAXA had three species as options – Arabidopsis, *Nicotiana benthamiana*, and Petunia, each with its own pros and cons [52]. The original plant, Arabidopsis had two main issues; the first was low transformation efficiency and the second were challenges in growing them at home under short daylight conditions [52]. *Nicotiana benthamiana*, a close relative of tobacco (but does not produce nicotine), can be easily transformed to produce stable lines, however, the main issue with this species was that the seeds available in the USA were commonly grown only in the research labs and were not found in the wild [52]. The unavailability of seeds in the USA posed greater ecological uncertainties and potentially higher ecological risks, and according to TAXA, it was not a wise decision to select this species [52]. Moreover, TAXA feared that USDA may also raise some concerns around this [52]. For Petunia, a commonly grown plant with a life cycle that did fit with TAXA's seed

production timelines, transformation protocols were established and the team was confident to make it glow [52].

TAXA, being a small start-up firm, was highly dependent upon the retention and addition of highly skilled resources [52]. In May 2015, while the glowing plant project was entering from its research phase to development phase, one of the key resources who was with TAXA since the inception, decided to leave the firm and join academia as it better aligned with his career goals [52]. Although this resource attrition had a substantial impact on the ongoing projects, Dr. Jihyun Moon, who had nearly twenty years plant research experience, took up the scientific leadership role to make sure that the R&D functions continued without interruptions and met the extended milestone dates for the shipment of products [52].

On July 2nd 2015, the White House released a memo stating that the three main agencies which regulate GMOs in the United States – USDA, EPA, and FDA, should review the Coordinated Framework for the Regulation of Biotechnology, which defined a comprehensive federal regulatory policy to confirm the safety of biotechnology products [53]. Some of TAXA's sources from Washington reported that this regulatory review was partly prompted by the Glowing Plant project and its Maker Kits [Refer Exhibit 3] were a topic of discussion in a meeting at the White House in early June [53]. Although the federal agencies had initially confirmed that TAXA's products will not be regulated, after the invent of gene editing tool – CRISPR/CAS9, there was a change in regulations to regulate all GMO plant products [53]. These changes in the political and legal climate had a significantly high impact on TAXA's business. The success of TAXA's crowdfunding campaigns rested on the fact that USDA does not regulate non-pest plants and hence they don't have any regulatory compliance costs [53]. However, the change in regulations coupled with technical, resource, and financial constraints had some extremely undesirable consequences on TAXA's overall business [53].

The shipment of some batches of finished products got cancelled

because the permits for shipment got rejected based on changes in regulations and the shipment of rest of the products got significantly delayed due to technical challenges faced during the development [54, 55, 56]. Meanwhile, TAXA conducted a survey to hear from its backers on which version of the glowing plant was their preferred choice and based on the survey over 95% of their supporters preferred Lux v2 version of the plant which was still under research phase [57, 58]. In order to ensure customer satisfaction TAXA decided to suspend the work on other versions and started to focus on Lux v2 [57, 58]. Evans realized that this would require him to raise additional funds for the research activities [57, 58]. In February 2016, TAXA launched the business of 'genetic engineering of plants as a service' (the TAXA Platform) with an aim to attract equity investors and he launched a non-accredited investor fund-raise in May [58, 59].

Even though TAXA's team were hit by setbacks one after the other Evans continued to keep his stakeholders and supporters informed of the status of all projects [60, 61]. He looked forward to raising funds through WeFunder campaigns and from the shipment of Fragrant Mosses [60, 61]. By July 2016, Evans and team had partly crossed the financial crisis point and raised just enough funds to get the Fragrant Mosses to market [60, 61]. He hoped that he could reinvest the money received from the sale of Fragrant Mosses to resolve the technical issues of the much awaited Glowing Plants [62]. In August 2016, James Anderson-Furgeson who holds a Ph.D. from UC Berkeley joined TAXA's technical team [63]. For a period of eight months TAXA continued to work on various projects i.e. multiple versions of Fragrant Moss, Glowing Moss, and Glowing Plant, solving technical issues one after the other [64, 65].

In April 2017, while TAXA and its supporters hoped to have Fragrant Moss almost ready for shipment, unfortunately, Evans had a bad news waiting for his investors [66]. The production strain of Fragrant Moss that was ready for shipment got contaminated and there was no single step that could have been done to resolve the issue and

continue with the shipment [66, 67]. Consequently, TAXA decided to downsize the team to ensure that they had enough financial runway to ship the moss [66, 67]. This translated to the fact that TAXA had to permanently stop working on their dream project 'The Glowing Plant' since Evans' plan was to use the revenues from the moss to fund the ongoing glowing plant research [67].

After a rough sail for about a year and a half, in July 2017, TAXA started shipping their first product, *Orbella* – the Fragrant Moss in a glass terrarium [68][Refer Exhibit 1, 2]. They shipped around 400 unit in two months, in three different flavors – Patchouli, Linalool, and Geraniol [68]. To celebrate this milestone with his team and backers, Evans hosted an event in San Francisco on August 3rd, 2017 where he planned to have an exhibit of some of the other interesting consumer products he had in the pipeline [68]. Antony Evans, an ambitious and strong-minded entrepreneur, did not lose hope on his dream project and was still determined to use the profits from the sale of Fragrant Moss to restart working on the glowing plant project [68].

**RISK FACTORS**

As listed below, TAXA had identified all the risks associated with their business and notified their investors regarding the same through their Annual Reports [as cited in *TAXA Biotechnologies 2016 Annual Report* – 17].

- *"The company is dependent upon the continued support and involvement of executive management, technical, and scientific resources.*
- *The company's operations could be adversely affected by a regulatory change. Changes to Government regulation may reduce the volumes and/or values of the products that the company seeks to sell.*
- *The development of new products is a complex and lengthy process and may not be completed within anticipated timeframes.*
- *TAXA is dependent on consumer demand for its products.*

- TAXA's future revenues are dependent upon the successful development of products.
- TAXA had recorded net losses in prior years as it has looked to develop its products. While TAXA expects to generate increasing revenues from its products in the future, the company may not be able to generate a net profit, or if it does generate a net profit, to sustain profitability.
- The company operates in a sector where other participants create competition.
- The company has limited liquidity available to fund its business.
- Although TAXA monitors the possible infringement or misuse of its trademarks, it is possible that third parties may infringe upon its intellectual property rights and could harm its reputation or commercial interests. In addition, TAXA's enforcement against infringers may be unduly expensive and time-consuming, or the outcome may be an inadequate remedy.
- TAXA also rely on trade secrets, including unpatented know-how, technology, and other proprietary information, to maintain its competitive position. TAXA seeks to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them. Despite these effort, in case of any breach of the agreement, TAXA may not be able to obtain adequate remedies.
- Some of TAXA's products exist in areas where, due to novelty, there are no legal precedents for interpreting regulations. As a result, TAXA may misinterpret regulations, which could result in financial or operational penalties.
- TAXA will have significant flexibility in applying the net proceeds of the Offering. Investors in TAXA will not have an opportunity to evaluate for themselves the relevant economic, financial, and other information regarding any investment or business activity undertaken by TAXA after the Offering.
- After the cancellation of Glowing Plant in April 2017, for which

*TAXA has taken nearly $600k in pre-orders, backers may demand refunds or initiate litigation.*"

**FUTURE OF TAXA BIOTECHNOLOGIES INC.**

TAXA uses an old technology which can be easily adopted by any other biotechnology company with a better financial, research and development, operational and marketing capabilities. With the emergence of a powerful genome editing tool – CRISPR/Cas9, tools for DIY bio-engineering will have significantly less scope. Moreover, in December 2017, Researchers from Massachusetts Institute of Technology (one of the partners of Broad Institute which owns the CRISPR/Cas9 Patent) have already created a glowing plant [5]. In that case, does it make sense for TAXA to spend more in their glowing plant project?

TAXA's business is dependent on consumer's demand for its products and has no control or influence over the market demand for its customer products [17]. This demand can be adversely affected by various external factors, which in turn will have a huge impact on TAXA's revenues and profitability. Their business is dependent on company's ability to sell genetically engineered plants without going through a regulatory review and any adverse regulatory change can negatively impact its business prospects and financial stability.

TAXA has limited liquidity available to fund its business. The funding required for its operations were obtained primarily through Crowdfunding Campaigns and Collaborative Research Agreements. Even if TAXA considers funding its future business through a combination of debt and equity financing, is there an assurance that such additional financing can be obtained as and when needed?

To a significant extent, TAXA's future depended on its ability to develop, manufacture and successfully commercialize new products in a timely manner [17]. The development of GMO products is inherently complex and risky and unfortunately, TAXA was not able to achieve it within the time and cost constraints or generate enough

revenue to reinvest into their business. The future of glowing plants was completely dependent on customer's response to TAXA's first product – *Orbella* Fragrant Moss [Refer Exhibit 1, 2]. Does Fragrant Moss have a good market? Would the sale of Fragrant Moss help TAXA to generate revenue to support their future business? Considering the complexities and risks involved in the development of GMO products, does TAXA have a viable Business Model?

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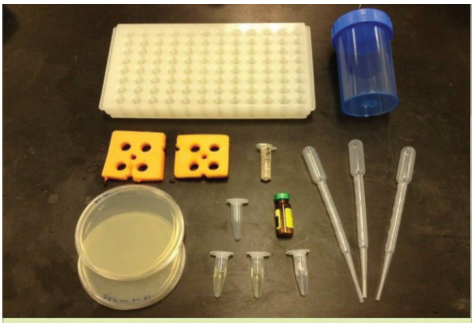
**Exhibit 1:** Orbella Fragrant Moss in a glass terrarium


*(Image Source: https://angel.co/projects/281286-orbella-fragrant-moss)*

**Exhibit 2:** Orbella Fragrant Moss – Packaging


*(Image Source: https://angel.co/projects/281286-orbella-fragrant-moss)*

**Exhibit 3:** Glowing Plant – Maker Kit



A maker kit so that you can genetically transform your own plant at home or at a lab like Biocurious or Genspace. The kit will contain the following:

- Full instructions for how to make a glowing plant
- Copy of the coffee table book with visual description of what you need to do
- A vial of Glowing Plant DNA
- Pre-poured LB plates (2 plates)
- Arabidopsis seeds
- Agro-bacterium
- Small pot and soil
- Silwet
- Nutrient solution
- Petri dish for germinating seeds

(*Image Source: http://blog.glowingplant.com/*)

# 20. Edge Therapeutics: Fast-tracking EG-1964 to Market or Not

**Edge Therapeutics: Fast-tracking EG-1964 to Market or Not**

**By: Aman Razack**

**April 8th, 2018**

On a surprisingly cold day at the tail end of March 2018, CEO of Edge Therapeutics Brian Leuthner and Senior Vice President and General Counsel Brad Middlekauff call in the rest of the management team for an emergency meeting. "I have called you all in today to discuss the future of the company," said Brian. This statement raised concern for many of the other executives on the board. "We will soon have a 92% loss on our market capitalization and will need to lay off a large amount of employees"[1]. This information greatly shocked everyone in the room. "We need to figure out a short-term solution to appease our investors," said Brad. "How could this drastic of a loss have happened in our stock" asked Liam Ratcliffe, a member of the Board of Directors. "We recently found issues with the side effects of our Phase III drug EG-1962," stated Brian. This posed a huge problem, as the promise shown by EG-1962 was the reason for the major market cap of Edge. There Brian and the rest of the management team seemed to be vacillating on what to do now that their highly touted drug candidate is discontinuing its trials. "We must figure out a way to get our next most ready product, in this case EG-1964 through trials as effectively as possible," said Brian.

As a someone who has over 25 years of experience in the market of hospital acute care, Brian is someone who has had to face adversity and tough situations before. Prior to being one of the Co-founders

of Edge Therapeutics, he also served as the CEO to Fontus Pharmaceuticals, the Senior Head of Marketing for The Medicines Company and the Director of Market Development for ESP Pharma [2]. His sales and marketing jobs at Glaxo Wellcome and Ortho Biotech also seemed to help him thrive in leadership roles where he helped launch critical care products and strengthen customer relations. All in all, the situation he and Edge currently find themselves in will require as much experience and tenacity as possible.

**Edge Therapeutics**

Edge Therapeutics Inc. is a biotechnology company based in Berkeley Heights, New Jersey. It was founded in the 2009 by now CEO Brian Leuthner and the Chief Scientific Officer R. Loch Macdonald. The aim of Edge is to develop and commercialize therapies to be used for the treatment of acute, life-threatening neurological conditions. Specifically, they were looking into compounds that would be able to target rare neurological conditions for which current methods of treatment were insufficient [3].

As of 2017 the company contained thirty-eight employees [4], making them rather small in size, but what they lacked in size they made up for in experience, like Brian Leuthner. The Chief Operating Officer, Daniel Brennan was previously the Vice President of Lundbeck's U.S. Neurology Business Unit and under his leadership he was able to launch four specialty products which caused the annual sales to grow from $60 million to $820 million. Senior Vice Preseident Brad Middlekauff also had great experience being the Chief Legal Officer at Kolltan Pharmaceuticals and the Senior Vice President and Medarex Inc [2].

With all of the experience from their executives, what Edge needed next was a novel product or process to break into this very saturated field. In June 2013, researchers brought forth very promising results with their microparticle formation named EG-1962, which is able to

treat aneurysmal subarachnoid hemorrhaging in the brain [5]. Also, in October 2016, they filed for a trademark on a novel way to administer drugs to the specific site of injury, which they called the Precisa Platform™[6].

The only issue was that they were using a good portion of their funding in Research and Development for EG-1962 and also for General and Administrative purposes. They had used $34.3 million for R&D purposes related to EG-1962 clinical development and $17.7 million for G&A purposes related to personnel costs, investor relations cost and legal and professional fees, at the end of 2017. This totaled to a net loss of $50.9 million at the end of 2017 [7]. Although they incurred a net loss at the end of 2017 and 2016, Edge still had $47.4 million in their reserves for any other costs

**Aneurysmal Subarachnoid Hemorrhage (aSAH)**

Subarachnoid hemorrhages are a very serious type of stroke that occurs in the subarachnoid space in the brain. It is caused by a ruptured brain aneurysm or a head injury. In a healthy brain, the subarachnoid space in between the brain and the skull contains cerebrospinal fluid, however, when an aneurysm occurs, blood is released into this space surrounding the arteries which increases pressure on the brain, damaging the brain cells [8]. Also, the artery that was affected is not able to transport oxygenated blood to the specific area of the brain that it was leading to, causing there to be a deprivation of blood, leading to a stroke and ultimately death of brain tissue. This process can be seen in Exhibits 1 and 2.

The amount of people affected each year by aSAH is growing at a staggering rate, especially in countries in the Western Hemisphere. Looking at the United States, there are about 30 000 people who suffer from a brain aneurysm each year, where about 40% are fatal. It has also been shown that women are more likely to suffer from brain aneurysms than men and that African American's and Hispanics are more susceptible than Caucasians. In addition, across the world there

are approximately 500 000 deaths each year from brain aneurysms with most of the victims below the age of 50 [9]. One of the most debilitating facts however is that of the people who do recover, about 57% will end up with a disability, causing lay offs from work.

There are a few specific ways which aSAH is diagnosed: the first being the use of Computed Tomography angiography (CTA) which constitutes the injection of a specific contrasting compound into the blood stream allowing the arteries in the brain. Another way is by lumbar puncture where a needle is inserted into the subarachnoid space of the spinal canal to determine if blood is in the cerebral spinal fluid. This procedure is usually performed as a secondary test if a regular CT scan does not show bleeding. The third way to diagnose aSAH is by Magnetic Resonance Imaging (MRI), which uses a magnetic field and radio frequency waves to give a detailed view of the soft tissues in the brain [8].

**Current Surgical Treatments Available for aSAH**

With the rise of aSAH and other stroke related illnesses, there will also be a rise in treatments to go along with it. It has been predicted that the cost of therapeutic technology relating to stroke and other brain diseases will be around $323 million with the treatment of acute stroke management estimated to be $1.5 billion, between 2015-2019. According to the report, "Emerging Global Market for Neurointerventional Technologies in Stroke" by Patrick Driscoll of MedMarket Diligence,

"Stroke is associated with costly long-term care, especially for a patient population that is typically older and more susceptible to its complications, but neurointerventional treatment have succeeded in both making a positive clinical impact and securing respectable revenue streams for manufacturers [10].

With that being said, one of the current treatments is the use of surgery. One of the surgical procedures that is used is surgical clipping, which involves opening the skull at the spot of the aneurysm

and then inserting a titanium clip around the neck to prevent the blood flow from entering. Another procedure is endovascular coiling, which involves the insertion of a catheter into an artery in the groin that is sent to the spot of the blood vessel burst, where titanium coils or liquid glue is packed into the aneurysm to prevent blood from entering [8]. The control of vasospasm is also of importance as it leads to the narrowing of the arteries and decreased blood flow in the area of the brain which the artery feeds (Exhibit 2). The monitoring of vasospasms is performed by a Transcranial Doppler (TCD) to measure the blood flow of the arteries (Exhibit 3) and can determine which arteries show vasospasm as well as the severity. The effects of vasospasm can lead to delayed cerebral ischemia (DCI), the restriction of blood flow, causing parts of the brain to die.

**Current Pharmaceuticals on the Market**

As can be inferred however, these procedures are highly invasive and would not be preferred by patients. Because of this, there has been the development of several drugs one of which, called nimodipine, has shown to have very positive effects on the treatment of vasospasm.

*Bayer: Nimotop*

Originally the drug was discovered and tested in 1983 by a group of scientists on a series of patients to determine whether or not nimodipine would reduce the severity of ischemic neurological deficits [11]. What they found was that the 56 patients given the drug did not suffer any worse neurological outcomes compared to the patients given a placebo.

This product was then developed into an oral pill by the pharmaceutical giant Bayer and was granted FDA approval in 2005. Called Nimotop®, the drugs' usage was to improve neurological outcome by reducing the severity and incidence of ischemic deficits by subarachnoid hemorrhaging. Specifically, this drug was known as

a calcium channel blocker. During contraction of the muscle tissue, calcium ions are needed to enter the muscle cells through depolarization, creating small currents ultimately causing the muscles to contract. By administering nimodipine, calcium ion transfer is inhibited, thus inhibiting the contraction of the muscles in the blood vessels [12].

The effect of nimodipine was shown to be very useful in patients who suffered from vasospasms but it also came along with several side effects such as: heart failure, vomiting and neurological deterioration to name a few [12]. This led to the development of drugs by other companies.

*Pfizer: Calan*

One of the competitors of Nimotop was Calan® and worked in a similar way to nimodipine. The name of the compound used in Calan is verapamil and it is also a calcium ion inhibitor. The way it works is by dialating the arteries in normal and ischemic regions thus increasing the amount of oxygenated blood that is delivered in patients with arterial spasms [13]. Although verapamil was mostly used for the treatment of vasospasm related to the heart, as what is was originally marketed for in 1984, it has recently been shown to be beneficial for treatment of cerebral vasospasm [14].

This however came along with some controversy in its use in cerebral vasospasm. One study conducted found there was a significant reduction in arterial blood pressure after inter-arterial injection14. There is also not enough research to prove that verapamil has a large clinical application.

*Amgen: Epogen*

A third therapeutic on the market is the use of the erythropoietin Epogen. This product is different from the two previously described since it uses glycoprotein instead of a chemical compound. For the past 30 years Amgen has been producing Epogen specifically for

dialysis patients and has been splitting the erythropoietin (EPO) market with Johnson & Johnson [15]. This market has been a growing one as well; it is expected that it will reach $11.9 billion by 2020 with a solid CAGR of 9.7% from 2014 to 2020 [16]. One of the reasons for this high growth is the fact that EPO drugs are used in Cancer and HIV patients who suffer from anemia after chemotherapy, and EPO's are used treat this.

In some early animal experiments, EPO's have also been shown to have a neuroprotective role in cerebral ischaemia. The mechanism for their action in decreasing vasospasm is not clearly understood however. Some proposed mechanisms are its effect to limit inflammation, stop cell death in surrounding tissue or upregulation of neuron production [14].

Even though there is a lot of potential for the adoption of EPO drugs, they are still only in animal trials for its use in vasospasms. There is still much work to be done, especially the use of large clinical trials, before this can be used as a potential treatment.

**EG-1962**

With all of this information on the market, Brian, Brad and the rest of the team wanted to figure out a way to administer an anti-vasospasm drug without the side effects of other drugs and procedures. With several years of research they were able to engineer a specific development platform which they coined the Precisa Platform. Precisa is a programmable, biodegradable, polymer-based therapeutic that is able to deliver compounds directly to the site of injury, which would potentially prevent side effects from other drugs [17]. To be specific, a therapeutic, is adhered to the surface of the Precisa microparticles and then administered via brain catheter. The microparticle is then able to release the therapeutic in a controlled manner, allowing for a one-time administration [Exhibit 4]. The polymer made up of poly (DL-Lactic-co-glycolide) (PLGA) is

then broken down into lactic acid, a naturally occurring product in the body.

The entire system composed of the Precisa microparticle and nimodipine makes up the EG-1962 product. As mentioned before, the current method of oral or intravenous dosing is known to cause serious side effects, one of the more serious is hypotension where blood flow is drastically decreased in the blood vessels. For this reason EN-1962 was made to deliver nimodipine to the brain as one single dose with drug exposure lasting 21-days, while also avoiding the dose-limiting side effects [17].

The previous animal trials were so promising that the United States FDA and European Commission both granted orphan drug designation for the treatment of aSAH. In the North American NEWTON phase 1/2 study, the tolerability and pharmacokinetics of EG-1962 was measured with the therapeutic administered via external ventricular drain (Exhibit 5) to 72 patients. What was observed after 90 days was that EG-1962 met all of the endpoints for safety, pharmacokinetics and tolerability and also 60% of the patients treated with the therapeutic showed favourable outcomes compared to the 28% administered oral nimodipine (Exhibit 6) [17]. Furthermore, the reduction in vasospasm, delayed cerebral ischemia, reduction in rescue therapies and shorter ICU times were all shown after the use of EG-1962, with no hypotension. With Phase 1 and 2 trials so successfully, EG-1962 looked like it was going to give extremely promising results in Phase 3, however this was not the case. It was determined that the Phase 3 study demonstrated a low probability of achieving statistically-significant difference compared to the standard care and was suggested to stop the study by the Data Monitoring Committee [18]. Although bad news, there were still some options that Brain and the rest of the management team had.

**Possibility**

Although their main product seemed to be bust, Edge still had another product on deck, EG-1964. This therapeutic would again aid

in neurological damage but more specifically it would be used to treat subdural hemotomas (SDH). SDH is the collection of blood on the outer surface of the brain and is usually caused by head injury. While this is not yet a leading neurological disorder, it is predicted that by 2030 there will be at least 60 000 people who suffer from SDH in the US alone [19]. However, the production and phase testing of EG-1964 still looks very far off.

This leads to Edge's most valuable product, its Precisa technology. The advantage of this type of technology is the fact that any compound is able to adhere to its surface; the microparticle just needs to be engineered so that the polymer-based formulations are adapted to the proper size, surface property, dose level and release profile [17]. With this type of technology, Edge could use other drugs with Precisa to administer drugs quicker and to their specified target more accurately. Moreover, the release rates of the drugs would be timed accurately thus making patients not have to worry about taking their drugs at specific times or over and underdosing. With this trademark, Edge will still be able to compete in the therapeutic industry, it however might take a little time.

**The Restart**

As Brian and the rest of the team sat in the conference room, they continued to mull over whether bringing EG-1964 to market would be the best idea. "I think the best idea would be to see how Eg-1964 does in its Phase 1 trials and not push it out as soon as possible," said Brad MiddleKauff. Looking around the table and observing the unanimous head nods, Brian then stated, "Now that we all agree on that, lets see what we can do about Precisa." The team then proceeded to brainstorm.

**Appendix**

Exhibit 1: Aneurysmal Subarachnoid Hemorrhage (aSAH). The blood

from the ruptured artery fills the subarachnoid space forming a blot clot and increasing pressure [8].

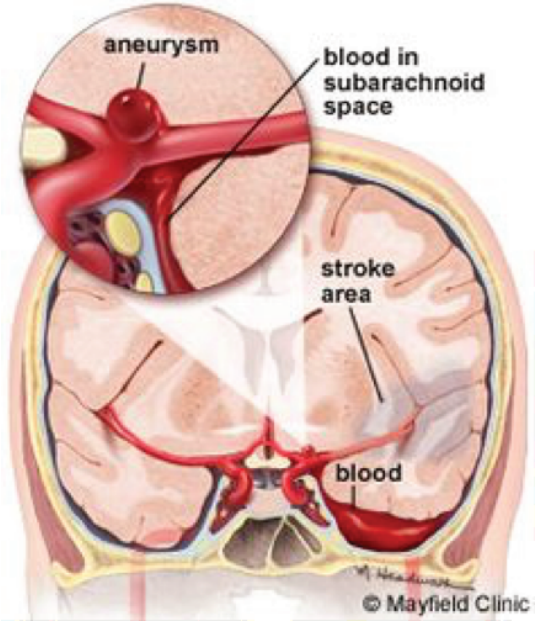



Exhibit 2: Diagram displaying the subsequent affects of a subarachnoid hemorrhage on one area of the brain [3].

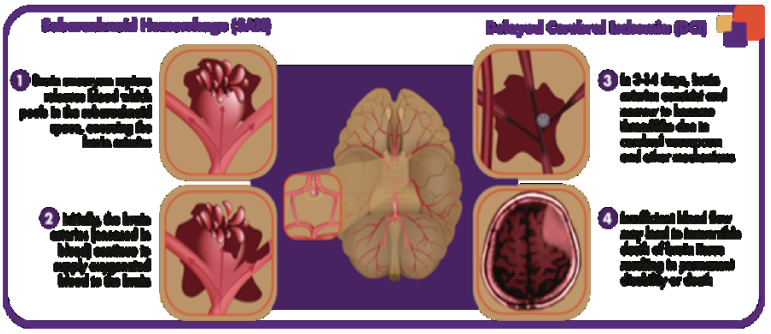


Exhibit 3: Transcranial Doppler probe (TCD) using ultrasound technology to examine cerebral arteries, looking for blood flow and diagnosing vasospasm [8].

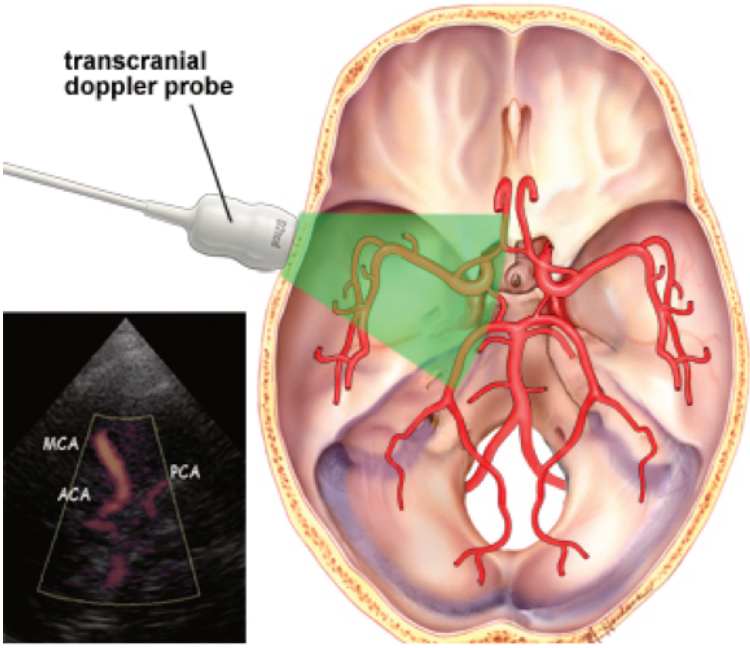



Exhibit 4: EG-1962 made up of Precisa microparticles and nimodipine showing the release of the drug and degradation of the polymer [3].

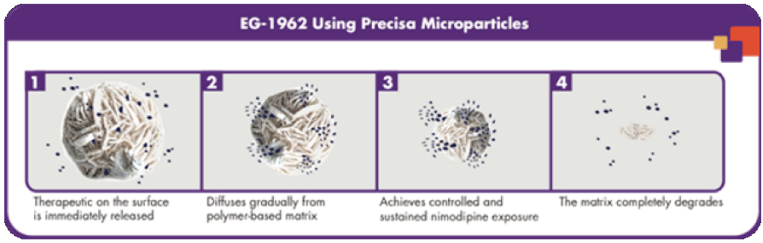


Exhibit 5: Depiction of external ventricular drain used to administer EG-1962 to specific area of the brain. Red arrows indicate areas where blood flows after aneurysm [3].

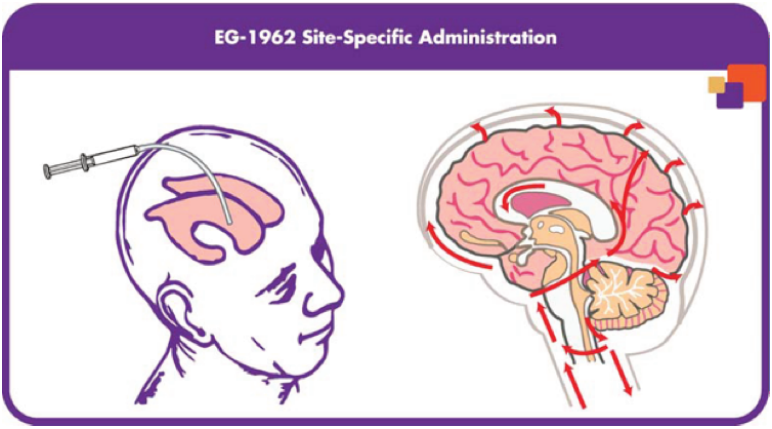
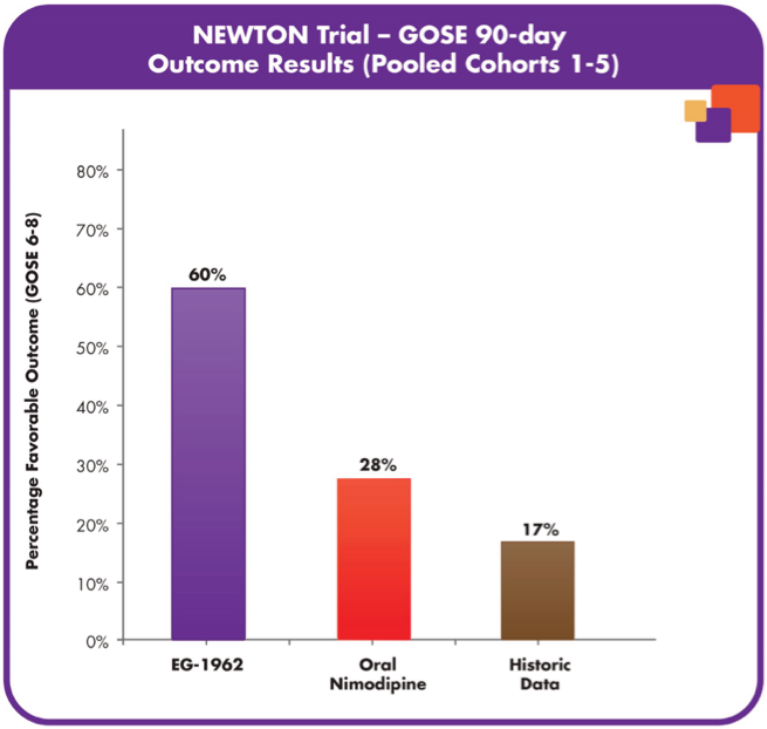



Exhibit 6: Percentage of favourable outcomes for EG-1962 and other drugs on 72 patients for 90 days [3].

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# 21. GlaxoSmithKline Zika Virus Vaccine: Coverage and Aid through Patient Assistance Programs

**GlaxoSmithKline Zika Virus Vaccine: Coverage and Aid through Patient Assistance Programs**

By: MAHAM HAFEEZ

Emma Walmsley sat in her office chair, preparing for the start of the meeting with the stakeholders about the much awaited Zika Virus Vaccine. She was the newly appointed Chief Executive Officer (CEO) of GlaxoSmithKline (GSK), and her job left little room for error. With several people inflicted with Zika Virus and its ever-progressing spread to the United States of America, the access of the vaccine to patients of all socio-economic status was important. Therefore, the establishment of the coverage of the drug despite its price and any actions required to ensure those unable to afford the vaccine have access was crucial. To decide on the coverage of the new vaccine and who gets which type of coverage from the organization, the Patient Assistance Program at GSK played a critical role.

**GlaxoSmithKline**

GlaxoSmithKline (GSK) was a research-based pharmaceutical company that provided products within their product segments that included Pharmaceuticals, Consumer Healthcare, and Vaccines (Bloomberg, n.d.). Pharmaceuticals, Consumer Healthcare, and Vaccines generated a total revenue of $17.28 billion, $7.75 billion, and $5.16 billion respectively (Bloomberg, n.d.). Even though vaccines accounted for the least revenue compared to other products (17%),

$5.16 billion remained to be a substantial amount. Therefore, the success of the vaccine segment of the company was important as the healthcare system's ideology shifted from disease treatment to disease prevention (Rheinberger, Herrera-Araujo, & Hammitt, 2016). GSK had several locations across the globe and were one of the largest pharmaceutical companies.

**Zika Virus Infection**

Zika virus was a mosquito-borne flavivirus that had impacted the United States of America (USA), Australia, and several countries in South America and Africa ("Infographic," n.d.). The mosquito capable of carrying Zika virus was called Aedes mosquito, which was found in abundance across USA ("WHO | Zika virus," n.d.). Zika virus had been around for 60 years, however, the outbreak in 2016, resulted in the World Health Organization (WHO) labeling it as a disease with "explosive pandemic potential" ("Infographic," n.d.). The virus was transmitted through mosquito bites, mother-to-fetus, sexual contact, and potentially blood transfusion ("WHO | Zika virus," n.d.). The disease symptoms were similar to those of dengue and chikungunya virus, which included fever, skin rash, conjunctivitis (eye inflammation), muscle and joint pain, malaise (general feeling of discomfort) and headache ("WHO | Zika virus," n.d.). The incubation period (exposure time) of the virus was unknown, however, upon the appearance of symptoms, the symptoms lasted only 2-7 days ("WHO | Zika virus," n.d.). No specific treatment was required to treat those infected due to the mildness of the viral symptoms ("WHO | Zika virus," n.d.). Therefore, the infected individuals were prescribed with plenty of rest, higher levels of fluid intake, and common medicines to treat the fever and pain ("WHO | Zika virus," n.d.).

The main issue with Zika virus was not the fact that it infected many individuals because of the mild nature of the symptoms. Instead, the growing link between Zika virus infection in pregnant women and its negative impact on the fetus was very concerning. There had been a growing consensus within the scientific community

that upon mother's infection, the virus caused neurological symptoms in developing fetuses ("WHO | Zika virus," n.d.). The virus was believed to cause microcephaly and Guillain-Barré syndrome in newborns, and associations with other neurological conditions in newborn were being tested ("WHO | Zika virus," n.d.). In fact in South America, after the 2013-2014 circulation period of Zika virus, the number of infants with neuronal birth defects increased from 2.86 infants per 1000 births to 58.8 infants per 1000 births in 2016 ("Risk of Zika Virus-Related Birth Defects in Pregnant Women," 2017). Most of the observed neurological conditions were the ones observed physically after birth, and other long-term neurological complications remained unclear, highlighting the potential impact of the virus on infants ("Risk of Zika Virus-Related Birth Defects in Pregnant Women," 2017). Therefore, governments across the globe were scrambling to produce a vaccine for Zika virus infection.

**Zika Virus Vaccine Development, Vaccine Affordability, and Disease Spread**

The increasing prevalence of Zika virus and its association with neurological symptoms in infants had promoted the need for the Zika virus vaccine development. However, pharmaceutical companies have been hesitant to invest in the Zika virus vaccine Research and Development (R&D) on the assumption that individuals will naturally build a resistance to the virus ("GSK jumps into Zika vax hunt on heels of Sanofi's deal | FiercePharma," n.d.). Nonetheless, political pressure had warranted the development of a vaccine ("GSK jumps into Zika vax hunt on heels of Sanofi's deal | FiercePharma," n.d.). Therefore, GSK had formed partnerships with National Institutes of Health (NIH), Sanofi, and Walter Reed Army Institute of Research (WRAIR) to fast-track the development of a Zika virus vaccine ("GSK jumps into Zika vax hunt on heels of Sanofi's deal | FiercePharma," n.d.).

The development of a vaccine was costly and time-consuming. On average vaccine development can cost around $US205-878 million

and can take up to 16 years, with 7.5 years being the average duration (Waye, Jacobs, & Schryvers, 2013). This leads into high prices for vaccines and with further rigorous regulation, the prices have only soared. Vaccines can range from as little as $US30 up to over $US145 ("The Price of Prevention: Vaccine Costs Are Soaring – The New York Times," n.d.). In fact over the decades, the federal costs incurred by US government alone has increased 15-fold over time regardless of the discounted prices ("The Price of Prevention: Vaccine Costs Are Soaring – The New York Times," n.d.). Sanofi's rejection to the US Army's negotiations to set an affordable price for Zika virus vaccine, even after being given a $43 million grant from the US Biomedical Advanced Research and Development Authority (BARDA), only raised further affordability issues ("The Battle Over a Fair Price for Zika Vaccines – Scientific American," n.d.). The current price set for Zika virus vaccine made it unaffordable for many US citizens ("The Battle Over a Fair Price for Zika Vaccines – Scientific American," n.d.). As a result, Sanofi's ability to secure further funding and an exclusive license to sell the vaccine was jeopardized ("The Battle Over a Fair Price for Zika Vaccines – Scientific American," n.d.).

The issue with high prices was that it made it unfeasible for many individuals to afford the Zika virus vaccines. The concern was further highlighted as the majority of the individuals affected by the virus were in South America and Africa, where poverty was more prominent. Several countries in Latin America faced various levels of poverty. Certain countries faced poverty rates of around 10% (Uruguay, Argentina, and Chile) while other countries such as Nicaragua and Guatemala faced higher poverty rates of 37% and 50% respectively ("10 Shocking Facts About Poverty in Latin America," 2016). Poverty rates were further made tricky as they not only varied from country-to-country, they also varied drastically from city-to-city within a country. Brazil, the country to first report the association between Zika virus and neurological abnormalities, was a prime example of the city-to-city poverty variation. In Brazil, Santa

Catarina had a chronic poverty rate of 5%, while Ceará had a rate of 40% ("10 Shocking Facts About Poverty in Latin America," 2016; "Risk of Zika Virus-Related Birth Defects in Pregnant Women," 2017). The importance of poverty consideration was further highlighted when contrary to general belief, the urban regions in these countries had higher poverty than the rural areas ("10 Shocking Facts About Poverty in Latin America," 2016; "Four Facts About Poverty in Latin America you Probably Didn't Know | HuffPost," n.d.). Even though the rate of poverty in rural locations may be higher, there was a higher number of individuals in poverty in the urban areas compared to rural ("10 Shocking Facts About Poverty in Latin America," 2016; "Four Facts About Poverty in Latin America you Probably Didn't Know | HuffPost," n.d.). This trend was clear in countries like Chile, Brazil, Mexico, Colombia and the Dominican Republic ("10 Shocking Facts About Poverty in Latin America," 2016). With an average individual earning only $4 a day in Latin America, the affordability of the vaccines was concerning ("10 Shocking Facts About Poverty in Latin America," 2016).

Access to Zika virus vaccines was also important for the poverty-stricken countries because the majority of the individuals with lower income lived in urban areas where population densities were higher, making disease transmission easier ("10 Shocking Facts About Poverty in Latin America," 2016; "Four Facts About Poverty in Latin America you Probably Didn't Know | HuffPost," n.d.). The incidence of disease was only increased as those living in poverty had poor living conditions. According to World Water Council, in Latin America, 77 million people lacked access to safe water or a water source altogether in their homes ("10 Shocking Facts About Poverty in Latin America," 2016). Moreover, it was estimated that 256 million people relied on latrines and septic tanks in place of basic sanitation ("10 Shocking Facts About Poverty in Latin America," 2016). The poor living conditions further added to the facilitation of environments suitable

for disease spread, which led to higher risks of incidences of disease contraction and spread.

Therefore, the scope of the market for the Zika virus vaccine, and the considerations necessary pertaining to the price and the affordability of the therapeutic was a multi-facetted concern.

**GlaxoSmithKline (GSK) Patient Support Program: GSK for you**

GSK for you program was a patient support program at GSK that provided assistance to those who were unable to afford GSK products. The type of aid that was provided was divided into three categories that included uninsured patients, patients with Medicare Part D, and vaccines ("GSKForYou | Patient Assistance Program," n.d.). They also had additional offers such as coupons and free trials to help patients in need gain access to quality medications ("GSKForYou | Patient Assistance Program," n.d.).

The free trails were applicable to only certain prescription medications that individuals with commercial insurance or without any insurance were eligible for ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). Those enrolled in any of the government-based insurance programs such as Medicare Part D in the USA were not eligible ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). The trial was also a one time offer for the prescriptions and the acceptance of the trial offer varied based on the pharmacy ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). Similar to free trials, the Dollars-Off coupons by GSK were offered to individuals with commercial insurance or without insurance at all ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). Those enrolled in any federal program like Medicare Part D were excluded from this offer ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). Those with insurance were covered only up to the amount that was not covered by their insurers, provided the value was less than that listed on the coupon ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). Those without insurance were covered up to the value listed on the

coupon ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.). The main goal of the coupons was to reduce any out-of-pocket costs associated with certain medications ("Coupons & Free Trial Offers for Medications | GSKForYou," n.d.).

The most relevant aid provided by GSK to their new Zika virus vaccine was the assistance provided under the vaccine segment for GSK for you program ("Patient Assistance for Vaccines | GSKForYou," n.d.). The program provided assistance to patients in gaining access to certain GSK vaccines ("Patient Assistance for Vaccines | GSKForYou," n.d.). Like all other patient support programs, there were specific eligibility criteria that were set for the patients ("Patient Assistance for Vaccines | GSKForYou," n.d.). To qualify for the assistance program, patients had to reside within the 50 states of USA, Columbia or Puerto Rico; could not have any third party insurance coverage; could only be enrolled in other federal programs like Medicare Part D; have had spent at least $600 on prescription medication through their Medicare Part D program; be of age 19 and over; could not be eligible for Puerto Rico's Government Health Plan Mi Salud or been denied from the program after application; and be within a specific house income that varied depending on family size and location ("Patient Assistance for Vaccines | GSKForYou," n.d.). The income criteria outlined by GSK can be found in Appendix I.

The eligibility criteria set forth by GSK posed several concerns. One major concern was that it was limited to only USA, Columbia, and Puerto Rico, while it was evident that those in South America also had a great need for such a program. In fact, about 20% of the individuals residing in Latin America and the Caribbean lacked access to health care due to poverty conditions ("10 Shocking Facts About Poverty in Latin America," 2016). Even if the program was to be deployed in these regions, certain considerations were required. The program in its current format faced several gaps and barriers; it was still inefficient (took long processing times; around 3-4 weeks), and did not work with any third-party insurers. To effectively launch

any patient support programs in a new location, GSK had to take the patient eligibility criteria, program cost, and program success indicators under consideration.

***Patient Eligibility Criteria***

The current eligibility criteria of the patient support program at GSK was heavily dependent on the socio-economic status of a patient and the impact the disease would have on the patient's ability to work. The patients also had to be over the age of 19 years ("Patient Assistance for Vaccines | GSKForYou," n.d.). These criteria proved concerning for individuals who did not meet these requirements but were still in need of the vaccine such as retired elderly or young children. The elderly did not have access to any income and were dependent on their children who themselves could not afford any vaccines or medications. The same applied to young children. The question was then how would these individuals who were dependents and could not access the vaccines be covered? Even though Zika virus caused only mild symptoms and affected pregnant women and their fetuses more severely, elderly and children had weaker immune systems. That meant that the severity of the symptoms was increased, and the virus could further compromise the immune system, leading to an increased risk of infection by other opportunistic viruses ("Are Seniors at Risk for Zika Virus?," 2016). Therefore, young children and elderly required vaccination as well, not only for their own health but also to avoid its spread to those around them. Moreover, the major risk associated with Zika virus infection was related to pregnant women; thus, the access priority of the vaccine to those already pregnant or planning on having children, and those around them was important. These considerations played an important role in identifying the right assistance eligibility and application priority criteria for the Zika virus vaccine.

The ineligibility of individuals carrying third-party insurers for the patient programs was also concerning as the likelihood existed that the vaccine would not be covered enough by the insurers as the

prices set by the pharmaceutical company were high. Therefore, despite having insurance coverage, a large subset of the population would not be able to afford the vaccine, rendering the concept of vaccination pointless.

Even after the determination of a better eligibility criteria, it was important to understand the level to which funding or coverage by GSK that would be provided. It was also important to determine that once individuals met the eligibility criteria, regardless of the income variations within the sub-set, would everyone receive the same amount of coverage or would it change based on income?

***Cost Estimation***

The feasibility of the program was also important for GSK to ensure the overall profit margins of the company did not suffer and to ensure sufficient allocation of funds. To estimate the costs associated with the program, the company needed to estimate the number of patients expected to buy the vaccine and the number unable to afford it without aid. In order to determine the costs associated with the program, many different forecasting models could be taken into consideration.

Some of the potential forecasting models included Dartboard methods, Workstation methods, Simple Spreadsheet methods, Analytic Spreadsheet methods, and Systems Dynamics methods (Cook, 2006). Each model had its own advantages and disadvantages. Dartboard method and Workstation method were two extreme type of forecasting styles within the pharmaceutical industry (Cook, 2006). Dartboard method heavily relied on the gut feeling that came with experience, while Workstation method relied heavily on huge amounts of data, which led to misinterpretations and confounded analysis (Cook, 2006). Simple Spreadsheet method, on the other hand, was a middle-ground approach that utilized spreadsheet software like Excel and combined it with forecast formulae to generate cost estimates. Therefore, Simple Spreadsheets was the most popular forecasting method for the pharmaceutical industry

(Cook, 2006). Analytic Spreadsheet method added a layer of complexity as it took the country-to-country variation under consideration (Cook, 2006). Systems Dynamics method incorporated the potential occurrences of relapse and repeated doses for medications under consideration (Cook, 2006).

Proper forecasting was important as previous pharmaceutical sales forecasts have either over-projected or under-projected sales (Cook, 2006). Any incorrect projections were likely to either stop the deployment of the support program or cut drastically into company's profits. Therefore, the costs analysis played a critical part in patients' ability to gain access to an important vaccine within poverty-stricken countries.

***Program Success: Key Performing Indicators (KPIs)***

Like any project deployed, it was important to judge the effectiveness and success of the project. To determine the success of the program, several key performing indicators (KPIs) could be considered. These KPIs included the number of patients that were served, the rate of applications reviewed, length of time spent on approval per application, and the accuracy of the forecasting model used.

Determination of the number of patients served and comparing it to the number of individuals living under the poverty line (expected patients who were eligible for the program) indicated the access of the program and how well individuals were informed by their healthcare professional about the vaccination options available to them and their affordability. This was indicative of the communication between the company and the healthcare professional in getting their jobs done effectively.

The rate of applications reviewed was indicative of the efficiency of the work done by the patient program employees. It was also indicative of the ease of the navigation of the program by company employees, patients, any insurance companies, and healthcare professionals. Any lapse in the rate would indicate areas of

inefficiencies in the newly deployed program. Gaining insights on the duration of the application process also provided insights into the inefficiencies of the program. Moreover, the understanding of processes that took longer than expected narrowed the specific problem areas for proper resource allocation in problem resolution. As a result, the overall efficiency and effectiveness of the program were expected to improve by setting the KPIs.

Forecasting accuracy was important in determining the actual costs of the program compared to expected. Ensuring accuracy in projections also ensured that the company funds were properly utilized to avoid any loss of revenue for the company.

The final overarching KPI that was set for the success of patient programs was the reduction in the global incidence of Zika virus infection and neurological abnormalities due to virus contraction by pregnant women.

With understanding all the considerations needed for setting the price of the Zika virus vaccine and any coverage plans for those in need, Emma Walmsley walked towards the door of the conference room. She knew the discussion would be long and many points would be raised. Going into the meeting, she knew that tackling the concerns of the advocacy groups like Doctors Without Borders and World Health Organization was going to play a key role in securing an exclusive license to the vaccine and commercializing the product.

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**Appendix I**

| **Maximum Monthly Gross Income** | | | | |
|---|---|---|---|---|
| **Household Size** | **48 states and Washington D.C.** | **Alaska** | **Hawaii** | **Puerto Rico** |
| 1 | $2,529.17 | $3,162.50 | $2,908.33 | $2,000.00 |
| 2 | $3,429.17 | $4,287.50 | $3,943.75 | $2,500.00 |
| 3 | $4,329.17 | $5,412.50 | $4,979.17 | $3,000.00 |
| 4 | $5,229.17 | $6,537.50 | $6,014.58 | $3,500.00 |
| For each additional person, add | $900.00 | $1,125.00 | $1,035.42 | $500.00 |

*The table was taken from GSK for you program website ("Patient Assistance for Vaccines | GSKForYou," n.d.)

# 22. Qvera: The #1 Interface Engine

**Qvera: The #1 Interface Engine**

Tanisha Shekdar

It was a beautiful spring day in April of 2008, and Sam Shapiro, President, and CEO of Qvera glanced out his office window in Kaysville, Utah located in the United States. Tom was in the middle of getting ready for an exciting meeting with his brothers and partners of the company: Ron Shapiro, Vice President and chief technology officer (CTO), Ben Shapiro, Director of Software Engineering for the company, Mike Williams, Vice President of Sales, Ken Ostrowski, Director of Strategic Development and Marketing, and Gary Meyer, Vice President of Customer Service. This consortium of executives was meeting up to discuss how to make history in the healthcare IT segment for both ambulatory and inpatient environments (Company History, n.d.).

What a time to be alive for the Shapiro brothers and Qvera! The company was eagerly approaching the commercial launch of its platform, the Qvera Interface Engine, QIE for short, which is a new interface engine that was built from the ground up. What was so great about this new interface engine was that not only did it benefit from the fact that the creators all had prior extensive experience with building an engine but also from the timing of its inception (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.). Qvera was able to take advantage of the latest data formats, connectivity requirements, and format standards by building into QIE the comprehensive support for the company and enhancing the

application to best utilize newer standards and formats used in the healthcare IT segment.

The Shapiro brothers hoped that, together, Qvera's new interface engine would be the easiest and most powerful tool for healthcare interoperability which would enable connecting the older legacy systems in hospitals with newer platforms and technologies; additionally, not only would Qvera aim to connect the two, the company would also make this connection simple, efficient, and easy to understand for all users. In the company's eyes, Qvera's QIE platform offered many benefits to those that wished to use it. The Qvrea Interface Engine held the potential to sufficiently drive the cost of interoperability in healthcare and lower the total cost of ownership.

Today's meeting with the group, however, was essential and held a special opportunity for everyone at the table to address their concerns and such about the health care interoperability tool and the segment in broader terms. What companies can Qvera partner up with to make the QIE a better and stronger tool? How will users be authenticated to access the data? And finally, how can patients, providers, and service locations uniquely be identified at the physical level for the sending and receiving systems? These were all questions that the team hoped to resolve to make their sole product the best one out there (Tong, 2016).

**Context: What is Interoperability?**

According to Health Information and Management Systems Society (HIMSS), the term interoperability is described as the extent to which systems and devices can exchange data as well as interpret that shared data (What is Interoperability?, 2017). Interoperability means the ability of health information exchange (HIE) systems to work together within and across organizational boundaries in order to advance the effective delivery of healthcare for both individuals and communities.

For two systems to be interoperable, they must be able to exchange data and also be able to present that data later on in such a way that it can be understood by a user (What is Interoperability?, 2017). These data exchange schemes and standards should allow data to be shared across various healthcare systems like clinician offices, labs, hospitals, and pharmacies.

**The Company's History**

Based out of Kaysville, UT, USA, Qvera is an experienced software company which tends to the needs of the healthcare IT industry. The company solely focuses on producing the most powerful and flexible interface engine on today's market. Initially, the company started off in healthcare IT consulting but the team realized that they needed an interfacing and integration tool that was not only intuitive to use but also flexible and powerful for users. When the team was unable to find one that fit all their requirements, they decided to build their own interface engine from scratch (Company History, n.d.). The engine they build initially was great for what was needed in 1999, but as healthcare IT evolved, so did the need for better tools. The company thus had the opportunity to re-form as Qvera and build a newer more up-to-date engine from the ground up (Company History, n.d.).

**General Challenges and Concerns With Legacy System Integration**

As businesses face growth and expansion, they also face the dilemma of integrating older legacy systems with newer technologies as well as web and mobile applications especially in the cloud (Legacy System Integration, 2017). The problem with legacy systems was that they were old and inflexible technologies which were put in place to resolve previous business challenges. Because of their long lifespans, these systems tended to be fragile, obsolete and were difficult to integrate with new cloud and web-based services. However, some

established legacy systems still remain in use to this day by companies because replacement of these systems is extensive and expensive processes (Legacy System Integration, 2017).

Additionally, maintaining older legacy systems is not only costly, it endangers businesses because it prevents further growth and expansion. This is because these systems are unable to provide users access to the latest technologies which makes it difficult to cultivate new businesses and ideas (Legacy System Integration, 2017).

One problem that many companies face is that replacing a legacy system is expensive as well as risky.Many enterprises are concerned with cloud integration security; this is because there is constant exchanging, transferring, and sharing of sensitive data. With Qvera, enterprise integrations are protected. Unauthorized access is blocked and sensitive information is secured (Legacy System Integration, 2017).

**The Ideal Solution**

Qvera offers a robust solution for businesses in the healthcare segment to solve the problem of legacy system modernization.

Qvera offers numerous benefits for its users:

– Low cost, low-risk process

– seamless and painless conversion

– Provides only solution with native 'Patient Not Found' functionality

– Simplifying interface development which provides lowest total cost of ownership

– No vendor lock-in

Qvera offers a seamless integration of modern and legacy systems which solves the problem of old infrastructure while also preparing companies and enterprises for future integration needs. With its simplified integration process and easy to use visual channel editor, which allows customers to visualize the flow of information and makes carrying out interface configurations quick and efficient,

customers can be up and be running within minutes (Legacy System Integration, 2017).

Built on a 21st-century technology stack, it offers features such as auto notification and update of the application, advanced interface monitoring functionality and features (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.)

Additionally, the concept of QIE was built with extensibility in mind. New technologies are constantly being integrated into the product which allows other third-party libraries to be amalgamated into QIE's scripting environment (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.).

**Visual Channel Editor**

The QIE's visual channel editor boils interfaces down to an intuitive VISIO type diagram (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.). This feature makes it simple for occupants in the healthcare segment to understand what is going on and to visualize the flow of data through the interface engine. Due to its simplicity, the visual channel editor drastically reduces interface development time and cost (Silicon Review Names Qvera 10 Fastest Growing Healthcare IT Companies in 2016, 2017).

The visual channel editor for QIE allows channels to be represented graphically as a serious of inter-connected notes. How messages flow through the channel is controlled by the connections between the channel nodes. Channel nodes include: source, condition(s), mapping(s), or destination(s).

**Qvera's Clientele**

Qvera targets clients which are in the healthcare sector; these consist of hospitals, clinics, imaging centers, and labs. Qvera's customers and partners are supported in the United States and the United Kingdom (Driving down the cost of Interoperability in

Healthcare: Qvera, n.d.). Currently, the company is partnered up with several large clients from each sector:

Healthcare Integrated Delivery Network and Hospitals – Baptist Health and Emerson Hospital, Baylor Scott & White

Technology Partners – Unified Imaging, Staywell, Restart

Solution Partners – HDConsult, EHR Integration Services

The Shapiro brothers and Qvera were looking into founding a partnership and reseller agreement with MedAllies, a leading national Direct network providing unlatching expertise in interoperability health information exchange (About, n.d.). By combining Qvera's interface engine with MedAllie's HISP platform, the partnership would be able to provide a completely automated transitions-of-care solution for their customers (New Partnership Announced with MedAllies, 2016).

**Awards and Certifications**

1. Qvera was ranked as the number one interface engine by black book research three years in a row from 2015 (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.).

2. ConCert Certification: Qvera was one of the first of four vendors to receive EHR (electronic health record) certification as well as it was the only company to receive ConCert certification (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.).

3. What is great about Qvera is that it is a 1-product company. This means that the QIE is the company's sole product allowing 100% of the focus to go towards constantly enhancing and providing customers with the most up-to-date functionality. CEO, Sam Shapiro, says: In order to provide the most powerful and flexible engine on the market, we had to focus 100% of our time and energy on this single product. This focus gives us the ability to react quickly to the ever-changing standards and requirements that our customers face and provide them with the tools and functionality they need to

quickly adapt and stay ahead (CIO Review Names Qvera One of 50 Most Promising Healthcare Solution Providers, 2016).

4. CIO Review: In 2015, Qvera was named as one of 50 most promising healthcare solution providers. QIE was deemed to be a "'cost effective' interface engine with 'exceptional usability.'" (Driving down the cost of Interoperability in Healthcare: Qvera, n.d.)

**Future Challenges**

Qvera is focused 100% on developing and making their sole product, the Qvera interface engine, the best interface engine on the market. The future for all platforms including Qvera is to provide the flexibility to create newer, extend, or update models to support evolving data acquisition needs. Additionally, the major challenge faced by platforms such as Qvera is to accomplish meaningful use as well as improve the overall care of patients – and to do this, functional interoperability needs to be improved by seamlessly transferring available data and needs from one source to the next (Biggest EHR challenges for 2018: Security, interoperability, clinician burnout, 2017).

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# 23. ETEPLIRSEN: A CONTROVERSIAL APPROVAL

ETEPLIRSEN: A CONTROVERSIAL APPROVAL

By Cherry Liu

**Background**

It was the spring of 2016, Doug Ingram, CEO of Sarepta Therapeutics, sat on his chair, waiting for the final decision to be made. He knows this is one of the most important moment of his life, and this could be the life and death situation for his company.

Eteplirsen, a drug for Duchenne Muscular Dystrophy (DMD), developed by Sarepta Therapeutics, has been under the spotlight for the past two years. Sarepta first announced the development of eteplirsen back in 2011. As the only drug on the market for treatment of DMD, this has raised the hope of many DMD patients and their family. After 5 years of clinical trials and review processes, eteplirsen finally got approved in 2016. Seemingly an exciting news, but is it really this simple?

On August 25, 2015, Sarepta Therapeutics announced that they have submitted the New Drug Application (NDA) for eteplirsen to the U.S. Food and Drug Administrationm(FDA). FDA completed eteplirsen's filing review and determined that it is permit for a substantive review. FDA also granted eteplirsen Priority Review status, which is offered to drug that is more beneficial than existing therapies.

On February 8, 2016, FDA announced that they would require additional time for the review of NDA for eteplirsen. The FDA pointed out that the major amendment to the NDA has been the 4-year

clinical data submitted in January 8, 2016 by Sarepta, which included the six-minute walk test (6MWT) and loss of ambulation data compared to historical control.

After almost 3 months of reviewing process, on April 25, 2016, FDA conducted the final meeting and the advisory committee voted 6-7 against the approval of eteplirsen, since they did not find sufficient evidence from clinical studies to show that eteplirsen could induce production of dystrophin to a level that is likely to produce clinical benefit. FDA also said that the advisory committee voted against finding substantial evidence from single historically controlled clinical studies which could indicate eteplirsen is effective treatment of DMD. In one additional question, the panel voted 5 to 7 against whether decisions to use the 6-minute walk test were an sufficiently objective measurement to allow for a valid comparison between patients and controls.

On June 6th, 2016, FDA requested Sarepta to provide additional dystrophin data, as measured by western blot that were generated from biopsies, as part of the evaluation of eteplirsen NDA. On June 27th, 2016, Sarepta submitted measured dystrophin data from 13 biopsy samples at both baseline and Week 48 to FDA for further evaluation.

On September 19, 2016, FDA finally approved eteplirsen for Duchenne muscular dystrophy.

**Duchenne Muscular Dystrophy**

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular degenerative disorder that causes severe muscle loss and premature death. The muscle weakness usually starts in the lower limb, and progressively spreading to the arms, neck and upper limb areas. Eventually, breathing failure caused by respiratory muscle dysfunction and cardiac dysfunction can lead to death before the age of 30. At present, DMD is estimated to affect approximately 5000 males worldwide. DMD is caused by a genetic mutation in the

dystrophin gene, which code for dystrophin protein. Dystrophin is responsible for proper muscle integrity and function. At present, treatments for DMD are mostly palliative, aiming to improve the patients' quality of life and delay disease progression. There is no curative therapy available.

Approximately 70% of the mutation are deletions of exons that leads to disruptions of the mRNA reading frame, causing premature termination codons and thus the production of non-functional dystrophin protein. As a result of the lack of dystrophin, muscle weakness usually starts before the age of 6, followed by loss of ambulation by the age of 15.

Becker Muscular Dystrophy (BMD) is a less severe form of muscle dystrophy, which is also caused by mutations in the DMD gene and possess similar symptoms as DMD. However, BMD usually is later onset and progress relatively slowly. This difference is attributed to different types of mutation on the DMD gene: the mutation in BMD does not disrupt the reading frame and thus BMD patients are able to produce partially functional dystrophin protein. Since severity of the disease is driven by the nature of mutation, ideas for potential treatment arises as that induction of exon skipping could potentially correct the reading frame, resulting in production of partially functioning BMD-type dystrophin protein.

**Alternative splicing & Exon-skipping**

Human DNAs are divided into introns and exons, with exons being the coding region of actually genetic materials and introns being genetic noise. Through alternative splicing, particular exons may be included or excluded into the final mRNA produced from that gene, and the introns will be discarded. As a result, the proteins translated from the mRNA will be different based on which exons are included. A genetic mutation could cause deletion of certain exons and thus alter the splicing process, interfere with the rest of gene being assembled.

Using small piece of synthesized DNA called oligonucleotides, it is possible to encourage the cellular machinery to skip an exon.

**Eteliprsen**

Eteplirsen is designed to address the underlying cause of DMD by allowing the production of partially functional dystrophin protein. Using oligonucleotide therapy, Eteplirsen enables the skipping of exon 51 and restoration of genetic mutation, which is shown to affect over 13% of the DMD patient population. This is by far the largest patient population in which single exon skipping is applicable. By skipping exon 51, a truncated but partially functional dystrophin protein can be produced, which significantly slow down disease progression and improve patients' quality of life. Eteplirsen is marked at about $300,000 per patient per year.

**The Clinical Trials**

**[1] Phase I/II clinical trials**

First phase I/II clinical trial was done in 2009. Eteplirsen was administered to 19 DMD patients intravenously, over a dose range of 0.5-20mg/kg/week for 12 weeks. Eteplirsen treatment was found to improve dystrophin expression in 7 of the 19 patients: six given 10–20 mg/kg/week and one given 2 mg/kg/week. Of the seven patients, three responded particularly well, showing an over 10% in dystrophin expression measured by Western Blot. However, the remaining four patients did not give appreciable results, and results from different assays did not agree with one another. Sarepta ascribed the result variability to genetic background differences and suggesting performing an extended clinical trial, as they believed the clinical benefit would only be visible upon prolonged treatment.

**[2] Phase II clinical trials**

Second clinical trial was conducted in 2011 as an extended clinical trial that responded to the shortfall of the last trial. A total of 12 DMD patients were recruited, with 4 patients in each cohort: patients with

30mg/kg/week eteplirsen, patients with 50mg/kg/week eteplirsen and placebo-treated cohort. The results from this study became the basis of FDA's decision. After 24 wees, patients treated with 30mg/kg/week of eteplirsen showed a 22.9% increase in dystrophin measured by IHC, and such an increase was not observed in placebo-treated group. However, since FDA found the IHC method questionable, additional testing was conducted on 11 patient biopsies from all cohorts after 180 weeks posttreatment. The result casted further doubts on earlier results as there was only 17.4% increase in dystrophin. Western blot was conducted to further confirm the study results. Western blot from the 11 patient biopsies showed only 0.93% increase after 180 weeks. As at least 10% of dystrophin increase is needed to translate into clinical benefit, FDA questioned whether the dystrophin level observed was "reasonable likely to predict clinical benefit".

Functional study through 6-munite walk test showed no significant improvement in ambulation for patients treated with 30mg/kg/week after 48 weeks. On the other hand, patients treated with 50mg/kg/week showed significant change after 48 weeks compared to placebo group. Although comparison of the eteplirsen-treated cohorts to historical controls after 3 years showed an improvement in the 6-minute walk test, two of the twelve patients actually lost ambulation during the study period. And thus FDA concluded that the action of eteplirsen was not sufficiently effective to yield clinical benefit.

**The controversial approval**

On September 19th, 2016, FDA decided to ignore the decisions from the advisory board and granted eteplirsen approval. The approval arose a major debate: "This drug is approved on the skimpiest, most pathetic data I've ever seen. It is going to set a precedent that is very uncomfortable," Diana Zuckerman, president of the National Center for Health Research said. Others who were happy about the approval also stated their reasons: The only two potential near-term treatment

for this disease were dismissed out of the hand by FDA earlier this year. If eteplirsen is rejected, DMD patients would have nothing on the market for this disease. Although it is a long shot, eteplirsen is still better than nothing. During eteplirsen's review process, hundreds of DMD activists descended on the FDA panel review, looking to put maximum amount of pressure on the reviewing committee. "Patients are crying out for the FDA to hear them: they are engaged and knowledgeable and only want the agency to do what is already in their power," wrote senators Dan Coats and Ron Johnson in a letter to the FDA.

However, many people stated that although eteplirsen is the only drug on the market that is proven to provide some clinical benefit, more clinical research is needed to prove its safety and efficacy, especially considering the price tag. Sarepta has announced that eteplirsen will cost ~US $300,000 a year on average, with the price varying depending on patient weight. The price seems reasonable for a rare disorder, but whether patient should spend so much on a drug with disputed efficacy is questionable. "Eteplirsen is indeed a landmark achievement for the DMD community. However, stronger evidence of efficacy is undoubtedly required to prove its place as a viable DMD therapeutic."

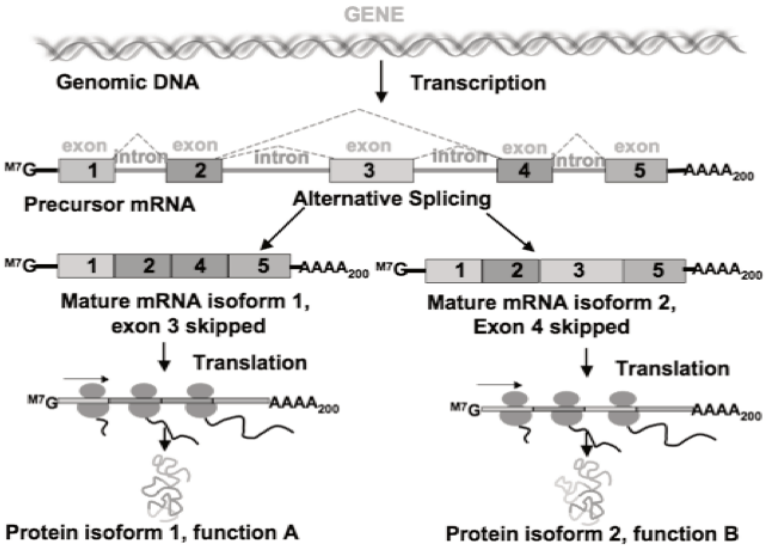
"The FDA's job is to get drugs out on the market that are proven safe and effective," bioethicist Art Caplan at New York University Langone Medical Center said. "In this case, there simply were not enough data in place from the corporate sponsor to make that possible. At the same time, companies shouldn't be deluding patients and families into thinking that they have enough data to go to the FDA. They shouldn't approach the FDA unless they truly have the available data to get approved. Relying on patient testimonials and lobbying is not the path to drug approval."

On the other hand, although much investment has been made in eteplirsen, it is only applicable to a highly specific subset of DMD

patients, as only ~ 13% of the DMD patients are amenable to exon 51 skipping.

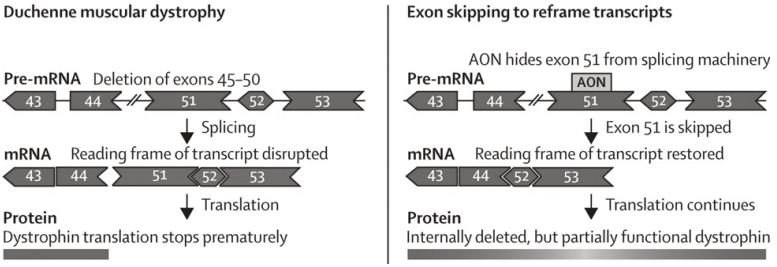
Some has also stated that the approval is not only bad for the patients, but also a major hit to Sarepta. Since eteplirsen is approved after a negative advisory committee panel review and rejection by regulators in the internal review, Sarepta could face a backlash from the industry as the approval is based on a deeply flawed 12-patient study. However, Sarepta believed in its drug and has stated that they does not want to stop at Eteplirsen as its one and only approval, and be forever the "controversial biotech company." The CEO of Sarepta, Doug Ingram, said to one of the reporter: "We think Exondys 51 is fantastic," Ingram said, "but it's part of a journey. We have some very lofty aspirations: We want to treat as close as we can to 100% of children with DMD and extend and improve their lives."

**Exhibit 1.** Alternative splicing



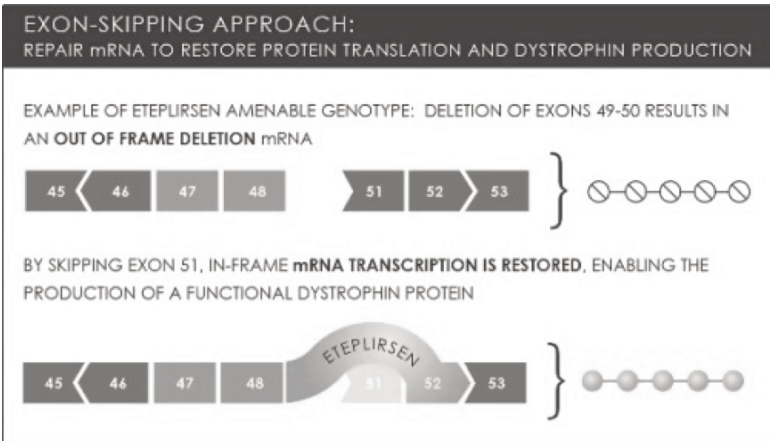
Source: Image retrieved from https://bitesizebio.com/10148/what-is-alternative-splicing-and-why-is-it-important/

**Exhibit 2. Genetic mutation of Duchenne Muscular Dystrophy**




Source: Image retrieved from: http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(09)70229-7/fulltext

**Exhibit 3**. Exon-skipping technology of Eteplirsen




Source: Image retrieved from: http://femscinerd.tumblr.com/post/

58964555523/combined-therapy-could-repair-and-prevent-damage

**Glossary**

**DNA** Deoxyribonucleic acid is nucleotides that carry genetic information in all living organisms

**mRNA** Messenger RNA is molecules that convey genetic information from DNA to ribosome

**Gene** A gene is part of the DNA that encodes function

**Exon** Portion of the gene that encode the mature RNA product that are eventually translated into protein products

**Intron** Portion of the gene that is not coding for genetic material and ultimately being removed during the splicing process

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# 24. KORSUVA: The Decisions Cara Therapeutics INC. made to Potentially Revolutionize Pain and Pruritus Relief

KORSUVA: The Decisions Cara Therapeutics INC. made to Potentially Revolutionize Pain and Pruritus Relief

**By: Luka Mihailovic**

When the creative team of Dr. Derek Chalmers, Dr. Frederique Menzaghi and Dr. Michael Lewis founded Cara Therapeutics Inc. in Stamford, Connecticut, in 2004, they created a company that would eventually be amongst some of the most promising young biotech firms of the early 21st century [1]. They centered this company on the development of a novel opioid-receptor acting painkiller that had the potential to provide the benefits of conventional opioids, without the risk of negative side effects and the possibility of abuse and addiction. This drug was developed as CR845 with the trade name KORSUVA and in 2018 it was in different phases of clinical trials in three main sectors; acute pain relief, chronic pain relief, and pruritus (severe itching) **(Figure 1)**. The results of these trials have shaped the decisions Cara has had to make moving forward in terms of which routes to take with KORSUVA, boiling down to which pipelines should they have continued to fund. Only over the past couple years, in 2017 and 2018, Cara has been forced to execute these critical decisions. Which of these sectors should Cara have devoted most of their focus to? Which areas should they have ignored altogether? And finally,

were there alternative routes, such as potential partnerships Cara could have taken to improve the development of their drugs?

**Significance of KORSUVA**

Optimizing Pain relief was one of the bigger challenges facing the field of medicine over the last couple decades. This is due to the fact that although we had effective drugs to treat pain, many of them belonged to the opioid family and thus came with a high risk of addiction as well as a variety of negative side effects. These drugs, such as morphine, codeine and oxycodone, were commonly prescribed to treat pain, mainly acute or temporary pain associated with soft tissue damage. This often occurs after surgery or through injuries and disease. They could also be used to treat chronic pain however they were used cautiously due to the fact that the benefits they could provide were outweighed by a number of harmful side effects. These included nausea, vomiting, sedation, constipation, and drowsiness [2]. In some cases respiratory problems occured, as well as analgesia, which is an increased sensitivity to pain. However, one of the larger issues associated with opioids was the possibility of addiction and dependence. The National Institute on Drug abuse had projected that somewhere between 26 and 36 million people abuse opioids worldwide in 2017. In the U.S. alone this was around 2.6 million people [3]. One might think that illegal drugs like heroin would make up the majority of this statistic, but the same article noted that an estimated 450,000 people in the United States were addicted to heroin to contribute, while 2.1 million cases involved prescription drug abuse. There were more than double the amount of deaths from opioid abuse annually in 2017 than in 2002 [4] **(Figure 2)**. This was clearly a major global issue that was only becoming worse with time. Steps were being taken to find better alternatives but there were also approaches targeting the way these drugs act. What if there was a drug that could alter how these opioids affected our bodies?

These opioids function through interactions with 3 main opioid

receptors. The opioids used today target Mu receptors that are located in the central nervous system, such as in the spinal cord and brain. This is what was believed to cause the negative side effects associated with these drugs, but was also the probable cause of addition development. There are however, other receptors located in the peripheral nervous system called kappa receptors that can potentially induce pain relief without these negative effects [1]. KORSUVA was developed by Cara as the first kappa opioid receptor agonist (KORA). This drug has high affinity towards these kappa receptors while ignoring the Mu receptors found in the central nervous system. This was attributed in part to the fact that KORSUVA is very poor at penetrating the blood-brain barrier. Thus KORSUVA has the potential to provide the benefits of traditional opioids such as acute and chronic pain relief, and anti-pruritus, without the myriad of negative side effects that usually come with these drugs.

**Financial Situation**

As of January 2018, Cara had not generated any profits from the direct sale of its products, and had been in a consistent state of research and development through clinical trials. Cara themselves have stated in a 2017 financial report, that they do not expect to generate revenue in the next several years. The only revenue they had generated to date had come from upfront licensing fees to other companies as well as milestone payments from these companies such as through completion of different phases of clinical trials of their licensed drugs. One of these companies was Maruishi Pharmaceutical Co., Ltd, that had paid a license fee of $15 million to research and develop KORSUVA in Japan as well as providing the possibility of up to $10.5 million in regulatory and clinical milestones. As of February 2018, Cara had received $3 million in these milestone payments. As part of this agreement Maruishi had also obtained 842,105 shares of Cara for another $8 million. Another company called Chong Kun Dang Pharmaceutical Corporation (CKDPC) had a similar agreement with Cara paying a $600,000 upfront license fee, up to $3.8 million

in milestones, and purchasing 69,444 shares for $400,000. These collaborations had contributed to Cara's total revenue as of February 2018 of $5.2 million [5].

Like most drug companies in clinical trial stages, Cara was in a state of consistent net loss. In the end-of-year financial report released in January 2018, they reported a net loss of $57.3 million in 2016 and $58.1 million in 2017 [5] **(Figure 3)**. This was due to the fact that they were still in the phases of research and development of their products. Research and development contributed $48.6 million in expenses for 2017 **(Figure 4)**. In total they had reached a deficit of $220.3 million. This was typical of a starting drug development company and the share price of 11.89 USD in March 2018 was relatively the same as it was in 2014 (12.9 USD). However these shareholders would eventually need to see a return on their investments and a shift in this direction would be reflected by positive data from clinical trials. Cara could not continue to fund all of their pipelines for KORSUVA using investor money on their own and they needed to make critical decisions about the future focus of their company. This involved careful analysis of the markets and efficiency of their pipelines for KORSUVA in terms of acute and chronic pain and pruritus treatment to determine which of these to continue funding and which to discontinue.

**Pain Relief Pipeline**

The treatment for pain management was generally linked to the intensity of pain the patient was suffering from. Mild to moderate pain was treated mainly through the use of non-steroidal anti-inflammatory drugs (NSAIDS) such as Advil or Tylenol. Mu opioids such as Oxycodone were only prescribed in patients suffering from moderate to severe pain, however in this area they were the only effective drugs to treat these conditions. This resulted in Mu opioids making up a huge portion of total prescription drug classes in 2017. IQVIA, a company devoted to providing medical data to companies involved with healthcare, stated that in 2017, the total market in

the United States for analgesics (pain relief drugs) was $45.5 billion which translated to 406 million prescriptions written in just that year. Opioids were a part of 53% of these cases and contributed to $6.9 billion in sales of 2017 [5] **(Figure 5)**. These cases are made up of acute pain, usually following surgery or injury and chronic pain.

**Acute Pain**

The International Association for the Study of Pain reported in 2017 that there were approximately 53 million outpatient surgeries, meaning immediate release after procedures, and 46 million inpatient surgeries, requiring overnight postoperative care. These cases involved 234.3 doses of IV injections of opioids including morphine, fentanyl and hydromorphone. This was a huge market that was dominated by a competitor with known flaws that potentially did not exist in KORSUVA. Those conventional opioids contributed in large part to 2 main postoperative symptoms that developed in patients that were given IV and oral Mu opioids. One was postoperative opioid-induced respiratory depression (POIRD) and the other was postoperative nausea and vomiting (PONV). The Journal of Anesthesiology News had reported that POIRD can occur in 29% of patients even if they show no other signs of ongoing symptoms. Another journal called the Best Practice & Research Clinical Anaesthesiology had reported that PONV can occur in 33% of patients given Mu opioids [5]. Both of these conditions were not only detrimental to the patients that experienced them, but also resulted in lengthened postoperative care and therefore increased hospital expenses. PONV was attributed to approximately $1 billion in postoperative healthcare costs. This again, represented how much expenses could be saved through the use of KORSUVA.

Now, the market for acute pain was huge, and KORSUVA had the potential to introduce itself as a serious competitor to conventional opioid analgesics, however in order to determine whether it was worth continuing funding of this postoperative pain management route, the efficacy of KORUSVA as well as its addition potential had to

be evaluated. KORSUVA proved highly effective in pain management in phase 1 and phase 2 clinical trials of 970 patients. Patients noted increased pain relief without any significant negative side effects other than increased urine output and slight facial tingling in some patients. This led to the initiation of phase 3 clinical trials of IV KORSUVA as analgesic in postoperative patients who underwent a variety of different abdominal surgeries in June 2017. 450 Patients were given two different does of KORSUVA (1.0 ug/kg and 0.5 μg/kg I.V.), as well as a placebo and were monitored and asked to score their levels of pain relief. This study is still going on and results were expected to be released in 2018 during the second quarter. The results of this study were critical. The U.S. Food and Drug Administration (FDA) had granted KORSUVA in IV form "breakthrough designation". This means that if these phase 3 trials proved to be effective, the FDA would improve and speed up the chances for approval. The FDA was notorious for strict regulation and analysis before they approved a potential drug. Tufts Center for the Study of Drug Development had estimated that the average cost of getting a new drug approved by the FDA was around $2.6 billion [6] **(Figure 6).** This was still much higher than the approximate $350 million Cara had spent so far on developing KORSUVA in all of its pipelines. Granted, they still needed funding for the completion of phase 3 trials before approval, but this was still much lower than the average cost. Therefore Dr. Derek Chalmers and his board of directors decided that this pipeline, using KORSUVA in IV form to treat postoperative pain was the main sector the company should devote its focus to.

An increase in funding of $12.1 million was devoted to this phase 3 trial as well as additional funding for a human abuse liability (HLA) trial to demonstrate the absence of abuse potential in patients given KORSUVA. Patients undergoing postoperative care were given KORSUVA and others were given the opioid pentacozine. Pentacozine is a Schedule IV drug that is much less addictive than common

opioids such as morphine. Patients were asked to score the 2 drugs in sections such as "over liking of the drug", "feeling high", and "possibilities of continual use". The study found that KORSUVA ranked much lower than this already less addictive drug. This study helped to launch KORSUVA into phase 3 trials, put it into the FDA radar, and increase the focus of the company into this area [5]. The company also decided that they would implement a sales team to market KORSUVA to hospitals across the U.S. following FDA approval. They have set the size of this team to 80 individuals to extend to a major portion of the physicians. They have also stated that they plan to organize a group of medical liaison officers and an underlying infrastructure as a foundation for marketing of KORSUVA.

**Chronic Pain**

Another potential target market for KORSUVA was as a chronic pain management analgesic. Long-term pain was mainly caused from injuries through accidents and the majority of cases involved lower back pain. These cases are usually treated with long-acting opioids such as oxycodone (Oxycontin) and hydrocodone or drugs that combine these opioids with NSAIDS such as Percocet and Vicodin. These drugs were usually taken by patients outside of the hospital setting and therefore oral formulations were more feasible than IVs. These NSAIDS were gradually being replaced by standalone Mu opioid agonists due to increased public awareness of liver toxicity issues associated with the common NSAID acetaminophen (Paracetamol), as well as FDA placing a requirement of warnings of possible cardiovascular complications on NSAID packaging in July 2005. However, similar to the cases of acute pain management, albeit to a greater degree due to long-term use, these Mu opioids still carried the potential for adverse negative side effects and the development of addiction. In addition to this, long-term use of these drugs could lead to the development of tolerance and therefore the need for continual increased doses and an amplification of those detrimental properties. In 2013, the FDA announced the implication

of a brand new set of safety labeling on opioid products as well the requirements of safety studies after drugs have been placed on the market in addition to before [7]. The DEA also regulates the security and distribution of most of these Mu opioids through the Controlled Substances Act. Therefore, if KORSUVA gained FDA approval for chronic pain treatment as well, and can bypass these regulations by proving the absence of the negative properties associated with Mu opioids, it would establish itself as a major player in chronic pain management.

This led to the development of an oral formulation of KORVUSA in a pipeline for chronic pain treatment, specifically running clinical trials in patients suffering from osteoarthritis that was expected to show huge promise. A Phase 2b trial was conducted in 2016 in which 476 patients with osteoarthritis in their hips and/or knees were given varying doses of KORVUSA in tablet form (1.0 mg, 2.5 mg and 5.0 mg) and asked to evaluate their pain relief. This trial however, generated the first negative results for KORVUSA as a pain medication. Only patients suffering from hip osteoarthritis (OA) and only those who received the strongest 5 mg doses noted a significant increase in pain relief. This resulted in a decrease of Cara Therapeutics stock by 40% on the day the trial data was announced. However this data showed that KORVUSA may still have potential to treat OA of the hip, but a new Phase 2b trial must be conducted with new dosage parameters and a focus on patients suffering chronic hip pain only.

Even though this oral KORVUSA pipeline to treat chronic pain has the potential to generate the most revenue post-commercialization, Cara came to the conclusion that they could not afford to devote more time and resources into this area on their own. They announced in the financial report for the 2017 fiscal year that they plan to seek partnerships with companies revolving around the chronic pain market in order to finance further pursuit into this sector. They would instead focus on the acute pain management pipeline if the

Phase 3 clinical trials proved successful, as well as the thirds potential market, for anti-pruritic medication.

**Anti-pruritic Pipeline**

The final pipeline Cara was involved with was in the field of anti-pruritics. These drugs were designed to alleviate intense itching that comes as a symptom of a variety of diseases. Itching was known to come from the release of substances called pruritogens from various peripheral cells of the body including some immune and nerve cells. Interestingly, it seemed that these cells regulated the release of these compounds through the same opioid receptors responsible for pain relief in traditional opioids; the mu opioid receptors. This was why prolonged opioid use such as through heroin addiction often led to increased itching in individuals. Now, the activation of kappa receptors through a drug like KURSOVA could counteract the effects of Mu receptor activation to relieve itching sensations.

According to IQVIA approximately 45 million Americans were diagnosed with an illness that pruritus as a symptom in 2013. Some form of treatment designed to act against pruritus was prescribed to 47% of these people. This added up to about 21 million prescriptions. There were also cases of uremic pruritus coming from patients on dialysis from diseases such as chronic kidney disease. Fresenius Medical Care, a healthcare company devoted to patients on dialysis projected that, in 2016, around 3 million people around the world were on some form of dialysis treatment and approximately 70% of them experienced renal or uremic pruritus [5]. Therefore these numbers showed Cara that this was obviously not as big a market as that for analgesics, but it was still a sizeable number of potential consumers. There were also no FDA approved drugs to treatment this condition and management was done through attempts to alleviate symptoms. There was also only one truly viable competitor (although this competitor was also not FDA approved) made by a company called Toray Industries called Remitch, however it was both a kappa receptor agonist and a mu receptor agonist. It therefore had the

potential to reduce itching in some areas and trigger it in others. It was also known to have the ability to cross the blood brain barrier and induce other negative side effects. Other treatments of pruritus included anti-depressants, anti-histamines and corticosteroids, but these too varied in their actual effectiveness from patient to patient. Cara had to examine effective was KORSUVA at treating these patients. Would it show the same huge promise as in acute postoperative pain management, or would it fail as the oral chronic pain form did?

KORVUSA had a very successful phase 2 trial in June 2016. Patients suffering from uremic pruritus were given KORSUVA injections as well as placebo and asked to rank their scores in terms of reduction of itching. These 174 patients actually experienced on average, a 68% reduction in overall itching. When given IV KORSUVA there was a 100% greater reduction in itching [5]. These results were very promising and led to the initiation of a phase 3 clinical trial in January 2018. 350 patients on hemodialysis as a result of being diagnosed with chronic kidney disease will be monitored over a 12 week period of treatment to evaluate the efficacy of KORSUVA [5]. These results will determine the steps Cara will take going forward in the anti-pruritic market and the expectations are very high.

**Final Decisions Going Forward**

There were many ups and downs on the road Cara took to establish itself in the anti-pruritic and pain relief market. They recognized that although their breakthrough drug KORSUVA had the potential to treat a variety of cases through different pipelines, as a young company they did not have the foothold and finances to back every single one. They had to make key decisions about how to handle each of their pipelines. Cara recognized that the market for pain management was massive and they had a product that had something every possible one of its competitors did not. They had a drug that could alleviate pain, without possible negative side effects or addiction potential. Initially this was the main focus after the

discovery of KORSUVA. They run the drug through clinical trials for both acute pain and chronic pain management, however they could not afford to continue both after their chronic pain pipeline proved that it needed further modification to continue. To address this, Cara will be seeking further partnerships or to license out their products for further testing by other companies such as Maruishi. This will allow them to focus on their successful acute pain pipeline on their own, a path that is currently under phase 3 trials and is generating high expectation. However, because their drug also functioned as an opioid, even if it passed every clinical trial and moved on to commercialization, it would still most likely be under strict FDA regulation. They could not afford to devote all their resources into pain management and found that KORSUVA can actually act on kappa receptors to act as an anti-pruritic. This led to even further pursuit into this new direction. Cara finally decided to devote the majority of its time and resources to two major sectors; using KORSUVA an analgesic for postoperative care and as an anti-pruritic in patients suffering from chronic kidney disease and on dialysis. They did this through careful analysis of both the markets in these sectors as well as the efficacy on their drugs. Cara Therapeutics has huge potential to assert itself in these markets as a provider of the first solely kappa opioid receptor agonist to provide a revolutionized form of pain relief without detrimental effects.

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**Exhibits**

Exhibits for Cara Case study

# 25. How Important is Privacy? – A Case on AncestryDNA

## How Important is Privacy? – A Case on AncestryDNA

BIOT 6610

Madison Veperts

It was an unusually cold December day in Lehi, Utah, United States, as Tim Sullivan, President, and CEO of AncestryDNA picked up the ringing phone. He was in a relatively good mood after having found out the total revenues for the year of 2014 were 619.5 million dollars ("Ancestry.com LLC Reports Fourth Quarter and Full Year 2015 Financial Results | Ancestry Corporate," n.d.). Unfortunately, this was not a pleasant phone call and his mood would change quite drastically. The police were on the other line with a warrant to seize the name of a customer of AncestryDNA (Rybak, n.d.). They had used one of Ancestry's public databases to search for a match of DNA that was found at a crime scene (Rybak, n.d.). Tim had no choice, but to hand over the name of Michael Ursy to the Utah police department (Rybak, n.d.).

After becoming the CEO of this company in 2005, Tim never thought it would ever come to this. When he first became the CEO, AncestryDNA had just opened a new head office with more than 700 employees ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). Their main focus was to connect family members and create genealogy family trees ("AncestryDNATM | DNA Tests for

Ethnicity & Genealogy DNA Test," n.d.). As technology started to improve and DNA sequencing of humans became something of the present and not the future, Ancestry started to move towards connecting people through genetics rather than surnames. It all started with the purchase of acquiring the DNA collection of GeneTree in 2012 (Genealogist, n.d.). GeneTree was the commercial arm of Sorenson Molecular Genealogy Foundation (SMGF), an independent DNA and genealogical research institution with a goal of demonstrating how the peoples of the world are related (Genealogist, n.d.). SMGF had collected more than 100,000 DNA samples that were donated from people around the world (Genealogist, n.d.). A year after that, they purchased the records of a South African genealogy website called Ancestry24 ("Ancestry.com | Ancestry 24," n.d.). From this company, they had received more than four million South African records ("Ancestry.com | Ancestry 24," n.d.). With these purchases, they were able to build a large enough database to start connecting family members by DNA and called this AncestryDNA.

AncestryDNA worked by having the customer send in a saliva sample done by spitting into a test tube ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). They then take this sample and analyzed it for more than 700,000 markers ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). These are known as genetic markers and are genes or DNA sequences that are well known (Elliott & Brodwin, 2002). People have many distinct genetic markers and together they can be thought of as a genetic fingerprint (Elliott & Brodwin, 2002). Every person has a different genetic fingerprint, but there are some genes within this genetic fingerprint that are common amongst everyone, as well as ones that are identical amongst family members (Royal et al., 2010).

The saliva samples sent in by the customer contain their DNA and a genealogical DNA test can be performed on it. From the beginning of

their testing, Ancestry used three different types of genealogical DNA tests, autosomal, Y-DNA, and mtDNA ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). The autosomal test looked at chromosomes 1-22; these are chromosomes that are inherited from both parents and all recent ancestors (Royal et al., 2010). This test also looked at the X-chromosome. This chromosome is used to follow a special inheritance pattern from paternal mothers (Royal et al., 2010). The Y-DNA test is done for just men since men have both a Y and an X chromosome, where woman have two X chromosomes (Royal et al., 2010). This DNA test looked at what is inherited from father to son to see a direct parental line. The final test Ancestry used was mtDNA. This test looked at the mitochondrial DNA, which is inherited from mother to child (Royal et al., 2010). This test can be done on both male and female and is used to determine the direct maternal line (Royal et al., 2010).

The autosomal DNA test had been used to determine ancestry from up to 3 times great-grandparents (Royal et al., 2010). It is known that half of a person's chromosomal DNA comes from each parent and so on and so forth. With this knowledge, a quarter of that persons DNA is from each grandparent and an eighth of their markers from each great-grandparent (Royal et al., 2010). After this, the inheritance becomes more random and unequal from more distant ancestors (Royal et al., 2010). AncestryDNA wanted to also look at a special path of inheritance and this was done using an X-chromosome DNA test. A female receives the only paternal X-chromosome since males only have one (Via, Ziv, & Burchard, 2009). That paternal male had to have received that X-chromosome from their mother since they received the Y from their father (Via et al., 2009). Therefore, this test can help show specialized inheritance for females. Another special path of inheritance AncestryDNA was testing was the mitochondrial DNA. Each person's mitochondria is inherited just from the mother (Via et al., 2009). This means that none of the DNA of the mitochondria

comes from the paternal side. This test, therefore, looks at the inheritance of the maternal side (Via et al., 2009). This can be done on both male and females. The final special path of inheritance is the Y-chromosome test and as mentioned above can only be tested on males and not females (Via et al., 2009). This test looked at the male line of lineage since each male passes on their only Y chromosome to their son. For a woman that wishes to see their direct paternal DNA lineage that goes further than just their father, they can ask a male in their family to take this test (Via et al., 2009).

Each of these tests is performed by a DNA sequencing machine called Illumina ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). This machine sequences are known variants of the genome at a particular location known as single-nucleotide polymorphisms (SNPs) ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). There are more than 700,000 SNPs in each person, but AncestryDNA only needed those 700,000 and therefore programmed the Illumina machine to only sequence the areas of the chromosome that they needed ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). AncestryDNA then used the data they acquired from this machine and compared the results to their large database. They compared the results by looking at how many SNPs are shared with a person ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). Each person has a different length of SNPs and the lengths are compared. The closer in length a person's SNPs, the closer they are related ("AncestryDNATM | DNA Tests for Ethnicity & Genealogy DNA Test," n.d.). This was how AncestryDNA created genealogy trees and connected long-lost relatives.

They had not just connected long-lost relatives; they had also created a public database of DNA that was searchable by anyone, this included the police (Chia, 2016). About 20 years ago in 1996, Angie

Dodge was raped and murdered in her own apartment in Idaho Falls, Idaho at just 18 years of age (Rybak, n.d.). The police arrived at the scene of the crime and found her brutally murdered and stabbed 14 times and left half-naked (Rybak, n.d.). There were no signs of rape, but the killer had ejaculated leaving behind a semen sample (Rybak, n.d.). This semen sample provided excellent DNA evidence. Unfortunately, the police were never able to find a match of this DNA (Rybak, n.d.). They did, however, manage to get a confession from Christopher Tapp. He admitted to being present during Angie Dodge's murder and told the police that he held her down while his friend, Mike, stabbed her (Rybak, n.d.). When the murder went to trial, he pleaded "not guilty" and his lawyer had tried to fight the charges saying the DNA left at the scene of the crime did not match Christopher Tapp's (Rybak, n.d.). The jury still found him guilty of the crimes of first-degree murder and rape and was sentenced 30 years to life in prison (Rybak, n.d.).

Fast forward to the present of December of 2014, due to the recent advancements made on DNA technology, the case of Angie Dodge had been reopened (Koerner, n.d.). The police believed that they could use this new technology along with Ancestry's public database search to find a match of DNA, and they did (Chia, 2016). They got a warrant and received the name of Micheal Ursy from AncestryDNA that matched the semen sample left at the scene of the crime (Rybak, n.d.). After further investigation, they believed Michael Ursy to not fit the description and age of this unknown killer, but they did find out he had a son (Rybak, n.d.).

Michael Ursy had donated his DNA to his church that was helping the Sorenson Molecular Genealogy Foundation (Rybak, n.d.). He had no intention of his DNA ever becoming a public searchable thing. After Ancestry bought GeneTree that owned SMGF, they now had all rights to their data to do what they pleased with it (Genealogist,

n.d.). Imagine Michael Ursy Jr.'s surprise when the police knock on his door and tell him they have a warrant to take him in for questioning on a murder that happened almost 20 years ago. He was even more surprised that they found him through AncestryDNA, something he had never heard of before or used (Rybak, n.d.). The police had questioned him and taken a sample of his DNA to do their own more accurate test (Rybak, n.d.). Fortunately for Michael Ursy Jr., the results came back negative and there actually was no match in the DNA left at the crime scene and he was released as a suspect (Rybak, n.d.). This may have been the end of the problems for Michael Ursy Jr., but for the CEO of AncestryDNA, Tim Sullivan, they had just begun.

News articles were written with titles such as, "DNA sample given to Ancestry.com leads to arrest in murder case", "Your relatives DNA could turn you into a suspect", "How safe is your DNA", and "Ancestry.com takes DNA ownership rights from customers and their relatives" (Blythe, 2015). None of these titles or articles had a positive message about AncestryDNA. There were various websites that reported that Ancestry.com had released the identity of the donor without a warrant (Blythe, 2015). This was untrue, but these websites had continued to snowball slandering AncestryDNA's name. Not only were these negative news reports hurting AncestryDNA's reputation, they were also causing people to look more closely at their privacy policy (Koerner, n.d.).

People did, in fact, find some suspicious things amongst the privacy policy of AncestryDNA. Some of the more controversial issues within the privacy policy of AncestryDNA were being written about in news articles online. For example, ThinkProgress wrote an article titled "Ancestry.com takes DNA ownership rights from customers and their relatives". In this article, they reveal that by submitting DNA to AncestryDNA, the person has agreed to "grant AncestryDNA and the Ancestry Group Companies a perpetual, royalty-free, world-wide,

transferable license to use your DNA, and any DNA you submit for any person from whom you obtained legal authorization as described in this Agreement, and to use, host, sublicense and distribute the resulting analysis to the extent and in the form or context we deem appropriate on or through any media or medium and with any technology or devices are now known or hereafter developed or discovered", (Winston, n.d.). Meaning they have the entire right of your DNA to exploit your genetic information. The customer who had given AncestryDNA their DNA still owns their own DNA, but so does Ancestry.com (Winston, n.d.).

Another controversial issue that was in AncestryDNA's privacy policy was that the personal "information derived from processing your DNA Sample through genomic, molecular, and computational analyses using various technologies, such as genotyping and whole or partial genome sequencing. Genetic Data is broader than just the results delivered to you when you use the AncestryDNA test and includes a range of DNA markers such as those associated with your health or other conditions", (Winston, n.d.). With this information "Ancestry.com warms customers, it is possible that information about you or a genetic relative could be revealed, such as that you or a relative are carriers of a particular disease. That information could be used by insurers to deny you insurance coverage, by law enforcement agencies to identify you or your relatives, and in some places, the data could be used by employers to deny employment", (Winston, n.d.). In Canada, there is a Genetic Non-Discrimination Act that grants Canadian citizens the legal right to refuse to undergo a genetic test, that it is prohibited for any person to require an individual to undergo a genetic test as a condition of providing goods, or entering a contract, as well as disclosure of results to employers or insurance agencies (Branch, 2017). Unfortunately, the U.S. had no such laws and Ancestry may provide information to employers or insurance companies.

With all of this information surfacing, Tim Sullivan had to make some drastic changes to the company. In 2014 after all these reports were being published, he decided to first shut down the public SMGF data search of DNA (Blythe, 2015). If anyone tried to find the website, they would see this message (Blythe, 2015):

"We regret to inform you the site you have accessed is no longer available.

Sorenson Molecular Genealogy Foundation (SMGF) was founded in 2000 with the philanthropic goal of helping connect mankind. It was the organization's goal through the sharing of genetic data, to show how the similarities we possess are greater than our differences. The site was created in the spirit of openness and it is in that spirit AncestryDNA purchased the DNA assets from SMGF to further its mission and support the intentions on which it was founded. Unfortunately, it has come to our attention the site has been used for purposes other than that which it was intended, forcing us to cease operations of the site.

We understand the site has been a helpful resource for genealogists and plan to advance the original vision of Mr. Sorenson by continuing to develop tools like ethnicity estimates, matching, DNA Circles, and New Ancestor Discoveries, which are connecting mankind. There are no plans to destroy the DNA that was contributed but have no plans to make the service available in the future.

Ancestry is committed to helping people understand their family's unique story and through AncestryDNA, make new discoveries about their family's past and cultural roots. Like the original founders of SMGF, Ancestry also believes one can have a better understanding of who we are and where we come from. Through our continued work

on family history and DNA, we will encourage the same mission of SMGF in hopes of making the world a smaller, more relatable place.

If you have any concerns, complaints, or questions about the SMGF study, or wish to withdraw consent to participate in the study, please contact AncestryDNA at:

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Member Services
1300 W Traverse Parkway
Lehi, Utah 84043
memberservices@ancestrydna.com
1-800-262-3787 or fax to 801-705-7001"

It was 2017 now and articles were still being published about the murder case that involved their data search as well as their privacy policy. This was unacceptable to Tim; he knew Ancestry needed to make big changes to stop this bad publicity. He knew the only thing that would solve this would be to change the privacy policy. As of December 2017, four years after his phone rang with the police on the other line, the policy changed ("Website Privacy Statement – Ancestry.ca," n.d.). They now do not share "your individual Personal Information (including your Genetic Information) with third-parties without your additional consent other than as described in this Privacy Statement. In particular, we will not share your Genetic Information with insurance companies, employers, or third-party marketers without your express consent", ("Terms and Conditions – Ancestry.ca," n.d.). However, if Ancestry "or its businesses are acquired or transferred to another entity (in whole or part and including in connection with any bankruptcy or similar proceedings), we will share your Personal Information with that entity. The promises in this Privacy Statement will apply to your Personal Information as transferred to the new entity", ("Terms and Conditions

– Ancestry.ca," n.d.). Currently, Ancestry is partnered with Calico, a company focused on longevity research and therapeutics (Bergen, 2015). This company has full access to the entire proprietary database of Ancestry.com (Bergen, 2015).

Ancestry also states that they "may hold records that contain your Personal Information that we are obligated to maintain as archives. Please direct any request to remove information from linked archival records to the responsible archival entity. We will consider requests for removal of Personal Information from the searchable indexes of the records we hold on a case-by-case basis and will endeavour to fully respect your requests to remove Personal Information. Additionally, some of your Personal Information may be included in other Ancestry members' family trees, which will only be removed if the other Ancestry member deletes it", ("Terms and Conditions – Ancestry.ca," n.d.). If the user chooses to delete their data from Ancestry, it will still be stored in their backup systems. "If you request that Ancestry delete your DNA Data, we will delete all Genetic Information, including any derivative Genetic Information (ethnicity estimates, genetic relative matches, etc.) from our production, development, analytics, and research systems within 30 days. To request the destruction of your biological samples, you must contact Member Services", ("Terms and Conditions – Ancestry.ca," n.d.). Once Ancestry deletes the users' data, it will persist in their backup systems for up to 6 months before it is overwritten. Their privacy policy was not perfect, but there had been a major improvement since 2014.

Despite all the negative press, the company managed to continue to increase revenue and grow its subscriptions and users. By 2015, the total revenues had increased 10.3% year over year ("Ancestry.com LLC Reports Fourth Quarter and Full Year 2015 Financial Results | Ancestry Corporate," n.d.). They sold over one million DNA test kits,

which was more than double the previous year and managed to grow their subscription base by 150,000 more users ("Ancestry.com LLC Reports Fourth Quarter and Full Year 2015 Financial Results | Ancestry Corporate," n.d.). By 2016 they managed to increase their first quarter revenues up 19.4% year over year and 21.2% on constant currency basis ("Ancestry.com LLC Reports First Quarter 2016 Financial Results | Ancestry Corporate," n.d.). Their subscriptions had also increased by 7% compared to the previous year ("Ancestry.com LLC Reports First Quarter 2016 Financial Results | Ancestry Corporate," n.d.). As shown in exhibits 1-8 of the Appendix.

Even though Tim Sullivan was able to grow AncestryDNA through the negative press, in late 2017, just after the privacy policy had been changed, he decided to step down as CEO ("Ancestry CEO Tim Sullivan Stepping Down | Ancestry Corporate," n.d.). It was unclear the reason why he would step down while the company's performance was so strong. It may have just been too much work trying to turn the company's reputation around. Either way, he seemed to have put a stop to the negative press and fixed the privacy issues… for now. The public concern for their privacy is only continuing to increase ("Survey Report," n.d.). With new reports of social media platforms changing their privacy issues and releasing sensitive information, citizens are becoming more aware of how important privacy is ("Top 5 Concerns To Focus On For Data Privacy Day," n.d.). Ancestry's privacy policy had improved, but there are still some very obvious loopholes. With that being said, there may be more issues that come to light and it is best they close those loopholes before something major happens. Everything may be great now, but maybe Tim Sullivan decided to step down as CEO before another serious privacy issue comes out and he has held responsible again. Maybe, just maybe, he made the right choice; only time will tell.

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Appendix:

Exhibit 1:

**ANCESTRY.COM LLC**
**CONSOLIDATED BALANCE SHEETS**

**(in thousands)**

| | December 31, 2015 | December 31, 2014 |
|---|---|---|
| | (unaudited) | |
| ASSETS | | |
| Current assets: | | |
| Cash and cash equivalents | $ 128,157 | $ 108,494 |
| Restricted cash | 2,412 | 49,086 |
| Accounts receivable, net of allowances of $997 and $540 at December 31, 2015 and December 31, 2014, respectively | 13,624 | 11,241 |
| Prepaid expenses | 12,228 | 9,830 |
| Other current assets | 6,288 | 1,813 |
| Total current assets | 162,709 | 180,464 |
| Property and equipment, net | 54,795 | 37,106 |
| Content databases, net | 282,281 | 282,815 |
| Intangible assets, net | 159,736 | 269,054 |
| Goodwill | 948,283 | 948,283 |
| Other assets | 13,956 | 3,175 |
| Total assets | $ 1,621,760 | $ 1,720,897 |
| LIABILITIES AND MEMBER'S INTERESTS | | |
| Current liabilities: | | |
| Accounts payable | $ 13,120 | $ 11,515 |
| Accrued expenses | 50,459 | 47,029 |
| Acquisition-related liabilities | 2,412 | 49,086 |
| Deferred revenues | 171,822 | 145,010 |
| Current portion of long-term debt, net | 7,087 | 46,537 |
| Total current liabilities | 244,900 | 299,177 |
| Long-term debt, net | 989,256 | 799,403 |
| Deferred income taxes | 59,809 | 110,184 |
| Other long-term liabilities | 46,877 | 16,406 |
| Total liabilities | 1,340,842 | 1,225,170 |
| Commitments and contingencies | | |
| Member's interests: | | |
| Member's interests | 422,603 | 666,830 |
| Accumulated deficit | (141,685) | (171,103) |
| Total member's interests | 280,918 | 495,727 |
| Total liabilities and member's interests | $ 1,621,760 | $ 1,720,897 |

Exhibit 2:

**ANCESTRY.COM LLC**
**CONSOLIDATED STATEMENTS OF OPERATIONS**

**(in thousands)**

| | Three months ended December 31, | | Year ended December 31, | |
|---|---|---|---|---|
| | 2015 | 2014 | 2015 | 2014 |
| | (unaudited) | | (unaudited) | |
| Revenues: | | | | |
| Subscription revenues | $ 149,396 | $ 139,693 | $ 584,075 | $553,810 |
| Service and other revenues | 28,214 | 15,469 | 99,030 | 65,734 |
| Total revenues | 177,610 | 155,162 | 683,105 | 619,544 |
| Costs of revenues: | | | | |
| Cost of subscription revenues | 26,419 | 24,556 | 103,051 | 95,899 |
| Cost of service and other revenues | 17,255 | 10,730 | 60,668 | 43,654 |
| Total cost of revenues | 43,674 | 35,286 | 163,719 | 139,553 |
| Gross profit | 133,936 | 119,876 | 519,386 | 479,991 |
| Operating expenses: | | | | |
| Technology and development | 24,971 | 21,677 | 97,105 | 94,221 |
| Marketing and advertising | 46,461 | 40,195 | 171,094 | 168,536 |
| General and administrative | 16,365 | 18,489 | 54,427 | 60,971 |
| Amortization of acquired intangible assets | 27,017 | 36,636 | 109,318 | 147,681 |
| Total operating expenses | 114,814 | 116,997 | 431,944 | 471,409 |
| Income from operations | 19,122 | 2,879 | 87,442 | 8,582 |
| Interest expense, net | (18,874) | (17,298) | (81,056) | (69,680) |
| Other expense, net | (105) | (512) | (334) | (368) |
| Income (loss) before income taxes | 143 | (14,931) | 6,052 | (61,466) |
| Income tax benefit | 13,369 | 7,416 | 23,366 | 42,738 |
| Net income (loss) | $ 13,512 | $ (7,515) | $ 29,418 | $ (18,728) |

Exhibit 3:

**ANCESTRY.COM LLC**

**(in thousands)**

| | Three months ended December 31, | | Year ended December 31, | |
|---|---|---|---|---|
| | 2015 | 2014 | 2015 | 2014 |
| | (unaudited) | | (unaudited) | |
| **Reconciliation of adjusted EBITDA and free cash flow to net income (loss):** [1] | | | | |
| Net income (loss) | $ 13,512 | $ (7,515) | $ 29,418 | $ (18,728) |
| Interest expense, net | 18,874 | 17,298 | 81,056 | 69,680 |
| Other expense, net | 105 | 512 | 334 | 368 |
| Income tax benefit | (13,369) | (7,416) | (23,366) | (42,738) |
| Depreciation | 5,306 | 5,636 | 21,823 | 21,498 |
| Amortization | 35,816 | 44,095 | 141,647 | 176,755 |
| Stock-based compensation expense | 1,968 | 2,008 | 7,683 | 8,004 |
| Adjusted EBITDA | $ 62,212 | $ 54,618 | $ 258,595 | $ 214,839 |
| Capitalization of content databases | (7,899) | (8,358) | (32,514) | (37,566) |
| Purchases of property and equipment | (5,169) | (2,712) | (15,117) | (21,821) |
| Cash paid for interest [2] | (26,028) | (23,227) | (62,831) | (60,450) |
| Cash paid for income taxes | (6,462) | (107) | (23,333) | (1,334) |
| Free cash flow | $ 16,654 | $ 20,214 | $ 124,800 | $ 93,668 |

Exhibit 4:

**ANCESTRY.COM LLC**
**Total Subscribers and Net Subscriber Additions**

**(in thousands)**

| | Year ended December 31, | |
|---|---|---|
| | 2015 | 2014 |
| | (unaudited) | |
| Total subscribers | 2,264 | 2,115 |
| Net subscriber additions | 149 | (25) |

Exhibit 5:

**ANCESTRY.COM LLC**
**CONDENSED CONSOLIDATED BALANCE SHEETS**
**(in thousands)**

| | March 31, 2016 (unaudited) | December 31, 2015 |
|---|---|---|
| **ASSETS** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 176,776 | $ 128,157 |
| Accounts receivable, net of allowances of $749 and $997 at March 31, 2016 and December 31, 2015, respectively | 13,858 | 13,624 |
| Prepaid expenses | 10,509 | 12,228 |
| Other current assets | 5,571 | 8,700 |
| Total current assets | 206,714 | 162,709 |
| Property and equipment, net | 71,351 | 54,795 |
| Content databases, net | 278,382 | 282,281 |
| Intangible assets, net | 143,027 | 159,736 |
| Goodwill | 948,283 | 948,283 |
| Other assets | 14,141 | 13,956 |
| Total assets | $1,661,898 | $1,621,760 |
| **LIABILITIES AND MEMBER'S INTERESTS** | | |
| Current liabilities: | | |
| Accounts payable | $ 15,859 | $ 13,120 |
| Accrued expenses | 53,731 | 52,871 |
| Deferred revenues | 187,874 | 171,822 |
| Current portion of long-term debt, net | 7,095 | 7,087 |
| Total current liabilities | 264,559 | 244,900 |
| Long-term debt, net | 988,656 | 989,256 |
| Deferred income taxes | 51,363 | 59,809 |
| Other long-term liabilities | 62,818 | 46,877 |
| Total liabilities | 1,367,396 | 1,340,842 |
| Commitments and contingencies | | |
| Member's interests: | | |
| Member's interests | 423,819 | 422,603 |
| Accumulated deficit | (129,317) | (141,685) |
| Total member's interests | 294,502 | 280,918 |
| Total liabilities and member's interests | $1,661,898 | $1,621,760 |

Exhibit 6:

**ANCESTRY.COM LLC**
**CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME**
**(in thousands)**

| | Three Months Ended March 31, | |
|---|---|---|
| | 2016 | 2015 |
| | (unaudited) | |
| Revenues: | | |
| Subscription revenues | $ 154,644 | $ 141,717 |
| Service and other revenues | 41,866 | 22,880 |
| Total revenues | 196,510 | 164,597 |
| Costs of revenues: | | |
| Cost of subscription revenues | 27,350 | 25,695 |
| Cost of service and other revenues | 24,410 | 14,266 |
| Total cost of revenues | 51,760 | 39,961 |
| Gross profit | 144,750 | 124,636 |
| Operating expenses: | | |
| Technology and development | 26,004 | 23,443 |
| Marketing and advertising | 51,800 | 43,177 |
| General and administrative | 15,350 | 11,455 |
| Amortization of intangible assets | 18,590 | 27,463 |
| Total operating expenses | 111,744 | 105,538 |
| Income from operations | 33,006 | 19,098 |
| Interest expense, net | (20,081) | (17,208) |
| Other expense, net | (169) | (263) |
| Income before income taxes | 12,756 | 1,627 |
| Income tax (expense) benefit | (388) | 1,167 |
| Net income | $ 12,368 | $ 2,794 |
| Comprehensive income | $ 12,368 | $ 2,794 |

Exhibit 7:

**ANCESTRY.COM LLC**
**(in thousands)**

| | Three Months Ended March 31, | |
|---|---|---|
| | 2016 | 2015 |
| | (unaudited) | |
| **Reconciliation of adjusted EBITDA and free cash flow to net income:**[5] | | |
| Net income | $ 12,368 | $ 2,794 |
| Interest expense, net | 20,081 | 17,208 |
| Other expense, net | 169 | 263 |
| Income tax expense (benefit) | 388 | (1,167) |
| Depreciation | 5,713 | 5,562 |
| Amortization | 27,581 | 35,106 |
| Stock-based compensation expense | 1,884 | 1,925 |
| Adjusted EBITDA | $ 68,184 | $ 61,691 |
| Capitalization of content databases | (6,220) | (7,400) |
| Purchases of property and equipment | (5,850) | (4,152) |
| Cash paid for interest[6] | (9,368) | (6,429) |
| Cash paid for income taxes | (461) | (205) |
| Free cash flow | $ 46,285 | $ 43,505 |

Exhibit 8:

**ANCESTRY.COM LLC**
**Total Subscribers and Net Subscriber Additions**
**(in thousands)**

| | Three Months Ended | | |
|---|---|---|---|
| | March 31, 2016 | December 31, 2015 | March 31, 2015 |
| | | (unaudited) | |
| Total subscribers | 2,372 | 2,264 | 2,219 |
| Net subscriber additions | 108 | 21 | 104 |

# 26. Queensland University of Technology: Funding a Golden Opportunity

As Alyson Summers and Shawn Baker strolled out of her office, Vidya Vasu-Devan, senior officer in program investment at the Bill and Melinda Gates Foundation, looked down at the information package that Alyson had left on her desk. The global development divisions had identified for the program investment department a novel opportunity with a focus on nutrition for human growth and development.

Alyson and Shawn had called this meeting to discuss the opportunity to invest in a small project affiliated with the Centre for Tropical Crops and Biocommodities(CTCB) run by professor James Dale and the Queensland University of Technology. This lab was seeking funding to develop a new vitamin A-rich banana that aligns with the current global development and nutritional aims of the foundation.

Vidya understood their enthusiasm with this new opportunity but was much more hesitant after years of experience with disappointing investment opportunities to take on this project at first glance. She knows that there were many external factors and internal factors that go into the success of a product and its adoption within its target market. She was also familiar with the past struggles bringing vitamin A-enriched products to market and knows that these social issues could hold back any potential future advancements in these areas.

Vidya had asked the global development division to provide her with an information package on the researchers, the product, and the market for this product to aid in her final funding decision.

## Professor James Dale

Professor James Dale was the inaugural director of the CTCB at Queensland University of Technology. This organization consists of approximately 50 researchers, and more than 25 postgraduate students working on projects ranging from gene discovery and genetic modification through to biomass fractionation, processing and value adding in the area of tropical crops(Dale, n.d.). The CTCB has collaborative projects with Syngenta and in Africa, Asia, Europe and the Americas in attempt to grow the global bioeconomy(Institute for Future Environments, n.d.).

Professor Dale has had a hand in biotechnology research for over 30 years with interest in the biofortification of bananas, molecular farming for high-value medical proteins and the development of disease resistance in genetically modified bananas, papaya; and sugar cane(Dale, n.d.). He and his research team. He has led international research and development programs within both South East Asia and the South Pacific with plans to expand international efforts to Africa(Paul et al., 2016). He is an inventor on nine granted patents or applications including the patent for GeneCo technology that was later sold to Affymetrix(Dale, n.d.). He was the founder and chief science officer of Farmacule Bioindustries, Australia's first molecular farming company that later merged with Aquacarorotene to form the first listed molecular farming company Leaf Energy(Retka Schill, 2012). Lastly, in 2004, James Dale was made an Officer in the Order of Australia (AO) for services to agricultural biotechnology(Dale, n.d.). Within the last 10 years, James Dale has experience bringing genetically modified and biofortified bananas to field trials within both African and Asian countries.

## Vitamin A

Vitamin A is a fat-soluble retinoid that is involved in immune function, vision, reproduction and cellular communication(Office of Dietary Supplements, n.d.). Vitamin A is critical for vision and the development of function within the eye. Vitamin A has also been linked to cell growth and differentiation in the heart, lungs, kidneys, and other organs proving essential in the growth and development of a human child (Ross, 2006). Vitamin A is available in the diet in two different forms, preformed vitamin A (retinol) and provitamin A carotenoids (α and β carotene) that are converted into vitamin A by various metabolic processes(Zimmermann & Hurrell, 2002).

The recommended dietary allowance (RDA) is the average daily level of intake sufficient to meet the nutrient requirement of nearly all healthy individuals. The RDA for Vitamin A increases steadily from birth until 14 years of age shown through increasing need for retinol activity equivalents (RAE) (Exhibit 1)(Office of Dietary Supplements, n.d.). RAE accounts for the different bioactivities of retinol and provitamin A within the diet of humans. The main source for provitamin A within a healthy diet is leafy green vegetables, orange and yellow vegetables, tomato products, fruits and some vegetable oils(Klein B. P. & Perry a. K., 2006). Whereas preformed vitamin A is mainly found in milk and eggs(Olson, 1987). Many different foods provide varying levels of vitamin A and a varied diet is important in obtaining an adequate level of vitamin A on a daily basis (Exhibit 2)(Office of Dietary Supplements, n.d.).

## Vitamin A Deficiency

Vitamin A deficiency is most common in developing countries because residents have limited access to foods containing vitamin A(Sommer, Hussaini, Tarwotjo, & Susanto, 1983). The World Health Organization has stated that 190 million preschool-aged children and 19.1 million pregnant women have do not receive enough vitamin A(Howson, Kennedy, & Horwitz, 1998). Vitamin A deficiency typically begins at a young age due to lack of vitamin A provided within their diet of breast milk. Chronic diarrhea can develop with vitamin A deficiency which leads to further nutrient loss and a more severe case of vitamin A deficiency(Sommer, Katz, & Tarwotjo, 1984). A common symptom of vitamin A deficiency is an abnormal dryness, and inflammation of the eye that causes the inability to see in low light or darkness(Sommer et al., 1983). Vitamin A deficiency is the leading cause of preventable blindness in children and increases the severity and mortality risk of infections.

Approximately 627,000 children die each year from deaths that could be prevented by vitamin A supplementation(Humphrey, West, & Sommer, 1992). There are 122 countries classified as having a moderate to severe public health problem with vitamin A deficiency in children age 5 and under (Exhibit 3) (WHO, 2009). The countries with the most severe public health issues involving vitamin A deficiency are geographically located within sub-Saharan Africa and South Asia. The countries within sub-Saharan Africa accounts for 61% of the total deaths attributable to vitamin A deficiency (WHO, 2009). Within Uganda alone, 28% of the population aged 6 to 59 months suffers from vitamin A deficiency(Fiedler & Afidra, 2010).

## Food Fortification

Food fortification is the public health policy of adding micronutrients to foodstuffs in order to ensure that minimum dietary requirements are met. The East Central and South African (ECSA)-Health Community agreed to the fortification of five staple foods(Exhibit 4 and 5) including the fortification of both sugar and oils with preformed vitamin A(Fiedler & Afidra, 2010). Subsequently, In 2004, the Uganda National Board of standards set the standard of 15mg per kg of oil(Fiedler & Afidra, 2010). Previous food fortification efforts have been directed towards the Asian populations affected by vitamin A deficiency. This effort was directed through a product known as golden rice that upon development received a bad reputation for its GMO nature by several social advocacy groups(Greenpeace, n.d.).

## Vegetable Oil Fortification

A study done by Fiedler and Afidra in 2010 reported that in 2007 Uganda imported 285 million metric tons of vegetable oil, 99.6% of which consisted of crude palm oil that was later processed into refined vegetable oil. This palm oil is imported from Malaysia and refined by two major companies, Mukwano and BIDCO. These two companies produced approximately 105,000 metric tons of refined vegetable oil in 2007 and significantly outperformed the other 26 vegetable oil producers in the Ugandan market. These smaller refineries only produce subnational or regional supply and therefore cannot compete with Mukwano and BIDCO on a national level. These two companies produce 85% of the countries output and that is used across the country and exported to surrounding countries. Both

facilities have previously expressed a commitment to Vitamin A fortification of vegetable oil(Fiedler & Afidra, 2010).

In this same study they found that in July 2004, Mukwano began voluntary fortification by addition of preformed vitamin A to its vegetable oil products with BIDCO following suit soon after in 2005. In a 2009 study, costs were estimated at US$277,834 for the annual incremental costs of vitamin A fortification with an upfront capital cost of $9,050 for each of these companies. This number can also be viewed as a US$5.29/metric ton increase in price of refined and enriched vegetable oils. Assuming that the cost increases are shifted onto the consumer by price increase, the maximum price increase to cover these costs is 8.02 UGX (US$0.0048). This is the equivalent of 0.26% of the retail price of 1 L of vegetable oil at the price it is sold within Uganda. According to the Uganda National Household Survey, 54% of Ugandan households purchase and consume vegetable oil. It was estimated that the average Ugandan household will pay an additional US$0.163 per year for fortified vegetable oil(Fiedler & Afidra, 2010).

## Sugar Fortification

In the Fiedler and Afidra study, they also determined that sugar production in Uganda has increased nearly twofold from 1998 to 2007 resulting in a 232,180-metric ton output of sugar in 2007. This output accounts for 77% of the 25644 metric tons of sugar consumed nationally by the Ugandan population. 83% of the Ugandan sugar output is produced by three mills; Kakira, Kinyara and Lugazi. Two of these companies stated that they did not want to oppose or be seen as opposing something that could improve the health of the Ugandan population, whereas the final company is unequivocally opposed to

the fortification of its product with preformed vitamin A. Due to these attitudes it looks as though it will have to be legally mandated before fortification by these companies will be implemented(Fiedler & Afidra, 2010).

This same study estimated that approximately 197,292 metric tons of sugar was produced by the top 4 sugar mills in Uganda. 58% of Uganda's 5.23 million households purchase sugar with an average consumption around 32.6g/person. The retail price of sugar for the Ugandan population is US$1.02 per kg. The addition of preformed vitamin A would cost approximately US$11.39 per metric ton of sugar to meet the standard previously set for the vegetable oil fortification. Assuming that the cost increases of fortification with preformed vitamin A are shifted onto the consumer by price increase, the maximum price increase to is 18.964 UGX (US$0.01139). This is the equivalent of 1.12% of the retail price of a kilogram of sugar at the price it is sold within Uganda. The average Ugandan household would pay an additional US$0.1355 per year for fortified sugar(Fiedler & Afidra, 2010)

## Rice Fortification

Golden Rice had been engineered to contain the genes necessary to produce beta-carotene in the grain. This product was developed by Ingo Potrykus and Peter Beyer originally in 1999. Syngenta scientists were able to enhance the beta-carotene level 23-fold in 2005(Paul et al., 2016). This was done by inserting two genes one from a species of soil bacterium as well as a gene from Erwinia uredovora that was later changed to a gene from maize in 2005 to improve function and overall beta-carotene level(Paul et al., 2016). This level of beta-carotene is enough to cover the recommended daily allowance for children and adults eating a rice-based diet(Tang et al., 2012).

Golden Rice was developed for use in the Philippines, where rice is a staple food eaten with many meals and low levels of vitamin A affect approximately 50% of children aged 1-16 years (Solon, Popkin, Fernandez, & Latham, 1978). However, the release of this product has been hindered by social advocacy groups against the use of GMOs. Greenpeace international has publicly stated in their report that:

I. The exact metabolic pathway for beta-carotene is poorly understood, and overexposure to vitamin A could have negative health benefits.
II. Malnutrition cannot be solved by Golden Rice and should be solved by an increased biodiversity of indigenous vitamin-rich crops and not genetically engineered crops
III. Natural strains of rice could be contaminated with GE rice through seed bank mixing, transport, and cross-pollination increasing the difficulty to eradicate Golden Rice if the need arose.

## The Golden Banana

Within Uganda, bananas are the principal staple fruit where consumption levels average 0.5kg per person per day to approximately 1 kg per person per day in some regions(Smale & Tushemereirwe, 2007). In East Africa, the staple banana is the East African highland banana that is prepared primarily by steaming or boiling for meal preparation. Alternatively, in West Africa, plantains are dominant and are usually fried or roasted for meal preparation(Fungo & Pillay, 2011). These bananas are a natural source of beta-carotene (10ug/g) (Mbabazi, 2015). However, they do not contain the levels needed to reach the recommended daily allowance needed to solve vitamin A deficiency within Uganda. The Fe'i bananas of Micronesia and Papua New Guinea contains significantly higher

levels of beta-carotene (340ug/g)(Englberger et al., 2006). Due to the low male and female fertility of domesticated bananas, conventional breeding of the Fe'i beta-carotene level into the East African highland banana is extremely difficult(Paul et al., 2016).

The CTCB turned to genetic modification to solve these breeding issues. Due to both the bioconversion of and the typical steaming and boiling processes these bananas go through the genetically modified "Golden Bananas" needed to contain 40ug/g to achieve the daily recommended allowance of vitamin A(Paul et al., 2016). Transgenic cavendish banana's expressing the banana phytoene synthase gene controlled by the ubiquitin promoter produced a banana with approximately 55.0 ug/g(Paul et al., 2016). The first Ugandan field trial from this program commenced in 2010. In 2012 the program progressed from the research to the development phase after refunding and expanded into India through collaborating with the Indian Department of Biotechnology(QUT).

## Banana Market: Uganda

Uganda is one of the worlds largest producers and consumers of bananas; producing approximately 7205 million kg per year(Komarek, 2010). This is not surprising because bananas occupy 38% of all agricultural land in Uganda, and contribute to both household food consumption and labor allocations with approximately 90 percent of Uganda's banana output consumed within the domestic market(Exhibit 6 and 7)(Smale & Tushemereirwe, 2007). Approximately 65 % of output is consumed on-farm by the producers, while only 35 % is sold to nearby markets and within Kampala. Large market margins exist, with the retail prices in Kampala double those received by farmers with little to no product

transformation during this time(Benson Todd, Mugarura Samuel, & Wanda Kelly, 2008). Transport costs are the highest associated marketing cost for the sale of bananas within this market; this accounts for around 80 % of total marketing costs(Smale & Tushemereirwe, 2007).

The adoption of both improved bananas and recommended farming practices have been examined throughout Uganda. It was found that low adoption rates (8.8%) for improved bananas was due to inferior cooking quality of the disease resistant hybrid bananas and the dissemination of products to mainly lowland areas(Smale & Tushemereirwe, 2007). Recommended farming practices are more widely adopted (11.6%-95.6%) with the highest of these adoption rates found near paved roads, showing that access to information and markets is important in the adoption of practices. In the past, these recommended farming practices and improved bananas have been provided by the government to improve public health and economic growth(Smale & Tushemereirwe, 2007).

## Opportunity

Currently, vitamin A deficiency poses a significant threat to both African and Asian developing countries where a simple solution has yet to be developed. Vitamin A deficiency affects women and children independent of wealth and affects all economic groups within Uganda(USAID, n.d.)

For the Ugandan Government and the Centre for Tropical Crops and Biocommodities, this presents a unique opportunity to improve the public health of this developing nation. In doing so, these companies must ensure that there is a high enough need for the

Golden Banana to warrant the Genetic engineering of a staple food within the Ugandan diet.

Many previous efforts to eradicate vitamin A deficiency within Uganda have proved ineffective due to the cost of adoption of these processes and the negative view of GMO products within global markets. Many individuals and organizations feel that this is a quick fix to the much larger problem of poverty and lack of a varied diet within developing countries(Greenpeace, n.d.). Additionally, organizations in the past have been opposed to the use of GMOs due to the many unknown factors that they pose.

Current Field trials show promise in the growth of Golden Bananas and adoption of these products within the Ugandan market(Dale, n.d.).

## The Task

The decision to fund the research behind and the development of a product is a critical task bringing new products to market within the biotechnology industry. This is no easy task, involving deep thought about the many economic, social, political, and technological factors that surround this market and product. Vidya Vasu-Devan knew that this would be no simple decision and that it was time to get to work.

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# Exhibits

| Age | Male | Female | Pregnancy | Lactation |
|---|---|---|---|---|
| 0–6 months* | 400 mcg RAE | 400 mcg RAE | | |
| 7–12 months* | 500 mcg RAE | 500 mcg RAE | | |
| 1–3 years | 300 mcg RAE | 300 mcg RAE | | |
| 4–8 years | 400 mcg RAE | 400 mcg RAE | | |
| 9–13 years | 600 mcg RAE | 600 mcg RAE | | |
| 14–18 years | 900 mcg RAE | 700 mcg RAE | 750 mcg RAE | 1,200 mcg RAE |
| 19–50 years | 900 mcg RAE | 700 mcg RAE | 770 mcg RAE | 1,300 mcg RAE |
| 51+ years | 900 mcg RAE | 700 mcg RAE | | |

* Adequate Intake (AI), equivalent to the mean intake of vitamin A in healthy, breastfed infants.

*Exhibit 1 Recommended Dietary Allowances for Vitamin A. Retrieved From https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/#en2*

| Food | mcg RAE per serving | IU per serving | Percent DV* |
|---|---|---|---|
| Sweet potato, baked in skin, 1 whole | 1,403 | 28,058 | 561 |
| Beef liver, pan fried, 3 ounces | 6,582 | 22,175 | 444 |
| Spinach, frozen, boiled, ½ cup | 573 | 11,458 | 229 |
| Carrots, raw, ½ cup | 459 | 9,189 | 184 |
| Pumpkin pie, commercially prepared, 1 piece | 488 | 3,743 | 249 |
| Cantaloupe, raw, ½ cup | 135 | 2,706 | 54 |
| Peppers, sweet, red, raw, ½ cup | 117 | 2,332 | 47 |
| Mangos, raw, 1 whole | 112 | 2,240 | 45 |
| Black-eyed peas (cowpeas), boiled, 1 cup | 66 | 1,305 | 26 |
| Apricots, dried, sulfured, 10 halves | 63 | 1,261 | 25 |
| Broccoli, boiled, ½ cup | 60 | 1,208 | 24 |
| Ice cream, French vanilla, soft serve, 1 cup | 278 | 1,014 | 20 |
| Cheese, ricotta, part skim, 1 cup | 263 | 945 | 19 |
| Tomato juice, canned, ¾ cup | 42 | 821 | 16 |
| Herring, Atlantic, pickled, 3 ounces | 219 | 731 | 15 |
| Ready-to-eat cereal, fortified with 10% of the DV for vitamin A, ¾–1 cup (more heavily fortified cereals might provide more of the DV) | 127–149 | 500 | 10 |
| Milk, fat-free or skim, with added vitamin A and vitamin D, 1 cup | 149 | 500 | 10 |
| Baked beans, canned, plain or vegetarian, 1 cup | 13 | 274 | 5 |
| Egg, hard boiled, 1 large | 75 | 260 | 5 |
| Summer squash, all varieties, boiled, ½ cup | 10 | 191 | 4 |
| Salmon, sockeye, cooked, 3 ounces | 59 | 176 | 4 |
| Yogurt, plain, low fat, 1 cup | 32 | 116 | 2 |
| Pistachio nuts, dry roasted, 1 ounce | 4 | 73 | 1 |
| Tuna, light, canned in oil, drained solids, 3 ounces | 20 | 65 | 1 |
| Chicken, breast meat and skin, roasted, ½ breast | 5 | 18 | 0 |

*Exhibit 2 Selected Food Sources of Vitamin A. Retrieved from https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/#en2*

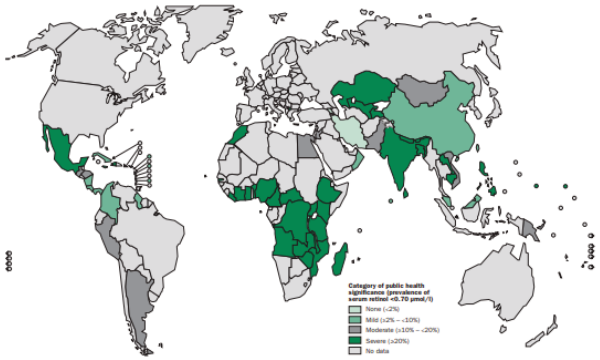



*Exhibit 3 Vitamin A deficiency as a public health problem by country 1995-2005: Preschool-age children. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/44110/9789241598019_eng.pdf;jsessionid=44848AEDE9350647C4E3D8F76FF17088?sequence=1*

| Commodity | Quantity consumed | Daily caloric intake | Share of caloric intake |
|---|---|---|---|
| | (kg/person/year) | (kcal/person/day) | (percent) |
| Plantains | 172 | 419 | 18% |
| Cassava | 101 | 300 | 13% |
| Maize | 31 | 266 | 11% |
| Sweet potatoes | 82 | 215 | 9% |
| Beans | 16 | 148 | 6% |
| Wheat | 7 | 42 | 2% |
| Rice | 4 | 53 | 2% |
| Other | | 1133 | 48% |
| Total | | 2360 | 100% |

Source: FAO. 2009a.

*Exhibit 4 Staple foods consumed in Uganda daily and their caloric values. Retrieved from https://ageconsearch.umn.edu/bitstream/58553/2/AAMP_Maputo_25_Uganda_ppr*

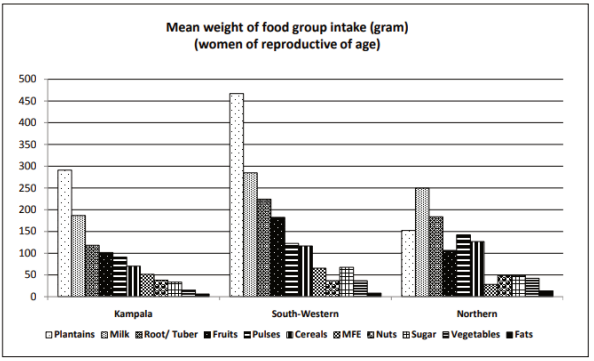



*Exhibit 5 Mean weight of food group intake in grams for women of reproductive age. Retrieved from http://www.gainhealth.org/wp-content/uploads/2014/04/44.-Uganda-2008-Food-Consumption-Survey-Report.pdf*

| Commodity | Production | Imports | Formal Exports | Imports as a percentage of apparent consumption | Formal exports as a percentage of production |
|---|---|---|---|---|---|
| | (1000 tonnes) | (1000 tonnes) | (1000 tonnes) | (percent) | (percent) |
| Maize | 1230 | 33 | 41 | 2.7% | 3.3% |
| Cassava | 4986 | - | 7 | 0.0% | 0.1% |
| Plantains | 9110 | - | - | 0.0% | 0.0% |
| Beans | 446 | 3 | 19 | 0.7% | 4.2% |
| Rice | 105 | 63 | 18 | 42.0% | 16.7% |
| Wheat | 17 | 365 | 1 | 95.8% | 7.4% |
| Others | 8867 | 523 | 513 | 5.9% | 5.8% |
| Total | 24761 | 986 | 598 | 3.9 | 2.4% |

Source: FAO, 2009b and FAO, 2009c.
Note: Apparent consumption is production plus imports minus exports and non-food uses. Average over 2005-07.

*Exhibit 6 Production and trade of food staples in Uganda. Retrieved*

*from https://ageconsearch.umn.edu/bitstream/58553/2/AAMP_Maputo_25_Uganda_ppr*

| | Uganda | | |
|---|---|---|---|
| | Elevation | | |
| **Type of participation** | **Low** | **High** | **All** |
| No Participation | 22.55 | 24.07 | 22.72 |
| Only sells | 31.92*** | 62.82*** | 35.38 |
| Only buys | 32.03*** | 5.21*** | 29.02 |
| Sells and buys | 13.50* | 7.90* | 12.87 |

*Exhibit 7 Percentage of households participating in banana markets by elevatio. Retrieved from http://cdm15738.contentdm.oclc.org/utils/getfile/collection/p15738coll2/id/125290/filename/125291.pdf*

# 27. Rebuilding the pipeline: Celgene and Juno Therapeutics

April 8, 2018

Adrienne Wan

## Introduction

Mark Alles, CEO of Celgene, sat at his desk on a cold January morning looking out the window of his office contemplating what Celgene's next steps would be. The press release had just been published about his appointment as Chairman of the Board of Directors of the company as Bob Hugin was set to step down after two years in the role and 19 years with the company.[1] Alles had been with the New Jersey-based company since 2004 working in different senior positions such as Global Head of Hematology & Oncology, Executive Vice President, and most recently, President and Chief Operating Officer.[1] It was now his turn to take up the mantle and lead the company into a new era of biopharmaceuticals.

In keeping with Celgene's vision of building an influential global biopharmaceutical establishment, with a focus on creating and bringing novel cancer, immune, and inflammatory treatments to

people, Alles would have to ensure long-term success through smart acquisitions of leading novel therapeutics. Celgene's portfolio consisted of drugs and biological treatments for blood and solid tumor cancers as well as immune and inflammatory diseases (see Exhibit 1).[2] They also had more than 45 other drugs in the development pipeline at various phases of clinical trials (see Exhibit 2).[3]

## The biopharmaceuticals industry and cancer therapies market

A 2016 report stated that biopharmaceuticals made up approximately one fifth of the entire pharmaceuticals market and produced around $228 billion in revenue globally. Growth is expected to continue as increasingly valuable investments are made, more patents are filed, and products constantly enter clinical trials each year.[4, 5] By 2023, the global biopharmaceuticals market is projected to be valued at $341 billion with a compound annual growth rate of 8.5% for the next five years.[6]

Some of the major challenges in this developing area are the complexity and expense of production costs as well as the increasingly strict regulations for therapy approval. Despite that, upcoming patent expirations for existing bio- and pharmaceuticals have created an environment for competitors to create biosimilars or generic version as well as emerging companies to break out into the market with their own novel products.[7] Johnson & Johnson, Roche, and Pfizer are the top three pharmaceutical companies from 2017 (see Exhibit 3).[8]

A 2015 report from the American Association for Cancer Research identified more than 830 cancer therapeutics in development, in

clinical trials, or awaiting US Food and Drug Administration (FDA) review. 106 of them were for treatment of leukemia, while 92 were for various lymphomas. Personalized medicine is a growing field of research for its ability to be tailored to a patient's specific condition while avoiding potentially adverse effects commonly seen with generalized therapeutics. According to this report, 73% of cancer therapeutics currently in development fell under the personalized medicine category.[9] Cancer therapeutics were overwhelmingly the leading area of research in 2016 with nearly 9,000 projects from a total of more than 20,000 (see Exhibits 4 and 5).[10]

## Celgene

Celgene has seen a lot of growth over the years both in number of employees and revenue (see Exhibits 6 and 7).[11] Despite their stock value rising over 150% in the past five years, a 32% drop had suddenly occurred in recent months (see Exhibit 8). Not only were there problems with drugs in the development pipeline, but they had to stop clinical trials of one after rejection from the FDA. Investors were growing concerned over the company's future.[12]

One of the major issues looming over the Celgene was that Revlimid, their most profitable drug for treating multiple myelomas which generated $8.2 billion in 2017 alone, would be going generic in 2022.[13] In order to continue to be both sustainable and profitable, Celgene would have to diversify their portfolio and look to the drug development pipeline for a new therapeutic very soon.

A prospective Crohn's disease drug, Mongersen or GED-0301, had failed in phase 3 clinical trials causing Celgene to contemplate continuing development on it after having already spent $2.6 billion in 2014.[14]

In 2015, Celgene had acquired Receptos, a leader in the treatment of immune and inflammatory diseases, for $7.2 billion in order to obtain Ozanimod, its latest multiple sclerosis drug still in development. John Newman, an analyst with Canaccord Genuity, said to investors that,

> "Despite the likely termination of the GED-0301 program, we still believe that Ozanimod will be a meaningful contributor to long-term revenues due to differentiation on cardiac safety versus Gilenya® [fingolimod]."[14]

The FDA had rejected its initial application due to insufficient data of the drug's application which has delayed its release.[15] In explanation of the refusal-to-file letter, Celgene stated:

> "[The FDA] determined that the nonclinical and clinical pharmacology sections in the [New Drug Application] were insufficient to permit a complete review."[16]

As a result, the projected peak sales were estimated to fall from $5 billion to $3.5 billion.[16]

## Cancer treatments

For years, global cancer rates have been rising due to increased life expectancy, lifestyle choices (smoking, exercise, diet, etc.), and environmental factors. It is one of the top leading causes of death in developed countries and is increasing in prevalence in less developed ones. It is expected that the global cancer therapeutics market will grow at a compound annual growth rate of 7.4% in the next four years resulting in an increase from $121 billion in 2017 to $173 billion in

2022.[17] The cost of cancer therapeutics has increased from $91 billion to $113 billion in 2016 alone.[18]

## Conventional cancer treatments available

*Surgery*: Depending on the type of cancer, doctors may be able to remove solid tumors from the patient. This is not possible for metastatic cancers that have spread or cancers of the blood like leukemia. Surgery can also be used to prevent (remove tissue that could become cancerous before it develops), diagnose (biopsy or tissue sampling), stage (determine the spread), and treat cancers (cure, debulk, etc.). The main risks are the same as those with any form of surgery: bleeding, clots, damage to surrounding tissue, infection, etc.[19]

*Radiation therapy*: High doses of high energy radiation are used to induce breaks in a cell's DNA leading to cancer cell destruction and tumor reduction. While it is usually a localized treatment, healthy cells in the nearby surrounding tissue can also be harmed by radiation. At the same time, cancer cells that have spread from the site are unaffected by the treatment.[20]

*Chemotherapy*: Doctors may use drugs to kill rapidly dividing cells (cancerous ones) systemically throughout the body. Chemotherapy can be used to cure or control cancers as well as ease symptoms of the disease. The specific drug(s) used will depend on the type of cancer, what stage it is at, the patient's age and health status, and if there is a history of previous cancer treatment in the past. While the main goal is to kill growing cancerous cells, chemo also affects healthy non-cancerous ones that are also rapidly dividing such as those located in the bone marrow, hair follicles, digestive tract, and reproductive organs.[21]

*Other treatments*:

- Virotherapy: using a viral vector to specifically target cancer cells of tumours to destroy them;
- Immunotherapy: stimulation of the immune system to promote its ability to fight transformed cells;
- Hormone therapy: treatment for cancers that use the body's hormones to proliferate like breast and prostate cancers;
- Stem cell transplant: a follow up procedure after radiation or chemotherapy has been used to destroy the patient's immune system – stem cells are transplanted to the individual to rebuild the immune system;
- Among others.[22]

## Chimeric Antigen Receptor – T-cell Therapy (CAR-T)

Chimeric Antigen Recepter – T-cell (CAR-T) therapy was a new area of research for treating patients with different types of blood cancers (see Exhibit 9). The first step in the process is to remove a portion of the patient's blood. The T-lymphocytes, a type of white blood cell vital for fighting infections and cancerous cells, are isolated and sent to a manufacturing facility or lab. There, the cells are genetically engineered to produce the chimeric antigen receptor on its surface. These novel receptors are exceptionally good at identifying cancer cells in the body allowing the T-lymphocyte to attack and destroy them. After the lab work is completed, the modified cells are returned to the patient for the therapeutic effects to take hold. The entire process is expected to take only a few weeks.[23] Their use has been

focused on blood cancers for now but work has been started to test its efficacy on solid tumours.[24]

New developments in biopharmaceuticals for treating blood cancers have a promising outlook.

> "[W]e are working to target cancer in a transformative way. On the one hand, you always want to improve current therapies. But you also want to leapfrog them when possible by investing in different technologies that may change the state of the disease more radically. We see the possibility of such a leapfrog moment with investigational [immunotherapies called] CAR-T cell therapies."[23]

When looking at CAR-T therapeutics and Celgene's in particular, Wim Souverijns, Celgene's Corporate Vice President of Global Marketing in Hematology and Oncology, continued,

> "... [they] are already having a tremendous impact on acute lymphoblastic leukemia, providing the chance for durable responses in kids with the disease. The same promise exists for lymphoma.... In multiple myeloma, where the nature of the disease is different, CAR-T cells may not be a cure but will probably help us control the disease better. The first data shown at the American Society of Clinical Oncology Annual Meeting earlier this year were impactful and strong. Now we're looking at longer-term follow-ups to confirm that our high expectations are warranted."[23]

One of the implications to consider with CAR-T therapy was that because it is a patient-specific procedure, it was also very expensive. In terms of the general therapy processes, the cell modification procedure could be complex, there were safety concerns once the cells had been returned to the patient, and because it was a new technology, the longevity of the therapy was uncertain. On top of

that, while it was not intended for solid tumors at this stage, it was believed to be one of the best strategies that oncologists have for fighting blood cancers.[25]

One question that investors and analysts wanted to know the answer to was, is there much demand for this therapeutic currently and what are the projected numbers in the future? It was believed that demand was high at about 7-10,000 people requiring treatment for blood cancers each year. There were only 22 sites in America certified to administer the treatment though this will increase as demand and development do.[25]

## Competition

While it was an emerging area of research in cancer immunotherapeutics, there were a few companies developing CAR-T treatments, some of which were already approved and available on the market.

Novartis' Kymriah (tisagenlecleucel) was the first CAR-T to be FDA-approved.[26] In a trial of 63 patients, 52 were in remission three months after treatment while 40 patients remained in remission one year later.[27]

Kite Pharma was another major contender who gained approval for their product Yescarta (axicabtagene ciloleucel) used to treat adults with large B-cell lymphoma and aggressive non-Hodgkin lymphoma. Recognizing the great potential it had, Gilead Sciences, Inc., a major North American biopharmaceutical company, bought out Kite Pharma for $12 billion in October of 2017.[25]

## Juno: JCAR015 and JCAR017

Founded in 2013, Juno Therapeutics was a small biopharmaceutical company working on hematological therapeutics. Seeing an opportunity to broaden their areas of research and gain stake in the novel treatment, Celgene invested $1 billion into development of Juno's CAR-T therapies in 2015 and the two announced a decade-long collaboration. Within two years, Celgene bought out 9.7% of the smaller company for $500 million.[28]

Juno had a very promising CAR-T therapy called JCAR015 that had been developed to treat acute lymphoblastic leukemia (ALL). ALL is a cancer of the white blood cells where they do not mature properly resulting in an abundance of underdeveloped dysfunctional cells in both circulating blood and bone marrow. It is most often diagnosed in patients under 20 years old.[29]

During the JCAR015 phase 2 clinical trials, three patient deaths had occurred due to cerebral edema, the buildup of excess fluid in the brain and spinal tissues causing swelling. The study was halted and Juno blamed the deaths on the pre-treatment that was common among many companies' protocols, rather than the therapy. Changes were made to the procedure to remove the suspected pre-treatment and upon hearing that, the FDA allowed the study to continue. Stock prices rose once more. Two more deaths occurred, again, due to cerebral edema which forced Juno to terminate all clinical trials.26

The first three deaths lead to the legal firm, Block & Leviton, suing Juno for failing to inform investors of all the details of the trials, like the deaths, knowing that it was important information. It was also alleged that the company was heavily selling stocks in the weeks before any announcements were made about the results of the experimental trials. The company denied these claims. In this time, Juno stocks fell from $50/share in the summer of 2016 to $23/share at early 2017 (see Exhibit 10).[26]

The five deaths that occurred during the clinical trials for JCAR015 were a major setback for Juno and forced the company to halt all testing. Investors were losing confidence in the company which caused stock prices to drop dramatically. In terms of drug development, Juno would have to reach further back into the pipeline for something that was not as far along requiring more time and money to regain their footing.[28]

Since then, Juno had been working on a new product, JCAR017, for treatment of large B-cell lymphoma and non-Hodgkin lymphoma.[30] JCAR017 was thought to have greater safety and efficacy since it used defined CD4 and CD8 cell populations. By doing so, researchers had greater control over cell growth which was thought to be the major issue with JCAR015. These modified cells targeted a specific surface protein found in B-cell malignancies, a different type of cancer for another subset of white blood cells.[28] So far, results have been positive with an overall response rate of 74%, or 14 out of 19 patients, at the three-month mark.[30] It is expected that JCAR017 will gain FDA approval in 2019 with projected peak sales of about $3 billion.[31]

Despite the improvements and optimistic outlook, not everyone was confident in JCAR017's potential. Brad Loncar, an investor analyst of novel cancer immunotherapies specifically, said,

> "I think they are making a mistake by relying on JCAR-017. [It is] unclear if Juno will in fact be best in class or even if it will matter. The way this deal succeeds is if Celgene/Juno becomes a leader in CAR-T version 2.0, 3.0, etc. many years down the line."[30]

## Celgene's options

In 2013, before the Celgene-Juno partnership, the former had begun a partnership with Bluebird Bio, another small biopharmaceutical

company developing a CAR-T therapeutic, bb2121, for targeting altered B-cells. 2016 clinical results showed that 56% of patients were in complete remission nine months post-treatment from a single dose. A few side effects were noted, but nothing fatal. Currently, the company has a second generation drug in the works.[32] Some have wondered, would working with Juno be a conflict to Celgene's first loyalties to Bluebird Bio? It turns out the two cell therapies had different molecular targets and did not occupy the same areas of the cancer therapeutics market so the overlap was not a serious concern. Between the two, analysts have projected Bluebird Bio's potential revenue over the next five years to be close, but marginally greater than Juno's (see Exhibit 11).[33]

Analysts have stated that Celgene's attempt to enter the CAR-T market was a smart strategy since a large part of its research was heavily focused on hematology and cancer therapeutics. The development of new collaborative products or existing therapies that work synergistically could boost sales for all the players involved. Not only that, but being one of the bigger biopharmaceutical companies in North America, Celgene had the marketing capabilities and sales force to commercially succeed.[34]

What would the acquisition of the remaining part of Juno mean for Celgene? Celgene would have complete control over JCAR017 as well as the other eight clinical and preclinical projects. Furthermore, the company would also gain 100% of revenue generated from these projects. Recent talks of a merger between the two had sent stock prices up (see Exhibits 12 and 13).[31]

Alles had the weight of carrying on the company on his shoulders and the decisions he had to make would no doubt define Celgene's success over the next decade. With the looming decision of how to ensure Celgene's future success and if Juno Therapeutics would be a piece of that puzzle, Alles turned away from the window and knew what to do.

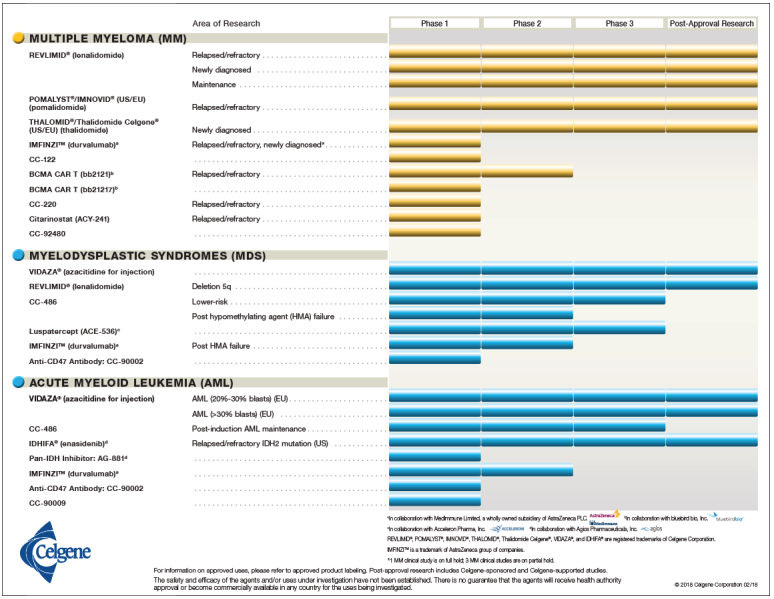
## Exhibits

**Exhibit 1** Current Celgene products and their indications

| Name | Indication |
|---|---|
| Abraxane | Metastatic breast cancer, metastatic non-small cell lung cancer, metastatic adenocarcinoma |
| Idhifa | Adults with relapsed or refractory acute myeloid leukemia (AML) |
| Istodax | Cutaneous T-cell lymphoma, peripheral T-cell lymphoma |
| Otezla | Adult patients with active psoriatic arthritis, moderate to severe plaque psoriasis |
| Pomalyst | Multiple myeloma |
| Revlimid | Multiple myeloma, transfusion-dependent anemia, mantle cell lymphoma |
| Thalomid | Multiple myeloma, erythema nodosum leprosum |
| Vidaza | Myelodysplastic syndrome |

Source: Celgene Corporation. (n.d.). Therapies. Retrieved March 3, 2018, from http://www.celgene.com/therapies/

**Exhibit 2** Celgene's current products in the pipeline by area of research and clinical phase


Area of Research
Phase 1
Phase 2
Phase 3
Post-Approval Research
MULTIPLE MYELOMA (MM)
REVLIMID® (lenalidomide)
Relapsed/refractory
Newly diagnosed
Maintenance
POMALYST®/IMNOVID® (US/EU) (pomalidomide)
Relapsed/refractory
THALOMID®/Thalidomide Celgene® (US/EU) (thalidomide)
Newly diagnosed
IMFINZI™ (durvalumab)*
Relapsed/refractory, newly diagnosed*
CC-122
BCMA CAR T (bb2121)*
Relapsed/refractory
BCMA CAR T (bb21217)*
CC-220
Relapsed/refractory
Citarinostat (ACY-241)
Relapsed/refractory
CC-92480
MYELODYSPLASTIC SYNDROMES (MDS)
VIDAZA® (azacitidine for injection)
REVLIMID® (lenalidomide)
Deletion 5q
CC-486
Lower-risk
Post hypomethylating agent (HMA) failure
Luspatercept (ACE-536)*
IMFINZI™ (durvalumab)*
Post HMA failure
Anti-CD47 Antibody: CC-90002
ACUTE MYELOID LEUKEMIA (AML)
VIDAZA® (azacitidine for injection)
AML (20%–30% blasts) (EU)
AML (>30% blasts) (EU)
CC-486
Post-induction AML maintenance
IDHIFA® (enasidenib)*
Relapsed/refractory IDH2 mutation (US)
Pan-IDH Inhibitor: AG-881*
IMFINZI™ (durvalumab)*
Anti-CD47 Antibody: CC-90002
CC-90009
*In collaboration with MedImmune Limited, a wholly owned subsidiary of AstraZeneca PLC.
*In collaboration with bluebird bio, Inc.
*In collaboration with Acceleron Pharma, Inc.
*In collaboration with Agios Pharmaceuticals, Inc.
REVLIMID®, POMALYST®, IMNOVID®, THALOMID®, Thalidomide Celgene®, VIDAZA®, and IDHIFA® are registered trademarks of Celgene Corporation.
IMFINZI™ is a trademark of AstraZeneca group of companies.
†1 MM clinical study is on full hold; 3 MM clinical studies are on partial hold.
For information on approved uses, please refer to approved product labeling. Post-approval research includes Celgene-sponsored and Celgene-supported studies.
The safety and efficacy of the agents and/or uses under investigation have not been established. There is no guarantee that the agents will receive health authority approval or become commercially available in any country for the uses being investigated.
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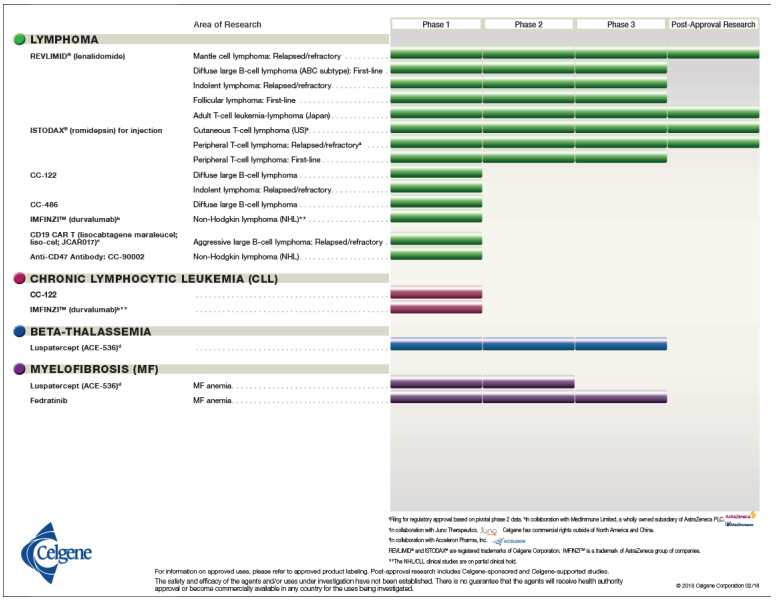
Area of Research
Phase 1
Phase 2
Phase 3
Post-Approval Research
LYMPHOMA
REVLIMID® (lenalidomide)
Mantle cell lymphoma: Relapsed/refractory
Diffuse large B-cell lymphoma (ABC subtype): First-line
Indolent lymphoma: Relapsed/refractory
Follicular lymphoma: First-line
Adult T-cell leukemia-lymphoma (Japan)
ISTODAX® (romidepsin) for injection
Cutaneous T-cell lymphoma (US)*
Peripheral T-cell lymphoma: Relapsed/refractory*
Peripheral T-cell lymphoma: First-line
CC-122
Diffuse large B-cell lymphoma
Indolent lymphoma: Relapsed/refractory
CC-486
Diffuse large B-cell lymphoma
IMFINZI™ (durvalumab)†
Non-Hodgkin lymphoma (NHL)**
CD19 CAR T (liscabtagene maraleucel; liso-cel; JCAR017)*
Aggressive large B-cell lymphoma: Relapsed/refractory
Anti-CD47 Antibody: CC-90002
Non-Hodgkin lymphoma (NHL)
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
CC-122
IMFINZI™ (durvalumab)†**
BETA-THALASSEMIA
Luspatercept (ACE-536)‡
MYELOFIBROSIS (MF)
Luspatercept (ACE-536)‡
MF anemia
Fedratinib
MF anemia
*Filing for regulatory approval based on pivotal phase 2 data.
*In collaboration with MedImmune Limited, a wholly owned subsidiary of AstraZeneca PLC.
†In collaboration with Juno Therapeutics.
Celgene has commercial rights outside of North America and China.
‡In collaboration with Acceleron Pharma, Inc.
REVLIMID® and ISTODAX® are registered trademarks of Celgene Corporation. IMFINZI™ is a trademark of AstraZeneca group of companies.
**The NHL/CLL clinical studies are on partial clinical hold.
For information on approved uses, please refer to approved product labeling. Post-approval research includes Celgene-sponsored and Celgene-supported studies.
The safety and efficacy of the agents and/or uses under investigation have not been established. There is no guarantee that the agents will receive health authority approval or become commercially available in any country for the uses being investigated.
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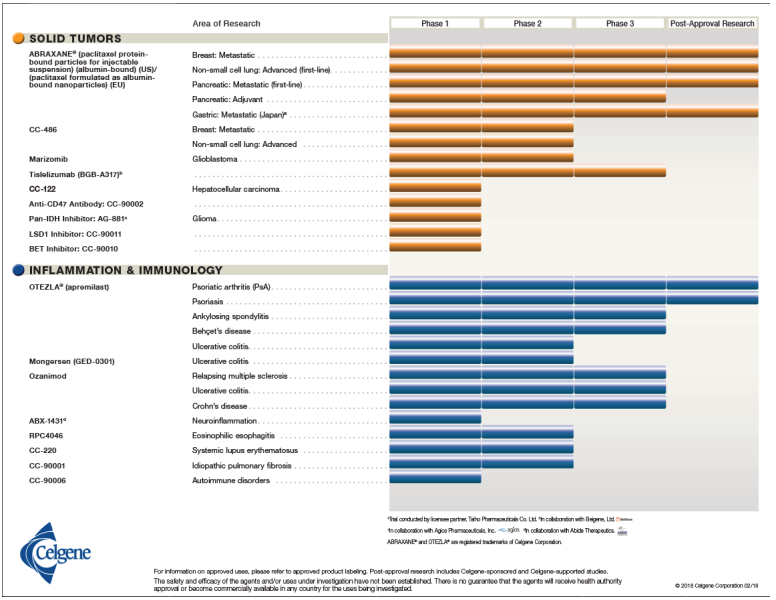
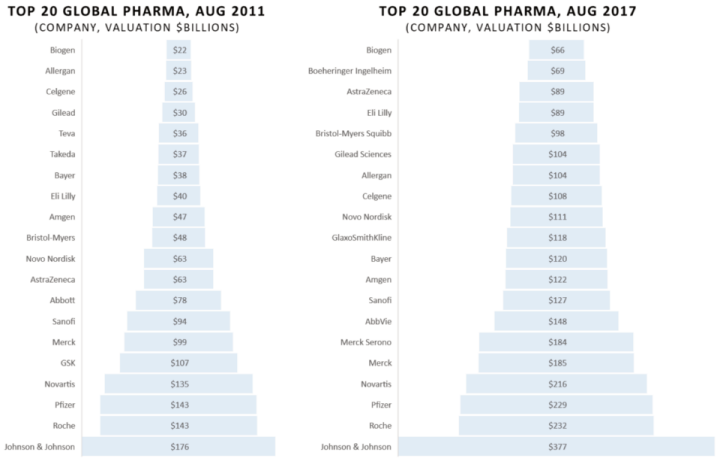


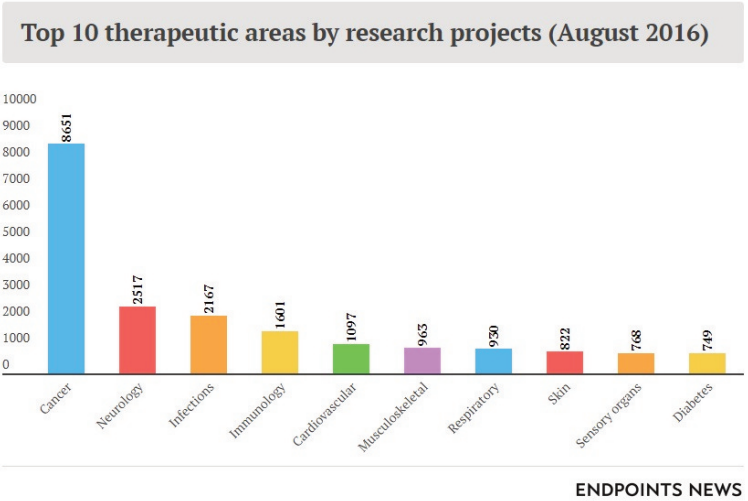

Source: Celgene Corporation. (2018, February 18). Product Pipeline. Retrieved March 29, 2018, from http://media.celgene.com/content/uploads/product-pipeline.pdf

**Exhibit 3** Top 20 global pharmaceutical companies, August 2011 and 2017




Source: Carroll, J. (2017, July 18). King cancer: The top 10 therapeutic areas in biopharma R&D. Retrieved April 6, 2018, from https://endpts.com/king-cancer-the-top-10-therapeutic-areas-in-biopharma-rd/

**Exhibit 4** Top ten therapeutic areas by number of research projects, August 2016




Source: Carroll, J. (2017, July 18). King cancer: The top 10 therapeutic areas in biopharma R&D. Retrieved April 6, 2018, from https://endpts.com/king-cancer-the-top-10-therapeutic-areas-in-biopharma-rd/

**Exhibit 5** Distribution of products and projects by therapeutic area of research and phase

| Therapeutic Area | Preclinical/ Research Project | Phase I | Phase II | Phase III | Filed/ Approved | Total Projects | Total Products |
|---|---|---|---|---|---|---|---|
| Blood | 293 | 78 | 104 | 59 | 3 | 537 | 394 |
| Cancer | 4,621 | 1,757 | 1,920 | 329 | 24 | 8,651 | 5,789 |
| Cancer, Blood & blood forming malignanci | 487 | 433 | 434 | 67 | 5 | 1,426 | 671 |
| Cancer, miscellaneous cancer | 1,826 | 100 | 85 | 21 | 2 | 2,034 | 1,679 |
| Cancer, Solid tumors, Bladder | 29 | 13 | 28 | 11 | 2 | 83 | 27 |
| Cancer, Solid tumors, Breast | 212 | 80 | 108 | 27 | - | 427 | 169 |
| Cancer, Solid tumors, Colorectal | 98 | 46 | 73 | 19 | 1 | 237 | 81 |
| Cancer, Solid tumors, Lung | 73 | 13 | 21 | 1 | - | 108 | 50 |
| Cancer, Solid tumors, Melanoma | 102 | 57 | 87 | 9 | - | 255 | 154 |
| Cancer, Solid tumors, Prostate | 146 | 39 | 86 | 10 | - | 281 | 217 |
| Cancer, Solid tumors, Other | 1,648 | 976 | 998 | 164 | 14 | 3,800 | 2,741 |
| Cardiovascular | 642 | 141 | 227 | 77 | 10 | 1,097 | 771 |
| Diabetes | 482 | 97 | 125 | 42 | 3 | 749 | 432 |
| Gastro-intestinal | 305 | 85 | 140 | 54 | 5 | 589 | 413 |
| Hepatic & biliary | 165 | 47 | 75 | 10 | 1 | 298 | 182 |
| HIV & related conditions | 186 | 30 | 39 | 13 | - | 268 | 218 |
| Hormone | 40 | 14 | 18 | 11 | 3 | 86 | 62 |
| Immunology | 1,157 | 200 | 176 | 60 | 8 | 1,601 | 1,153 |
| Infections | 1,603 | 195 | 252 | 109 | 8 | 2,167 | 1,659 |
| Miscellaneous | 916 | 174 | 116 | 58 | 6 | 1,270 | 1,152 |
| Musculoskeletal | 582 | 142 | 163 | 63 | 13 | 963 | 606 |
| Musculoskeletal, Rheumatoid arthritis | 165 | 55 | 52 | 13 | 2 | 287 | 125 |
| Musculoskeletal, Osteoarthritis | 62 | 17 | 31 | 12 | 1 | 123 | 90 |
| Musculoskeletal, Other | 355 | 70 | 80 | 38 | 10 | 553 | 391 |
| Neurology | 1778 | 320 | 287 | 119 | 13 | 2,517 | 1,899 |
| Neurology, ALS | 76 | 7 | 17 | 4 | 1 | 105 | 53 |
| Neurology, Parkinson's disease | 183 | 37 | 24 | 4 | 2 | 250 | 212 |
| Neurology, Alzheimer's disease | 276 | 68 | 52 | 23 | - | 419 | 277 |
| Neurology, Spinal cord injury | 45 | 7 | 9 | 2 | - | 63 | 43 |
| Neurology, Traumatic brain injury | 64 | 3 | 6 | 1 | - | 74 | 70 |
| Neurology, Other | 1,134 | 198 | 179 | 85 | 10 | 1,606 | 1,244 |
| Psychiatry | 261 | 76 | 100 | 29 | 2 | 468 | 331 |
| Reproduction | 133 | 23 | 59 | 27 | 1 | 243 | 189 |
| Respiratory | 567 | 126 | 181 | 50 | 6 | 930 | 609 |
| Sensory organs | 486 | 69 | 152 | 57 | 4 | 768 | 567 |
| Skin | 428 | 103 | 222 | 59 | 10 | 822 | 624 |
| Surgery | 72 | 9 | 18 | 8 | 1 | 108 | 100 |
| Urinary tract | 146 | 37 | 50 | 23 | 1 | 257 | 183 |
| Total Projects | 14,863 | 3,723 | 4,424 | 1,257 | 122 | 24,389 | |
| Total Products | 11,012 | 2,618 | 2,660 | 932 | 111 | | 17,333 |

Source: Carroll, J. (2017, July 18). King cancer: The top 10 therapeutic areas in biopharma R&D. Retrieved April 6, 2018, from https://endpts.com/king-cancer-the-top-10-therapeutic-areas-in-biopharma-rd/

**Exhibit 6** Summary balance sheet for years 2008-2017

| Year End (Dec) | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total assets ($B) | 4.45 | 5.39 | 10.18 | 10.01 | 11.73 | 13.38 | 17.34 | 26.96 | 28.09 | 30.14 |
| Total liabilities ($B) | 0.95 | 0.99 | 4.18 | 4.49 | 6.04 | 7.79 | 10.82 | 21.05 | 21.49 | 23.22 |
| Total equity ($B) | 3.49 | 4.39 | 5.98 | 5.51 | 5.69 | 5.59 | 6.52 | 5.92 | 6.60 | 6.92 |
| Number of employees | 2441 | 2813 | 4182 | 4460 | 4700 | 5100 | 6012 | 7140 | 7132 | 7467 |

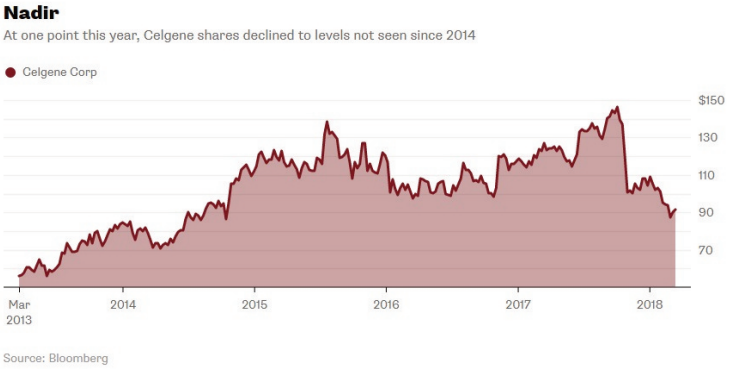
Source: Celgene Corporation. (n.d.). Financial information. Retrieved March 15, 2018, from http://ir.celgene.com/financials.cfm

**Exhibit 7** Summary income statement for years 2008-2017

| Year end (Dec) | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|
| Revenue ($B) | 2.25 | 2.73 | 3.58 | 4.84 | 5.43 | 6.48 | 7.64 | 8.9 | 10.92 | 12.82 |
| Total net income ($B) | -1.53 | 0.78 | 0.88 | 1.32 | 1.46 | 1.45 | 2.00 | 1.60 | 2.00 | 2.94 |

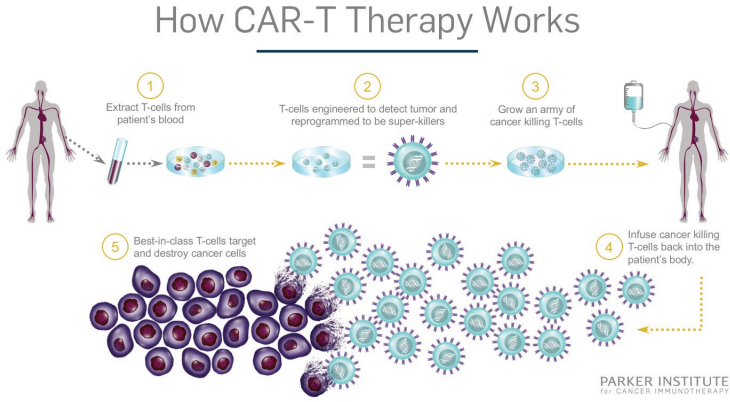
Source: Celgene Corporation. (n.d.). Financial information. Retrieved March 15, 2018, from http://ir.celgene.com/financials.cfm

**Exhibit 8** Celgene stock value from March 2013-March 2018




Source: Nisen, M. (2018, March 14). People Are Talking About a Celgene LBO; That Should Worry It. Retrieved March 19, 2018, from https://www.bloomberg.com/gadfly/articles/2018-03-14/celgene-lbo-talk-should-worry-it

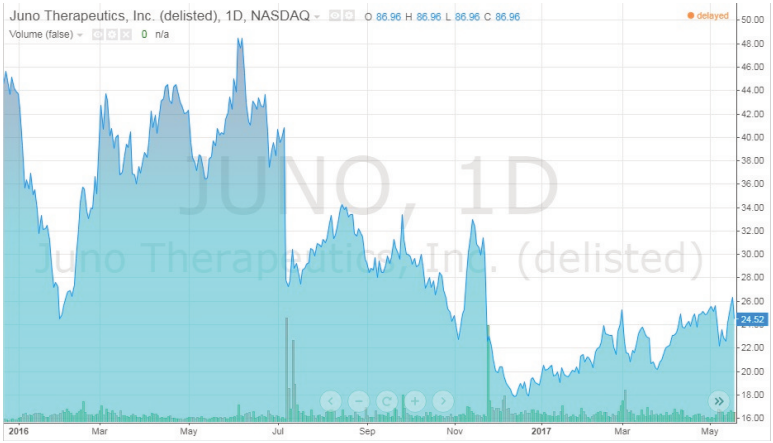
**Exhibit 9** How Chimeric Antigen Receptor – T-cell (CAR-T) therapy works




Source: Parker Institute. (2017, August 17). CAR T Therapy How It Works Final. Retrieved March 31, 2018, from https://www.parkerici.org/2017/08/30/leukemia-cancer-free-

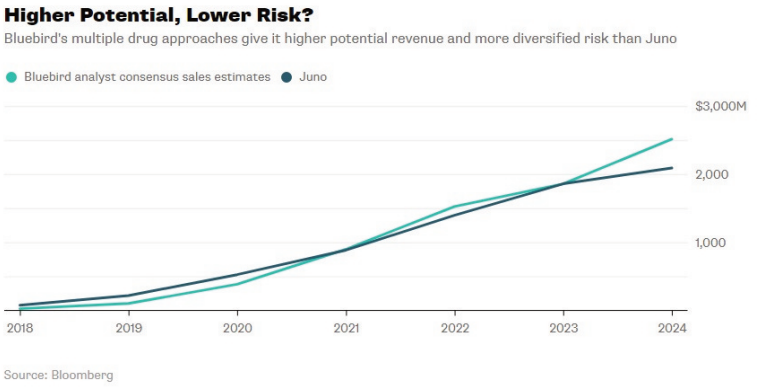
how-car-t-immunotherapy-saved-emily-whitehead/car-t_therapy-how-it-works_final/

**Exhibit 10** Juno stock value from January 2016-May 2017




Source: ADVFN. (n.d.). JUNO THERAPEUTICS, INC. (JUNO). Retrieved April 7, 2018, from https://www.advfn.com/stock-market/NASDAQ/JUNO/chart/trading-view

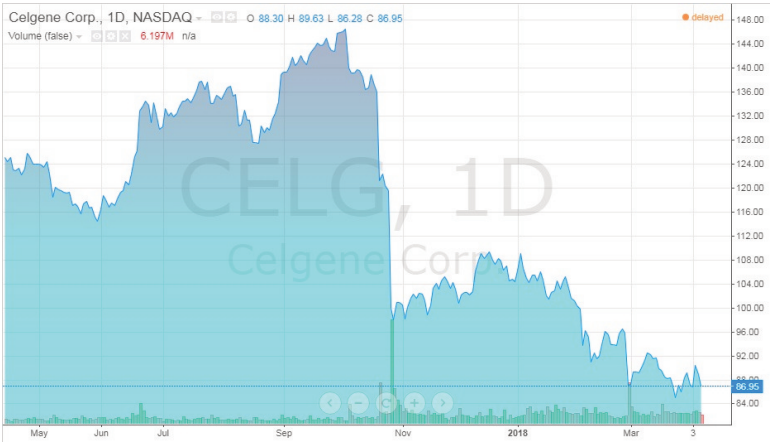
**Exhibit 11** Bluebird Bio and Juno projected revenue from 2018-2024




Source: Nisen, M. (2018, January 21). Bluebird Bio Shouldn't Be Blue.

Retrieved March 8, 2018, from https://www.bloomberg.com/gadfly/articles/2018-01-22/celgene-juno-deal-bluebird-bio-shouldn-t-be-blue

**Exhibit 12** Celgene stock value from April 2017-April 2018




Source: ADVFN. (n.d.). Celgene (CELG). Retrieved April 7, 2018, from https://www.advfn.com/stock-market/NASDAQ/CELG/chart/trading-view

**Exhibit 13** Juno stock value from April 2017-April 2018


Source: ADVFN. (n.d.). JUNO THERAPEUTICS, INC. (JUNO). Retrieved April 7, 2018, from https://www.advfn.com/stock-market/NASDAQ/JUNO/chart/trading-view

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## Appendix

On March 6, 2018, Celgene announced it had completed the acquisition of Juno Therapeutics in a $9 billion deal contingent on the latter reaching specific regulatory and commercialization milestones.[40]

> "The acquisition of Juno builds on our shared vision to discover and develop transformative medicines for patients with incurable blood cancers. Juno's advanced cellular immunotherapy portfolio and research capabilities

strengthen Celgene's global leadership in hematology and adds new drivers for growth beyond 2020." – Mark Alles, Celgene CEO, on the partnership.

"The people at Juno channel their passion for science and patients towards a common goal of finding cures by creating cell therapies that help people live longer, better lives. Continuing this work will take scientific prowess, manufacturing excellence and global reach. This union will provide all three." – Hans Bishop, Juno CEO, on the partnership.[41]

The two acquisitions Celgene made in early 2018, Impact Biomedicines for $7 billion and Juno for $9 billion, had begun to instill confidence in investors. They could see that the company was no longer completely relying on Revlimid's success and that it was serious about rebuilding the drug development pipeline. Despite the issues Celgene and Juno faced in the months leading up to the merger, analysts expect the company's share value to rise 28% with improved earnings over the next two years.[12]

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## Endnotes

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# 28. Okanagan Specialty Fruits & the Arctic® Apple

By K. J. Britto

## Setting the Scene

Imagine this scenario: You have had a long Monday, waking up with just enough time to get your lunch ready and make it out the door to work. After a long and stressful morning, you get to the break room for lunch, ready to enjoy the nice, crisp apple you cut up and packed in the morning. Only to discover the surface to be mushy and brown. Some part of you knows it is still edible, but it looks so unappetizing that you push it aside for discrete disposal later. You think to yourself 'if only there was a way that my apple would not turn brown before I could eat it.' Well there is.

## Introduction

The Arctic® apples, a product of Okanagan Specialty Fruits (OSF), was designed in a way that prevents the primary browning process in apples from occurring ("How'd we 'make' a nonbrowning apple?" n.d.). This means that the apple stays crisp and looks fresh for a longer period of time, despite exposure or physical damage ("How'd we 'make' a nonbrowning apple?" n.d.). However, the Arctic® apple is a genetically modified organism (GMO) which, as a label, brought its own issues and problems to the product and always has a negative

impact on reception and spread of the crops involved. This issue is one that plagues many crops in the agricultural industry. To combat the negative attention of a GMO reputation OSF came up with many unique solutions and strategies, some of which have the potential to change the ways GMOs are approached in the future.

## Okanagan Specialty Fruits

The company was founded in 1996 by Neal and Louisa Carter in Okanagan Valley, BC. Neal Carter had previously worked as a bioresource engineer, focused on helping third world countries enhance food security ("Meet Our Team" n.d.). It was during this time he became convinced of the importance in biotechnology and genetically engineered (GE) crops for helping farmers deal with the increasing demand for food ("Meet Our Team" n.d.). This led to the founding of OSF ("Meet Our Team" n.d.).

## The Apple Industry

At the time OSF was founded Neal Carter noticed some things ("Meet Our Team" n.d.). He was concerned with how it was flatlining and stalling compared to others that were seeing growth and innovation ("Arctic® Apples: more apples for consumers," n.d.). With society becoming increasingly 'on-the-go' the agricultural and food industries had to modify their products to fit these new needs ("Nonbrowning GM apple cleared" n.d.).

However, the apple industry faced a unique issue. If the apples were cut and packaged they would slowly brown, looking unappetizing and spoiled (Lane, n.d.). The only way to prevent this

was to treat the apple slices with a collection of chemicals to prevent this (Armstrong, n.d.). However, consumers were often wary of consuming these products, additionally, these chemicals used and cause minor irritation and health issues in certain groups of people (Armstrong, n.d.) ("Nonbrowning GM apple cleared" n.d.). This represented a huge area of opportunity to enter if a working product could be developed ("Nonbrowning GM apple cleared" n.d.).

OSF learned about a project in Australia to produce non-browning potatoes to reduce food loss and waste ("Meet Our Team" n.d.). Neal decided that this would be a huge potential avenue of exploration in order to develop the apple product and approach the market ("Meet Our Team" n.d.) . Once the technology involved was licensed by OSF trials to produce the Arctic® apple began in 2003("About OSF – OK Specialty Fruits," n.d.).

## The Arctic® Apple

As stated earlier the Arctic® apple is a GMO that was produced by OSF as a non-browning apple (Armstrong, n.d.). However, the actual genes involved in this process are from the apples themselves, the genetic engineering involved used genes derived from apples themselves (Armstrong, n.d.).

The enzyme responsible for the browning process in response to physical damage or exposed flesh in Polyphenol Oxidase (PPO) (Armstrong, n.d.). This enzyme is naturally found in many plant species and is thought to be a natural defense against insects (Armstrong, n.d.) ("Consumer, environmental groups," n.d.). In Arctic® apples RNA interference (RNAi) is used to reduce PPO to less than 10% of what would typically be found ("How'd we 'make'," n.d.). RNAi involves using another RNA molecule to terminate the synthesis of the original RNA molecule and is a natural way to control gene

regulation in many species ("How'd we 'make'," n.d.). OSF scientists added these genes to the apple varieties to downregulate PPO synthesis and create the Arctic® apple("How'd we 'make'," n.d.).

This is an important part of the Arctic® apple brand as the varieties use genes that produce a product that silences the PPO enzyme, and then get degraded (Armstrong, n.d.). As such, there is no remaining structure or protein that can be ingested which might raise concerns among consumers (Armstrong, n.d.). Additionally, the final product contained no added or artificial pest resistance enzymes derived from bacterial species (Armstrong, n.d.). This means that it does not produce its own pesticides, and as a result, it Arctic® apples did not have to be reviewed by the U.S. Environmental Protection Agency (EPA) (Armstrong, n.d.).

The process for generating the Arctic® apple started in 2003, submissions to regulatory agencies were made as early as 2010 but crops and orchard were still being monitored and examined for any new data ("About OSF," n.d.). OSF highlights that third-party crop consultants were used to manage and track the orchards progress ("About OSF" n.d.). This was because OSF wanted to submit as much data as possible to the respective regulatory agencies for clear transparency around the Arctic® apple ("Agricultural," n.d.).

## The Regulatory Process

By 2011 the Arctic® Golden Delicious apple and the Arctic® Granny Smith apple had entered the review process in both Canada and the United States of America (U.S.A.), and both were approved in 2015 ("Nonbrowning GM apple cleared," n.d.). The Arctic® Fuji apple was approved for U.S.A. sales in 2016 and Canadian sales in 2018 ("Nonbrowning GM apple cleared for market," n.d.).

During the first submission (the Golden Delicious and Granny

Smith varieties) the apples participated in a public feedback program within the Canadian Food Inspection Agency (CFIA) and the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (USDA APHIS) ("How does a genetically engineered food get to the Canadian market?" n.d.) ("How does a genetically engineered food get to the U.S. market" n.d.) ("Canada seeks public input on Arctic® Apples" n.d.) ("U.S. regulator seeks comments on biotechnology-produced nonbrowning Arctic® apple" n.d.). This allowed both agencies as well as OSF to receive public (and expert) opinions and insight on the apples which was considered regarding their approval on the market ("Addressing common misconceptions," n.d.). OSF took advantage of these surveys by addressing the questions, comments, and concerns that were brought up by the individuals involved ("Addressing common misconceptions of Arctic® orchards and fruit," n.d.). Altogether, the typical review process for a GMO product, in both Canada and the U.S.A. would take around 2-3 years ("How does a genetically engineered food get to the Canadian market?" n.d.) ("How does a genetically engineered food get to the U.S. market" n.d.).

Additionally, in 2015 APHIS allowed the Arctic® apple to gain a deregulated status, meaning that they believe it does not pose a plant pest risk to other crops or plants in the US ("U.S. to deregulate," n.d.). This was done after APHIS focused on a number of issues around the plant, including potential cross-pollination, effect on biological organisms, effect on the physical environments, potential for weakened defense systems and increased susceptibility to disease ("U.S. to deregulate," n.d.). Finding no difference between the Arctic® apple and a non-GE apple APHIS provided the Arctic® apple with a deregulated status ("U.S. to deregulate," n.d.). This allows OSF to plant and distribute the Arctic® apple without restriction ("U.S. to deregulate," n.d.).

## Opinions and Opposition

2011 also OSF conduct their own surveys among potential consumers across Canada, with 1000 adults participating in this survey (Brooks, n.d.). The individuals polled were self-identified 'apple-eaters' and differed in age, education and income levels (Brooks, n.d.). Overall 62% of people surveyed thought that a non-browning apple was a good idea, while those opposed or indifferent were closely split (Brooks, n.d.). People who liked the idea of the Arctic® apple stated that the appeal was in "...would be visually appealing, fresher, last longer (and thus save money), and would result in more people eating more apples..." (Brooks, n.d.). After the initial survey respondents were then educated on the process on how the Arctic® apple was produced (Brooks, n.d.). Post education the number of people who thought the apple was a good idea and were interested in buying it increased (Brooks, n.d.). This demonstrated to the team at OSF that education of potential consumers can go a long way to improving the appreciation of their product. Following this, OSF has maintained a running blog that regularly provides insight to the company and related news, as well as their frequently asked questions (FAQ) page that addresses common questions ("OK Specialty Fruits," n.d.).

However, not all people were enthused about the Arctic® apple. That includes organizations like the US Apple Association, the Northwest Horticultural Council, and the BC Fruit Growers Association, all of which sent letters to the regulatory bodies involved to reject OSFs application for potential market disruptions ("Nonbrowning GM apple cleared," n.d.). Organisations have argued that the apple will be put it front and center for the GMO labeling debate ("Nonbrowning GM apple cleared," n.d.). Chris Schlect, then president of the Northwest Horticultural Council said "Apples are a symbolic product. It's a fruit that a mother gives to a child going to school, gives to a child going to school." ("Nonbrowning GM apple

cleared," n.d.) These groups all operate within the industry and have vested interests in keeping potential competitors bay, as well as concerns about the safety of their own crops. Once approval in the states was evident US apple released this statement "We are confident from the assurance we've received from Okanagan that they intend to stand by their pledge to clearly identify their apples in all marketing and packaging, enabling customers to choose between GM and non-GM apples." ("Nonbrowning GM apple cleared," n.d.) Again, highlighting the issues around the term GMO and how they affect the Arctic® apple.

Other corporations entered the fray later on in the movement. Fast food giants Wendys and McDonalds, as well as baby food company Gerber, have all stated they have no plans to use the Arctic® apple in their products ("McDonald's, Gerber," n.d.) ("3 Companies Say," n.d.). Upon reviewing the letters, however, Neal Carter had this to say, "The conclusion that either of these companies has 'rejected' Arctic apples is clearly false," ("McDonald's, Gerber," n.d.) Carter believes the language used implies that there may be a possible future where these organizations are open to the possibility of using the Arctic® apple ("McDonald's, Gerber," n.d.).

Organisations such as the "Friends of the Earth", an environmental group committed to keeping GMOs out of foodstuffs were even less enthused of the progress the Arctic® apple was making ("Scientists, environmental and consumer groups," n.d.). The comments they raise include the fact that this trait only serves a cosmetic purpose and therefore it may be risky in pursuing a GMO option with potential for harmful effects ("Consumer, environmental groups call on," n.d.).

The disparity towards the Arctic® apple grew once the approval was made, a decision that some say happened to fast ("Scientists, environmental and consumer groups," n.d.). Lisa Archer of "Friends of the Earth" said, "Despite the USDA's flawed approval of the GMO apple, there is no place in the U.S. or global market for genetically engineered apples." ("Scientists, environmental and consumer

groups," n.d.) Scientists associated with these groups worry about the preciseness of the RNAi method and what other genes it has the potential to affect ("Scientists, environmental and consumer groups," n.d.). These concerns were elevated further after APHIS granted a deregulated status to the Arctic® apple ("Consumer, environmental groups call on," n.d.). The main argument is that the USDA and FDA approvals were done based solely on data provided by the company ("Consumer, environmental groups call on," n.d.).

## Safety Concerns

Opposing groups raised many concerns regarding the Arctic® apple. Their primary concern was that cross-pollination of the GMO apple with other trees will remove the organic status of those trees ("Engineered Apples Near," n.d.). This could affect whole orchards as it may remove the organic status of those apples ("Engineered Apples Near," n.d.). This can affect the market, both domestically and internationally ("Engineered Apples Near," n.d.). OSF countered this by saying that cross-pollination is not a worry when it comes to apples (Brooks, n.d.). Imported and native American apples have interacted for years with no lasting harmful effects (Brooks, n.d.). Working with independent consultants OSF demonstrated that bees rarely travel outside the range of known food sources (Brooks, n.d.). They maintain the contamination of seeds would be detectable due to the infrequency in which it occurs (Brooks, n.d.). OSF also argues that if cross-pollination did occur only the seed, which is not consumed, would be contaminated and the fruit would contain no traces of the Arctic® modification (Armstrong, n.d.).

Another safety concern groups had with the Arctic® apple is the lack of PPO produced ("Consumer, environmental groups call on," n.d.). Since PPO is still believed to be involved with defense against

pests' individuals are concerned that lack of PPO will lead to more susceptibility as well as the need for higher pesticide use ("Consumer, environmental groups call on," n.d.). OSF argues that the regulation status granted by APHIS shows that the crop is not more susceptible to pests ("Addressing common misconceptions," n.d.). However, opposition maintains their stance because the orchards used by APHIS to test the apple were maintained with the use of herbicides, pesticides and fungicides meaning the data obtained should be declared inconclusive ("Nonbrowning GM apple cleared," n.d.). These concerns are legitimized because non-organic apples are reputed to have the highest pesticide levels ("Scientists, environmental and consumer groups," n.d.). Anti-GMO groups worry that the Arctic® apple growers may be forced to use even more of these chemicals to protect the crop with the natural ("Scientists, environmental and consumer groups," n.d.). OSF rebukes this by stating that that function of PPO can be seen in other crops that produce PPO is high amounts, apples had already naturally lower amounts of PPO and it may just be remnants from when the fruit was wild (Armstrong, n.d.).

A final concern is the variableness of the RNAi method of gene silencing, which is what is used to produce the Arctic® apple phenotype (non-browning) ("Scientists, environmental and consumer groups," n.d.). Opposition scientists worry that the targeting mechanism may not exclusive effect genes linked to PPO and therefore affect other genes and enzymes ("Scientists, environmental and consumer groups," n.d.). This can have a negative effect on the plant overall as it may throw the internal systems out of balance ("Scientists, environmental and consumer groups," n.d.). Anti-GMO advocates also stated the trait acquired is still purely cosmetic and can be mimicked using a vitamin C source and calcium ascorbate ("Scientists, environmental and consumer groups," n.d.). As such they see no reason to manipulate the genes and potentially produce unintentional adverse effects ("Scientists, environmental and consumer groups," n.d.).

## The Okanagan Specialty Fruits Approach

The team at OSF took a novel approach to a controversial market, perhaps learning from their early work and their corporate peers. They came up with a strategy of education and transparency ("Agricultural biotechnology," n.d.).

When sold the Arctic® apple packages will labels indicating that they are Arctic® apples, but not indicating that they're GMOs, as well as a QR code that, when scanned, takes consumers to a webpage discussing the benefits and safety of consuming the apple ("Nonbrowning GM apple cleared," n.d.) ("Arctic® apples," n.d.). This allows potential customers to become educated within the store and make their decisions right there. This webpage is part of an entire website dedicated to the Arctic® apple product, which provides consumers with a lot of information about the apple, the way it was made, apples in general and much more ("Arctic® apples," n.d.). This website also connects consumers to the OSF website.

The OSF website is structured in a similar way. Users can browse information about the OSF team and company history ("OK Specialty Fruits," n.d.). They can also learn more about the scientific practices behind OSF, Agricultural biotech, and their apple supply chain ("OK Specialty Fruits," n.d.). The team at OSF also has a permanent blog on the website, with posts written by members and other people highlighting the safety, and potential of OSF and the Arctic® apple, as well as all the steps it took to get approval and a de-regulated status ("OK Specialty Fruits," n.d.).

Lastly, OSF has been very transparent with their application process ("Agricultural biotechnology," n.d.). They have used third-party consultants to perform the management and testing of the Arctic® apple products ("Agricultural biotechnology," n.d.). They also provided everything that was required and requested by the regulatory bodies involved, and participated in voluntary studies and

public surveys to provide people with information and receive feedback ("Agricultural biotechnology," n.d.) ("U.S. regulator seeks comments," n.d.) ("Canada seeks public input," n.d.).

OSF also pushes the Arctic® apple as being convenient and healthy, something that the modern consumer would appreciate (Lane, n.d.). Being sold exclusively in sliced forms the Arctic® apple is targeted to people who want a healthy food on the go (Lane, n.d.). OSF did this primarily because of the rise in popularity of ready foods and meal prep kits, as well as the low amount of pre-prepped products that exist in the apple market (Lane, n.d.) ("OK Specialty Fruits," n.d.).

## Acquisition

In 2015 American biotechnology company Intrexon acquired OSF, realizing the potential of the independent company ("About OSF," n.d.). Intrexon has committed to the Arctic® apple and other crops that OSF has in its experimental pipeline ("About OSF," n.d.). OSF states that its mission to improve the efficiency of food production while increasing consumer appeal is supported by Intrexons mission to improve the quality of life and health on the planet ("About OSF," n.d.).

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# 29. Therapure Biopharmaceuticals: The Risky Decisions of a Growing Company

## Therapure Biopharmaceuticals: The Risky Decisions of a Growing Company

By: Kevin Romanick

### Background

The outlook for Therapure Biopharmaceuticals Inc. was very promising in the summer of 2015. Nicholas Green, president and CEO of Therapure, had led the first-of-its-kind biopharmaceutical company through another outstanding year, establishing itself amongst the top 100 companies of the Profit 500 List of Canada's fastest growing companies (Therapure Biopharma Inc., 2015). Indeed, Therapure had a great performance record, and was recognized as one of the fastest growing manufacturing companies in Canada.

In early 2016, Therapure began experiencing growing pains. They had recently received $20 million in funding from Feddev Ontario's Advanced Manufacturing Fund, and sought to expand the company's research and development (R&D) division, Therapure

Innovations (Therapure Biopharma Inc., 2015). Expansions in R&D meant pushing the company into a high stakes arena, where drug discovery can make or break a company.

To this point, Therapure had succeeded in developing three novel therapeutics. Two of these drugs had already passed FDA approval to begin phase I clinical trials. Green knew the potential risks associated with drug development, but he also knew that getting either of these drugs to the market meant substantial gains for the company, and ultimately an opportunity for Therapure to establish itself amongst the multinational pharmaceutical entities.

What Green didn't know was the long-term plans that parent company Catalyst Capital Group Inc. had in store for Therapure. Would they provide financial security while Therapure pushed new drugs into clinical trials? Or would Catalyst pull out of this high risk investment?

## Company History

*Overview*

Therapure Biopharmaceuticals Inc. is a Canadian biopharmaceutical company that was established in 2007. The Mississauga based company acquired its state of the art 130,000sq ft facility from the former Hemsol Biopharma Inc. Therapure was funded through private equity, with Catalyst Capital Group Inc. as the major shareholder. Catalyst uses a "loan to own" strategy, acquiring the discounted debt of failing companies, taking over the business, then selling at a profit after improving operations (Bloomberg, 2017; Delevingne & Tivak, 2018). Catalyst acquired Hemosol Biopharma Inc., a large scale manufacturer of protein therapeutics, in 2005 (Grant, 2007). Hemosol's crippling debt forced them to lay off 50 of their 75 employees and the company eventually filed for insolvency in

2005 (Grant, 2007). After acquiring Hemosol, Catalyst restructured the company, expanded the facility and operating capabilities, and renamed the company Therapure Biopharmaceuticals Inc.

Therapure opened their doors in 2008 as the first Canadian company of their kind (Therapure Biopharma Inc., 2008). Therapure was initially a contract development and manufacturing organization (CDMO) for complex therapeutics, but later divided the company into three separate divisions. The two additional divisions, Therapure Biologics and Therapure Innovations focussed on plasma protein therapeutics, and drug research and development, respectively. Thomas Wellner, the CEO at conception, had strategically structured the company in a way that allowed for rapid expansion. Having Therapure split into three divisions meant that they could form partnerships with other firms for the CDMO division, where they could generate steady revenue through large scale production of protein therapeutics, and finance their research and development division using this revenue stream.

*Therapure Biomanufacturing*

Therapure's CDMO business, Therapure Biomanufacturing, makes up the bulk of the company and serves as the company's primary revenue generator. The Therapure Biomanufacturing business model addresses a major challenge in the Canadian biotechnology industry; the need for Canadian start up companies to seek resources outside of the country to manufacture products (Therapure Biopharma Inc., 2008). Therapure Biomanufacturing operates by forming partnerships and long term contracts with other biopharmaceutical and biotech companies who have developed effective therapeutics, yet lack the manufacturing capabilities to bring their drugs to market. The CDMO division is highly flexible and capable of handling a wide variety of pharmaceutical contracts, from cell-line development to protein purification. The division's ability to tailor their manufacturing processes to each individual customer's needs is

reflected in the CDMO division's initial performance (Therapure Biopharma Inc., 2008).

*Early Successes & Growth*

Less than a year after their doors opened, Therapure signed several major contracts with a variety of clients. Early partnerships with companies like BioVectra Inc. saw the development of proprietary purification techniques for the production of new drug delivery mechanisms (Therapure Biopharma Inc., 2009). Other partnerships with firms such as LFB Technologies saw the development of plasma derived medicinal products (Therapure Biopharma Inc., 2009). In the first two years of business, Therapure had established enough partnerships and development service contracts to see signficant earnings, setting the bar high for subsequent years. With Thomas Wellner at the helm, Therapure sought to max out manufacturing capacity using an aggressive revenue growth plan for 2009 and beyond (Therapure Biopharma Inc., 2009).

As part of Wellner's aggressive growth strategy, the company initiated two new divisions, the first of which, Therapure Biologics, was formed from the acquisition of plasma protein purification technology from Upfront Chromatography A/S. This proprietary technology, called PlasmaCap EBA, enabled Therapure to drastically improve efficiency and precision in the extraction of plasma proteins (Therapure Biopharma Inc., 2013).

The third division, Therapure Innovations, specializes in drug discovery, research and development. Specifically, Therapure Innovations have developed novel protein therapeutics for treatment of liver cancer, anemia, and hepatitis, some of the most difficult to treat conditions in modern society (American Society of Clinical Oncology, 2017). This division has three pipeline drugs to treat these conditions, TBI302, TBI304H, and TBI301. Of these drugs, TBI302 and TBI304H have been approved by the FDA to commence phase I clinical trials (Therapure Biopharma Inc., 2015).

*Failed IPO & Buyout*

The addition of Therapure's Biologics and Innovations divisions imposed a financial stress on the company early in 2016. To remedy this, Catalyst Capital Group, having control of the company, stepped in and attempted to take Therapure public with an initial public offering (IPO). The proposed IPO had the company valued at $867 million, however many pundits viewed this critically, suggesting it was overvalued (Delevingne & Tivak, 2018). The overvaluation of Therapure resulted in a failed attempt to hold an IPO, and consequently, Catalyst began searching for alternative ways to secure funding for Therapure Innovations. As a result, Catalyst agreed to sell off Therapure Biomanufacturing and Therapure Biologics in a joint venture between 3SBio, a Chinese biotechnology company, and CPE Funds for $290 million, a valuation of less than half of Catalysts 2016 company valuation (PBR, 2017; Delevingne & Tivak, 2018).

## The Pharmaceutical Industry

*Challenges in Big Pharma*

The Canadian pharmaceutical industry is a volatile climate and has experienced several challenges in the past decade. Canadian pharmaceutical market growth has been declining since the 2008 Great Recession, which saw a number of companies declaring bankruptcy or being acquired by larger multinational companies (Government of Canada, 2014). In addition to a global financial crisis and economic downturn, the lack of new successful drugs, slow uptake of new products, more rigid drug approval processes, and loss of market exclusivity have culminated in decreased market growth (Government of Canada, 2014). To handle market declines, pharmaceutical companies have restructured their companies to diminish the effects.

*Emergence of Contract Service Providers*

As large multinational companies such as Pfizer, Merck, and Johnson & Johnson look to cut costs, production has been moved to emerging markets overseas (Government of Canada, 2014). Employment in pharmaceutical manufacturing has contracted 8% since 2007, with approximately 27,000 employees nationwide (Government of Canada, 2014). Manufacturing facilities of several multinational entities (AstraZeneca, Pfizer, Novartis, Roche, Shire and Teva) have been shut down in Canada and moved to emerging markets such as China (Government of Canada, 2014). With global pharmaceutical companies decreasing their level of direct investment by outsourcing production, contract service providers have began to fill vacant facilities. For example, Teva Pharmaceutical's Montreal facility was sold to Halo Pharmaceuticals in 2012 after moving production to China. Similarly, Pfizer sold its Arnprior facility to Korean-based Keata Pharma, both of which are contract service providers (Government of Canada, 2014).

*Biotech & Specialty Pharma*

Another way that pharmaceutical companies have coped with difficult economic conditions is by investing in biotechnology and specialty drugs. There are currently 532 biotechnology companies in Canada, representing a $4.2 billion dollar industry (Therapure Biopharmaceuticals, 2017). By 2012, biologics and specialty drugs such as protein therapeutics lead growth in Canadian sales by market segment, boasting a 12.4% growth rate (Government of Canada, 2014).

In these economic conditions, companies with pre-established CDMO business strategies, and producers of protein therapeutics and specialty drugs were at a significant advantage. Given the high demand for these complex products, small biotechnology firms could form partnerships with contract service providers to scale up production.

## Therapure's Market Position

While the pharmaceutical industry markets were a nightmare for large multinational companies, companies that could quickly change their business models were highly successful. For example, prior to market declines, Roche invested heavily in specialty therapeutics and emerged amongst the top ten corporations by annual sales in Canada for the first time ever, grossing over $700 million per year, with a compound annual growth rate (CAGR) of 3.9 from 2007 to 2010 (Government of Canada, 2014).

*A Good Fit*

In the midst of the unique situation affecting the Canadian pharmaceutical industry, Therapure excelled as one might have expected. As a biopharmaceutical and specialty therapeutics corporation whose emphasis was on their CDMO division, this was the ideal market for Therapure based on their business model. Furthermore, Therapure was equipped with the facility, equipment, and expertise needed to produce large quantities of product for partners of their CDMO division. With these capabilities, Therapure secured several large contracts and was growing at a time when most companies were struggling to keep their doors open. By 2017, Therapure ranked 115th of the Profit 500 List of Canada's fastest growing companies, their fourth year consecutively (Therapure Biopharma Inc, 2015).

*Difficult Decisions*

The long term plan for Therapure would see the three-division company producing products for partners while also producing their own line of novel therapeutics. With three pipeline drugs in development, Therapure Innovations was at a crossroads with their R&D. They could invest heavily in their pipeline drugs and potentially see significant returns, or they could divest their R&D division and focus on their CDMO. Most companies were not investing in their

R&D due to high costs and unsteady economic climates. The industry had seen a significant declines in R&D growth, and even contracted 0.9% in 2009 (Government of Canada, 2014).

To make matters worse, Therapure would need hundreds of millions, if not billions of dollars to finance clinical trials for their pipeline drugs. In 2014, the cost of drug development had increased by 146% since 2003, averaging a staggering $2.6 billion dollars (Mullin, 2014). When Catalyst had valued the company at $867 million, an initial public offering (IPO) appeared to be the best way to gather funding for clinical trials. However, Catalyst ultimately pulled off the IPO, citing volatile markets, while critics speculated that the failed IPO was a result of Catalyst's inaccurate valuation (Baigorri & Deveau, 2017). Why the IPO failed did not matter anymore, Therapure needed money, and needed it fast if it were to continue with its R&D division.

The failed IPO meant two things, 1) Therapure would not have enough money to finance clinical trials under their current business model, and 2) company expansion was becoming less of a reality. Therapure's parent company, Catalyst Capital Group, saw this as an opportunity to pull out it's investment by divesting the CDMO division, and hired Wells Fargo & Co. to help find a buyer (Baigorri & Deveau, 2017).

When Catalyst sold Therapure Biomanufacturing and Therapure Biologics to 3SBio and CPE Funds for $290 million in September of 2017, Nicholas Green was left with Therapure Innovations and their three pipeline drugs. Despite Catalyst's move to dismantle the company, Green maintained a positive outlook. In a press release with Therapure, Green said:

> "This transaction is exciting for the future of Therapure and for the Canadian biopharma industry, it will be a powerful enabler for further growth and expansion of both 3SBio and Therapure in high growth areas of the market through our combined capabilities. This will put us in a stronger position

to lead, innovate and grow, and further support our current and future clients."

From Green's perspective, the acquisition of Therapure Biomanufacturing and Therapure Biologics by 3SBio meant that all of Therapure's remaining resources could be funneled towards drug development.

## Drug Development

*High Risk, High Cost & Long Waits*

Drug development is an extremely expensive endeavour, with costs ranging from $1 billion to $3 billion, and averaging near $2.6 billion in 2014 (Institute of medicine, 2009; Mullin, 2014). Drug development is not only expensive, it is a painfully long process to bring a drug to market, and the probability that the drug makes it to the market is very low (Bains, 2004).

The process begins with the disease. R&D aims to discover everything there is to know about a particular disease, ultimately identify ideal drug targets (what the drug will act upon). Once the disease is fully understood, high throughput screens assess millions of chemicals in search of the molecule that interacts with the disease target (Bain, 2004). Once a molecular candidate is identified, it will go through preclinical testing, where drug toxicity, distribution, metabolism, and excretion will be studied. If the drug is not toxic on animal models, including mice and primates, it will be approved by the FDA for phase I clinical trials (Bain, 2004). Pre-clinical drug development has a 69% failure rate, takes approximately 4 years to complete, and costs upwards of $400 million (Bain, 2004).

Clinical trials are the most expensive and time consuming components of drug development. In Phase I clinical trials, drug efficacy and pharmacokinetics are studied in a small, healthy

population. If the drug is found to be effective and safe, it will proceed to phase II clinical trials, where the drug is tested on a small group of patients carrying the disease of which the drug is meant to treat. Again, if the drug is found to be effective and safe, the drug will move forward to phase III clinical trials. To this point, phase I and phase II clinical trials require $400-500 million, have 75% and 35% failure rates respectively, and take 2-3 years each to complete (Bain, 2004).

Phase III clinical trials are the single most expensive component of the drug development process, with costs exceeding $350 million (Bain, 2004). Phase III clinical trials assess the drug's safety and effectiveness in a large and diverse population, in addition to looking for adverse effects. It serves to validate dosages and formulations, and provides the first platform for marketing material. Phase III clinical trials have a failure rate of 58% and take approximately 2 years to complete (Bain, 2004). Upon successful completion of clinical trials, pharmaceutical companies typically launch massive marketing campaigns and begin selling at high prices as they look to gain returns on their longterm, high risk investment.

## All Their Eggs in One Basket

With a sleeker Therapure that had fewer moving parts, Green could thoroughly re-assess the company's needs. To be successful, Therapure Innovation needed to find success with at least one of their pipeline drugs, and needed to finance clinical trials. Having 3SBio's newly acquired facilities in-house made production of the therapeutics fast and cost effective. Downsizing the company to a single R&D firm meant fewer expenses, and the company could function for longer on less. To this day, Therapure Innovations has no money coming in, and needs new revenue streams.

In the long term without external investors, Therapure Innovations

cannot afford to bring their three drugs to market, however, they may be able to bring one drug to the market. If Therapure Innovations can succeed in bringing just one of their candidate drugs to market, they will generate enough revenue to continue operations. This may be accomplished through private investors, or by going public with an IPO. An IPO would bring in an estimated $100 million, according to company insiders (Baigorri & Deveau, 2017). Additional funding may be secured by selling off the remaining pipeline drugs to other companies who can develop them. On March 28th 2018, Therapure Innovations announced that the company confidentially submitted a draft registration statement on Form F-1 with the U.S. Securities and Exchange Commission (SEC), relating to the proposed initial public offering of its common shares. The IPO is expected to commence after the SEC completes a thorough review (Business Wire, 2018).

## Company Buyout

*The Buyout Fever*

Therapure's proprietary drug candidates increase the company's value significantly, positioning Therapure for a buyout by a larger pharmaceutical company. In what has been termed the "Biotech Buyout Fever," 2017 saw several major pharmaceutical companies buying out smaller biotech (Brush, 2017). Takeda Pharmaceuticals bought cancer drug biotech company Ariad Pharmaceuticals for a 75% premium, resulting in a 400% increase in Ariad's stock value (Brush, 2017). Derma Sciences, another biotech company, jumped 40% after being acquired by Integra LifeSciences, and CoLucid Pharmaceuticals jumped 32% after its acquisition by Eli Lilly and Company, a global pharmaceutical giant (Brush, 2017). These trends are expected to continue well into 2018 and beyond, as large

pharmaceutical companies struggle to accommodate the rapidly changing industry.

*Stale Industry*

This trend is due in part because large pharmaceutical companies are running out of ideas for drug development. In 2016, the FDA approved only 22 new drugs, none of which were "blockbuster" drugs ((drug revenue exceeds $1 Billion per annum) Brush, 2017). Brian Skorney, a biotech analyst from Baird Equity Research, suggested that pharmaceutical companies are going stale and experiencing an "innovation gap," as few new revenue generating products are being developed (Brush, 2017). Big pharmaceutical companies will look to fill these gaps by acquiring other companies.

*Wanted: a New Home*

Therapure Innovation is in a situation that begs for a buyout. With two drugs ready to begin phase I clinical trials, a larger pharmaceutical company could acquire the company and immediately begin clinical trials, wasting no time on R&D. Therapure must raise hundreds of millions of dollars to initiate clinical trials, while the chance of any drug candidates reaching the market remains dreadfully low (Bains, 2004). A buyout would provide Therapure with stability and opportunity to develop new therapeutics while their current pipeline drugs are undergoing clinical trials, ultimately maximizing the possibility of a drug reaching the market.

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# 30. CRISPR Therapeutics – Novel Use of CRISPR/Cas9 Technique in Disease Therapy

VIOLA HALDER

## *CRISPR Therapeutics – Novel Use of CRISPR/ Cas9 Technique in Disease Therapy*

### A Case Study

Created by Viola Halder

Since the advent of CRISPR/Cas9 based genome-editing technology, researchers have been quite excited about its potential applications including gene deletion, gene regulation, mutated gene repair for chronic disease therapy and much more (Menn, 2017; Tycko, Hess, Jeng, Dubreuil, & Bassik, 2017). On a slightly chilly morning – October 28, 2013 –Emmanuelle Charpentier, Rodger Novak and Shaun Foy decided to do something about this. They founded CRISPR Therapeutics (CRISPR Tx) with the mission to find and develop transformative gene-based medicines for serious diseases using CRISPR/Cas9 gene editing platform fill the void that existed in CRISPR based therapeutics (CRISPR Therapeutics, 2018a). Emmanuelle Charpentier stated in a recent interview with Alyson

Weidmann the reason behind CRISPR Therapeutics (Weidmann, 2018):

> I am very excited about the potential of CRISPR-Cas9 for the treatment of serious genetic diseases for which there is currently no cure but also for cancer or infectious diseases. This is one of the reasons I co-founded CRISPR Therapeutics.

## The Company

CRISPR Tx started with its headquarters in Zug, Switzerland, where all of their efforts were put into research and development activities in determining CRISPR based therapeutic strategies (SEC, 2016). Initial market development was accomplished, substantial capital was raised and, in 2014, foundational intellectual property, for the use of CRISPR in human therapeutics, underlying the research was licensed to CRISPR Tx and its subsidiaries (SEC, 2016). CRISPR Tx formed CRISPR Therapeutics Limited in the United Kingdom on February of 2014 for select business operations, and CRISPR Therapeutics Incorporated in Cambridge, Massachusetts, USA for research and development operations, both wholly-owned subsidiaries (CRISPR Therapeutics, 2018a; SEC, 2016).

The goals of CRISPR Tx were outlined (see Figure 1) and included the following (CRISPR Therapeutics, 2017b):

1. Focus on the hematopoietic system (related to blood) through *ex vivo* (within cells, but outside of the body) approaches
2. Pursue select therapies requiring *in vivo* (within cells, inside the body) approaches
3. Foster relationships with Bayer and Vertex (using joint ventures

and collaborations)

4. Advance our position to become leaders in the field of gene editing

As of June 2016, CRISPR Tx has raised almost $140 million, with $38 million in B-series funding (CRISPR Therapeutics, 2017a). Part of the B-series funding was from pharmaceutical firms such as GlaxoSmithKline, Vertex Pharmaceuticals and Bayer and biotech companies such as Celgene and New Enterprise Associates (CRISPR Therapeutics, 2017b). See Figure 2 for visual representation. In October 2016, after their initial public offering, the company was able to raise an additional $56 million (Gallo, Jr, Sarata, & Cowan, 2018). The company also participates in joint ventures and collaborations with a variety of different companies to find cures for diseases such as Cystic Fibrosis, Sickle cell disease, severe combined immunodeficiency and haemophilia (CRISPR Therapeutics, 2017b). CRISPR Tx also partnered up for a joint venture with Bayer AG to create a new company – Casebia Therapeutics – whose sole purpose was "to discover, develop and commercialize new breakthrough therapeutics to cure blood disorders, blindness, and congenital heart disease" (CRISPR Therapeutics, 2015). Part of the agreement included that Bayer would provide $300 million in research and development investments over the next five years for the joint venture while taking a stake in CRISPR Therapeutics for $35 million (CRISPR Therapeutics, 2015). As of March 23, 2018, CRISPR Tx's market capitalization was $2.049 million (Bloomberg®, 2018).

The team at CRISPR Tx consisted of experts in not only CRISPR/Cas9 technology, but also in gene editing, stem cell biology, advanced drug delivery technologies, RNA interference and gene silencing (CRISPR Therapeutics, 2018a). Scientific Advisors and Investors included Stephen Elledge (renowned expert in DNA repair and damage responses), Craig Mello (Nobel Laureate in the discovery of RNAi – form of gene editing) Matthew Porteus (renowned expert in

gene edition) and Dan Anderson (famous for early works in CRISPR *in vivo* delivery) (CRISPR Therapeutics, 2017b). With these and many more experts in the field, CRISPR Tx was well on its way to create CRISPR based therapeutics for serious human diseases. Charpentier stated that (Weidmann, 2018):

> It is our aim to better understand … mechanisms and generate new findings in basic science that can possibly be translated into new biotechnological and biomedical applications, e.g., genome editing tools or anti-infective strategies.

## The Technology

Targeted mutations in the mammalian genome have been the focus of genetic research since the 1980s, creating the field of genome editing (Dow, 2015). The methods related to genome editing has been the recent focus for scientists, regardless of the fact that the field is not novel (Dow, 2015). Scientists have discovered techniques that have become efficient, specific and versatile over the years (CRISPR Therapeutics, 2017b). The primary goals were to discover a technique which could allow for site-specific mutagenesis in eukaryotes (comprised on animals, plants and fungi) (Jiang, Bikard, Cox, Zhang, & Marraffini, 2013) while also providing genome editing strategies in other organisms (Gilbert et al., 2013).

A few techniques that have been the forefront of genome editing, prior to CRISPR/Cas9 system, were zinc finger nucleases (ZFNs) and TAL effector nucleases (TALENs) (Gaj, Gersbach, & Barbas III, 2013). Both had the capacity to modify genes with the induction of double-strand breaks in DNA (cutting both strands of the DNA within a cell) (Gaj et al., 2013). Once the DNA is cut, DNA repair mechanisms within the cell where damage has incurred are recruited to repair

the specific genomic locations (Dow, 2015; Gaj et al., 2013). Regardless of the potential associated with ZFNs and TALENS, there are some limitations to the technologies that have frustrated scientists (Dow, 2015). For both techniques, the process required to engineer the molecules associated are quite difficult and require long and expensive steps (Dow, 2015). Aside from that, there is an intellectual property wall that exists with regards to ZFNs, that makes it challenging for scientists to apply it easily (Dow, 2015). CRISPR/Cas9 does not have these drawbacks and can be used with relative ease and accuracy.

CRISPR/Cas9 construct was discovered to be the immune system used by bacteria and other prokaryotic organisms to fight against foreign invaders (Cong et al., 2013). The system uses an RNA-dependent system (guide RNA) for sequence-specific detection and silencing of invading nucleic acids (Jinek et al., 2012). The CRISPR/Cas9 system add to the CRISPR array as the host prokaryote comes across foreign DNA (Jinek et al., 2012). The CRISPR array is formed into a CRISPR RNA (crRNA); The crRNA guides the Cas9 protein to a particular location on the DNA to allow Cas9's endonuclease activity cleave (cut) both strands of DNA, causing a double-strand break (DSB) (Cong et al., 2013). After the DNA is cut, the cell depends on the DNA damage repair mechanisms of the host to repair the damage and return the cell to normal function (Cong et al., 2013). Cong and his colleagues (2013) created the most efficient version of CRISPR/Cas9 system (CRISPR 2.0) by discovering the important components of the original to work in mammalian (humans, mice, etc.) cells. In this version, the construct includes the Cas9 protein and a small guide RNA (sgRNA) is used to replace the crRNA (Cong et al., 2013).

While the biological definition is difficult to understand at the basic level, another way to define CRISPR/Cas9 is basically as a set of molecular scissors that can cut DNA. Then, the cell's own repair machinery can repair the cut which results in disruption or deletion a disease-causing gene or correction that gene if the desired DNA is

added as a template (CRISPR Therapeutics, 2018a). A second analogy can compare CRISPR/Cas9 technique to two keyboard shortcuts used sequentially: CTRL-F, followed by the delete key. The sgRNA functions as CTRL-F to find the target DNA of interest, and the Cas9 protein functions as the delete key to delete the DNA of interest (Menn, 2017).

Furthermore, the patent war that has existed between the Broad Institute and University of California, Berkley (UC Berkley) since 2016 (Hamermesh & Preble, 2016) has officially been resolved as of January 2018 (Servick, 2018). The Broad Institute won the patent rights in the United States but are still on the battlefield in the European landscape; they have planned to file an appeal to overturn the revocation decision (Servick, 2018). That being said, Emmanuelle Charpentier, along with Dr Ines Fonfara and the University of Vienna entered into a patent assignment agreement in November 2014 which was under investigation for interference (SEC, 2016). However, since the European Patent Office (EPO) revoked the Broad Institute's claim for the patent, it is assumed that the EPO intends to grant the patent to UC Berkley and its affiliates (such as CRISPR Tx) (Mukherjee, 2017).

> The patent would cover uses in multiple cell types, including humans – the main focus of companies developing treatments for everything from cancer to HIV/AIDS and various genetic disorders using CRISPR.

See Figure 3 for more details.

This technique has the benefit of being efficient, specific and versatile (CRISPR Therapeutics, 2017b) as outlined in Figure 4. Therefore, CRISPR/Cas9 has the implication that genes – which serve as the blueprint of all life – are not predetermined; they can be controlled, changed and moulded when needed.

## The Problems and Solutions

While CRISPR/Cas9 technology has existed since its discovery in the early 2000s (Jinek et al., 2012), two problems existed. One, the technique still had to be used in humans; there needed to be a way to allow for the CRISPR/Cas9 construct to enter the cells that required genome editing without harming the rest of the body. This was made clear by Dr Feng Zhang, one of the scientists who discovered the non-prokaryotic uses of CRISPR (Weidmann, 2018):

> One of the persistent challenges facing the field of genome editing is the need to be able to deliver systems with all the elements needed to efficiently and precisely integrate a DNA template into the intended location of the genome.

George Church, the principal investigator in a lab responsible for establishing CRISPR platforms for engineered organs, agreed with Dr Zhang in stating (Weidmann, 2018):

> It would be nice to have higher efficiency delivery *in vivo* [inside the body] …

A few solutions were proposed by CRISPR Tx in order to solve this dilemma. First, an ex vivo strategy was explored in order to allow for CRISPR/Cas9 based therapeutics to succeed (CRISPR Therapeutics, 2018b). Figure 5 depicts what may happen in such a strategy: damaged cells harvested from the body (autologous or self-donated), then CRISPR is applied to them – the single gene is edited as required, and finally the edited cells are transplanted back into the patient where they can function normally (CRISPR Therapeutics, 2018a).

This problem was further explored by Dan Anderson, made famous for his early works in CRISPR *in vivo* delivery (CRISPR Therapeutics, 2017b; Yin et al., 2016). It was discovered, by him and others working within the company, that viral and non-viral means of CRISPR/Cas9

construct delivery into the cells can be achieved with variable results (CRISPR Therapeutics, 2018b; Yin et al., 2016). In this situation, as seen in Figure 5, the CRISPR/Cas9 construct is packaged inside a delivery vehicle of some sort and this vehicle is delivered into the body – either to the organ of interested or into the blood so it can travel systemically throughout the body (CRISPR Therapeutics, 2018a). Figure 6 outlines the different non-viral and viral delivery vehicles that were identified for use in CRISPR based therapy. These were established using various joint venture and collaborations with MIT, CureVac and StrideBio (CRISPR Therapeutics, 2017c, 2017d, 2017e).

Both *in vivo* and *ex vivo* strategies require further research to determine which will result in greater success. Research is also required for the different *in vivo* delivery vehicles to determine which offers the greatest benefit while reducing any unwanted toxic effects.

The second problem was to determine what type of diseases would be ideal for discovery and development of CRISPR based therapeutics? There are over 10,000 human diseases that are monogenic – a single gene in the human DNA that is mutated, causing 1 in every 100 babies to be born with the disease (Genomic Resource Centre, 2018). Tay Sachs, Cystic Fibrosis, Huntington's disease, Sickle Cell disease (SCD) and Thalassemia are a few examples of such diseases (Genomic Resource Centre, 2018). Monogenic diseases have been at the forefront of clinical and scientific research. Scientists were curious to research whether CRISPR/Cas9 can be used to address genetic defects to determine if genetic editing is an option or not (CRISPR Therapeutics, 2018a). CRISPR Tx established some *in vivo* therapies based on research for Sickle Cell disease (SCD) and b-thalassemia.

There are over 300000 babies born with SCD and over 60000 babies born with b-thalassemia (Genomic Resource Centre, 2018). Both diseases are hemoglobinopathies because they cause mutation with the globin subunit (part) of haemoglobin, part of the red blood

that carries oxygen and is quite important (Genomic Resource Centre, 2018). Both diseases are monogenic – a gene in chromosome 11 is mutated (changed) for both – which causes blood to be inefficient in transporting oxygen where required (Genomic Resource Centre, 2018). Both diseases are associated with anaemia (low red blood cell volume resulting in pale skin and exhaustion), pain and early death (CRISPR Therapeutics, 2018a). One approach to reducing symptoms is to go through a blood transfusion to replace the damaged cells, which increase the number of hospital stays as well as expensive (CRISPR Therapeutics, 2018a).

CRISPR Tx created an *ex vivo* CRISPR/Cas9 based therapy – denoted CTX001 – utilizing the fact that fetal haemoglobin has shown positive results in dealing with hemoglobinopathies.Increase in the levels of foetal haemoglobin in the blood has been known to alleviate morbidity and mortality rates for both SCD and β-thalassemia while decreasing transfusion requirements (Musallam et al., 2012; Powars, Weiss, Chan, & Schroeder, 1984).

> CTX001 is an investigational CRISPR gene-edited autologous hematopoietic stem cell therapy, in which a patient's hematopoietic stem cells are engineered to produce high levels of foetal haemoglobin in red blood cells to alleviate transfusion requirements for β-thalassemia patients and painful and debilitating sickle crises for sickle cell patients. – Emmanuelle Charpentier (Weidmann, 2018).

This novel CRISPR based therapy is currently in clinical trials in Europe for β-thalassemia and USA for SCD.

## Current Pipeline/The Future

Currently, CRISPR Tx has eleven potential CRISPR based therapies

in their pipeline at various stages of research (See Figure 7) (CRISPR Therapeutics, 2018b). They are either in vivo or ex vivo, and range from being causing DNA disruptions to correct mutated genes by adding the appropriate repair template (CRISPR Therapeutics, 2018a). The potential therapies also range from being wholly owned by CRISPR Tx, to being in collaboration or a joint venture with other therapy based companies such as Vertex or Casebia (CRISPR Therapeutics, 2018a). The 4 major areas for CRISPR based therapies include (i) ex vivo programs of hematopoietic cells, (ii) ex vivo programs for immuno-oncology (using the built-in immune system to fight cancer cells), (iii) in vivo programs targeting the liver and (iv) in vivo programs targeting muscle and lung systems (CRISPR Therapeutics, 2018a). Conclusion

CRISPR Therapeutics took advantage of a void that exists in the field of genomic research by bridging the gap between scientific research and the biomedical community. Emmanuelle Charpentier knew that she and her colleagues had to take advantage of the potential associated with CRISPR/Cas9 technology. She was aware that the potential applications including gene deletion, gene regulation, mutated gene repair for chronic disease therapy and much more were quite exciting and a challenge that she and all her colleagues were more than willing to take up.

When asked about the future of CRISPR technologies, Emmanuelle Charpentier was quite excited about its prospects (Weidmann, 2018):

> The CRISPR-Cas technology is extremely versatile. For this reason, it was adapted around the world where scientists are applying the technology for the basic understanding of mechanisms of life in a large diversity of cells and organisms and are working on potential future applications.
>
> I am very excited about the potential of CRISPR-Cas9 for the treatment of serious genetic diseases for which there is

currently no cure but also for cancer or infectious diseases. This is one of the reasons I co-founded CRISPR Therapeutics.

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# Figures

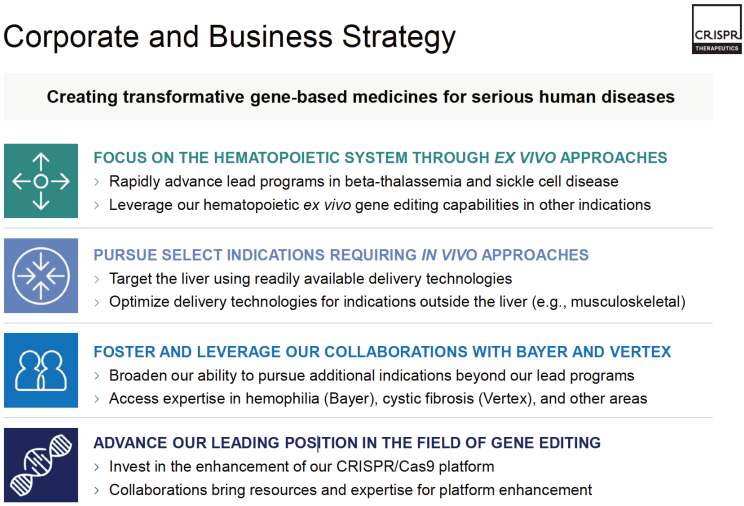


*Figure 1: CRISPR Therapeutics Corporate and Business Strategies outlined in the Corporate Overview* (2017)

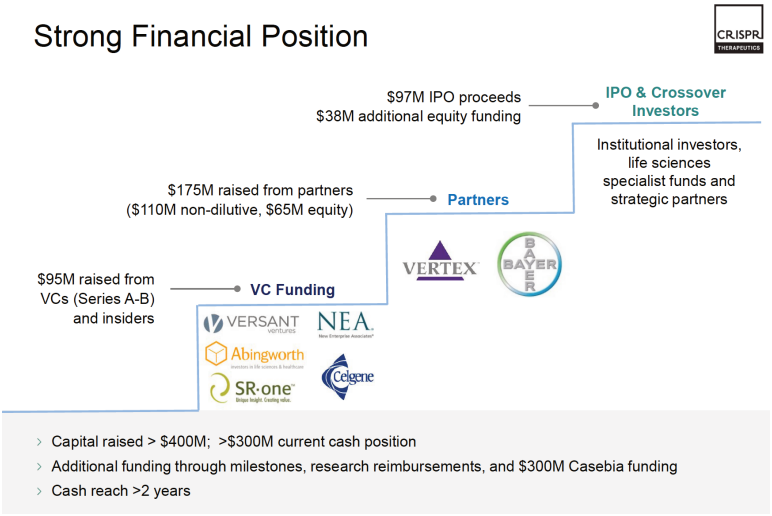


*Figure 2: Financial Strategies utilized by CRISPR Therapeutics (CRISPR Therapeutics, 2017b)*

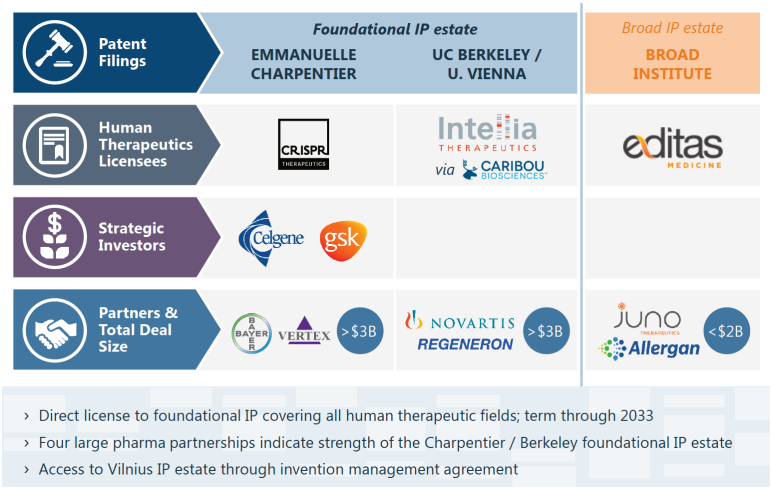


*Figure 3: Intellectual Property, licensing and strategic investors associated with CRISPR Therapeutics (CRISPR Therapeutics, 2018b).*

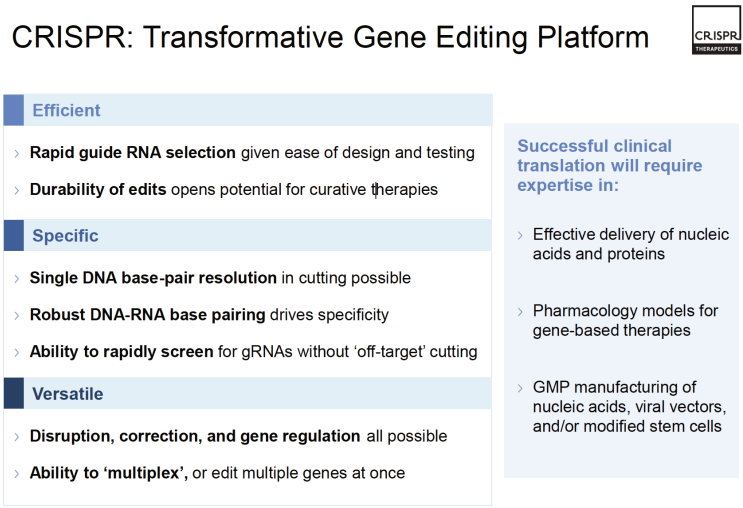


*Figure 4: CRISPR Therapeutics have aimed to take advantage of these properties of CRISPR*

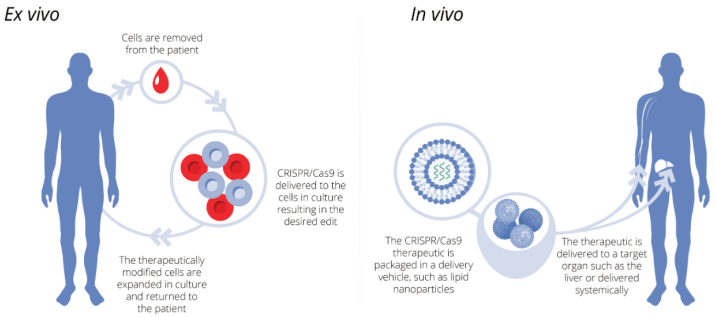


*Figure 5: Ex vivo and in vivo strategies for utilizing CRISPR/Cas9 for disease therapy as outlined by CRISPR Therapeutics (CRISPR Therapeutics, 2018a).*

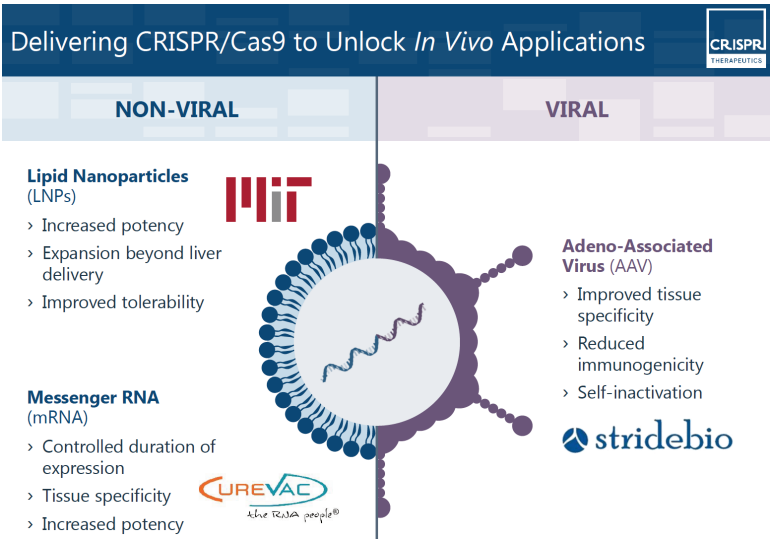


*Figure 6: In vivo non-viral and viral delivery vehicles usable for CRISPR based therapy (CRISPR Therapeutics, 2018b)*

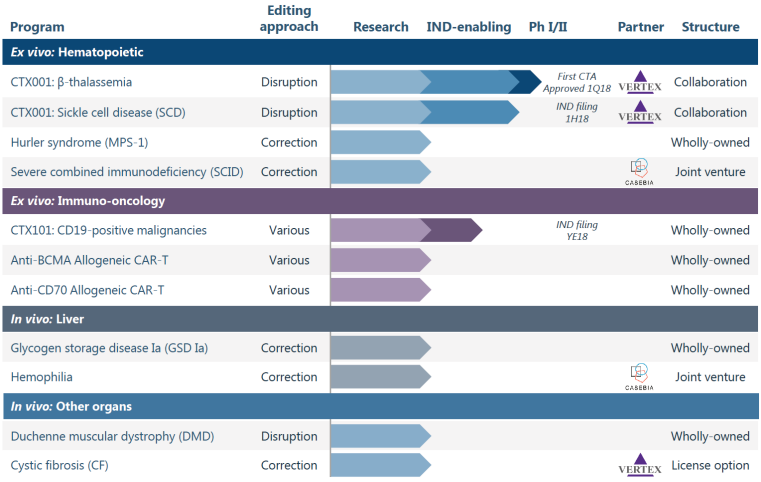


*Figure 7: Current product development pipeline for CRISPR Therapeutics as of January 2018 (CRISPR Therapeutics, 2018a)*

# *CRISPR Therapeutics – Novel Use of CRISPR/Cas9 Technique in Disease Therapy*

# 31. Vertex Pharmaceuticals

## Vertex Pharmaceuticals

By Allan Humphrey
April 08, 2018

### Introduction: Living with Cystic Fibrosis

Jillian McNulty of Ireland has a story similar to that of many others who suffer from Cystic Fibrosis. Both in her childhood and adult life she's had to visit the hospital at least once a month, at the easiest of times, but during the hardest, she would spend 12-13 straight weeks there. The hospital visits were for any number of symptoms including malnutrition, chronic indigestion, extreme difficulty in breathing or for life-threatening lung infections. These conditions were so severe that Jillian and her family were considering a lung transplant to help alleviate these symptoms, something that would be difficult to obtain, due to a shortage of donors and the cost to her family. It was around this time, in 2015, that Jillian's doctor prescribed her a new drug that was just on the market. The drug, Orkambi, promised to treat more patients than any previous treatment for cystic fibrosis to date. It also claimed to target the cause of the disease rather than just treating the symptoms, which is what, up until now, Jillian had been receiving during her long hospital visits. Within months after starting Orkambi Jillian's health had improved drastically, the debilitating symptoms that she had been suffering her whole life were slowly cleared away.

Two years after starting treatment Jillian managed to stay hospital visit free for over 12 months, and even after contracting swine flu, an infection that surely would have killed her before, she was capable of fighting the infection and made a full recovery. This drug changed her life for the better, something that many Cystic Fibrosis patients are still desperate for (Ryan, 2016).

The drug, Orkambi, was developed by a pharmaceutical company called Vertex Pharmaceutical from Boston Massachusetts. Vertex's current company goals have been to develop treatments for Cystic Fibrosis that go beyond just trying to sustain the patients by treating the symptoms. This was not an easy task for Vertex. To start, Cystic Fibrosis is a complicated disease, that has implications from the genetic level all the way to full tissue organ and systemic conditions. Secondly, before going all in on Cystic Fibrosis, Vertex was not doing well, either finically or on the drug discovery front.

This report aims to tell the story journey of Vertex Pharmaceuticals, from their start as a small biotech start-up, and through their ups and downs as a company over the past decade. The purpose of the report is to see why certain decisions (and lucky breaks) were made that ultimately lead to their current success. Before the story of Vertex can be told, the complexities of Cystic Fibrosis and developing drugs for rare conditions need to be considered.

## Cystic Fibrosis: One Disease, Many Complications

Cystic Fibrosis (or CF), is a disease that has a long history, with the first evidence of cases going back hundreds of years. In the past, the cause of CF was not clear. With many different symptoms and manifestations of the disease, it was difficult to understand the

disease and also problematic to treat medically (Nick, 2012). Today, a much better understanding of CF exists due to breakthroughs in genetic/molecular technologies and diagnostic techniques.

While it was always understood that CF was genetically linked and spread through heredity, it wasn't until 1989 the one specific gene was identified, named the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene. While it may seem that this condition should be simplistic, with only a single gene being implicated in CF, it turns out that there are many (over 2000) mutations that have been identified in humans, with 127 of these directly linked to causing CF, thus adding to the complexity of treating CF. The CFTR gene codes for the CFTR transport protein which helps shuttle chloride ions into and out of cells ("Understanding CF | Vertex Pharmaceuticals," n.d.). Basically, it is responsible for maintaining the balance of salt and mucus content on the inside and outside of cells. Some tissues are more susceptible to a damaged CFTR system, such as the lungs, where mucus can build up and restrict airways, causing difficulty breathing. There is also an increased risk of infection as the mucus cannot be easily removed from the lungs as normal, allowing pathogens to be trapped and do damage. CF also has effects in other tissues of the body including the digestive systems (liver bile production and pancreas activity) which leads to an inability to absorb nutrients which manifests in many different malnutrition issues ("Understanding CF | Vertex Pharmaceuticals," n.d.).

Ultimately, these conditions mean that people that suffer from CF have significantly shortened life spans, around 39 years on average (Davies, Alton, & Bush, 2007). This makes finding a treatment that deals with the underlying cause of CF and not just the after effects very important to those suffering from this disease.

## Challenges with Treating Rare Diseases

Besides the biological complexity of CF, the challenge of treating the disease also comes from its status as a 'rare disease'. A disorder is considered rare when less than 200 000 people are affected by it (ICON, 2018). Cystic Fibrosis is considered a rare disorder with only approximately 75 000 people (in USA, Europe and Australia) diagnosed with it ("Understanding CF | Vertex Pharmaceuticals," n.d.). Like most rare disease this creates challenges for drug development.

The first challenge is a financial one. Drug discovery and approval processes are expensive and time-consuming, costing on average around $500 million can take anywhere from 5-15 years (depending on the drug and disease) (Shimasaki, 2014). A rare disease that affects a smaller number of people also have a smaller potential market and therefore it is difficult to justify the cost of investment to develop these drugs. This is especially true when considering the risk that many drug trials fail, with only 13.8% of drugs making it from initial discovery through to approval (Cross, 2018). Secondary challenges also exist with rare drug discovery, such as having fewer people available for clinical trials to meet the FDA approved standard (Fagnan, Gromatzky, Stein, Fernandez, & Lo, 2014).

Given these challenges for rare diseases, previous treatments for Cystic Fibrosis did not target the genetic or molecular cause of the symptoms but rather physicians used already developed and approved drugs and treatments to treat the symptoms directly. Some examples include antibiotics to treat lung infections, anti-inflammatories to reduce airway restriction as well as nutrient supplementation to deal with malnutrition due to poor absorption (Davies et al., 2007). One can imagine that these are only a temporary solution and CF patients needed a drug that could treat the cause.

# Vertex Pharmaceuticals: Roller-coaster Pharmaceutical Development

Vertex Pharmaceuticals originated as a small pharmaceutical start-up company that was founded in 1989 by Josh Boger. Originally opening in Cambridge, Massachusetts, it was riding the new wave of biotech innovation from the previous decade, with new molecular technologies opening up new avenues for studying disease and drug discovery. With many team members coming from other large pharmaceutical companies, Vertex wanted to take a different approach to developing drugs. Their method was unique as they heavily invested in research and development into the diseases they wanted to develop drugs for and they specifically focused on using new techniques that utilized computer software to identify potential drug targets base on molecule structure. Using this unique model they wanted to develop breakthrough drugs that tackled difficult diseases where there weren't current treatment options. They wanted to be different than Big Pharma, they wanted to generate revenue but also help people (Boston, 2001). Another key to their strategy was Boger's focus on tackling many different projects at once. His thought that having many drug developments in the pipeline may help if one fails during trials, there is another candidate that's already in development.

Although they struggled at first, the members of the team did not want their company to be bought out by a large pharmaceutical company, they had all worked there before and had faith that their model would work (Macaluso, 2014). Their first focus was on anti-viral drugs but they had little success at first leaving the start-up low on resources. The company then went public in 1991, to raise funds (making around $25 million dollars). They used this capital to focus their efforts on HIV treatment since HIV was still an emerging disease in that era (Boston, 2001). This decision seemed to pay off as

their drug Agenerase was approved in 1999 by the FDA and began to sell in the following year. By the end of the year 2000, their annual revenue was at its highest ever at $26.9 million (Griffith, 2001). Vertex stock had also shot up to it's highest point in history with shares in December 2000 closing at $78.48 up from $13.56 from the year prior ("Historic Stock Lookup | Vertex Pharmaceuticals," n.d.).

Vertex did not rest on the success that Agenerase had brought and continued their strategy to invest in research and development for a number of drugs. They understood that you cannot rely on the success of one drug to sustain you, with competitors and generics coming down the pipeline which will cut into Agenerase sales. One of the main focuses for Vertex research investment was Hepatitis C. The Hepatitis C research had already been in development and was starting to show promise, and with the boost from Agenerase's success, they could continue to develop it. However, the drug was still many years off from being approved and with a few other failed projects Vertex's stocks began to sink over the next few years (closing at $9.21 in December 2003) ("Historic Stock Lookup | Vertex Pharmaceuticals," n.d.).

During this time Vertex had also started projects involving Cystic Fibrosis. In 2001, when vertex had acquired the company Aurora Biosciences their CF research took another step forward due to a 40-million-dollar collaboration that existed between Aurora and the Cystic Fibrosis Foundation (CFF) (Higgins, LaMontagne, & Kazan, 2007). With funding from CFF and expertise in the area from Aurora team, the CF projects remained in Vertex's pipeline; however, these were not the main focus for Vertex. There were a lot of complications surrounding developing drugs for CF given that it was a rare disease. They did not want to divert too many resources from their other projects since developing drugs for rare diseases is risky and they did not want to lose the confidence of their investors. There were also concerns from the CFF since the funding wasn't originally meant to go towards a for-profit company like Vertex, but they continued to

support the research since the foundation's ultimate goal is to find a cure for the disease (Weisman, 2016).

Over the next decade Vertex ran into problems with many of their projects failing to make it through to clinical trials, however, in 2011 they finally saw a second successful drug make it through approval. This was for the Hepatitis C drug, Incivek, which at this point had been in development for the past 15 years (Macaluso, 2014). This was a much-needed break for the company and it was reported that it was the first time that the company was regularly profitable. The Incivek drug was something of an overnight success, with Vertex total pharmaceutical sales reaching over $585 million dollars up from the previous quarter's sales of $75 million (Feuerstein, 2011). The drug had the designation of the "fastest selling drug in history" when it sold over a billion dollars within its first year of sale (Macaluso, 2014). Vertex's stock at the end of October 2011 closed at $43.99 which was the highest it had been since the 2001 spike ("Historic Stock Lookup | Vertex Pharmaceuticals," n.d.).

Even with the successful launch of the drug Vertex would still have to endure challenges. While Incivek success seemed like the beginning of a new start for Vertex, the horizon of its sales suddenly seemed bleak. A competitor drug, Sovaldi (from Gilead Sciences) was set to be released. This drug had a better efficacy and was sold a cheaper price. This quickly battered Incivek sales and by 2012, Vertex's stocks were down 50% from the previous year (Herper, 2017). For a company that took over 22 years to see a regular profit and had invested over $4 billion dollars in drug development over that time period, it seemed doomed to cave now that their flagship Hepatitis C drug was being destroyed by the competition. However, thanks to Vertex's focus on having many projects in the pipeline, and a change in leadership, they were still in the game

## Enter Jeffery Leiden

For those in the biotech and pharmaceutical industry, Dr. Jeffery Leiden needs no introduction. He had an illustrious academic career, starting from elementary school (where he skipped a grade), to high school (which he left early after being accepted to university during his junior year). This trend of academic excellence continued and he had earned both PhD. in biological sciences and a Medical Degree from the University of Chicago before the age of 25 (Huggin, n.d.). Leiden's accolades continued into his career, where he became a seasoned cardiologist, and then stepped into the biotech realm where he saw the successful launch of arthritis and HIV drugs during his tenure as CEO at a pharmaceutical company called Abbot Laboratories (Herper, 2017).

As Leiden entered Vertex in 2012, they were struggling due to the unfortunate circumstances surrounding the quick success but the immediate drop in their drug Incivek. He was still interested in working with Vertex, since they had a reputation of being research focused in the past, with a real passion for discovering breakthrough drugs. Leiden wanted to reignite this part of the company with their Cystic Fibrosis projects.

## Vertex and Cystic Fibrosis: A Shift in Focus

During the 2000s Vertex had mostly focused on getting Incivek onto the market; however, they still had a team working away on Cystic Fibrosis projects that were acquired 10 years earlier with the Aurora Biosciences acquisition. This team, like most Vertex projects, focused heavily on researching the disease and not just drug development. This research into the genetics and on the CFTR gene (which had

been ongoing for the past 12 years) paid off as the team had found a molecule that offered CF treatment that was targeting the actual protein malfunction due to mutation. This drug, called Kalydeco, would gain FDA its approval right before Leiden started as CEO. It targeted the CFTR protein directly, allowing it to let some chloride ions through (where defective CFTR does not) and thus returns the salt and mucus balance of the membranes to alleviate symptoms in the lungs and pancreas. It was the first breakthrough Cystic Fibrosis drug that looked to address the cause of CF and not just deal with the symptoms (Herper, 2017).

While it was a breakthrough, it was not enough to save the company from the failing Incivek, with Kalydeco only doing around $317 million in its first year (compared to Incivek's billion dollars in the same time frame). This is because the drug only worked for a small percentage of the CF patients (around 3000) and because only a small percentage are affected by the mutation that Kalydeco deals with. This is where targeting a rare disease can be financially dangerous, you need to be able to treat a good portion of those affected, otherwise, your drug will have to be very expensive to cover costs.

Leiden did what he could to save the company, by cutting costs through a workforce reduction of 15% (Herper, 2017). However, Leiden saw the potential in CF treatment and research. The team was already working on other promising CF projects at Vertex, and with their monopoly on the genetic research, this could be the area where they would have the lead. This coupled with the fact that there was still money coming in from the Cystic Fibrosis Foundation (funding had increased to $125 million), meant that Leiden did not need as much from investors, who had begun to lose faith in the company after the Incivek debacle (Garde, 2017). Another advantage he saw was that a focus on one disease, where they have the monopoly, would mean that they could reduce spending on advertisements and funnel that back into the research and development. With pharmaceutical

companies traditionally spending anywhere from 27-33% of budgets on advertising, this was an opportunity for substantial savings for Vertex (Staton, 2013).

Leiden's plan with CF was to continue to further understand the genetic causes and find targets that would help more CF patients than Kalydeco alone. All this focus on CF research paid off as Vertex's second drug Orkambi, was approved in 2015. This drug may not have been as effective of a treatment in relieving CF symptoms compared to Kalydeco, but it did target a mutation that was more common in people with CF and thus could treat more patients, around 25 000 worldwide. In 2016 Kalydeco and Orkambi generated $1.7 billion for Vertex (Tirrell, 2017), and upwards of $2 billion in 2017 (Garde, 2017). Vertex stock at the end of 2017 closed at its highest to date $149.86 and continues to rise in 2018 ("Historic Stock Lookup | Vertex Pharmaceuticals," n.d.). It seemed that Leiden's strategy worked out for Vertex, saving them from going under just a few years earlier.

## Price Point Controversy

One of the main reasons the CF drugs are able to support Vertex, despise them being targeted towards the low install base of CF patients, is how expensive they are. With Kalydeco costing a patient upwards of $300 000 a year, calling it very expensive is an understatement. One of the risky things Leiden did was to price Orkambi equally has high (at about $272 000 a year). Even though Orkambi was a less effective treatment, it actually could treat many more patents meaning the revenue it could generate was substantial at that price point (Herper, 2017). There is a lot of controversy over Leiden setting this high price point for the drug. Many people see this as taking advantage of CF patients since there are no other options

currently available. Also, given that much of this research was funded by the CFF, whose original goal was to fund the non-profit Aurora Biosciences to find a CF cure, there was concern from those who donated to and support the CFF.

There is concern Cystic Fibrosis Foundation still supports Vertex's endeavours with the Foundation pledging $75 million in 2016 and future payments of $6 million a year (Weisman, 2016). While the foundation also benefits from royalties during the negotiation, which can be seen as good since the CFF has many programs to help people with CF, there is a lot of criticisms as to why they don't pressure Vertex to lower prices (to allow more people access to the drug); or even why they continue to fund Vertex's research now that they are profitable themselves (Weisman, 2016). Some felt that their goals were being overlooked due to potential profits.

Even so, these prices are what allow Vertex to thrive and Leiden was seen as a company saviour as they were not only profitable but generating sustainable revenue. The argument that Leiden and Vertex makes is that although they are now profitable they continue to invest 9 out of every 10 dollars back into CF research. Their next goal is to treat 90% of people who suffer from Cystic Fibrosis but the research into their new combination therapies is expensive (Tirrell, 2017).

There are also attempts from Vertex to improve their public relation which include them starting their own CF programs to give back to the community from their profits. These include scholarship and award programs to CF students ("Cystic Fibrosis Programs," 2017). Even so, Jillian McNulty, who has benefited greatly from Orkambi still has mixed views on the company and the drug cost. On one hand she says that all of the hospital stays and other drugs would quickly add up to a price that is comparable to the yearly costs of Orkambi; but, on the other hand she says "it is difficult for her to see friends with CF struggling because they can't access Orkambi, while she is reaping its benefits" (Ryan, 2016).

## Future Directions and Suggestions for Vertex

The current projects for Vertex all involve Cystic Fibrosis and the combination therapies that are in development. Vertex hopes generate new treatments and drug combinations to help over 90% of CF patients over the next few years (Tirrell, 2017). Their immediate goals are all focused on gaining approvals on combination therapies for their current Orkambi and Kalydeco drugs. This strategy is in line with their "all in for CF" strategy that Leiden brought to the table. Their final goal with CF treatment is to have one pill that a patient can take and be asymptomatic (Tirrell, 2017).

One suggestion for Vertex is to attempt to develop a few drugs in different categories and get them through the first few stages of the approval process. While the Cystic Fibrosis focus saved Vertex from going under 7 years ago, the only reason they had that option in the first place was because of their founder's stance of developing a diverse portfolio of drugs. Reinvesting some of their revenue into drugs outside of the Cystic Fibrosis category will allow them to be diverse in drug discovery, and could have the potential of producing another breakthrough.

## Conclusions

Vertex is a company that has had its ups and downs over the past 30 years but they have shown great tenacity during these trials and tribulations. While there are many things that lead to them to the

company they are today, it seems that there are three key factors continued to their current success. The first is the focus on research and development to understand a disease and drug beyond just efficacy. This allowed them to obtain knowledge for the rare disease of Cystic Fibrosis, and they became a world leader in its drug development. The second was keeping their drug targets diverse. This sustained them between their three breakthroughs, from HIV to Hepatitis C and finally having the CF projects to fall back on when Incivek fell out from under them. The last factor was Leiden's choice to go "all-in" with the CF development. Rather than looking at the rare disease as challenging, he saw the advantages that Vertex had over the competition when developing drugs for this disease. These key factors and a little luck are what drove Vertex from the small startup to the billion dollar company it is today. Hopefully, Vertex can continue to develop CF drugs to reach their goal of eradicating the disease, while also finding a price point that works for more people.

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# 32. Pond Technologies Inc. - Target Markets

*Pond Technologies Inc. - Target Markets*

**by Amna Alam**

It was a 2008 article in the Washington post that first fueled Steve Martin's inspiration behind Pond Technologies Inc. in Markham, Ontario. The article indicated that algae was a promising alternative to fossil fuel derived biofuels, and that it could pave the way for greener and more renewable energy [1]. A mere twelve hours later, Martin started growing algae in a coffee cup, taking the first stock from the film growing on his swimming pool. Humble beginnings propelled Martin into the biofuels industry, through numerous programs funded by the government and private investors. Aptly named Pond Biofuels at the time, it wasn't until 2016 that the company reached a crossroads – one that would prompt them to adopt a new name: Pond Technologies Inc.

A few years after starting the original company, it became clear to Martin that algal biofuels were not as close to being adopted on a large scale as he had hoped. While the government and large energy companies were interested in investing in research into the creation of renewable transportation fuel, the high capital costs associated with the resources required for producing biofuels left little room for profit. Mainly, Martin found that while they had proprietary technology that would allow for efficient and rapid algal growth, this new industry that they were trying to tackle was not ready to leave fossil fuels entirely behind. Therefore, Martin wanted to expand the scope of the company and shift it from simply producing biofuels to creating other algal technologies, as demonstrated by the change in

company name. The question that then remained was: Which algal products industry would be best to aim towards, such that it could provide sources of revenue but also remain in line with the original vision of the company for cleaner products from algae?

**Industry (Algae Products)**

Algae has been known to have applications across several industries. Globally, the algae products market was projected to reach approximately $3 billion USD by 2022 with a compound annual growth rate of 6.7% from 2017-2022 [2]. The largest share of the market was claimed by biofuels, but overall, nutraceuticals were growing at the fastest rate. These were followed by other applications such as cosmetics and bioplastics.

*Key Trends*

Growing demand for renewable and sustainable energy: By 2024, the largest sector of the algal products industries was projected to be biofuels, primarily in response to the awareness of the harmful effects caused by burning fossil fuels [3]. The Canadian government launched the Clean Air Agenda in 2007, looking towards fostering innovations that reduced greenhouse gas emissions and reduction of fossil fuel use in favor of renewable energy sources [4]. Included alongside solar, wind and hydropower were energy products derived form plant biomass.

The Asian Pacific Partnership (APP), had also implemented climate programs to foster innovations that would mitigate or possibly reverse the harmful effects of fossil fuel use. Altogether, the APP was made up of countries such as the United States, Korea, Japan, and more, which produced 62% of the world's cement, 65% of the world's smoke, and 60 % of the world's steel [5] In 2009, Pond Technologies received funding by the APP to create a pre-commercial pilot algal photobioreactor that would be powered by carbon dioxide emissions released by the St. Mary's Cement facility in Ontario [6].

Growing demand for natural products: Data from a 2015 Statistics Canada survey indicated that 45.6% of Canadians had used a form of nutritional supplement in the past year [7]. The most common types of these supplements included vitamins, omega-3 fatty acids, fibers and antioxidants. A 2011 survey projected that the largest increase in the natural health products industry was to be whey protein, omega-3 fatty acids, glucosamines, probiotics and sterol esters [8]. The major trend in the market was the shift in buyer power from baby boomers to millennials, who were more likely to expect nutritional information on the foods they were consuming, as well as becoming generally more health conscious [9]. With this, the nutraceuticals and functional foods industry saw an increase in the global market, and is projected to be almost $600 billion by 2025 [10].

**Company History and Algal Technology**

Pond Technologies Inc. was founded in 2008, when it was initially named Pond Biofuels. It was created by Steve Martin, who served as Senior Scientist at EXFO Photonics Solutions, a company that specialized in developing optics systems. His background made him an expert at helping to identify the ideal light conditions required for growth of algae strains under study [11]. Together with a gradually growing staff of project managers, sustainability experts and engineers, Pond Biofuels was able to receive numerous funds from the Canadian government and private investors [6]. They created a proprietary photobioreactor that caused algae to grow at a rapid rate due to novel light technology, as well as other relevant patents that offered the company strong IP protection [11]. With the large biomass of algae, they could extract fuels such as biodiesel (from the fats), and bioethanol (from the carbohydrates) [12]. Exhibit #1 shows the company's patented photobioreactor.

The breakthrough for the company came when it received funding from the APP (Asia-Pacific Partnership) to create a pre-commercial pilot algal photobioreactor that was powered by carbon dioxide

emissions released by the smokestack at St. Mary's Cement facility in Ontario [6]. Smokestack emissions from the plant fed directly into the photobioreactor, where carbon dioxide supply was used for the growth of algae strains that were known to produce high saturated fat content. Initially aimed at creating biofuels on a large scale, it was this project that indicated to Martin and his colleagues that algae's applications can be applied to different industries. And so, in 2014, Pond Technologies Inc. emerged, ready to target new sales channels.

**The Technology**

Algae consisted of a group of single-celled aquatic microorganisms that relied on light energy, water, and carbon dioxide in order to growth through photosynthesis [12]. These organisms were found to produce oils and carbohydrates in larger quantities in comparison to other land plants, making them a promising source for biofuels (See Exhibit #2 for yield data) [12. 13]. Once refined, the oils or carbohydrates could be converted into sustainable forms of diesel and ethanol, which were shown to produce fewer harmful emissions of carbon dioxide and nitric oxides in the atmosphere compared to their fossil fuel derived counterparts [12]. The oil, protein, and carbohydrate content per overall biomass varied across species, and depending on the desired end-product, an algal species that produces the largest quantity of the unrefined molecule could be chosen. For example, for the production of biodiesel, which is created from unsaturated fats, scientists would cultivate *Neochloris oleoabundans* and *Schizochytrium sp.*, two species known to produce large quantities of unsaturated fats per overall biomass [12]. See Exhibit #3 for oil content of various algal species.

Closed vessel systems called photobioreactors were used to facilitate the rapid growth of algae, by providing control over factors such as light, temperature, water supply, and carbon dioxide content [12]. Bioreactors also decreased the overall risk of contamination that was associated with open cultivation systems, such as outdoor

ponds [12]. This strict control made large-scale production of algae economically feasible. Pond Technologies had a patented algae platform that could grow algae at a fast rate by taking advantage of its response to light [14]. As an expert in optics, Martin and fellow engineers constructed an artificial LED system that exposed algae to strobing light [14]. The constant flickering of the lights indicated to algal cells that days are shorter, leading to an increase in the organism's biomass and oil production, the latter of which could be dried, filtered and refined for use as transportation fuel [14].

The ability of algae to sequester carbon dioxide from the air and use it as a nutrient for its own growth has significant implications in the clean energy industry. It could not only mitigate the greenhouse gas emissions that were released by industrial facilities with smokestack, it could also use this to create oils which can be used as a cleaner oil that itself emits fewer green house gasses. The remaining biomass also had relevant uses: aside from fats, algae also produce protein and antioxidants that held importance in the nutraceutical and health supplement market [12]. One large disadvantage that algal biomass production faced was the high capital and operational expenditure that was associated with algal cultivation in photobioreactors [12].

**The Opportunities**

Up until 2013, Pond Biofuels had focused on cultivating carefully chosen algal species and extracting unsaturated fats (only single bonds in their chemical structure) for biodiesel production and carbohydrates for bioethanol production [15]. However, the company soon realized that the amount of nutrient resources required to get algal biofuels on the commercial level was far higher than they could supply with their own funds. With Martin's background in optics, they were able to create patented technology that would increase the rate at which algae grew; however, they had no immediate solutions for the amount of carbon dioxide that was needed. Initially, they had

been able to chemically alter dissolved glucose to release ethanol and carbon dioxide, the latter being used as a nutrient for algal growth (see Exhibit #4 for the chemical reaction) [16]. This resource was needed in great quantity and led to a high running cost for overall cultivation of the algae, which increased further when considering the manufacturing and operational costs of the photobioreactor itself. Martin decided that the company needed to tap into revenue streams that would allow it to mitigate some of the capital cost associated with the algae cultivation, and they had to look no further than algae's other benefits outside of biofuel production.

Martin intended on delving deeper into the algal products market, specifically that of natural algal health products and pollution control in the energy industry. The biology of the species they had structured their technology on prevented them from initially being able to approach both industries. The first was an issue they were already familiar with based on their experience at the St. Mary's cement facility: in order to grow algae on a commercial scale, large amounts of carbon dioxide were required [17]. Secondly, depending on the type of species of algae they chose, different valuable products could be derived [12]. The market they would choose to attempt to establish themselves in depended on these two factors.

The main decision that the company had to make was to decide whether they should go towards the fast-growing nutraceuticals industry, or to remain in the energy industry and capitalize carbon sequestering? Both of these came with their own benefits and limitation, making it a difficult decision for Pond Technologies Inc.

**Potential Sales Channels and Strategies**

1. *Nutraceuticals Industry*

As the company had not delved into the nutraceuticals market in

their research initiatives, the outreach from nutraceutical companies was not as large as that in the energy industry. The angle taken at the start of the company, when it was still called Pond Biofuels, was to produce renewable energy. However, Martin knew that the value of algal biomass was too great not to consider entering the nutraceutical market. Specifically, in their novel photobioreactor's ability to produce algae on a rapid scale in comparison to outdoor systems, the company could provide the raw materials required for the production of supplements for nutraceutical manufacturers [11].

To start, algae species that produced high quantities of the desired molecules for supplement production were preferred. *Chlorella* and *Spirulina* species-derived nutraceuticals were already on the market in Canada, and Pond Technologies had the potential to follow suit [19]. These algal species produced unsaturated fatty acids, which are preferred forms of omega-3 on the market. Most importantly, an antioxidant called Astaxanthin which is derived from algal species such as *Haematococcus sp.*, saw a surge in public interest and was readily incorporated in carotenoid supplements [19].

Pond Technologies Inc.'s strategy for this market was to produce the desired molecules in their in-house facility in Markham, and to sell the products to manufacturers [11]. In doing so, they were responsible for supplying their own resources, including large quantities of carbon dioxide. It would become the company's responsibility to use carbon dioxide derived from dissolved glucose. Therefore, capital expenditure associated with algae's production was not likely to be mitigated.

Additionally, the algal strains that Pond Technologies had used up to this point were aimed towards biofuels production. The company had conducted extensive research on algal species that produced unsaturated fatty acids, as well as large quantities of carbohydrates [20]. However, the nutraceuticals industry placed more importance on protein, fiber, and unsaturated fatty acids that made up omega-3 [8]. Overall, the demand for the molecules that particular algal

species could produce were high, but came with limitations associated with large resource costs, and the company having to work with new algal species.

With these limitations taken into account, Pond Technologies Inc.'s calculations suggest that despite an estimated capital expenditure of $1.6 million per bioreactor and an additional $600,000 of operating costs per year, the cashflow would be positive in 18 months, if targeting customers that required biomass from *Chlorella* and *Spirulina* species, as well as raw Astaxanthin [8]. With the nutraceutical market projected to be worth over 500 million in the coming years, this was not an opportunity that Pond Technologies wanted to dismiss [10]. These market estimations are presented in Exhibit #5.

*Company*: *Neptune Wellness Solutions* [11, 21]

A Quebec based company specializing in manufacturing customized formulations of natural health products using healthy extracts from marine species and terrestrial seeds. The unsaturated fatty acids used in omega-3 oils (different from saturated fatty acids used in biofuel production) was a product of algae that served as an important ingredient in the gel-capsule formulations for this company. The red-pigmented antioxidant, Astaxanthin, was also valuable in preserving the quality of capsules by protecting them from light and heat, as well as providing health benefits of fighting off harmful effects on the body due to ultraviolet rays and converting harmful UVB rays into vitamin D. Production of these valuable compounds in Pond's facility had the potential to create revenue by selling to this company, which itself sold raw materials to other manufacturers.

2. *Pollution Abatement in the Energy Industry*

As growing concerns for greenhouse gas emissions take place around the world, Pond Technologies discovered a niche market that would not only take advantage of their breakthroughs in algal research, but also feed back into the company for the production of value products that the company could sell for profit.

Steve Martin was aware that algae could sequester carbon dioxide from the environment and use it as a nutrient for its own growth. In fact, in 2014, the company had done just that by installing their photobioreactor adjacent to St. Mary's Cement [6]. However, after the successful implementation of Pond's photobioreactor at the facility, Martin understood that carbon capture could serve as a sales channel on its own. By licensing their technology and selling their proprietary equipment to industrial facilities across North America, they could not only create a revenue stream, they could also cut back on cost of resources such as carbon dioxide, as well as use the produced algae into bioethanol, biodiesel, and other valuable products. In this way, the company would not lose sight of its original pursuit for renewable energy.

This sales channel did not work on a small scale, such as providing energy for a single house or furnace, as the net energy consumed would be far greater than the net energy produced. However, on a larger scale, and by targeting industrial emitters that produced over 25,000 tons of carbon dioxide per year, Pond Technologies had a way of settling into the niche market. There were over 10,000 large industrial emitters across North America, providing a large potential customer base [22].

The main reason value products could not overlap with the nutraceuticals market (omega-3 unsaturated fatty acids and protein) were because the algal strains that Pond had been working with in the industrial settings produced molecules more suitable for production of biodiesel and bioethanol. These included saturated fatty and carbohydrates. Without the limitation of using "clean" carbon dioxide, Pond Technologies had the potential to not only

sequester air pollution, but also to continue creating an alternative energy source. On the other hand, this entailed that Pond was restricted by producing only forms of biofuels, which Martin had already discovered was not currently as established as the nutraceuticals industry. In targeting this industry, Martin found that even though fossil fuels were not ready to be discarded for other alternative biofuels, he could mitigate their harm and continue to collaborate with the government and private investors to create innovations that would make algal biofuels economically feasible [22].

*Company: Markham District Energy* [23]

By late 2016, the city of Markham had also shown an interest in collaborating with Pond Technologies. The proof-of-concept project at St. Mary's Cement had shown enough promise that Markham District Energy was eager to work with the company on potential energy systems. MDE was involved in providing heating and electricity to city-wide infrastructure, and wanted to use the company's photobioreactors to sequester carbon dioxide emissions form industrial facilities and produce algal biomass that could be burnt as a heating source.

The CEO of MDE, Bruce Ander, was a former chair of the International District Energy Association, and also wanted to further Pond's network globally by introducing the company's breakthrough technology to other members of the group, which spanned across 26 countries.

This was a significant advantage as it promised an increase in the company's profit potential.

*Company: Stelco Canada* [24]

This Ontario based steel company provided products for transportation and infrastructure construction across North America, and was looking for a way to continue to reduce their carbon footprint without significantly decreasing their production

value. Sujit Sanyal, Chief Operating Officer at Stelco Canada knew that Pond Technologies Inc. had become a leader in the carbon abatement sector. He said that a partnership with Pond Technologies Inc. could "demonstrate the potential for the steel industry to utilize science and innovation to make significant reductions in greenhouse gas emissions.... Our intention is to divert thousands of tonnes carbon from our operations while making Stelco more competitive and environmentally sustainable" [24]. This view was seconded by Steve Martin, who foresaw partnerships with heavyweight emitters like Stelco Canada leading to "transforming their GHGs into significant revenue streams" for Pond Technologies [24]. Stelco Canada hoped to start a project with Pond Technologies Inc. in creating the first ever commercially sized carbon-abatement system.

**Future Challenges and Questions**

Martin knew that regardless of which industry his company chose to focus on in the coming future, algae products would contribute not only to the financial wellbeing of the company, but also add value to the environment by fostering the production of green products. In 2008, when he had first read the article in the Washington Post, the goal had been to create green energy to replace fossil fuels. As the company grew, he found that perhaps conquering it was still further down in the pipeline, but that algal products could mitigate several of the harms that came with using fossil fuels, or even create green products in an entirely different sector. Despite finding himself in a place he hadn't anticipated with his company, he felt that expanding the applications of algae, and fostering research into its many benefits was certainly the best way to go.

Having always been the idea man, he thought about how he could take algae further. Was there was a way to introduce genetic modification into the equation? Could he find a way to alter an algal cell's genome such that it could not only increase the production of molecules required for the nutraceuticals industry, but enhance the

production of those required for the energy industry? Would that prove to be the ultimate solution in establishing Pond Technologies Inc. in both markets, or would the public opinion on large scale production of transgenic organisms prove to be a setback?

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**Exhibits**

**Exhibit #1**: Pond Technologies Inc.'s 25,000L Photobioreactor


Source: Votorantim Cementos News [25].

**Exhibit #2**: Oil and Ethanol Yield Comparison Between Microalgae and Land Crops

a) Comparison of some source of biodiesel:

Comparison of some sources of biodiesel

| Crop | Oil yield (L/ha) | Land area needed (M ha)[a] | Percent of existing US cropping area[a] |
|---|---|---|---|
| Corn | 172 | 1540 | 846 |
| Soybean | 446 | 594 | 326 |
| Canola | 1190 | 223 | 122 |
| Jatropha | 1892 | 140 | 77 |
| Coconut | 2689 | 99 | 54 |
| Oil palm | 5950 | 45 | 24 |
| Microalgae[b] | 136,900 | 2 | 1.1 |
| Microalgae[c] | 58,700 | 4.5 | 2.5 |

[a] For meeting 50% of all transport fuel needs of the United States.
[b] 70% oil (by wt) in biomass.
[c] 30% oil (by wt) in biomass.

b) Ethanol production capacities by various feedstock, (L/Ha)

| Feedstock | Ethanol Yield |
|---|---|
| Switch grass | 10,760 |
| Sugar beet | 5,010–6,680 |
| Corn | 3,460–4,020 |
| Sweet sorghum | 3,050–4,070 |
| Cassava | 1,050–1,400 |
| Wheat | 2,590 |
| Corn stover | 1,050–1,400 |
| Algae | 46,760–140,290 |

Sources: a) Chisti, 2007 [12]; b) Grandview Research [13].

**Exhibit #3**: Oil Content of Some Microalgae

Oil content of some microalgae

| Microalga | Oil content (% dry wt) |
|---|---|
| *Botryococcus braunii* | 25–75 |
| *Chlorella* sp. | 28–32 |
| *Crypthecodinium cohnii* | 20 |
| *Cylindrotheca* sp. | 16–37 |
| *Dunaliella primolecta* | 23 |
| *Isochrysis* sp. | 25–33 |
| *Monallanthus salina* | >20 |
| *Nannochloris* sp. | 20–35 |
| *Nannochloropsis* sp. | 31–68 |
| *Neochloris oleoabundans* | 35–54 |
| *Nitzschia* sp. | 45–47 |
| *Phaeodactylum tricornutum* | 20–30 |
| *Schizochytrium* sp. | 50–77 |
| *Tetraselmis sueica* | 15–23 |

Source: Chisti, 2007 [12].

**Exhibit #4:** Chemical reaction for the conversion of glucose into ethanol and carbon dioxide


Source: Essential Chemical Industry website [16].

**Exhibit #5**: Pond Technologies Inc.'s Nutraceutical Revenue Model

## Nutraceutical Revenue Model

| 5 YEAR REVENUE TARGET | GROSS MARGIN | CASH FLOW POSITIVE |
|---|---|---|
| $99MM | 80% | 18 months |

| BIOREACTOR SIZE | CAPEX/UNIT | OPERATING COSTS/YEAR/UNIT |
|---|---|---|
| 65,000L (approx. 1 Shipping container) | $1.6MM | $600K |

| | Astaxanthin | Chlorella | Spirulina |
|---|---|---|---|
| Price per tonne | $160,000 | $25,000 | $15,000 |
| Revenue per bioreactor | $3.8 MM | $1.2 MM | $0.9 MM |
| # of bioreactors | 18 | 14 | 14 |
| Target revenue in 5 years | $69.1 MM | $16.8 MM | $12.6 MM |

Source: Pond Technologies Inc – Corporate Presentation [11].

# 33. The French Pharmaceutical Giant: A case study of Sanofi

## The French Pharmaceutical Giant: A case study of Sanofi

By: Naheen Imtiaz

April 8, 2018

On Thursday, February 19th2015, Sanofi finally announced that the search for their CEO came to an end which started on the Fall of 2014 and took a four month period after which it declared that Dr. Oliver Brandicourt would be taking over as their current CEO replacing Chris Viehbacher. The former CEO was fired after having series of disputes with the board members, especially with the chairman of Sanofi, Serge Weinberg, who questioned his way of work ethics and the alleged disputes were due to the problems with communications and management style.

Mr. Viehbacher's exit from Sanofi was disappointing to many of the investors of the company with whom Viehbacher used to go along well. The investors acknowledged that he was indeed successful into making Sanofi more like an innovative and dynamic company when it was lacking these, bringing back the company's drug development

process to its previous glory, and was acting more like a traditional company to survive than to gearing up with their rivals. However, his departure occurred at a time when the company was facing a crucial moment in the diabetes business and was at stake at profit in the US.

**History of Sanofi before Dr. Oliver Brandicourt took charge**

Sanofi, formerly known as Sanofi Aventis, is a French multinational pharmaceutical company and is one of the fifth largest in generating revenues from prescription sales of drugs. It has a high class R&D organization and the company holds a superb reputation for its drug discovery and development status providing therapeutic solutions over a range of diseases to improve the quality of life. The company covers vaccines as well and its division Sanofi Pasteur is undoubtedly the world's largest manufacturer of vaccines. Sanofi is known as Sanofi Aventis Canada Inc. which is situated in Laval, Quebec and its Canadian division Sanofi Pasteur is located in Toronto, Ontario. Still having a world class R&D operation, there were no new drugs in the pipeline for Sanofi and that is when Chris Viehbacher was appointed as the CEO of Sanofi from December 2008. The company was going through a rough patch- with a lot of its patented drugs were soon going to lose the patent and will have to face patent expiry of the key drugs which was going to put at stake more than one-third of their revenue when Mr. Viehbacher took in charge. Pharmaceutical experts felt that Sanofi was lacking behind in the race to keep up with the changes in the pharmaceutical and biotech industry where other leaders were performing far better than Sanofi and that it was being run more like a traditional French company based in Paris than a competitive health leader.

Viehbacher was focused to transform the image of Sanofi to once its glorious R&D and make it a dynamic healthcare leader. The company focused on making new strategies with its R&D, management, emerging markets as well as focusing on non-prescription drug sectors. It declared a sales of 7,438 million euros

for Q2 2009 as compared to 6,689 million euros in 2008 when Viehbacher was in action. Its stock value also went high and this was surprising as just the year before, i.e. in 2008, Sanofi's stock had been considered the worst among its peers/rivals. Sanofi was the third largest pharmaceutical company of the world in the year 2009. However in 2013 when most of Sanofi's key drugs had to face patent expiry, its revenue fell.

**Biotech Boom- A strategic plan**

In order to revitalize Sanofi's R&D sector, Chris Viehbacher decided to depend on Regeneron to conduct and help Sanofi in R&D and compared to the French multinational giant, Regeneron was a much smaller biotech company based in USA. This did not go too well with the board members who questioned how Viehbacher was planning to help drive the growth of Sanofi who did not opt for mega mergers but still was making a multi-billion dollar collaboration with a smaller biotech company in comparison to Sanofi. In 2014 Sanofi paid about $1 billion to Regeneron to conduct research on their behalf as back in 2013 Sanofi lost most of its patented drugs and was about to enter generic sales. Chris's goal was to use Sanofi's skills and Regeneron's expertise to help bring the change into Sanofi's R&D which it was desperately trying to make better and brought out emerging products into the market.

**The many faced problems**

Despite all his efforts, he was finally showed the door on late 2014. In the same year the state filed suit against Sanofi when native Hawaiians were dying at an increased rate due to reasons of cardiovascular death for marketing the drug Plavix (Clopidogrel) as an anti-blood clotting agent for patients who suffered stroke or heart attack whereas the company knew that this drug would not work for the majority of the population in Hawaii. This lawsuit could make

Sanofi come under a difficult phase as the drug company should have tested and trialed a drug in all different kinds of population.

Sanofi again came under limelight for the wrong reasons. It had to pay a fine of 40.6 million euros for making disparagement strategies about other company's product and spreading false news about it in order to slow down the drug development process of competing generic drugs. French Competition Authority (FCA) found out about Sanofi's disparagement practices and the company had to pay whopping amount of fine whereas they could have focused more on how making their products more dynamic. Recently Sanofi partnered with Viela Bio which is a spin off company of global drug giant AstraZeneca to help aid in Sanofi's research program. Analysts saw a lot of potential in Viela Bio to become a leading biotech company as it was successful to raise a lot of money for its funding, $250 million, from investors and questioned Sanofi's future that it was again partnering with a company, like it partnered with Regeneron, which could become their competitor in the future.

**Innovation in the healthcare environment**

Sanofi was focused on bringing quality medicines and effective treatment for the whole world and Canada was a core part of it. It wanted to meet the healthcare needs of Canadians and wanted to go for intellectual property protection regime as the Canadian innovative pharmaceuticals had no effective right of appeal when they face challenges with IP. Hugh O'Neill, president and CEO of Sanofi Canada said that the challenges with loss of patent exclusivity was needed to be met in order to deliver value to the Canadian healthcare system. He emphasized that Sanofi would be focusing more for a sustainable long term growth rather than following the traditional pharmaceutical business model. They wanted to have an effective discussion coupled with effective measures taken by the government as insufficient government policies with patent exclusivity was causing generalization of branded drugs even though

they were still under patent protection. This situation was threatening Sanofi's R&D investments, capital expenditures and job creation opportunities. Sanofi wanted to focus on this issue so that they can grow the Canadian market to a more sustainable one and does not fall behind with respect to their other international divisions.

Lantus, Sanofi's novel recombinant human insulin analog approved for use in high blood sugar control in patients with Type 1 and Type 2 diabetes, was one of its highest selling drug with sales above $7 billion in 2015. In 2009, Sanofi for the first time launched an eco-friendly insulin pen in Canada to provide safe and more efficient use of insulin instead of taking insulin shots with a needle. Diabetes is one of the chronic disease affecting more than two million people in Canada and it is estimated that one-third of the population do not know that they are vulnerable to this condition. According to Canadian, diabetes condition, Canadian healthcare system spend an estimated $13.2 billion each year to treat diabetes and its complications and by the year 2020, the cost would be mounting up to whopping $19.2 billion per year. Sanofi brought an added advantage to themselves as well for Canadians with the launch of this medicine pen as one of the first country in the world to do so to achieve sustainable control of the blood sugar level.

Some of the highlights of the new Canadian strategy included:

- Wider understanding about the needs of the patient, physicians, policy makers
- Creating a sustainable model to deliver greater savings of the country spend on healthcare by investing in product positioning
- Providing services and support to the patient by making a network or connection with them
- Collaborating with the marketers to target the right patient for the patient
- Securing the best possible results for Canada's healthcare

system and the patients.
- Spreading awareness about diseases and the significance of disease prevention.

**Sanofi Pasteur**

Sanofi's constant struggle in the pharmaceutical market led to being questioned about its future and growth. The French drug maker had to sell its bone marrow transplant drug (Sargramostim) plant in January 2018 for $60 million as it seemed that they were having a hard time figuring out their constant challenges with R&D and as a result they could not target this drug market anymore, thereby selling it. So the company was inclined to focus on its largest division, the vaccines sector, Sanofi Pasteur.

**Scandals of Dengue Vaccine**

WHO reported that that it would review the safety data of Sanofi's dengue vaccine after the French pharmaceutical giant announced that their vaccine could actually worsen the condition of dengue in some cases. This came as a shock and surprised the drug market as news evolved that by using the vaccine severe infections could arise which was actually supposed to be treated as a dengue vaccine whereas it was reported to worsen the disease. The Philippines Government would be taking legal actions against Sanofi and suspended massive immunization program which was taking place in Philippines. An estimated 830,000 school children were reported to be vaccinated by this drug and Philippines was asking the company to fund the treatment of the children who developed severe form of dengue after vaccination. This alarmed the pharmaceutical industry as Sanofi announced that infection rate could rise to about 90% more in patients who had been vaccinated, and being liable on Sanofi came under scrutiny as protests went on in Philippines and experts

questioned if it was really liable to be depended on Sanofi and its treatment anymore.

Sanofi brought this vaccine to the market as a very promising and effective vaccine for dengue, a disease which affects millions of people by mosquito bite especially in the developing world, but the scenario became delicate when Sanofi found out that dengue can backfire after using their vaccine. The Philippines government paid $69 million to Sanofi for this vaccines and was planning to take legal actions against Sanofi. Atleast 20 children have died, allegedly after using the vaccine since Sanofi's declaration and the victim's parents have accused the dengue vaccine as the cause of death of their children. Sanofi was expecting a net loss of 100 million euros from this vaccine as a result of diminished. This dengue vaccine was sold in over 11 countries with massive immunization taking place in Philippines and Brazil. Philippines government started investigations about it. Sanofi spent about 20 years to bring this vaccine to the market as world's first ever dengue vaccine which costed them 1.5 billion euros ($1.78 billion). Two other dengue vaccines were in line in the last stage of clinical trials and this situation could threaten Sanofi's future sales of these dengue vaccines. Despite this scandal, Sanofi's vaccines by Sanofi Pasteur made more than 5 billion euros in net sales year.

**The challenges**

As Chris Viehbacher exit from being the CEO of Sanofi, Oliver Brandicourt took up his place. Oliver being the new CEO of Sanofi was welcomed by many analysts. He took charge of Sanofi at a critical situation when it was busy to launch its products into the market which investors were looking forward to it to revitalize growth of Sanofi after long periods of no innovation and lack of R&D dynamicity. The chairman of Sanofi, Serge Weinberg, welcomed him to Sanofi and felt he was the right choice among all as he had a record 28 years pharmaceutical industry experience among which working

with Pfizer, Bayer were notable before joining Sanofi. Though Mr. Brandicourt had all the commercial and scientific experiences and had an international professional background, he had to face a number of challenges.

From building a good relationship with the board members and investors to defending Sanofi's place in the market specially the diabetes market was among the most important of them all. Former CEO Chris Viehbacher had a good rapport with the investors and this was the point that everybody was looking forward to as Oliver Brandicourt needs to stay along not only the board members but also with the investors who wanted to see that how he can make a difference regarding Sanofi's difficult phase in making an increased growth. Lantus, the anti-diabetic drug, brought in more than a fifth of Sanofi's revenue in 2014 and it was considered the world's best-selling insulin. But there were to dangers to this business. One was that Lantus was about to lose its patent exclusiveness and the rivals have been targeting this product for a long time, making cheaper drugs than Lantus and producing its biosimilar version and the other was that since it was one of the widely used drugs, insurers were trying to make a much tougher way to make price negotiations. Lantus was under a lot of pressure in the US for this second reason. All these factors made Sanofi predict that their drug sales might not be profitable than the previous year. Oliver Brandicourt also needed to make sure that he kept the drug pipeline like an on-going process for Sanofi to bring in new and improved products into the market. He had a lot of cups to be filled and needed to ensure that he maintained his previous successes like that at Pfizer in bringing cholesterol lowering medicines to the market. His past experiences should prove to be advantageous for Sanofi as it was preparing to tackle up with the current scenarios of the pharmaceutical and biotech business.

**The Promises and the Future**

Sanofi was awaiting approval for Toujeo Insulin from US FDA to launch a better version of the world's best-selling diabetic drug, Lantus, into the market. Clinical trials showed promising results of this new drug and Sanofi remarked it can dominate the diabetes market once again with this drug. They also developed Praluent with Regeneron Biotech, a new injectable cholesterol lowering drug and Sanofi stated that it would prove to be a key drug for their business targeting the statins markets as this drug was supposed to be better tolerated in patients with statin intolerance and making them a leader in this sector as well. Praluent showed results of overall fewer deaths cutting down 15% deaths associated with patients who received only statin treatment and were not responsive to this therapy. As a marketing strategy, Sanofi also planned to sell this drug at a cheaper rate for high risk patients with increased cholesterol. They offered lower the price upto 69% in exchange that insurers and pharmacies broaden their medicine coverage to more number of patients. Experts thought this strategy could be used to establish Sanofi as a leader of the future pharmaceutical industry and Sanofi was had clinical data reports to support their claim. Sanofi also had two new dengue vaccines which were present in their pipeline in the late stages of drug development.

However, Sanofi's fourth-quarter sales of 2017 fell 10.8% at constant exchange rates to $1.64 billion though the total sales increased 4,1% and to 8.7 billion euros. The sales of diabetes and heart disease sector went down 20% in the fourth quarter of 2017 as diabetes sales were facing competition due to patent loss and generic business of their product from the competitors, especially in the US. Still Sanofi was trying to be a leader in an emerging field. It made two outstanding deals and took over on two big companies to be an outstanding achiever in rare blood disorder treatments. In 2018, the French pharmaceutical giant took part in one of its biggest deal since 2011 acquiring the US biotech company Bioverativ for $11.6 billion. Sanofi

agreed to buy in cash all of the outstanding shares of Bioverativ for $105 per share.

Analysts felt this deal should have been too expensive for Sanofi to bear as its shares fell 3.4%, making the stock the worst performer on France's index. However Sanofi felt that this would make their successful return to deal making after years of major takeover failures. Sanofi was also successful in cracking a deal to buy Belgium's Ablynx who develop drugs for rare blood diseases for 3.9 billion euros ($4.8 billion) and beat their rival Novo Nordisk who wanted to acquire Ablynx first. Novo Nordisk said it was not ready such a big amount to crack the deal with Ablynx whereas they generate more revenues than Sanofi does. Sanofi last bought the US biotech company Genzyme in 2011 for about $20 billion and in 2016 it lost to Pfizer to on buying the California based cancer specialist Medivation. Last year it also lost to Johnson & Johnson another biggest rival of Sanofi to take over Actelion, the Swiss Biotech Company. Oliver Brandicourt felt that with acquiring these companies, Sanofi could become an emerging leader in the market of rare disorders associated with blood. They had managed to face the challenges in the US market with their diabetes drug facing generic competition and with the dengue vaccine making the infection even worse and analysts and experts have questioned about their growth in their R&D sector, bringing new drugs in their pipeline. Investors also questioned Sanofi's costly acquiring of two major acquisition deals in their crucial moment.

Oliver Brandicourt stated that Sanofi would be ready to launch upto 18 new drugs by 2020. Sanofi said that annual sales of rare blood disease treatment drug market was around $10 billion. 181,000 people had been affected worldwide by this rare blood disorder. So, Sanofi targeted to execute their strategic goals with the launch of hemophilia drugs in the market which is projected to be grown more than 7% per year upto the year 2022.

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***Exhibits***

**Exhibit 1**: Diabetes statistics in Canada

| Key Statistics[1] | 2015 | 2025 |
|---|---|---|
| Estimated diabetes prevalence (n/%) | 3.4 million/9.3% | 5 million/12.1% |
| Estimated prediabetes prevalence in Canada (n/%) (age 20+) | 5.7 million/22.1% | 6.4 million/23.2% |
| Estimated diabetes prevalence increase (%) | 44% from 2015-2025 | |
| Estimated diabetes cost increase (%) | 25% from 2015-2025 | |

Source: Diabetes.ca [ http://www.diabetes.ca/how-you-can-help/advocate/why-federal-leadership-is-essential/diabetes-statistics-in-canada]

**Exhibit 2**: List of some of the top pharmaceutical companies with revenues greater than $10 billion

| Rank | Chg | Company | 2017 USD billions | 2016 USD billions | 2015 USD billions | 2014 USD billions | 2013 USD billions | 2012 USD billions | 2011 USD billions |
|---|---|---|---|---|---|---|---|---|---|
| 1 | – | Johnson & Johnson NYSE: JNJ | 76.50[1] | 71.89[2] | 70.10[3] | 74.30[4] | 71.31[5] | 67.20[6] | 65.00[7] |
| 2 | ▲ 1 | Roche OTCQX: RHHBY | 57.37[8] | 50.11[9] | 47.70[10] | 49.86[11] | 48.53[12] | 47.80[13] | 45.21[14] |
| 3 | ▼ 1 | Pfizer NYSE: PFE | 52.54[15] | 52.82[16] | 48.85[17] | 49.61[18] | 51.58[19] | 58.99[20] | 65.26[21] |
| 4 | – | Novartis NYSE: NVS | 49.11[22] | 48.52[23] | 49.41[24] | 58.00[25] | 57.36[26] | 56.67[27] | 58.57[28] |
| 5 | ▲ 1 | Sanofi NYSE: SNY | 42.91[29] | 36.57[30] | 36.73[31] | 43.07[32] | 42.08[33] | 46.41[34] | 44.34[35] |
| 6 | ▲ 1 | GlaxoSmithKline LSE: GSK | 42.05[36] | 34.79[37] | 29.84[38] | 37.96[39] | 41.61[40] | 39.93[41] | 41.39[42] |
| 7 | ▼ 2 | Merck & Co. NYSE: MRK | 40.10[43] | 39.80[44] | 39.50[45] | 42.24[46] | 44.03[47] | 47.27[48] | 48.05[49] |
| 8 | ▲ 1 | AbbVie NYSE: ABBV | 28.22[50] | 25.56[51] | 22.82[52] | 19.96[53] | 18.79[54] | – | – |
| 9 | ▲ 1 | Bayer FWB: BAYN | 27.76[55] | 25.27[56] | 24.09[57] | 25.47[58] | 24.17[59] | 24.30[60] | 23.11[61] |
| 10 | ▲ 5 | Abbott Laboratories NASDAQ: ABT | 27.39[62] | 20.85[63] | 20.41[64] | 20.25[65] | 21.85[66] | 39.87[67] | 38.85[68] |

Green boxes= profit; Green arrow= position upwards

Red Boxes= loss; Red arrow= position fell

Source:En.wikipedia.org[ https://en.wikipedia.org/wiki/List_of_largest_pharmaceutical_companies_by_revenue]

**Exhibit 3**: List of the Largest selling drugs with revenues over $5 billion in 2015

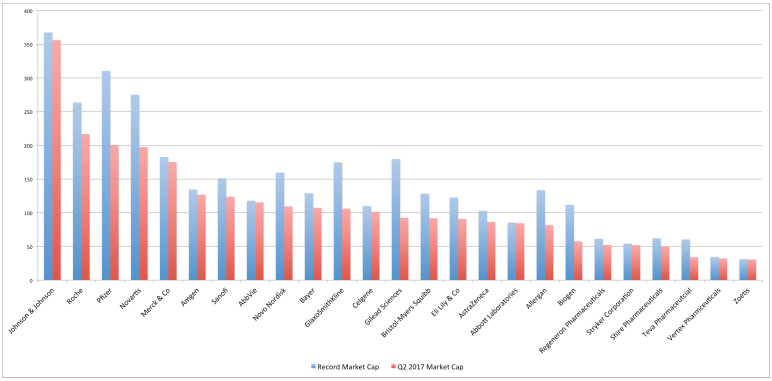
| Rank | Drug | Trade name | Type | Main indications | Company | Sales (USD millions/year) | Δ vs 2014 |
|---|---|---|---|---|---|---|---|
| 1 | Adalimumab | Humira | Biologic | Rheumatoid arthritis | AbbVie Inc. | 14,012 | 1,469 |
| 2 | Ledipasvir/sofosbuvir | Harvoni | Small molecule | Hepatitis C | Gilead Sciences | 13,864 | 11,737 |
| 3 | Etanercept | Enbrel | Biologic | Rheumatoid arthritis | Amgen<br>Pfizer | 8,697 | 4,009 |
| 4 | Infliximab | Remicade | Biologic | Crohn's Disease<br>Rheumatoid Arthritis | Johnson & Johnson | 8,355 | 1,487 |
| 5 | Rituximab | Mabthera<br>Rituxan | Biologic | Lymphoma<br>Leukemia<br>Autoimmune disorders | Roche | 7,115 | 1,456 |
| 6 | Insulin glargine | Lantus | Biologic | Diabetes mellitus | Sanofi | 7,029 | 51 |
| 7 | Bevacizumab | Avastin | Biologic | Metastatic cancers | Roche | 6,751 | 270 |
| 8 | Trastuzumab | Herceptin | Biologic | Breast cancer | Roche | 6,603 | 265 |
| 9 | Lenalidomide | Revlimid | Small molecule | Multiple myeloma<br>Myelodysplastic syndromes | Celgene | 5,801 | 821 |
| 10 | Sofosbuvir | Sovaldi | Small molecule | Hepatitis C | Gilead Sciences | 5,276 | (5,007) |
| 11 | Fluticasone propionate/salmeterol | Seretide<br>Advair | Small molecule | Asthma<br>Chronic obstructive pulmonary disease | GlaxoSmithKline | 5,227 | (778) |
| 12 | Rosuvastatin | Crestor | Small molecule | Cardiovascular diseases | AstraZeneca | 5,017 | (495) |

Source: En.wikipedia.org [ https://en.wikipedia.org/wiki/List_of_largest_selling_pharmaceutical_products]

**Exhibit 4**: List of Largest independent biotechnology and pharmaceutical companies based on market capitalization

Source: En.wikipedia.org [ https://en.wikipedia.org/wiki/List_of_largest_biotechnology_and_pharmaceutical_companies]

**Exhibit 5**: Graphical representation of top 25 biotechnology companies based on market capitalization for Q2 2017




Source: En.wikipedia.org [ https://en.wikipedia.org/wiki/List_of_largest_biotechnology_and_pharmaceutical_companies#/media/File:Top-25_Biotechs_Mkt_Cap_(Q22016).png]

**Exhibit 6**: Quarterly earnings surprise history of Sanofi

| Fiscal Quarter End | Date Reported | Earnings Per Share | Consensus EPS* Forecast | % Surprise |
|---|---|---|---|---|
| Dec2017 | 02/07/2018 | 0.62 | 0.69 | -10.14 |
| Sep2017 | 11/02/2017 | 1 | 1 | Met |
| Jun2017 | 07/31/2017 | 0.74 | 0.74 | Met |
| Mar2017 | 04/28/2017 | 0.76 | 0.73 | 4.11 |

Source: Nasdaq.com [ https://www.nasdaq.com/earnings/report/sny]

**Exhibit 7**: 2017 Results of Sanofi (Source: Sanofi.com: https://www.sanofi.com/media/Project/One-Sanofi-Web/sanofi-com/en/investors/img/2017_results_EN_web.pdf)

Company Sales and Business EPS
2017 Sales- 35,055 million euros
2017 Business EPS- 5.54 euros

**Exhibit 8**: Sales of Global Business unit of Sanofi (Source: Sanofi.com: https://www.sanofi.com/media/Project/One-Sanofi-Web/sanofi-com/en/investors/img/2017_results_EN_web.pdf)

- General Medicines & Emerging Markets- 14,048 million euros
- Sanofi Genyme (Specialty Care) – 5, 674 million euros
- Diabetes and Cardiovascular- 5, 400 million euros
- Sanofi Pasteur (Vaccines)- 5, 101 million euros
- Consumer HealthCare- 4, 832 million euros

**Exhibit 9**: Sales by Geography (Source: Sanofi.com: https://www.sanofi.com/media/Project/One-Sanofi-Web/sanofi-com/en/investors/img/2017_results_EN_web.pdf)

- US: 11,855 million euros
- Latin America: 2, 837 million euros
- Europe: 9, 525 million euros

- Eurasia: 1, 242 million euros
- Africa and Middle East: 2, 326 million euros
- Asia & South Asia: 3, 732 million euros
- Rest of the world: 3, 417 million euros

**Exhibit 10**: R&D Pipeline summary (Source: Sanofi.com: https://www.sanofi.com/media/Project/One-Sanofi-Web/sanofi-com/common/docs/investors/Sanofi_IR_Pipeline&CTSlides_Q42017Final.pdf)

| | Phase 1 | Phase 2 | Phase 3 | Registration | TOTAL |
|---|---|---|---|---|---|
| Immuno-inflammation | 2 | 5 | 5 | 1 | 13 |
| Oncology | 9 | 3 | 5 | 0 | 17 |
| Rare Diseases | 1 | 4 | 2 | 0 | 7 |
| Multiple Sclerosis, Neurology, Gene therapy | 3 | 2 | 2 | 0 | 7 |
| Diabetes | 1 | 2 | 4 | 0 | 7 |
| Cardiovascular Diseases | 2 | 2 | 1 | 0 | 5 |
| Infectious Diseases | 0 | 1 | 0 | 0 | 1 |
| Vaccines | 2 | 6 | 3 | 2 | 13 |
| TOTAL | **20** | **25** | **22** | **3** | **70** Total Projects |
| | | **45** | **25** | | |

# 34. VALANX BIOTECH

VALANX BIOTECH –
Superpower your protein
by Alina M. Einetter,
March 2019

Imagine you are working on in a research lab that develops new anti-cancer drugs. You just found a substance highly toxic for cancer cells which seems to have promising properties to cure certain types of cancer! The last missing step is to transport this highly toxic substance to the tumor cells in a patient's body only. So, you are trying to get your substance fixed to a transporter protein which specifically targets cancer cells. You tried to get it done for already a long time and the head of department wants to see some results. Moreover, the company you are working for is already under pressure because it did not come up with new drugs. As a result, there is not that much money of the foundation left to start experimenting on a new conjugation technology. Then, at a certain point you think to yourself 'if only there was a way, I could make a stable conjugation to this very specific transport protein!' If you are ever in this situation, well there is a solution to your problem….

This solution is called SnapIt! SnapIt is a synthetic amino acid which enables different types of conjugations, linkages and immobilisations of a protein ligand interaction. The company owning the patent of this new technology is called VALANX and was founded by Michael Lukesch (CEO) and Patrik Fladischer (CSO), an Austrian researcher team studying in Graz, Austria in 2017. (1,2) While researching for their final thesis they came up with a great invention which they called 'SnapIt'. This is a synthetically produced amino acid which is very small and shows to have several applicable advantages.(3) On their website they cite *Louis Sullivan*, 1896:

‘Whether it be the sweeping eagle in his flight, or the open apple-blossom, the toiling work-horse, the blithe swan, the branching oak, the winding stream at its base, the drifting clouds, over all the coursing sun, **form ever follows function**, and this is the law.’ They mainly focus on the part ‘form ever follows function’ and turned it into their new technology.

The amino acid can be incorporated in the protein of choice at every position by using *E.coli* as an expression system. Using *E.coli* offers many advantages, because it is the most common used bacterium in research, is highly studied and analysed and also occurs naturally in our guts. Placing SnapIt in a protein shows to reform known techniques and give rise to many new approaches regarding protein research.(3)

The team around VALANX engineered an *E.coli* strain which incorporates the synthetic amino acid SnapIt at every desired location in the desired protein. This specific incorporation facilitates subsequently the attachment of further molecule to this amino acid.(4)

*The click chemistry*

The click chemistry is commonly described as a high yielding and simple to perform reaction to form a conjugate between a substrate of choice (often a reporter molecule) with a specific biomolecule. This method is considered to be highly efficient, whereas only by-products, which can be removed easily, are generated and it requires merely mild synthetic conditions. Usually a click chemistry reaction is non reversible, but the VALANX amino acid makes it possible, that it still is reversible and furthermore they claim, that their technology is the fastest click reaction ever.(5,6)

They state, that their technology of producing this amino acid is very cost effective, because they ‘use nature’ to produce them. Other than their competitors who add reactive groups to residues of the protein, they form this synthetic amino acid and incorporate it into

the protein itself. They use an expression system instead of complex procedures which lowers the price of costs. (4)

***The possibilities* VALANX *offers up to now***

*Antibody-drug conjugates* ADC

ADC is the abbreviation for Antibody-drug conjugates which is a novel method to specifically transport drugs to and attack malignant cells like cancer cells. This dual therapy constitutes of a monoclonal anti body and a toxic drug which degrades or attacks the cancer cells. Both parts on its own do not function properly in the cancer treatment, whereas in combination the seem to have a huge impact on the viability of those cells. The antibody on its own does not have any impact to the cells and the drug on its own is highly too cytotoxic to be prescribed to a patient, because it attacks all cells in an unspecific way. The ADC leads to a cancer cell targeted treatment and furthermore to fewer or no side effects.

In course of the treatment the Antibody-drug conjugates enter the body and target the cancer cells by docking to certain receptors on their surface. After the docking, the highly potent cytotoxic drug is released and kills the cancer cells.

Already approved ADCs like Cetuximab (Erbitux) and Trastuzumab (Herceptin) were used to treat autoimmune diseases and cancer infecting the gastrointestinal tract, head, neck and breast. These drugs bind to the cancer cells and cause the blocking of these signal receptors which are usually responsible for receiving growth favoring signal molecules. Consequently, this leads to the shrinking of the tumors. (7)

The first ever ADC drug called brentuximab vedotin (brand name Adcetris) was FDA approved in 2011 showing, that this treatment is relatively novel. (8)

Even though these drugs seem to offer a great opportunity to fight cancer, there are still some struggles which complicate their development. Firstly, the perfect corresponding monoclonal antibody

hast to be found to guarantee to locate correct cells and secondly, a stable and appropriate conjugation between the monoclonal antibody and the drug must be built up. (7) VALANX facilitates the conjugation with their SnapIt amino acid and promotes consequently the step towards the perfect ADC therapy. Furthermore, the synthetic amino acid can be incorporated into the protein at specific locations and also more units of it can be attached which leads to an increased drug to antibody rate (ADR). This rate tells how many potent cytotoxic residues can be attached to the antibody. (4)

*PEGylation of therapeutic peptides and proteins*

Proteins offer a lot of positive effects for their use in the medical and therapeutic field because they are highly specialized for their possibility of binding substrates or other proteins, as well as their several activities. But there are still some challenges when being used in the patient related therapy: their short half-life time. (9) This parameter determines the time when half of the protein amount is degraded or excreted by the patient. Half-life time of a protein like Nesprin in the blood stream is within an average of a few minutes to few hours. (10) With a PEG conjugate the half-life can be increased to several hours or even days. By increasing the half-life time, a frequent dosing of the medicine and consequently kidney damage because of degrading the protein, can be limited or prevented. Furthermore, the cost of the medicine and immunological responses can be obviated.

However, the addition of a polyethylene glycol polymer (PEG) is called PEGylation and the following reaction mechanism shown in Figure 2. this figure also presents the main configuration of the polymer which consists of a repeating C-chain and a functional group. This method is the technology of choice for extending the protein's half life as well as for bringing more positive features along with it. It renders the protein more flexible, hydrophilic, less toxic,

variable in size and shields the substrate from proteases and recognition by the immune system. The FDA 'generally approved as safe" PEG increases the hydrodynamic radius and lowers the rate of renal clearance. While Jonathan K. Dozier et altri. state 'Installing a single PEG chain at a defined site in a protein is challenging' in their paper, VALANX facilitates this problem by using its novel synthetic amino acid which can be easily incorporated into the protein at every location. (4,9)

*Directed immobilization for biosensors*

Biosensors, biochips, drug screening, microarrays, biomedical implants, ... they all have one thing in common: a protein-ligand interaction which leads to a detection signal. The assembly of such a trial unit consists of a surface where receptor molecules can be immobilised and bound. Most commonly the material of such surfaces is a polymer or silicon which anchor the receptor molecules easily. The interaction between such a surface and the receptor must be highly stable and controllable to achieve reliable results. The ligands bind the corresponding biologically active receptors on the surface and facilitate a signal transduction to convert the event of binding to a measurable signal. This interaction between the protein and the ligand is highly specific, because also the orientation of the receptor protein plays a huge role. The receptor must present the active binding site in a way that the ligand can easily be bound to it, otherwise an accurate result is achieved. For example, if you want to bind an Antigen to an immobilized antibody, the antigen-binding site must be oriented towards the antigen, otherwise no interaction might happen. It therefore follows, that the difficult part is to immobilize the receptor correctly to the surface. (11) VALANX facilitates this event by again, using their synthetic amino acid in the immobilisation step to create a site-specific chemical binding and does this in a cost-effective way too. The company usually offers the

receptor proteins which bind correctly to the surface. This is a rapid method to develop reliable biosensors.

*Oriented immobilisation of biocatalysts*

Enzymes and proteins usually occurring in nature have limited function because they work as a single unit and therefore are often not able to meet the requirements for a large-scale application. Therefore, biocatalyst research brought up a new idea of immobilising enzymes to a surface to for a homogenous layer of protein activity. These experiments led to a huge increase in the protein's activity. For example, an immobilised lipase shows 50 times more activity when it is immobilised to a surface. To further increase the ability of these protein estimate, the enzymes are oriented in a way, that they present their binding site to the ligands. This procedure favours the accessibility of the proteins and increases the activity at a 3-fold in solution. (12)

***Conclusion***

VALANX is a highly promising new start-up with its roots in Austria, a small country in the middle of Europe. There are not that many companies trying to make their way up to the top by starting in Austria. Therefore, the government tries to encourage new start-ups by offering assistance and aid money. Using an *E.coli* strain to produce proteins for you is nowadays one of the most used standard operations in protein engineering, but incorporating a new synthesized amino acid is novel. Their biotechnological approach combines protein engineering, medicine and biology to create a solution to a huge problem. SnapIt might assist or complete in future many more applications in the medical field. With their special *E.coli* strain it is possible to make proteins with another amino acid then the 20 naturally occurring ones. So, it might be imaginable that it can also incorporate other molecules into proteins.

A huge advantage is outsourcing the production of your protein,

because it can save you time and money. If you don't have to care about the production, you can focus on the development of the procedure and drug itself. As they claim on their website, it seems to be an affordable procedure to generate these conjugates so that one can do many experiments and not just focus on one protein, because the costs are so high, that one can't afford different experimental concepts. The number of future applications is vast, and we still don't know in which areas it will be usable.

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# 35. Roche Strategies to Tackle Biosimilar Issue

*by Neethu Shaji Saji*

It was a nice day in spring 2019, Roche CEO, Severin Schwann was reading monthly reports about the recent developments of the company preparing for a meeting with investors later that afternoon. The investor's meeting was scheduled immediately after FDA approved the fourth biosimilar of Herceptin produced by Pfizer in the U.S. This meeting is very important for Roche to give confidence to the investors and educate them about the strategies Roche has taken over the years to prepare for the biosimilar competition. "I am confident that I can convince investors about the strong strategies taken by Roche to tackle the biosimilar competition" says Severin Schwann [1].

Three of Roche biologic cancer drugs: Avastin, Herceptin, and Tarceva are coming off patent in the U.S during the 2019-20 time period [2]. Biotech drugs or biologics are drugs that are either partially or completely made from living cells. Due to this reason, biosimilars to biologics are complex to develop compared to generics of chemically synthesized small molecule drugs [3]. FDA describes biosimilar as a biological drug that is almost identical to its reference drug in all clinically relevant structure and function. A little bit of variation is acceptable in clinically non-relevant structures [3]. Biosimilars are made by companies other than the innovator companies once the reference drug comes off patent protection.

Bevacizumab sold by Roche under the brand name Avastin is an anti-angiogenic drug, that prevents the formation of new blood vessels that bring nutrients to cancer cells. This drug is all set to come off patent in the U.S. in July 2019 and the EU in 2022. [4].

Trastuzumab sold under the brand name Herceptin is a monoclonal antibody that is used in the treatment for breast cancer. The patent for Herceptin has already expired in 2014 in the EU and will expire in 2019 in the U.S. [5]. This drug brought revenue of 7 billion USD to Roche in 2018 [6]. Erlotinib hydrochloride with the brand name Tarceva is an epidermal growth factor receptor inhibitor that is used to treat patients suffering from several types of cancer. [7]. This drug will come off patent in the U.S. in November 2020 and in the EU in March 2020 [8].

These three drugs together generated $100 billion in their lifetime from the U.S. [2] and a total of 19 billion USD to the company's revenue in 2017 [9]. These figures represent a significant portion of Roche's revenue. In 2018, they added $ 7 billion to Roche's revenue just from the U.S. [2] So, the patent expiries of these three biologic drugs will pave the way for the entry of biosimilars to the market and this will significantly impact the revenue these drugs bring to the company.

In addition to patent expiries, Roche will also lose the royalty money it collects from many companies from this year. Royalty money is from 'Cabilly patents'- that was originally granted to Genentech in 1983 for inventing a reaction step involved in the cell-based drug production [6]. Roche acquired Genentech in 2009 [10]. This patent allowed Roche to collect royalty fees from companies that used this step in their drug manufacturing process. In 2017, Roche collected about $840.4 million from its 'Cabilly royalties' [6]

The series of patent expiries of blockbuster biologic drugs and the expiration of Cabilly patents will significantly decrease the revenue generated by Roche from these sources. But Schwann is confident that the company can overcome the current situation. He says "We can overcome the biosimilar erosion curve" [11].

**Roche history**

Fritz Hoffmann-La Roche, who believed in the potential influence of pharmaceuticals in treating diseases foundedRoche on

October 1st, 1896, in Switzerland [12]. During the time period from 1897 to 1914, the company grew significantly and started several offices in Germany, London, and New York. The company experienced losses during the first world war due to the boycott of Roche products in Germany [12]. During the 1920s, 30s and early 40s, the company flourished by its sales of vitamins. Roche diversified its pipeline and started focusing on antimicrobials, antidepressants, and anti-cancer drugs during the 1950s and early 60s [12]. The company extended its interest to biotech industry during the early 2000s. Today, Roche is a leader in diagnostics and pharmaceuticals [12]. Roche's drug sales dominate in the fields of cancer, neuroscience, immunology, and microbiology [13].

**Biosimilars in Market**

In 1984, Drug Price Competition and Patent Term Restoration Act also known as Hatch-Waxman Act was passed which allowed the sales of generic versions of chemically derived drugs in the U.S. once the traditional small molecule drugs came off patent [14]. Unlike biologics, these small molecules drugs are synthetically made by a series of chemical reactions. The biologic drugs did not come under this law, so the biotech companies enjoyed a monopoly in the market and gained a high–profit margin. Due to the high price of biologic drugs and the increasing cost of treatment, things started to change in the late 2000s. In March 2010, U. S president Barrack Obama signed Affordable Care Act, that opened the market for the biosimilars of biologic drugs in the U.S. This act granted biosimilar drug maker's easier access to the market once the reference biologic drug comes out of patent [15, 16].

This was a huge shock for the pharmaceutical companies because the biosimilar companies now have access to the billion-dollar biologic market. The introduction of biosimilars can significantly affect the sales of brand name due to the low price of biosimilars. They also provide similar effects as the brand name itself. The low price of biosimilars can be attributed to less research needed

as most of the work is done by the innovator companies including testing of 1000s of molecules to come out with one successful drug. Since the law passed in 2011, several pharma companies that owned the market of some blockbuster drugs had lost it to biosimilar competitors. All the biotechnology and pharmaceutical companies started coming up with different strategies to protect their patents and thus extend the market monopoly as long as possible. Keeping patent life longer was important for them due to the increased price of research and decrease in the launch of new drugs.

The first biologic drug patented by Roche did not expire in Europe until 2013 and in the U.S until 2018; Mabthera expired in 2013 in Europe and in 2018 in the U.S [17]. This gave Roche a couple of years to come up with strategies since the law changed in 2010.

The strategies they adopted to deal with the patent crisis are discussed below.

**Evergreening- by thickening of patents**

Evergreening is a strategy that pharma companies adopt to extend patent protection and prevent biosimilars from creating a market competition for the drug [18]. In the pharmaceutical world, inventors make slight modifications to the original drug or find a new use for it and patent the modified version [18]. The new patent extends the protection period thus preventing the launch of new biosimilars. The different ways by which Roche obtained new patents for their old drug include:

1. Patent new uses for old drugs: is a strategy that is often used by the innovator companies to drive up the sales of old drugs or drugs coming out of patents. This will prevent biosimilar entry by extending the protection by patenting new functions for older drugs [19]. For example, i) Avastin was previously approved for treating colorectal cancer, lung cancer, breast cancer, renal cancer, brain cancer, and some eye disease [20]. In 2018, it was granted the approval to be used for ovarian cancer [21] (ii) Actemra/RoActemra was approved for the treatment of a type of juvenile idiopathic arthritis in 2018 [21] (iii)

MabThera/Rituxan, previously treated some autoimmune diseases and some cancers was recently approved to treat moderate to severe pemphigus vulgaris [21][22].

2. New formulations: Another strategy to drive up the dropping drug sales is combining an old drug with a relatively new drug developed by Roche in combination therapy [19]. The biosimilars may not act exactly the same way as the brand name when taken with the newer drugs in the combination therapy. Schwann says, "This strategy gives the company a chance to differentiate, to raise the standard of care, and to get in earlier lines of treatment" [23]. Tecentriq (new drug) in combination with Avastin(old drug), paclitaxel, and carboplatin (chemotherapy), is approved to be prescribed for cases with metastatic non-squamous lung cancer with no epithelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations [21]. Herceptin biosimilars are all set to enter the market in the U.S by this year, but Roche filed several additional patents on combination therapy so that the protection could potentially be extended until 2033 if granted [24].

*Major patent grants in 2018 and pending approvals for patents are shown in Exhibit I and II.

**Cutting Jobs and Operational Costs**

Roche recently announced some job cuts in the U.S. and Europe. In Europe, they plan to stop some of the company's operations [25]. These layoffs and operational shutdowns are part of the cost cut strategy in response to recent revenue loss from blockbuster drugs [25].

**Acquisitions to strengthen the drug pipeline and access new technologies**

Another strategy adopted by Roche is to form partnerships with companies that develop promising drugs and technologies by acquiring them. Roche acquired Foresight VISION4 (2017), Ignyta Inc (2017), Foundation Medicine, Inc. (2018), Tusk Therapeutics (2018), and Spark Therapeutics (2019 [26]. Out of these five recent

acquisitions, Ignyta Inc and Tusk Therapeutics are developing drugs that fall into Roche's traditional cancer business. On the other hand, Foresight VISIO4 is a company that developed a retinal drug delivery method known as port delivery system [27]. Roche fully acquired Foundation Medicine Inc for 2.4 billion USD in June 2018 where Roche already had a share of 57% from 2015. This acquisition gave Roche access to Foundation Therapeutics genomic profiling technology which can be utilized in the field of personalized medicine approach [28].

Earlier in 2018, Roche acquired Flatiron Health, that owns an oncology-based data platform. Roche's acquisition of Flatiron, which is a relatively new company was driven by the need to improve the results of oncology drug clinical trials [29]. Traditionally, oncology was one of Roche hot spot, but in today's situation where drugs are coming off patents and show signs of losing the market to biosimilars, Roche needs to maximize the efficiency of clinical trials by finding the right cohort of cancer patients for their future trials. This is where Flatiron technology becomes valuable for Roche. Flatiron collects unstructured oncology data from multiple labs and other repositories which will help to recruit people for clinical trials [29]. Using this data is not an easy path for Roche as there are strict regulations for a pharma company to use results acquired by a U. S provider [29].

The Flatiron's oncology data services, when combined with the genomic profiling technology developed by Foundation Medicine, will help Roche to increase the success of their clinical trials and bring more drugs into the market. Finding the right cohort of patients for the trial increases the speed at which the clinical trials are done and save millions of dollars for the company.

In February 2019, Roche acquired Spark Therapeutics for $ 4.8 billion. Spark Therapeutics mainly focuses on gene therapies for diseases like blindness, hemophilia, lysosomal disorders, and neurodegenerative diseases that have genetic origins [30]. "The fit

of Spark and Roche is really excellent. It provides us with a broad portfolio and expertise across the value chain," said Schwann [31]

**Diversify the pharmaceutical division with strong drugs**

Roche is now focusing on diversifying their current drug pipeline because the competition in the oncology field is increasing. Traditionally, most of Roche's blockbuster drugs were cancer drugs. The strong launch of Ocrevus in Multiple Sclerosis and Hemlibra for hemophilia A are examples of this diversification process [32]. Even though only about 40,000 people in the world suffer from hemophilia A, Hemlibra is an expensive medicine that can cost up to $492,000 per year for a patient of 140 pounds [33]. Through Hemlibra, Roche plans to enter the $10 billion industry of hemophilia A drug market [33]. Ocrevus was approved by FDA in 2017 to treat patients with multiple sclerosis. This was a huge success and partially compensated the loss caused by biosimilars [34]. Severin Schwan describes Ocrevus as "the most successful launch in the history of Roche" [34]. It added a whopping 1.4 billion Swiss franc to Roche's revenue in less than one and a half years since its launch [34]. Schwan is happy with the success of Ocrevus, Hemlibra, and new cancer drugs in the market which are Perjeta, Alecensa and Tecentriq [34]. "In the first half of the year, both our pharmaceutical and diagnostics divisions achieved very strong results. Given the very good, continuously growing uptake of our new medicines, we are well on track to rejuvenate our portfolio. The growth of our business will continue, also beyond the current year" says Schwann [34].

Roche has a number of drugs in the pipeline for neurodegenerative disorders like Alzheimer's disease, Autism, Parkinson's disease, and Huntington's disease, where the focus of other companies is becoming comparatively decreasing [32] [35].

*Exhibit III and IV shows Roche's current drug pipeline and clinical trials.

**Roche Controversary in India**

Sometimes the strategies Roche executed to keep the

market monopoly did not always end with a happy note. An example of this is the case against Roche in India. Biocon and Mylan filed a lawsuit against Roche in the Delhi supreme court alleging that Roche abused its dominant position in India to prevent biosimilar competition for Herceptin in India. Roche sold Trastuzumab in India under the brand name Herceptin from 2002 to 2012 [36]. It withdrew Herceptin from the Indian market in 2012 and introduced two cheaper versions: BICELTIS and HERCLON. In 2014, two generic versions of Herceptin CANMAb and HERTRAZ was brought to the market by Biocon and Mylan, after which Roche's market share declined [36].

In 2014, Roche sued Biocon and Mylan alleging that the new drugs did not meet the guidelines for biosimilars and thus cannot claim that their drugs are biosimilars to Roche's Herceptin [37,38,39]. Roche successfully sued biosimilar companies in this lawsuit and halted their sales in India [37,38,39]. The regulatory agencies in India later lifted the ban for CANMAb and HERTRAZ and allowed their re-entry to the market. In 2016, Biocon and Mylan filed a lawsuit against Roche claiming that they used their dominant position as the largest market share holder for Herceptin in India to influence regulatory authorities and spread misinterpretations as a means to keep the biosimilar competitors out of market [37,38,39]. In 2017, the competition commission of India (CCI) ordered an investigation in response to the allegations made by Biocon and Mylan. [37,38,39]. If the allegations are proven, it will be a setback for Roche in India.

**More Potential Strategies to Compensate Biosimilar Competition**

Some other strategies Roche could implement are:

- Reduction in price

Reduced price of biosimilars is the main incentive that encourages people to opt for biosimilars over brand names. Reducing the price of the drugs when they come off patents can decrease the number

of people switching to biosimilar version and also discourage the companies from bringing biosimilars to the market. This is because patients will be less likely to switch to a biosimilar if they get the brand name drug for a comparable price as that of a potential biosimilar.

- Enter the generic business

Roche possesses high-class infrastructure for developing drugs and state of art types of equipment for research & development of drugs. The generic industry is estimated to be about $380.60 Billion by 2021 [40]. Recent developments in the biosimilar market and legal battles show that how hard the innovator companies tried to stop biosimilar entries they eventually made it to the market. So, it would be a good idea for Roche to enter the generic or biosimilar business or even acquire companies making biosimilars.

- Some other strategies of evergreening like focusing on specific stereoisomers

Stereoisomers are mirror images of each other [19]. Patenting by stereoisomers is another strategy Roche can use to improve patent life. This means if both stereoisomers have similar effects, then they can patent one stereoisomer first and then later the other stereoisomer [19].

- Enter avenues with limited competitions

Orphan drugs- These are the drugs that are developed to treat diseases that are rare. The low numbers of patients are often combated with the higher price, and incentives provided by many countries to develop orphan drugs. The innovator company of orphan drugs often receives some tax exemptions, extended patent protections, and grants from the government [41]. Limited incentives

and low prevalence of the diseases can discourage biosimilar development in this field thus allowing the innovator companies to enjoy a market monopoly for a longer time.

- Focusing on high success clinical trials

Clinical trials can often be very costly. If the company can improve the success of clinical trials, the cost of drug development can be reduced. This money can then be used to bring the drug cost down in the relevant market with high biosimilar competition. As discussed above, the technologies acquired by Roche like that of Flatiron's oncology data services can help them select the right cohort of patients for oncology clinical trials and increase their success rate and avoid rejections from FDA. This strategy is applicable to any field where they plan to launch drugs.

"I am sure we will overcome the biosimilar incursion through our new drugs and other strategies" [42] saying this Mr. Schwann went back to prepare his talk for the investor's meeting later that evening. He was confident that the strategies Roche implemented, the new strong sales of new drugs, the increase in 2018 sales despite the biosimilar entry will convince the investors that the company is in the right trajectory.

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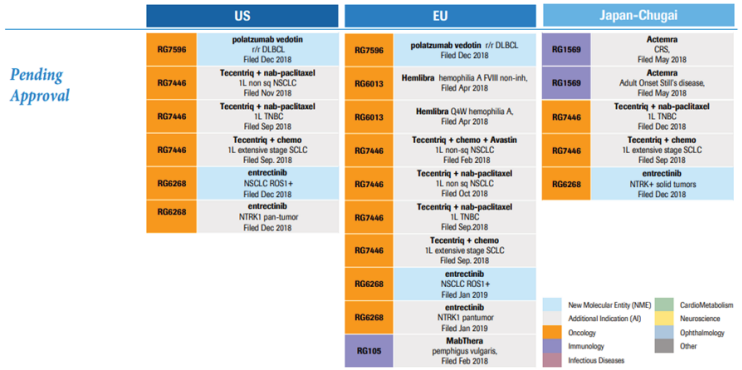
Exhibit I. Major Pending Approvals 2019




Source: https://www.roche.com/dam/jcr:d6a6a8a5-d42b-4678-9bf3-aa69bf00d535/en/irp190131-annex.pdf (Retrieved on April 11th, 2019).

Exhibit II. Major Patent Approvals 2018

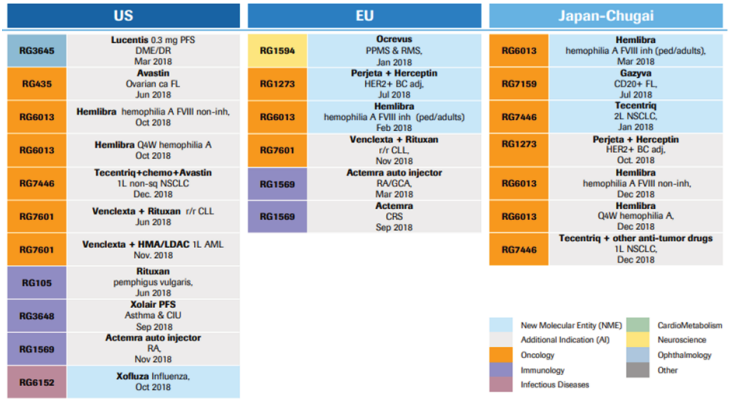



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Exhibit III. Cancer Immunotherapy Pipeline Overview

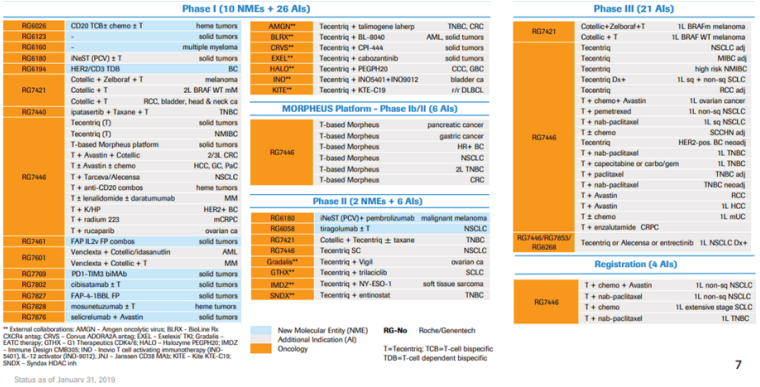


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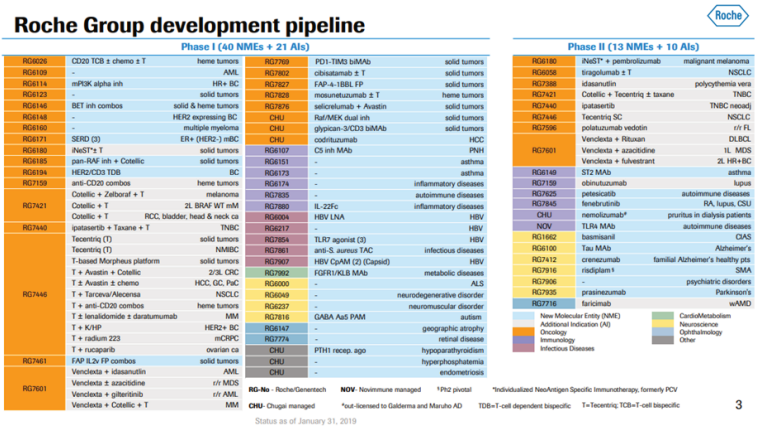
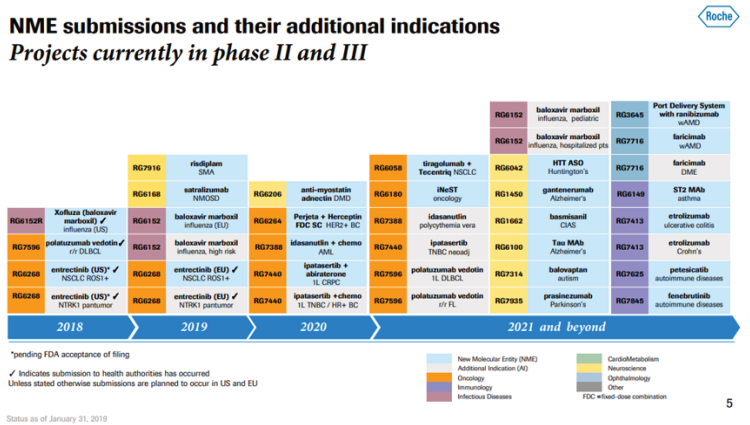
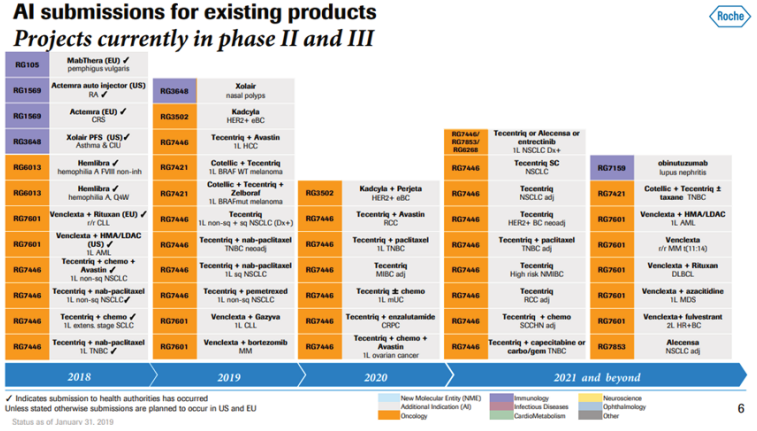
Exhibit IV. Roche Developmental Pipeline & Clinical Trials


Roche Group development pipeline
Roche
Phase I (40 NMEs + 21 AIs)
RG6026 CD20 TCB ± chemo ± T heme tumors
RG6109 - AML
RG6114 mPI3K alpha inh HR+ BC
RG6123 - solid tumors
RG6146 BET inh combos solid & heme tumors
RG6148 - HER2 expressing BC
RG6160 - multiple myeloma
RG6171 SERD (3) ER+ (HER2-) mBC
RG6180 iNeST*± T solid tumors
RG6185 pan-RAF inh + Cotellic solid tumors
RG6194 HER2/CD3 TDB BC
RG7159 anti-CD20 combos heme tumors
RG7421 Cotellic + Zelboraf + T melanoma
Cotellic + T 2L BRAF WT mM
Cotellic + T RCC, bladder, head & neck ca
RG7440 ipatasertib + Taxane + T TNBC
RG7446 Tecentriq (T) solid tumors
Tecentriq (T) NMIBC
T-based Morpheus platform solid tumors
T + Avastin + Cotellic 2/3L CRC
T ± Avastin ± chemo HCC, GC, PaC
T + Tarceva/Alecensa NSCLC
T + anti-CD20 combos heme tumors
T ± lenalidomide ± daratumumab MM
T + K/HP HER2+ BC
T + radium 223 mCRPC
T + rucaparib ovarian ca
RG7461 FAP IL2v FP combos solid tumors
RG7601 Venclexta + idasanutlin AML
Venclexta ± azacitidine r/r MDS
Venclexta + gilteritinib r/r AML
Venclexta + Cotellic + T MM
RG7769 PD1-TIM3 biMAb solid tumors
RG7802 cibisatamab ± T solid tumors
RG7827 FAP-4-1BBL FP solid tumors
RG7828 mosunetuzumab ± T heme tumors
RG7876 selicrelumab + Avastin solid tumors
CHU Raf/MEK dual inh solid tumors
CHU glypican-3/CD3 biMAb solid tumors
CHU codrituzumab HCC
RG6107 C5 inh MAb PNH
RG6151 - asthma
RG6173 - asthma
RG6174 - inflammatory diseases
RG7835 - autoimmune diseases
RG7880 IL-22Fc inflammatory diseases
RG6004 HBV LNA HBV
RG6217 - HBV
RG7854 TLR7 agonist (3) HBV
RG7861 anti-S. aureus TAC infectious diseases
RG7907 HBV CpAM (2) (Capsid) HBV
RG7992 FGFR1/KLB MAb metabolic diseases
RG6000 - ALS
RG6049 - neurodegenerative disorder
RG6237 - neuromuscular disorder
RG7816 GABA AaS PAM autism
RG6147 - geographic atrophy
RG7774 - retinal disease
CHU PTH1 recep. ago hypoparathyroidism
CHU - hyperphosphatemia
CHU - endometriosis
Phase II (13 NMEs + 10 AIs)
RG6180 iNeST* + pembrolizumab malignant melanoma
RG6058 tiragolumab ± T NSCLC
RG7388 idasanutlin polycythemia vera
RG7421 Cotellic + Tecentriq ± taxane TNBC
RG7440 ipatasertib TNBC neoadj
RG7446 Tecentriq SC NSCLC
RG7596 polatuzumab vedotin r/r FL
RG7601 Venclexta + Rituxan DLBCL
Venclexta + azacitidine 1L MDS
Venclexta + fulvestrant 2L HR+BC
RG6149 ST2 MAb asthma
RG7159 obinutuzumab lupus
RG7625 petesicatib autoimmune diseases
RG7845 fenebrutinib RA, lupus, CSU
CHU nemolizumab# pruritus in dialysis patients
NOV TLR4 MAb autoimmune diseases
RG1662 basmisanil CIAS
RG6100 Tau MAb Alzheimer's
RG7412 crenezumab familial Alzheimer's healthy pts
RG7916 risdiplam¶ SMA
RG7906 - psychiatric disorders
RG7935 prasinezumab Parkinson's
RG7716 faricimab wAMD
New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases
CardioMetabolism
Neuroscience
Ophthalmology
Other
RG-No - Roche/Genentech
NOV- Novimmune managed
¶ Ph2 pivotal
*Individualized NeoAntigen Specific Immunotherapy, formerly PCV
CHU- Chugai managed
#out-licensed to Galderma and Maruho AD
TDB=T-cell dependent bispecific
T=Tecentriq; TCB=T-cell bispecific
3
Status as of January 31, 2019
Roche Group development pipeline
Roche
Phase III (11 NMEs + 35 AIs)
RG3502 Kadcyla HER2+ aBC
Kadcyla + Perjeta HER2+ aBC
RG6264 Perjeta + Herceptin FDC SC HER2+ BC
RG7388 idasanutlin + chemo AML
RG7440 ipatasertib + abiraterone 1L CRPC
ipatasertib + chemo 1L TNBC/HR+ BC
RG7421 Cotellic + Zelboraf+T 1L BRAFm melanoma
Cotellic + T 1L BRAF WT melanoma
RG7596 polatuzumab vedotin 1L DLBCL
RG7446 Tecentriq NSCLC adj
Tecentriq MIBC adj
Tecentriq NMIBC, high risk
Tecentriq Dx+ 1L sq + non-sq NSCLC
Tecentriq RCC adj
T + chemo + Avastin 1L ovarian cancer
T + pemetrexed 1L non-sq NSCLC
T + nab-paclitaxel 1L sq NSCLC
T ± chemo SCCHN adj
Tecentriq HER2+ BC neoadj
T + paclitaxel 1L TNBC
T + capecitabine or carbo/gem 1L TNBC
T + paclitaxel TNBC adj
T + nab-paclitaxel TNBC neoadj
T + Avastin 1L HCC
T + Avastin RCC
T ± chemo 1L mUC
T + enzalutamide CRPC
RG7446/RG7853/RG6268 Tecentriq or Alecensa or entrectinib 1L NSCLC Dx+
RG7601 Venclexta + Gazyva 1L CLL
Venclexta + bortezomib MM
Venclexta r/r MM t(11:14)
Venclexta + HMA/LDA 1L AML
RG7853 Alecensa NSCLC adj
RG3648 Xolair nasal polyps
RG7413 etrolizumab ulcerative colitis
etrolizumab Crohn's
RG6152 Xofluza influenza, high risk
Xofluza influenza, hospitalized pts
Xofluza influenza, pediatric
RG1450 gantenerumab Alzheimer's
RG6042 HTT ASO Huntington's
RG6168 satralizumab NMOSD
RG6206 anti-myostatin adnectin DMD
RG7314 balovaptan autism
RG3645 port delivery system with ranibizumab wAMD
RG7716 faricimab DME
Registration (3 NMEs + 8 AIs)
RG6013 Hemlibra¹ hemophilia A w/o FVIII inh
Hemlibra¹ QxW hemophilia A
RG6268 entrectinib NSCLC ROS1+
entrectinib NTRK1 pantumor
RG7446 T + chemo + Avastin¹ 1L non-sq NSCLC
T + nab-paclitaxel 1L non-sq NSCLC
T + nab-paclitaxel 1L TNBC
T + chemo 1L extensive stage SCLC
RG7596 polatuzumab vedotin r/r DLBCL
RG1205 MabThera¹ pemphigus vulgaris
RG6152 Xofluza ¹ influenza
¹ Approved in US
New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases
CardioMetabolism
Neuroscience
Ophthalmology
Other
RG-No Roche/Genentech
NOV Novimmune managed
CHU Chugai managed
*out-licensed to Galderma and Maruho AD
FDC=fixed-dose combination
T=Tecentriq; TCB=T-cell bispecific
TDB=T-cell dependent bispecific
4
Status as of January 31, 2019

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# 36. Centocor: Commercializing Monoclonal Antibodies

**Centocor: Commercializing Monoclonal Antibodies**

On a beautiful late April day in 1991, Hubert Schoemaker's family holiday was abruptly interrupted by a phone call he had been dreading. David Kessler, the head of the FDA, was on the line tasked with passing on some unfortunate news – Centoxin, the drug that Schoemaker had staked his company's reputation and future on, was rejected for approval pending further clinical trials (1q). This news was the culmination of a devastating few months for Schoemaker's biotech company Centocor. Stock prices had plummeted as uncertainty grew around Centoxin's approval status, and public opinion on Centocor's future was at an all time low. This was uncharted territory for the upstart biotech company, which had experienced enormous success since its inception in 1979. Even Schoemaker, known for his optimism, could not hide his devastation at the news. He knew that in order for the company to survive, drastic changes would be needed.

**Centocor: Background Information**

Centocor was borne in 1979 of a partnership between Hilary Koprowski, an immunologist and virologist who was serving as director of the Wistar Institute, and Michael Wall, an electrical engineer from MIT and serial entrepreneur (1). This partnership was

created out of a desire to capitalize on the commercialization of a revolutionary new product biotechnology product; monoclonal antibodies. For the first time, researchers had developed antibodies that were immortal, produced in a standardized way, and could be engineered to specifically attack only desired epitopes or "targets" (5). The implications were widespread – mAb's had potential as both diagnostic tools and targeted therapeutics. As the director of a renowned immunological research centre, Koprowski was well aware of the impact mAb's were likely to have within these markets, having successfully developed mAb's against various diseases in his own lab (1). Koprowski decided to team with Michael Wall to build his own company and commercialize these innovative biotechnology products. With Koprowski's scientific expertise coupled with Wall's industry connections and business savvy, Centocor was poised for success.

Hubert Schoemaker, a biochemist from MIT with valuable experience in commercializing diagnostics, was soon recruited on as the CEO of the company. Schoemaker would prove crucial to the company. During is tenure, Centocor would undergo dramatic changes on the path to commercial success and, eventually, enormous uncertainty.

**Initial Strategic Planning**

Initially, Centocor viewed diagnostics as their target market when developing mAb products. This decision was driven by a variety of factors. Firstly, the potential market was very large, with a valuation at $2 billion (1). Additionally, diagnostics were much easier to develop than therapeutics. The added benefit of not being directly used in the human body meant a much easier regulatory path to approval

for these products as well, reducing the cost of development and time to market. All of these factors lead the team to believe that they could achieve revenues of $17 million in the diagnostics market by 1984 (1). Therapeutics were therefore seen as a long term strategy, with revenue from diagnostics being used as a tool to reach this goal.

While the diagnostic market was able to offer initial benefits over therapeutics, it was not without its challenges. The market was highly competitive, with with major players like Roche and Pfizer at the forefront. These companies were much larger than Centocor, with higher operating budgets and well established products available. Additionally, diagnostic tests available could only be analyzed through proprietary instruments, further solidifying the hold these major players had on the market (1). The executive team at Centocor were well aware that they would not be able to compete with these companies independently. Instead of relying on in house research and product development to gain a foothold in the market, Centocor based its strategic business plan on a collaborative approach. This meant that rather than developing competitive technologies themselves, the company would focus on building relationships and licensing agreements with labs that were producing promising results within the mAb diagnostic field. By leveraging the networking abilities and academic connections of the board members, it was believed that Centocor would be able to save money on original research and bring products to market at a much quicker pace (1).

Thus the plan was in place – fund promising research in exchange for licensing agreements on the technology produced, in order to quickly and efficiently bring products to market and build revenue. While less expensive than developing products in-house, this strategy still required a significant amount of capital in order to fund the research labs deemed worthy. Luckily, Schoemaker and Wall were successful in this regard. The company was able to raise significant

capital through both private investment and public offerings, with their largest public offering bringing in $100 million in capital (1). This placed Centocor in a promising position for penetrating the diagnostics market.

**Early Success**

Centocor enjoyed a high level of initial success using this business model. Widespread and diverse licensing agreements allowed the company to gain broad market penetration and establish a foothold in the mAb diagnostics market. Following this strategy of collaboration, Centocor was able to grow its research collaborations from 15 in 1985 to 80 in 1990 (1). These partnerships involved labs from across the world, allowing Centocor to grow its brand globally. The success of this strategy is evidenced by comparing the company's growth in terms of sales and in-house R&D funding. During this period of growth, Centocor saw a fivefold increase in sales, while R&D funding had remained constant annually (7). Additionally, partnerships with high-profile companies within the market were established. This allowed Centocor to take advantage of these companies well-established distributions channels, eliminating the need for Centocor to spend time and energy on large-scale marketing and distribution of its products (1).

A number of products were instrumental to the initial success of Centocor. The first two diagnostic tests to achieve market success were for gastrointestinal cancer and hepatitis B. Both of these tests were produced by research funded in academia by Centocor – the former from the Wistar Institution, and the latter from Massachusetts General Hospital. These tests achieved regulatory approval quickly and sold well, providing a massive ROI from initial

study funding for Centocor. Other products soon arrived from the Centocor pipeline, further bolstering the company's market position. Diagnostic tests for ovarian cancer, breast cancer and colorectal cancer proved exceedingly popular (in fact, all three tests are still used today) (1). Again, these products were all licensed from various research institutes. This represented a remarkable success story in biotechnology commercialization – Centocor had grown to the point of generating $50 million in revenue by 1985, and by 1990 had a 25% market share in mAb based cancer diagnostics (1).

**Movement to Therapeutics**

With the company strongly established and profitable in the diagnostics industry, Schoemaker and his team of executives decided the time was right to move into the therapeutics market. This had always been the goal of the company – their ambition was to become a large pharmaceutical player in the same vein as Bayer and Merck. To achieve this, Centocor would need to produce a blockbuster mAb based therapy. This was no easy task – therapeutics derived from mAb had never been developed, and whether they would prove effective remained to be seen. Additionally, commercialization of such products would require significantly more resources than diagnostics, as clinical trials and regulatory approval were more rigorous and cost intensive. Penetration of a market where costs and logistical hurdles were so prominent was undoubtedly a risky move for Schoemaker. The rationale was that while the risks were large, the enormous potential payoff of having successful therapeutics provided enough incentive to move forward.

After evaluating of many candidate therapeutics, Schoemaker believed that Centocor had their blockbuster mAb therapeutic in 1988. This drug candidate, dubbed "Centoxin", would be used to treat

septic shock caused by Gram-negative septic bacteria. This was a major health concern during the 1980s, killing 100 000 people annually and costing $10 billion to the healthcare system (2). Centoxin was meant to solve this problem, while simultaneously establishing Centocor into a pharmaceutical powerhouse. With projected sales of $400 million in its first year, it seemed a great candidate to propel Centocor into the future (2).

Along with a change in market came a change in strategy at Centocor. Schoemaker believed that the enormous revenue potential of Centocor and growing resources available at his company warranted a departure from the traditional collaborative approach. Centocor intended to develop Centoxin on their own, without help from major collaborative partnerships with big pharmaceutical companies. This move was intended to maximize revenue for Centocor, as well as establishing necessary systems within the company for their evolution into a major pharmaceutical player (2).

This transformation would come at a significant cost. In the absence of a major pharmaceutical partner, Centocor would have to develop its own manufacturing facilities, distribution channels, sales force, clinical trial system and R&D facilities for Centoxin. This would require major capital expenditures. From 1986 to 1992, Schoemaker was able to raise $500 million for this purpose (2). Of this total, $450 million was spent on running clinical trials, creating a sales force and constructing two manufacturing plants (2).

Early indicators gave reasons for optimism. An initial randomized trial of Centoxin was found to reduce both Gram-negative sepsis and mortality by 39% and 47%, respectively, without any adverse affects (3). Centocor had submitted the drug to the FDA to begin the regulatory process, and by 1991 the FDA advisory board had

unanimously recommended approval (3). The drug had been approved throughout much of Europe, and even the US army had placed a large order for use in the Gulf War. Expectations were high at Centocor, and the company was confident their drug would soon be brought to market.

**Unfortunate News**

Unfortunately, things did not stay optimistic for long. A number of issues would soon arise casting serious doubt over the viability of Centoxin. The earliest indicator of trouble was the loss of a patent battle between Centocor and Xoma, a close competitor, over the proprietary mAb used against sepsis. Centocor, being a relatively new company with little experience in patent battles, had decided to forego settlement and fight Xoma tooth and nail. This decision resulted in a huge loss of time and money which the company could not afford to waste(2). Additionally, questions about the efficacy and safety of Centoxin had begun to arise. A variety studies were being published reporting adverse safety affects in animal models as well as an inability to recreate effective treatment results in lab (4). The culmination of these events was an indication by the FDA in 1992 that additional clinical information would be needed before Centoxin would be approved. This news spelled disaster for Centocor. Financial markets were sent into turmoil – share prices plummeted 19% upon the report, representing a $675 million loss in Centocor's market valuation (3).

This was the predicament Schoemaker found himself as he contemplated the phone call he received. His company was now on the verge of collapse – share prices had decreased from $60 a share in December 1991 to $6 a share in April 1992 (6). Additionally, Schoemaker knew the company's cash burn rate of $50 million per

quarter was no longer sustainable (6). With his biotech start-up company, once so successful, hanging in the balance, Schoemaker called his executive team together for a fateful meeting. How could the company survive this financial disaster? Were therapeutics worth pursuing? What management style and culture shifts were needed to keep the company alive? These were the questions lingering as Schoemaker and his team members considered drastic measures to save their fledgling company.

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# 37. K&N's: A Vertically Integrated Business Approach

Khalil Sattar while reading newspaper in veranda in his house in northwestern, Pakistan on Sep. 2011 started thinking of his dream of a happy and healthy nation.

Khalil Sattar established poultry business “K&N’s” in Pakistan in 1964 with his wife Naushaba Khalil (hence the name K&N’s). In September 2011, K&N’s was now run with his son Adil K. Sattar(1). Khalil started K&N’s with the single mission “to provide better nutrition for the health and happiness of the nation”.

K&N’s was one of the largest broiler-chick producers and the market leader for the processed chicken products in Pakistan, in 2011, with the projected sales of US$ 250 million. It was unbelievable for international visitors to the company’s facilities to see world-class poultry producers in a country with political and economic challenges. Khalil and Adil not only successfully handled those challenges but also ran an industry that was regularly challenged by diseases, poor quality standards, an uncertain regulatory and tax environment, and wet market.

K&N’s earned confidence among consumers through quality and food safety and it was, therefore, the top choice of consumers and international food-food service operators such as KFC (Fig.1) which promoted K&N’s in its advertisements. Sattar’s always wanted to do more in this industry by increasing the percentage of broiler chicks they produced for processing operations. They also felt that their business could grow more by increasing the volume of chicken and by offering comparably low cost to compete for the wet market.

Rapid urbanization, a growing middle class, and a rising number of women working outside the home raised demand for processed

products which assisted K&N's to achieve its goal and to keep focused on domestic market demand. K&N's without degrading wet-market stayed focussed on its goal to provide "Safe and Healthy chicken" which positioned it as a top-selling chicken brand in Pakistan.

K&N's was interested to expand its business strategies at the international level but OIE (Organization of Animal Health) banned the export of poultry from Pakistan in 2006 due to the bird flu epidemic. The ban was lifted in 2008 but each country visited Pakistan to further verify the safety and health of poultry before accepting imports.

UAE approved K&N's for import of poultry and poultry products in 2011 after the ban was lifted. After that, other neighboring countries like Afghanistan and Saudi Arabia, Oman also approved import from K&N's, Pakistan. Sattars' were concerned with the imports to these rich states, as these markets looked temporary to them because of their wealthy government which could decide to have their own poultry industries any time as wealth was not an issue for them to raise any industry locally.

Sattars' were looking for avenues to enter into the western market with strong footing as they were fascinated with the large Halal food market which was growing rapidly in the west such as the U.S., the U.K, and France where there was real potential to grow and also people enjoyed higher incomes than Asia. But they were not sure if the Pakistani company could do business in western countries or would K&N's meet western standards of the market?

The company efficiently worked on gaps it had in its business to be more cost efficient so by 2011 it was the only fully vertically integrated poultry industry (Fig. 2) in country which had its own broiler-chick producers in the country, the largest broiler grower, the largest chicken processor, and the market and brand leader for processed chicken and value-added chicken products, with their own feed mill. In order to gain more confidence of customers, K&N's realized a video on their website in which birds were being

slaughtered in a truly Islamic way. The company was working with the basic objective of providing safe and healthy proteins to meet the nutritional needs of citizens. Khalil believed that it was the only source of animal protein that can feed the nation in a cost-effective manner (2).

Khalil, who was a chairman and CEO of K&N's, was looking matters related to his business on a daily basis and later in 1997 Adil, joined as executive director after completing his undergraduate degree in agricultural economics and business management with classes in poultry science at Cornell University. Strategy development and its effective implementation were taken care of by Sattars themselves. They hired a large and experienced senior management team to support them. They had 4,134 staff members in 64 facilities in 2011 all around Pakistan. In 2011, the business employed 4,134 people in 64 facilities located around Pakistan (Fig.3 for a map of K&N's locations) (3)

K&N's, in 2011, categorized its vast business into two areas for internal management purposes: K&N's Poultry, which had parent stock production unit, day-old chicks, feed and broilers, and K&N's Foods to control processed chicken and ready-to-cook and fully cooked chicken products.

1. **K&N's Poultry**

K&N's Poultry consisted of parent-stock production, day-old chick production, and broiler growing, as well as a layer breeding business which produced an average of 1.8 million chicks per week, including 1.55 million broiler chicks, 210,000layer chicks, and 40,000 broiler parent stock in 2011(1).

The company used around a quarter million of the chicks for its own farms and another 130,000 were placed with contract growers to be raised for K&N's Foods which were advised by K&N's on farming

and feeding, with regularly monitoring the health of contract-grower flocks. K&N's also supplied its broiler-chicks to Pakistan's independent broiler growers for sale to the wet market or to smaller poultry processors.

The other challenges, to the industry, were; disease control, access to quality feed, and a generally low priority attached to product quality and food safety. K&N's tackled these challenges strategically by raising the broiler houses away from parent flocks and from other producers in order to reduce the threat of disease. K&N's developed its own quality assurance laboratory and had its own feed mill, to provide safety and healthy chicken all over Pakistan. Sattars also established the K&N's Poultry Diagnostic & Research Institute in 1989 with the support of the U.S. Agency for International Development (USAID) which had internationally trained experts capable of diagnosing problems of bird disease and productivity and was also conducted tests on feed and feed raw materials. This integration resulted in improved quality and quantity of business (4).

**2. K&N's Foods**

K&N's Foods comprised of produced products including whole chickens, bone-in cuts, premium boneless meat, and value-added chicken products such as kebabs, nuggets, sausages, and deli-style cold cuts, and smoked meat. All its products were frozen. The company operations were certified under HACCP and ISO 9001: 2015, USDA, HALAL, FSSC (5)

There was much demand for processed products by consumers for which broilers were brought in special trucks to the processing unit where they were slaughtered before processing into various value-added chicken products. Ready-to-cook products, easy cook and quick-serve products were specialty items of the company which brought more convenience to the consumers. These included nuggets, burger patties, croquettes, shami kebabs, chicken sausages, cold cuts, and smoked meats, Chicken Tikka Chunks, which were

spicy bite-sized pieces of chicken good for topping pizzas, salads, or sandwiches (Fig. 4. for product images).

Innovations and continuous investment in marketing gave K&N's a reputable position in processed chicken. It earned consumer's confidence by providing safe and healthy chicken products in the markets over many years. It also raised consumers awareness level who previously preferred wet market shifted towards safe & healthy chicken products. Halal slaughtering in K&N's was in question by consumers which were resolved by providing video that showed all slaughtering process at the company's website www.KandNs.com, to promote public confidence and satisfaction. It also got two Halal certifications which were mentioned on the website as proof for consumers.

Many retail outlets were opened in 2003 to facilitate the consumers and by 2011 there were 68 stores located at different locations in the country. Due to the absence of an organized retail market in the country, the company could not find experienced retail workers to hire in the initial opening of the stores, but this was overcome by providing a clearly defined manual of all procedural handling and operating instructions. All the stores were connected with the main location at Lahore through video cameras to monitor and ensure that retail manual was being followed by the staff. In case of any negligence, the stores were visited by Adil to investigate the reason.

The company also introduced "The K&N's Way Club" to accelerate its penetration and encouraging its existing customers to turn their most loyal customer. It also got good recognition through advertising on TV, radio, print, outdoor media. Sattars' knew that the middle class was their real market, so they talked to them directly to increase that market which would increase their business.

K&N's earned its name in Pakistan due to its quality products in the market. It won the National brand of the year award each year since 2006(4). KFC, McDonald, and Nando's also approved K&N's quality

chicken and K&N's was 100% sole supplier of chicken to these international restaurant franchises and many of the domestic restaurants in Pakistan in 2011(1).

K&N's had price control upon its products as compared to its competitors such as wet market where the prices fluctuated through the year. K&N's was the market price leader for chicken.

Khalil and Adil were successful by having a complete vertically integrated strategy for their business. The company grew substantially between 2001-2010 where it produced broilers chicks from 24.5 million to 80 million, processing meat rose from 3,500 tons to 28,000 tons. Sattars started exploring to extend their business to adjacent countries and also to invest in the global market for Halal products to fill the gaps at the international level.

Domestic growth of the company was improving on one hand but was also having challenges due to the wet market. The wet market had the advantage of the slaughtering of chickens where the customers were sure that the birds were halal when slaughtered in their presence. But with the investment from foreign retailers and improvement in the upper and upper middle class shifted the wet market trend quickly.

Other challenges included were the competition with the imported chicken in 2011. Malaysia and Pakistan had trade agreement for import of finished poultry products which caused local producers to import from there for the retail market. Another challenge was safety and quality provision of the food services which costed more to costumers as compared to other options where cost was low, and quality was not much problem.

Khalil had invested heavily for the nation to provide nutritious and safe protein sources which were unfortunately still protein deficient. Would it be a successful approach to stay focused on the Pakistani market to reach his goal? How could he get more customers for processed products? How could the purchase be improved, were few of the future concerns of the company?

Neighboring countries were importing poultry meat and products from K&N's after the ban from poultry export from Pakistan was lifted but Khalil was more interested to grow his business in global market, to exploit more opportunities and build relationship globularly but the questions, like could it be affordable for him to have the same model in another country? Would it be good or bad for the people of Pakistan? were difficult for him to answer. But Khalil found a wider opportunity to tap the global market for Halal foods.

Provision of Halal food was always a big problem for Muslims living in Europe and U.S and increasing number of Muslims in these areas could help Sattars gain their goals. There were few other companies already offering Halal products such as Nestlé was the largest producer of Halal products in the world, also Tesco and Carrefour had also Halal offerings (1). It seemed a big market to Khalil as halal slaughtering was not available everywhere in the world. Also, Halal certification was another area where he could work to get more costumers.

Muslims consumers needed guaranteed halal products when buying groceries in non-Muslims countries which were not easy to have appropriately slaughtered according to Halal requirements in those countries, so Khalil found this market had great potential to grow. K&N's got credibility in Pakistan due to its high standard of services and reliable source of safe and healthy chicken, got approval in U.S and Europe to serve its processed products.

Retailers from other countries like Spain also visited K&N's facilities in Pakistan to investigate its supply opportunities who were surprised to see the standards, logistics, food processing and distribution business in a company in Pakistan which was comparable to any western company.

Khalil and Adil took advantage of the global Halal market but they wondered whether Halal products be welcomed? would it be practical for a company in Pakistan to do business in Europe and U.S?

It was due to their devotedness and continuous hard work that K&N's got established units at UAE and U.S(6).

Khalil, while sitting in veranda in his home in the northern Pakistan, with Adil told him that his request on behalf of PPA (Pakistan Poultry Association) had been approved by Government where he requested the government to support poultry industry by providing incentives to exporters and by changing tax regimes to promote Pakistan as a meat exporter to other Muslim countries. He was further assured that the Government would support this industry and would work on his proposal. This sounded him as a big achievement to get to his goal to see Pakistan prosperous and healthy one day.

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*Fig.1*
*Customer*
*Advertising*

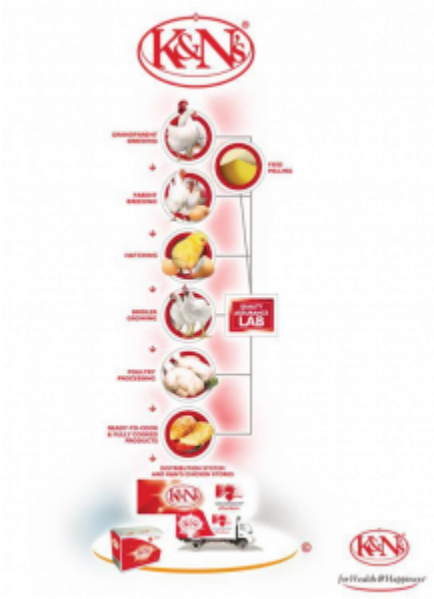



*Fig.2 K&N's Business Structure*

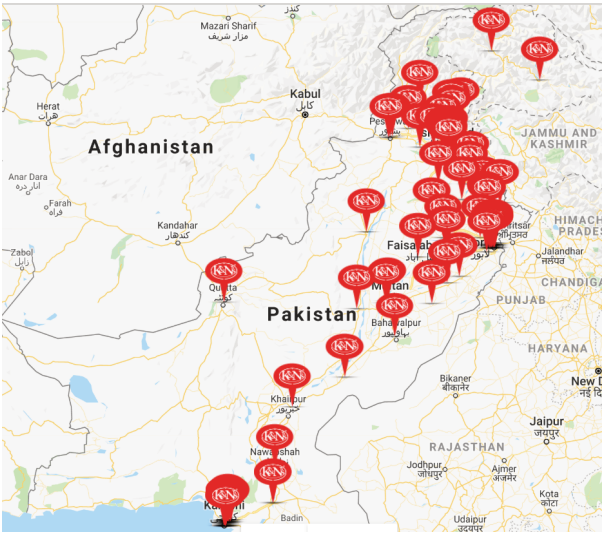



*Fig.3 K&N's Locations map.*


*Fig.4 (Processed Products)*

# 38. FDA Crisis for Pfizer: The Impact of an FDA Warning On the Company

Hetal Patel
April 9th, 2019

On an early February morning, researchers running the post-marketing clinical trial for Pfizer's rheumatoid arthritis drug, Xeljanz, had discovered a potential safety concern. After notifying the FDA, a safety alert had to be issued. Pfizer's media team got to work on writing up a statement for immediate release.

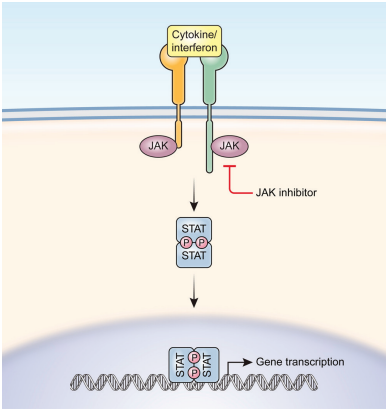
**About Rheumatoid Arthritis**

Rheumatoid arthritis is a common chronic autoimmune disease that affects 1 in 6 Canadians over the age of 15 (UCB Canada, 2019). On a global scale, its prevalence is around 0.3-1% (World Health Organization, 2016). As the population ages, this number is expected to increase (Cross et al., 2014). Rheumatoid arthritis occurs when the immune system starts to attack its own body tissue (Mayo Clinic, 2019). Currently, the trigger for this immune response is unknown (Mayo Clinic, 2019). The disease is associated with inflammation of the synovial membrane, autoantibody production, and deterioration of bone and cartilage around the joint (Mayo Clinic, 2019). This disease generally occurs around ages 20-40 and can be a disabling condition as it can cause deformities (World Health Organization, 2016). Rheumatoid arthritis also increases the potential for developing things like cardiovascular complications, infections, and cancer (Mayo Clinic, 2019).

Currently, there is no cure for rheumatoid arthritis, however early treatment of the disease has been shown to help with the remission of the symptoms (Mayo Clinic, 2019). Typically the drugs prescribed are disease-modifying anti-rheumatic drugs (DMARDs) (Mayo Clinic, 2019). These drugs work by slowing down the progression of the disease to prevent further damage to joints and tissue (Mayo Clinic, 2019). Examples of the most commonly prescribed DMARDs include methotrexate, leflunomide, and hydroxychloroquine (Mayo Clinic, 2019). A newer class of DMARDs falls into the biologic categories. They work by targeting the part of the immune system that triggers the inflammatory response in joints (Mayo Clinic, 2019).

**Xeljanz**

Xeljanz (tofacitinib) is a biologic drug developed by Pfizer for the treatment of rheumatoid arthritis. This drug differs from conventional treatment methods as it is a Janus kinase inhibitor. Janus kinase (JAK) is an enzyme that is part of the pro-inflammatory response (Macfarlane & Todd, 2014). Xeljanz works by inhibiting the JAK enzyme from sending off a pro-inflammatory signal (Macfarlane & Todd, 2014). Xeljanz comes in a tablet format, therefore it offers a new route of administration as the previous therapeutics were injectables (Baldock, Baynton, Baskett, & Bailey, 2018). Xeljanz is the first JAK inhibitor to be approved by both the FDA and Health Canada for the treatment of rheumatoid arthritis (Drugs.com, 2016; Pfizer, 2018)

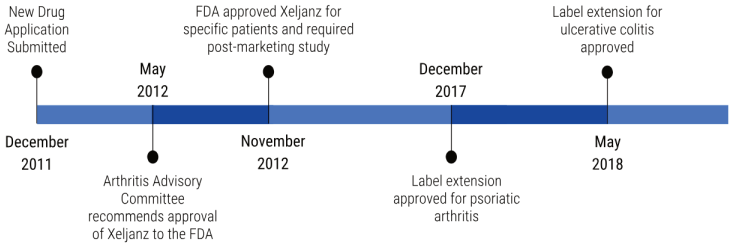



The JAK inhibitor binds to the active site, therefore preventing any downstream reactions from occuring. This ultimately prevents the production of pro-inflammatory compounds (Gadina, 2013).

**FDA Approval Timeline**

Once the phase III clinical trials were completed, Pfizer first sent in their new drug application for Xeljanz in December of 2011. Then in May 2012, the Arthritis Advisory Committee recommended the approval of Xeljanz to the FDA. Six months later, the FDA had approved the drug for patients that had Rheumatoid Arthritis and did not respond well or could not tolerate to methotrexate (Pfizer, 2012). However, the FDA did require that there is a boxed warning on the product to highlight the safety concerns with the drug (Drugs.com, 2012). Additionally, the FDA also wanted Pfizer to conduct a post-marketing clinical trial (Drugs.com, 2012). These studies are done to learn more about the long term effects and other safety concerns related to Xeljanz (Drugs.com, 2012; FDA Biologics Evaluation and Research, 2018). These safety concerns include cardiovascular events, cancer, and certain infections (Drugs.com, 2012). The study looks at patients over the age of 50 with one cardiovascular risk factor (Pfizer, 2019). Pfizer also wanted to get a label extension on Xeljanz. Label extensions essentially allow the drug to be utilized for the treatment

of other diseases. The first extension that was approved by the FDA was for treatment of psoriatic arthritis in 2016 (Drugs.com, 2017). The second extension that was approved was for the treatment of ulcerative colitis in May 2018 (Drugs.com, 2018). The higher dose of 10mg twice a day is approved for ulcerative colitis patients (Baldock et al., 2018).




**Performance of Xeljanz**

Other than the post-marketing study, the approval was obviously great news for Pfizer. Everything at this point seems to be looking up and the drug was set to be very profitable. Researchers had said that the JAK class of drugs was expected to more effective than the other classes of drugs used in this area (Helfand, 2018). Analysts had predicted that this drug was set to disrupt the market for rheumatoid arthritis anti-inflammatories (Helfand, 2018). They had stated that the drug was going to take up 24% of the rheumatoid arthritis market (Helfand, 2018). The analysts predicted correctly as Xeljanz quickly became one of Pfizer's leading brands in their innovative health segment. It even exceeded the profit estimates for the second quarter of 2018 (CNBC, 2018). By the end of 2018, Xeljanz sales were up 37% compared to 2017, which was primarily from rheumatoid

arthritis sales (Pfizer, 2019a). Pfizer had reported that they expected strong growth into 2019 with the help of key products including Xeljanz (Pfizer, 2019a). With this, they decided to spend over 60 million on commercials in December and January (Bulik, 2019). These commercials were targeting patients with rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.

**Safety Warning Issued**

In February of 2018, the Rheumatology Data Safety Monitoring Board (DSMB) issued a safety alert in response to a link found between the higher dose of Xeljanz (10mg twice a day) and an increase in pulmonary embolisms (Pfizer, 2019). This prompted the FDA to issue a safety alert for the drug. In response, Pfizer reduced the dose the patients in the trial to 5mg twice a day. Following the FDA's lead, Health Canada issued its own alert for the drug (Government of Canada, Health Canada, 2019). The European Medicines Agency was not far behind and did the same (Liu, 2019).

**Implications**

The warning issued by the FDA comes at a critical time for Pfizer for many reasons. The first being that Pfizer will soon lose exclusivity for one of its blockbuster drugs called Lyrica in June of 2019. This drug generated close to $5 Billion (USD) in 2018 alone (Forbes, 2019). It is expected that the losses in sales from this will impact Pfizer into 2020 (Crumly, 2019). The impact on their financials will be huge since they are expected to lose over two billion in Lyrica sales this year (Pharmaceutical Technology, 2018). This means that Pfizer needs other drugs to perform well to help meet their financial goals in the future.

Another concerning factor that puts more pressure on the performance of Xeljanz is that their current rheumatoid arthritis drug called Enbrel is experiencing a decline in sales. This decline has actually brought down the companies inflammation and immunology

portfolio (Packer-Tursman, 2017). The decline comes after the availability of the first biosimilar for Enbrel and reductions in prices in Europe (Market Realist, 2016). Thus, Pfizer was expecting Xeljanz to soften the blow of the decline (Packer-Tursman, 2017).

Lastly, the fact that other pharmaceutical companies are coming out with their own JAK inhibitors also puts a great deal of pressure on the performance of Xeljanz. The first company to release a JAK inhibitor after Pfizer was Eli Lilly, with their drug Olumiant, in June 2018 (Pharmaceutical Technology, 2018a). AbbVie and Gilead/Galapagos are currently in the late stage approval process for their JAK inhibitors (Pharmaceutical Technology, 2018a). The drugs offered from AbbVie and Gilead/Galapagos are the biggest threat as they have better safety profiles when compared to Xeljanz (Pharmaceutical Technology, 2018a). More specifically, the drug being developed by Gilead/Galapagos was actually found to have a low incidence of blood clots (Taylor, 2019), which is the side effect currently plaguing Xeljanz.

**Class-wide Issue or Just a Xeljanz Issue?**

The increase in pulmonary embolisms may not be directly caused by Xeljanz. In fact, the root of the pulmonary embolisms might be a class-wide issue, meaning it would be associated with all JAK inhibitors (Market Insiders, 2018). This also means that other companies will be facing similar regulatory hurdles when trying to get to market. However, the fact that Xeljanz already has a black box warning on the label causes more concerns with patients and physicians. Adding on another warning about the potential for blood clots could make selling Xeljanz much harder (Renauer, 2019).

**The Future**

It is very clear that the FDA warning comes at a critical time for Pfizer. The post-marketing clinical trial is set to be completed later in 2019 (Liu, 2019). The conclusions from the study could potentially

result in Pfizer pulling the stronger (10mg twice a day) dose from the market, discontinuing the use of Xeljanz for rheumatoid arthritis, or completely removing the drug from the market.

If the higher dose is banned, it could impact sales from ulcerative colitis. The higher dose was only just recently approved for the treatment of ulcerative colitis. Patients on this medication are required to take 10mg twice a day for the first couple of weeks for effective therapy (Renauer, 2019). Since it is new on the market for ulcerative colitis, there are concerns with the fact that this warning will impact Pfizer's ability to grab a good portion of that market (Renauer, 2019).

The impact on Pfizer could be substantial if the results of the study conclude that the drug should no longer be used for the treatment of rheumatoid arthritis. As mentioned, the drug is a strong performer in the rheumatoid arthritis market. With Pfizer's loss of exclusivity for their blockbuster drug Lyrica, the next few years for could underperform for the company. Furthermore, if the drug is forced to be completely removed from the market, then these implications will be exacerbated. Whatever Pfizer chooses to do next will impact the success of Xeljanz.

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# 39. Micron Waste Technologies: Turning Cannabis to Water

**The Food Waste Crisis**

There is a significant problem with food waste around the globe. It is estimated almost 50% of all food produced is wasted[1]. While many countries have adopted strategies to combat this crisis Canada is seriously lagging behind[1]. This is not only wasteful but has major consequences for both the environment and economy[1]. When you consider Canada's vast geography, and the distance food must travel, there is a significant cost to business and a large amount of greenhouse gas released just for the distribution of food that is ultimately wasted. In addition, the food that is wasted is sent to landfills or compost where additional fossil fuels are burned for its transport. At landfills, methane gas is released upon anaerobic degradation of the waste. Organic waste in landfills results in about 4% of our annual greenhouse gas release[1]. Compost represents an improvement; however, it takes up large amounts of space and requires a long time for complete degradation. In addition, compost requires uncontaminated organic waste which is hard to supply with current waste separating behaviours[1]. When all cumulative costs are considered (energy, labor, etc..), food waste is estimated to cost the Canadian economy up to $100 Billion each year[2].

Several companies have responded to the food waste crisis by developing food waste digesters to break down food waste into water that meets municipal discharge standards. ORCA is an international

company that uses a proprietary set of microbes to digest food waste into water. However, the resulting water must be discharged down sewers and is treated by municipal wastewater systems[3]. While their technology is incredibly scalable with a small option for restaurants, and 3 larger model sizes[3], there are fees that must be paid due to the compounds left in the discharged water[4]. This ultimately offsets some of the cost savings from avoiding landfills. A solution to this trade-off has been developed by a company called Micron Waste Technologies. Micron is an innovator in this field who developed a waste digester that offers a real competitive advantage.

## An Introduction to Micron Waste Technologies

> **"It has always been Micron's intention to create a system that was not only best-in-class but one that re-invented that class entirely," [5] – Alfred Wong (President, Micron Waste Technologies)**

Micron Waste Technologies Inc. is a Vancouver, Canada based biotech company with $6 million in capital[5]. Since their start in 2006, they have been looking to revolutionize the waste treatment industry. In February of 2017, results were announced from a pilot operation of Micron's waste digesting system in Richmond, BC. Exova, a third party which analyzed the results, indicated the water output from the system far exceeded municipal wastewater discharge standards[6]. Micron's patented on-site waste digesting system far exceeds the performance capabilities of competing products such as ORCA. Through a three-step process, the Micron system will digest waste until the resulting water is 99.94% clean (Exhibit 1)[7]. Competing products, such as the Orca, can only achieve 60-65% digestion efficiency which results in water that is far dirtier. The superior performance of the Micron product is due to initial digestion using

proprietary enzymes to render water 95% clean and then a final water treatment to produce 99.94% clean water[7]. Superior water cleanliness is the main advantage of the Micron system. While the resulting water is not potable, it can still be recycled for other uses such as in agriculture or released into municipal sewers without having to pay the fees associated with dirty water discharge[7]. These innovations in waste management demonstrate Micron's ability to create best-in-class technology. The innovative transformation process is demonstrated in Exhibit 1.

After the success of their pilot program in Richmond, BC the company hardened its commitment to advancing waste management practices in Canada by joining the National Zero Waste Council of Canada[8]. This council is led by businesses who are aligned with the common goal of improving waste management strategies across the country[8]. In October 2017, Micron began trading common shares on the Canadian Stock Exchange (CSE) at a price of $0.30 under the ticker symbol "MWM"[9]. Then in November, Micron entered into a Memorandum of Understanding with T&T supermarkets to explore opportunities to incorporate their waste digesters within the company[10]. T&T, part of Loblaw Companies Ltd., is the largest Asian grocery chain in Canada, with stores across the country[10]. At the same time, the company announced the lease of a manufacturing, warehousing and distribution facility in Delta, BC[10]. This highlighted the end of 2017 and a very busy year for Micron Waste Technologies in bringing their system from R&D to commercial use. The company's attitude in 2017 is best represented in a quote from the CEO of Micron during this time:

> **"This is an extremely exciting moment in our development"..."We intend to expand into other sectors looking to improve the operational and cost efficiencies of**

**their organic matter disposal, such as cannabis and quick-serve food markets"[10] – Rav Mlait (Former CEO, Micron Waste Technologies)**

This quote foreshadowed what would become the primary focus of Micron in 2018 and beyond.

**Venturing into the Cannabis Industry**

Cannabis was set to be legalized in Canada on October 17, 2018. During this time, companies such as Aurora Cannabis, who previously supplied the medical marijuana market, were scrambling to increase production in order to supply the anticipated increase in demand offered by the recreational cannabis market. An increase in cannabis production results in an increase in cannabis waste. Cannabis waste consists of the organic waste generated from cannabis cultivation and production. This waste contains active pharmaceutical ingredients (APIs) such as THC and CDB11 which must be degraded due to their detrimental environmental effects[23].

On January 15, 2018, Micron announced the completion of a strategic investment by Aurora cannabis to develop the world's first cannabis waste management system. The companies agreed to optimize Micron's technology for treating cannabis waste and a trial began at the "Aurora Mountain" facility near Calgary[12]. This moment represented a significant opportunity for Micron since upon a successful trial Aurora could agree to purchase additional units for its other facilities. At the time, Aurora Cannabis Enterprises Inc. was operating three facilities with a combined size of 892,000 square feet, with a fourth facility in production in Quebec[12]. It was later reported in September 2018 that the trial at the Mountain facility was a success[13]. The optimized cannabis waste digester named the

"Cannavore" was able to treat organic waste and denature APIs using a proprietary process to render wastewater 99.4% clean and recycled for use in cannabis irrigation systems. This demonstrates Micron's ability to treat specialized waste and create cost-savings for its clients. Aurora followed through on their agreement with Micron and committed to purchasing units for its other sites[13]. The Cannavore represented a significant cost-saver for Aurora since it no longer had to deal with off-site treatment[13], this is critical in an industry that is growing and very competitive. Incorporation of the Cannavore into Aurora's production process should effectively lower the per-gram cost of producing cannabis. In addition, the Cannavore is a mobile unit that operates from inside a 40ft. shipping container which enables it to be deployed in a variety of environments on land or at sea[21].

> **"We are very pleased with the outcome of the trial and are now moving into commercialization and will begin selling units to the wider cannabis industry" [13] – Alfred Wong (CEO, Micron Waste Technologies).**

The timing of the announcement of the successful trial was impeccable since legalization was set to occur in the next month. Micron had also been awarded an Industrial Design Certificate for from the Canadian Intellectual Property Office (CIPO) for its Food and Cannabis Waste Digester which demonstrates the digester is a one-of-a-kind product[14]. The design patent is valid for up to ten years and covers the unique design features of the unit[14].

> **"Receipt of the CIPO Industrial Design Certificate is further testament to Micron's innovation in agricultural and**

**organic waste processing biotechnology and engineering"[14] – Alfred Wong (CEO, Micron)**

So far, the company's success in 2018 has brought them a lot of attention and a lot of recognition. The successful partnership with a large company like Aurora comes with considerable brand recognition for Micron. With this in mind, Micron was seeking to expand the market for its "Cannavore" units.

**Exploring the United States Cannabis Market**

Currently, the United States has 33 states with medicinal cannabis legalized, while only 10 states have legalized recreational cannabis[15]. Medicinal cannabis in the United States had a significant market value of over USD 10 Billion in 2018 and is expected to increase to USD 24 Billion in 2025 (Exhibit 2)[16]. Compared to the Canadian cannabis market, at an estimated $4-6 Billion market value, the United States could be potentially much more lucrative for Micron[17].

Recognizing the opportunity south of the border, Micron filed for a US Patent. US Patent 10,144,044 was secured in January of 2019 and protects the bioprocess and compositions of Micron's food and cannabis waste digester technology[18]. With an adjusted expiration date in 2036, the company will have a lot of time to spread into the U.S. market while continuing to grow their Canadian client base[19]. In pursuit of their goals to enter the U.S. cannabis market, Micron partnered with Quest Resource Management Group LLC, a waste management group currently operating in every state[20]. Quest's services encompass a variety of industries including the cannabis industry and using its extensive market reach it will be able to accelerate Micron's entry into the U.S. market. Micron is currently working with BC Research Inc. to manufacture more Cannavore

units[21]. BC Research Inc. supports companies through technology scale-up and commercialization[22]. In the cannabis market, Micron estimates they can achieve a 20-30% profit margin by selling or renting their Cannavore units[23]. In addition, the company is researching the nutrient contents of residual solid waste from Cannavore operations for potential use as a fertilizer, therefore creating another value-added product[23].

**Where Will They Go Now?**

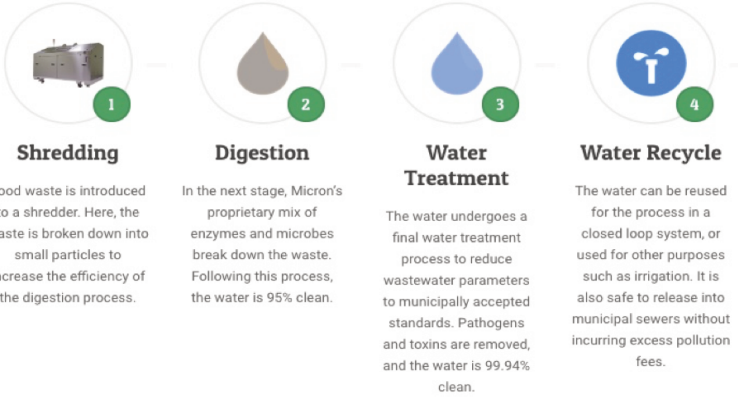
Micron's success with Aurora attracted interest from many other industries looking for waste management solutions, including municipalities, breweries and the agriculture industry[23]. On January 16, 2019, the company announced Alfred Wong would be taking over the role of President and CEO of Micron, a role previously held by Rav Mlait[21]. Alfred Wong is planning to focus on commercialization and expanding into new industries.

> **"I am honored to lead the Company forward as we transition to full-scale production and revenue generation."[21] – Alfred Wong (CEO, Micron Waste Technologies)**

Micron has accomplished a lot since the completion of the pilot project in 2017. However, it will not be easy to meet the production goals of all of their new partnerships while simultaneously exploring new markets. Will President and CEO Alfred Wong be able to maintain the growth of Micron and successfully lead the company through a production scale-up of its Cannavore units? Will Micron Waste Technologies be able to incorporate their waste digester successfully into other industries? Only time will tell.

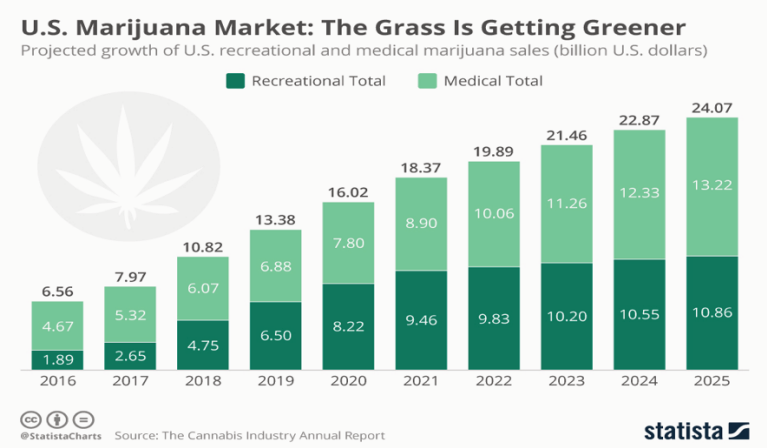
**Exhibits**

**Exhibit 1: Transforming Organic Waste to Water for re-use: A 4 Step Process.**




Source: Micron Waste Technologies. (2017). *Technology*. Retrieved from: https://micronwaste.com/about-2/technology-2/

**Exhibit 2: United States Cannabis Market Projections.**




Source: Statista Charts. (2018). U.S. Marijuana Market: The Grass Is Getting Greener. *The Cannabis Industry Annual Report*. Retrieved from: https://www.statista.com/chart/12406/us-marijuana-market-the-grass-is-getting-greener/

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# 40. Epidermolysis bullosa – Rare Disease and big Business

**Epidermolysis bullosa – Rare Disease and big Business**

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Winter semester 2019

The company Paragon Bioscience was founded in 2010 by Jeff Aronin, who serves as chairman of the company [1]. The intention of Paragon Bioscience is to found other companies with the goal to develop orphan drugs. “When we find an opportunity for life-changing care, Paragon forms and incubates companies to develop those therapies,” said Mr. Aronin [2]. One of these companies created and supported by Paragon is Castle Creek Pharmaceuticals in 2015. Paragon Bioscience invested a total amount of $122.5 million to found Castle Creek. “Paragon founded Castle Creek with the vision to deliver transformative therapies to patients with rare genetic dermatologic diseases, including Epidermolysis Bullosa Simplex,” said Paragon Biosciences CEO Jeff Aronin [3].

**Epidermolysis Bullosa (EB)**

EB is considered one of more than 6 000 rare diseases. A rare disease is defined by the U.S. Food and Drug Administration (FDA) as a disease which affects less than 200 000 people in the United States (US) [4]. In the US the likelihood that a child is born with EB is 1 to 20 000, however it is estimated that roughly 15 000 to 20 000 people suffer on EB in the US. The three main subtypes of EB are EB simplex (EBS), Junctional EB (JEB) and Dystrophic EB (DEB), where EBS occurs at most. All these variations show mutations in genes which are responsible for the production of proteins that are needed

within the skin to hold the different skin layers together. The proteins act as a "glue" or as "anchors" between the skin layers and with the absence of the correct forms of these proteins, due to the occurrence of mutations, the appearance of painful blisters can be a consequence [5].

In EBS the mutations occur in the genes *KRT5* and *KRT14* which lead to improper formation of the keratin 5 or keratin 14 proteins and consequently to an instable intermediate filament network (IFN). Subsequently, keratin aggregates are formed and eventually basal keratinocytes rupture when physical stress is applied and that lead to blisters and wounds. A positive feedback loop of the inflammatory signaling pathway could be observed in *in vitro* studies, induced by keratin aggregates which lead to an enhanced secretion of interleukin 1β (IL-1β) and eventually lead to an increased expression of the defect keratin 14 protein [6].

EBS can be inherited in two different ways. Autosomal dominant, where one parent is also affected by EBS. The other inheritance possibility is autosomal recessive, where each parent carries the gene mutation on one allele but both parents are healthy. Another way is that the mutation is spontaneously introduced into the genome of an infant [7].

Currently, there is no cure for patients with EBS available. There are approaches to delete the gene mutations in skin cells with gene editing techniques or transplantation of skin cells or stems cells without mutations. However, these therapies are still in their very early stages and decades away to become a common treatment method.

**Castle Creek**

Castle Creek's office is located in New Jersey since 2015. Their focus is to develop and provide patients with drugs for the treatment of orphan diseases. Often, there are no drugs against severe rare diseases available [8] Currently, Castle Creek has four different drug

candidates in the development stage for the treatment of rare genetic dermatologic diseases, including Vitiligo. They proclaim that their own drug candidates have the potential to enter the market within the next 2-3 years [9]. The most advanced drug candidate in the clinical trials is a 1% diacerein cream for the treatment of EBS. "With no approved treatment available, patients may be unable to participate in many daily activities and often experience severe pain", said Amir Tavakkol, executive vice president and chief development officer at Castle Creek Pharmaceuticals [10].

Jeff Aronin the CEO of Paragon Biosciences was awarded in 2018 by Best in Biz as innovator of the year for his 20 years engagement to identify unmet patient needs and develop novel drugs for the treatment of orphan diseases. Until yet Jeff Aronin could achieve to receive 13 Novel Drug Approvals by the FDA for the companies he had formed [11].

**Diacerein**

Diacerein (CCP-020) is a small molecular weight compound and is the drug that is currently under development by Castel Creek for the treatment of EBS. The goal of this drug is not to cure EBS but to decrease the pain by accelerating the healing process of patient's blisters and wounds. *In vitro* studies revealed that diacerein is able to down regulate the IL-1β signal pathway which lead to a decrease expression of the protein keratin 14 and a more stable IFN and less disrupted basal keratinocytes [6].

In June 2018 Castle Creek announced the launch of a pharmacokinetics (PK) study by treating the first EBS patient with a 1% diacerein cream. This phase 1 trial should be performed as a global study in the United States and Europe with 16-20 enrolled EBS patients including infants, children and adults for a treatment duration of 10 days. The goal of this study is to assess PK, safety and adverse events of the 1% diacerein ointment. "There has been no treatment available and most of the EB community is excited

to participate in anything that will give researchers knowledge of the disease as a whole," said Dr. Aída Lugo-Somolinos, principal investigator at UNC-Chapel Hill [12].

An already completed phase 2 study about the treatment with 1% diacerein cream was published in the "Journal of the American Academy of Dermatology". The study was performed in US, France and Austria and showed advantages in the healing of blisters and wounds of EBS patients by applying Caste Creek's drug. In this study 17 patients with EBS from four different countries were treated with the 1% diacerein cream. After a treatment of 4 weeks the results were compared to the initial status by counting blisters in a certain body area. It was predefined that it is clinical meaningful if there is a reduction of at least 40% blisters observed. The goal could be achieved in 60% of the EBS patients treated with 1% diacerein cream. During the application no negative effect could be related to the drug. However, the number of patients in this study was very low and more studies have to be performed to confirm these positive results [6].

Recently, another phase 2 study to test the 1% diacerein cream (TWiB's code name: AC-203) application was nearly completed in Taiwan. The study was performed by TWi Biotechnology Inc. (TWiB) an international partner company from Castle Creek. They announced in January 2019 that the last patient of the trial is already enrolled. The goal was also to assess the efficacy, safety and reduction of blister area. It is expected that the report with the outcome of this study will be released in the second quarter of 2019. "We are committed to bring AC-203 treatment to EB patients and believe the results of this study will be an essential step for future global registration trial in partnership with Castle Creek Pharmaceuticals," said Calvin Chen Chief Executive Officer of TWiB [13].

**Attractive market: Rare diseases**

“Fast Track designation is an important milestone in our development program for CCP-020 and reinforces the critical unmet need for patients who are living with the risk of severe blistering and skin erosion associated with EBS,” Amir Tavakkol, PhD, executive vice president and chief development officer at Castle Creek Pharmaceuticals [14].

The US Orphan Drug Act from 1983 ensure the financial benefit of developing drugs for rare diseases. Nowadays, also the European Union (EU) and Japan have similar laws which include incentives and decrease taxes to support the development of drugs for the treatment of rare diseases. In the US there is a 7 years marketing exclusivity for orphan drugs and in the EU a 10 years marketing exclusivity from approval on, respectively. The R&D costs for orphan drugs are lower compared to non-orphan drugs, especially the expenses in phase 3 can be 50 to 75% less. This is an essential amount of money for companies in the drug development flied, considering that the total expenses to launch a new non-orphan drug on the market are estimated to hit $2.6 billion with a success rate of less than 12% in the clinical trial phases [15]. The US and EU support companies with grants for the clinical trials, tax credit discounts, protocol -, administrative – and procedural assistance for small and medium companies, makes the field of orphan drug development an attractive market for these companies. However, seven of the top ten orphan drug owners are considered as big pharma companies. The fact, defined by legislation, that clinical trials can be performed in a shorter time range due to the lower number of test subjects in the clinical trials compared to non-orphan drugs is another incentive. Although, the overall demand on orphan drugs is small the average annual cost per patient for an orphan drug is very high. Considering the 100 top orphan drugs, the average costs per patient and year was in the US in 2017 with $147,308 significantly higher compared to $30,708 for non-orphan drugs. This is an opportunity for orphan drug producers to generate high revenue.

The annual market growth rate for orphan drugs is two-fold higher compared to non-orphan drugs. In 2024 it is expected that the orphan drug market has a volume of $262 billion [16] [17].

**Big Pharma vs small Biotech Companies**

Since, the Orphan Drug Act and other orphan drug supporting laws in Europe and Japan, facilitate the development of rare diseases treating medicines, this class of drugs became a more and more attractive business. Also the fact that it is possible to sell orphan drugs for much higher prices compared to non-orphan drugs draws the attention of big pharma companies to the market with small patient numbers.

The costs and trial size advantages in the development of orphan drugs offer a chance and possibility for smaller Biotech companies owing a lower budget to run clinical trials. However, if an orphan drug achieves beneficial outcome and it seems to be a promising medication, a big pharma company often makes efforts to purchase the license of the drug or even try to acquire the whole company. The Biotech company Genzyme launched a highly effective drug named Cerezyme on the orphan drug market for the treatment of Morbus Gaucher, a rare genetic disease which has a negative impact on the organ function. The treatment cost with Cerezyme was $300,000 per patient and year. As a result Genzyme could achieve sales over $700 million for their orphan drug in 2010. Consequently, Sanofi, a Big Pharma company, purchased Genzyme in 2011 and incorporated the smaller Biotech enterprise into their company [18] [19].

**Setback and Outlook**

By visiting the homepage of Caste Creek it is a bit odd that the last news release about the ongoing study of 1% diacerein was from October 2018. Then I found an article from “Endpoint News” with the title “Fresh from a $72M raise, Jeff Aronin’s new lead rare disease drug is flagged as a failure”. In an email statement Castle Creek’s

Co-founder, Michael Derby announced the termination and currently failure of the phase 2 study for the diacerein cream. After an assessment from an "Independent Data Monitoring Committee" Castle Creek had to terminate the pursue of their drug for the treatment of EBS due to lack of statistical robustness on efficacy [20]. The drug application is possibly related to cause Diabetic nephropathies, a serious kidney-related complication which negatively impacts the removal of waste products and fluid from the body [21]. However, Castle Creek allowed the patients which were enrolled in the phase 2 studies to continue the treatment of 1% diacerein cream in an open-label extension trail. Michael Derby also proclaimed that they will continue the development of the 1% diacerein cream with the start of a phase 3 study, although the phase 2 study is currently discontinued. With another investment of $71.8 million in October 2018, they try to find appropriate safety and efficacy results to get approval for phase 2. Michael Derby commented the termination of phase 2 study as followed, "showed several positive trends in key efficacy measures and a benign safety profile that strongly support continued phase 3 development of this potential treatment, which is our plan" [20].

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# 41. IBM Watson Health: Managing Partnerships to Improve Personalized Medicine

By: Lauren Jagus

Watson, an artificial intelligence machine developed by International Business Machines (IBM) Corporation, was heavily promoted by the company as being able to revolutionize the medical industry.[1] However, approaching on its ten year anniversary, Watson has failed to deliver on this claim. In September 2016, the partnership between a leading cancer institute, MD Anderson Cancer Center, and IBM that was created with the mission of eradicating cancer through improving personalized medicine has been put on hold.[2,3] This decision was made public prior to the release of an audit report of MD Anderson, indicating that the Cancer Centre had paid IBM $62 million for the project that was originally estimated to cost $2.4 million.[4] Speculation within the industry formed stating that Watson was recommending "unsafe and incorrect" cancer treatments.[5] This ultimately led to the general manager of IBM's health division, Deborah DiSanzo, stepping down from her position.[6] Despite this failure, the technology and medical industry continue to form partnerships on the basis that artificial intelligence can deliver on its claims.[6] Companies need to create transparent partnerships and advertisements to improve the outcome of successive projects.

## International Business Machines Corporation

Charles Flint and Herman Hollerith founded the Computing-Tabulating-Recording Company (C-T-R), on June 16th, 1911 (Exhibit A).[7] The C-T-R emerged with the development of their tabulating machine that could count and track information.[7] In 1914, Flin and Hollerith recruited Thomas J. Watson Sr. to work as the general manager of the company.[7] Ten years later, Watson renamed the C-T-R to IBM to redefine and expand the company's potential applications within information technology.[7] Watson, an important employee for IBM, said, "The future of this business, gentlemen, and our future success, depends to a great extent on the progress we make along the lines of development, and along the lines of expansion into new fields and into lines we are not touching today… We must progress and we can't do it any other way. We can not stand still on development work".[7]

IBM continues to be a prominent producer of hardware and software services.[7] Their most notable products include the automated teller machine (ATM), the magnetic-core memory and the floppy disk.[7] In addition, Arthur Samuel, a computer scientist at IBM developed, helped develop machine learning and artificial intelligence.[8] It was in 1959 that Samuel demonstrated that computers could be programmed to play checkers and learn from their past games to improve their abilities.[8] This led to the company developing the chess-playing machine Deep Blue.[9] The programming abilities of Deep Blue was successful in defeating the chess master, Garry Kasparov, in 1997.[9] Since then, IBM has devoted many resources to machine learning.[9, 10]

In 2004, IBM developed a new challenge to improve information technology.[10] This challenge was question-answering (QA) technology, which would benefit many industries.[10] Similar to Deep Blue, IBM gained worldwide attention as their computer scientists

worked on creating a computer system tackling QA technology to compete on the game show *Jeopardy!*.[10, 11] David Ferrucci began developing a computer system called Watson in 2006.[10, 11] After undergoing initial tests that consisted of reviewing previous *Jeopardy!* episodes, Watson debut on the show in 2011 where it defeated long-time *Jeopardy!* Winner, Ken Jennings.[10]

Ferrucci programmed Watson to have the ability to process natural language of unstructured data, which is known as DeepQA, formulate and evaluate hypotheses, and learn from previous interactions (Exhibit B).[11] This allows Watson to be an accurate and precise machine.[11]

## IBM Watson Health

In April 2015, IBM Watson Health was created to provide solutions to data analytics within the healthcare industry.[12] At the time, physicians and researchers were burdened by the amount of time required to clean and normalize data in order to draw conclusions.[12] Physicians spend approximately 6 hours of their working day interacting with health data and it is estimated that the amount of health data will double every two years, furthering this burden.[12, 13] Watson and its DeepQA were positioned to decipher health data, genomic data and social determinants of health to improve personalized medicine through increasing the accuracy and precision of treatment options.[12]

The ability of Watson to improve personalized medicine was demonstrated in a study conducted in 2018 at the Manipal Comprehensive Cancer Centre in India.[14] In addition to the quantity of health data, oncologists struggle with keeping up to date with the rapid changes in science that affect treatment guidelines and new drug approvals.[14] Personalized medicine has been shown to improve

treatment options for individuals with cancer, as an individual's genome can provide insights on therapies that will be most effective to reduce tumour growth.[14, 15] However, this requires oncologist to sort through health data, including recent publications in scientific literature and case studies.[14, 15] Researchers programmed IBM Watson for Oncology to acquire knowledge from scientific literature, protocols, patient charts, and test cases from the Memorial Sloan Kettering Cancer Centre.[15] Within this study, IBM Watson analyzed 638 breast cancer patients between 2014 and 2016 and recommended personalized treatment options.[14] These recommendations were compared with the oncologist at the Manipal Comprehensive Cancer Centre and the results of the study showed IBM Watson was able to recommend a concording treatment with the oncologist in 93% of the cases.[14] In addition to the recommendation, Watson provides journal articles from scientific literature to support its decision.[14]

Hospital and physicians have been quick to pick up and utilize Watson within their practices.[13] Hospitals that have fewer oncologists rely more heavily on Watson for recommendations and can alleviate the health inequalities by providing the best practice to individuals who do not have access to highly trained specialists.[16] The cost of Watson varies between $200 and $1000 per patient, depending on the additional products and services.[13] For example, a hospital can purchase additional consulting help and allow access to electronic medical records.[13]

IBM Watson Health has continued to conduct additional studies to support the potential of artificial intelligence in revolutionizing medicine.[12] Applications expand beyond genomics, including improving drug discovery, clinical trial matching and insurance coverage.[12]

## MD Anderson Cancer Center and IBM Watson Health

The partnership between the two organizations, MD Anderson Cancer Center and IBM Watson Health, was developed to create an Oncology Expert Advisor (OEA).[4] The goal was to help community patients, who are treated by community oncologists, receive the same high-quality care as the specialists at MD Anderson would deliver.[4] Waston would provide community oncologist with scientific literature and personalized treatment options for their patients.[4, 12] In addition, Watson would provide clinical trial matching for patients if applicable.[4] As stated by the project leader, Dr. Lynda Chin, the project was designed to "'transform how medicine will be practiced, by leveraging artificial intelligence' to elevate the standard of cancer care world-wide".[4]

## What Went Wrong? The Downfall of MD Anderson Cancer Centre and Watson Health

The project between MD Anderson Cancer Centre and Watson came to a close due to delays, mismanagement and overspending on the budget (Exhibit C).[13] Shortly after MD Anderson announced the closing of this project, an audit conducted by the University of Texas revealed many procurement violations involving outside consultants (Exhibit D).[4, 13] The Cancer Centre was working with the consulting firm, PricewaterhouseCoopers (PwC), however, many of the services, such as supply chain management and information technology governance, required for the OEA did not follow the hospital protocol or were not within the scope of the project.[4]

Other reports indicated that the problem was inherent to Watson

and its artificial intelligence ability.[13] Specifically, Chin said that her team had difficulties with integrating Watson with the idiosyncrasies found in a medical record, such as acronyms, shorthand phrases, and different styles of writing.[13] This required the doctors to more spend time teaching Watson to read a medical record and extract important information.[13] They also faced struggles with employing Watson into clinical and routine practices of nurses and physicians as this was a new technology.[13] Lastly, Watson did not have access to every medical institution and this created a relatively small patient pool.[13] This affected Waston's ability to generalize trends and to determine patterns, as a small patient pool does not accurately represent or allow for inference of all patients types.[13] These patterns are critical for improving personalized medicine.[13]

IBM also experienced drawbacks from the closing of this partnership.[13] This is represented through their declining revenue within its cognitive services, where Watson Health is classified, for 21 consecutive quarters.[13] IBM has since implemented strategies to support their cognitive services as they view Watson Health as a growing $200 million market.[13, 17]

## Disadvantages of Artificial Intelligence

The disadvantages and limitations of artificial intelligence were brought to focus after MD Anderson Cancer Centre and IBM Watson Health terminated their partnership. Many criticize IBM for advertising false capabilities of Watson that were not developed yet.[1, 3, 6, 13] Essentially, Watson and other artificial intelligence systems are only able to perform tasks they are programmed or trained to do.[13] Reports indicated that Watson was struggling with learning the different forms of cancer and this resulted in the recommendations of inappropriate treatment options.[13] However, for Watson to

recommend the best treatment options, its operating system must be updated.[13] As mentioned earlier, treatment guidelines and drug approvals can be changed rapidly prior to an overwhelming amount of published scientific literature that would allow Watson to update autonomously.[18, 13] Instead, this would require hospital staff to be familiar with updating Watson, which is not likely as machine learning is a highly complex field.[13] This ultimately creates a challenge for artificial intelligence to be used in the medical industry.

In addition, IBM was criticized for not conducting clinical trials prior to the launch of Watson Health to show scientific evidence of its capabilities.[13] This is largely due to regulatory agencies not requiring clinical trials for software applications.[13] Customers were incentivized to purchase Watson Health due to the value it provides through helping physicians manage a large amount of health data per patient.[13] Watson Health was launched in 2015, however, IBM did not start publishing scientific literature on the application until 2017.[12] To date, studies have predominately been conducted by paying customers of IBM and there have been no randomized clinical trials.[13]

Physicians have also indicated that Watson is biased towards the United States and their clinical practices, as it was trained by physicians at the Memorial Sloan Kettering Cancer Center in New York.[13] Despite the many physicians in other countries indicated that states they were hesitant to use Watson, it has been widely accepted.[13] Currently, more than fifty hospitals across five continents have partnerships with IBM to use Watson for genomics, oncology and clinical trials.[13]

## Future Partnerships

IBM has been a high-profile information technology company for over a century.[7] Their recent involvement in artificial intelligence and

the development of Watson Health has the potential to contribute to their legacy by providing benefits to many industries, including medicine.[1, 12] However, IBM has lost hospital clients due to the news surrounding the failure of IBM Watson Health and the MD Anderson Cancer Centre.[6] This is occurring at a problematic time for IBM as they face high competition from other information technology companies, including Amazon, Apple, Microsoft and Google who have formed partnerships with biotechnology and pharmaceutical companies.[6]

While there is still a debate on whether artificial intelligence has a place in the medical industry, this case highlights how two companies did not operate transparently and this ultimately led to the demise of their partnership. Interdisciplinary partnerships are becoming more common, especially within health and technology, and companies need to develop strategies to form and maintain successful partnerships. What strategies could IBM and MD Anderson Cancer Centre implement to avoid repeating this mistake? What can emerging partnership between health and technology companies learn from this case?

**Exhibit A.** A summarized timeline of IBM.

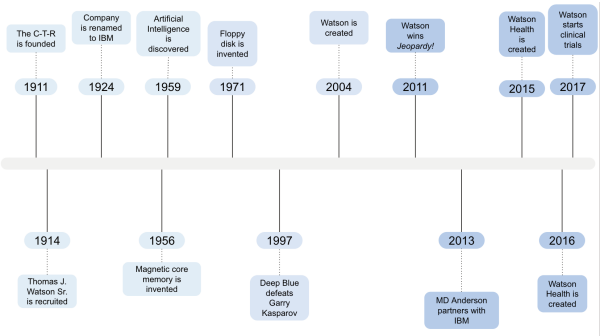

**Exhibit B.** A step-by-step depiction of how IBM Watson processes a question to determine an answer.[11]

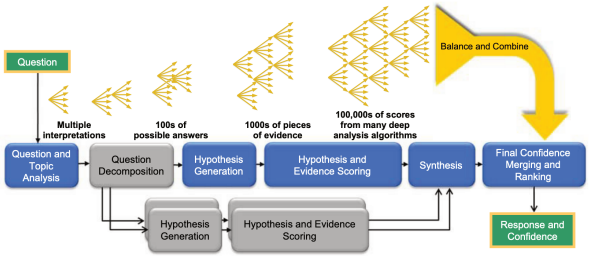


**Exhibit C.** Financial statements from the OEA project between MD Anderson Cancer Centre and IBM.[4]

The University of Texas System Audit Office
Special Review of Procurement Procedures Related to the
M.D. Anderson Cancer Center Oncology Expert Advisor Project

**Appendix C**
Funding Sources (through August 31, 2016)

| FUND USED | Fund Type | Current Fund Steward / Department | Current Free Balance (8/31/2016) | Contract | Total Paid from Fund | Most Recent Payment |
|---|---|---|---|---|---|---|
| Genomic Medicine Initiative | Restricted Gifts | Lynda Chin, Genomic Medicine | $ 43.19 | PwC Network Democratization | $ 71,923.37 | Jun-16 |
| | | | | PwC Value Capture | $ 630,140.00 | Feb-14 |
| Artificial Oncology Intelligence | Education & General | Chris Belmont, Inst IT Programs | n/a | IBM Watson | $ 15,600,000.00 | Feb-14 |
| | | | | PwC Business Plan | $ 2,223,702.88 | Aug-13 |
| Big Data Platform/TRA[1] | Designated Funds/ Restricted Gifts | Michael Antonoff, Enterprise Business Svc | $(1,513,121.20) | PwC BDI Bridge | $ 2,201,803.00 | May-16 |
| | | | | PwC Network Democratization | $ 2,459,482.91 | May-16 |
| Bosarge Apollo Watson Fund | Restricted Gifts | Lynda Chin, Genomic Medicine | $ 330.00 | IBM Watson | $ 2,000,000.00 | Dec-14 |
| | | | | PwC Value Capture | $ 1,699,920.00 | Feb-14 |
| Low OEA Promo Video | Restricted Gifts | Lynda Chin, Genomic Medicine | $ 60.00 | PwC Value Capture | $ 149,940.00 | Feb-14 |
| Oncology Expert Advisor Development Fund[2] | Restricted Gifts | Andrew Futreal, Genomic Medicine | $(9,772,671.53) | IBM Watson | $ 11,985,559.94 | Feb-15 |
| | | | | PwC Network Democratization | $ 12,896,174.26 | Apr-16 |
| OEA Democratization | Restricted Gifts | Lynda Chin, Genomic Medicine | $ 23.44 | PwC Network Democratization | $ 424,976.53 | Jun-16 |
| Jordan Network Democratization Pilot[2] | Restricted Gifts | Lynda Chin, Genomic Medicine | $ 41.67 | PwC Network Democratization | $ 84,958.33 | Jun-16 |
| Lung OEA | Restricted Gifts | John Heymach, Moon Shots Disease Sites | $ (300,000.00) | IBM Watson | $ 9,800,000.00 | Aug-16 |
| Various Donors/Research | Restricted Gifts | Lynda Chin, Genomic Medicine | $ 41.67 | PwC Network Democratization | $ 84,958.33 | Jun-16 |
| | | | | | $ 62,113,459.55 | |

[1] Donor pledged $34.85 million towards the OEA project in October 2013. As of August 31, 2016, $15 million remains uncollected by MD Anderson.
[2] Donor pledged $500,000 towards the OEA project in March 2014. As of August 31, 2016, $400,000 remains uncollected by MD Anderson.

**Exhibit D.** The procurement and vendor violations listed in the University of Texas Audit Report.[4]


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# 42. Big Pharma and Biotech: A match made in heaven?

*A look at mergers and acquisitions as strategies for sustainable growth in the pharma industry.*

*Source: The Pharma Letter*

*Authored by Nadine Abraham*
*April 09th 2019*

## In the hot seat – Bristol-Myers Squibb


*Screenshot of Jim Cramer (right) interviewing Giovanni Caforio (left) CEO of New York based pharmaceutical giant, Bristol-Myers Squibb. BMS had just signed a large merger with Celgene valued at $74 billion dollars. Retrieved from: https://www.cnbc.com/video/2019/03/06/bristol-myers-ceo-celgene-merger-will-generate-more-innovation.html*

"Okay, Giovanni, I'm going to look you in the eyes, and I'm going to ask you a question".

Giovanni Caforio, the CEO of Bristol-Myers Squibb remains stoic and poised amidst the interrogation he's received so far from Jim Cramer host of the show "MAD MONEY" (CNBC Markets). Bristol-Myers Squibb had recently been the centre of attention following a controversial merger signed with the biotech giant, Celgene.

"Were you approached by another company, and rather than become a part of that company, you decided to stay independent and bought Celgene for a ton of money so that any potential acquirer would no longer pursue you?"

When asked this question Giovanni simply smiles and replies, "Jim

this is not a defensive deal…[sic] we are creating an even stronger Bristol-Myers Squibb – well positioned for long term growth". (CNBC Mad Money, 2019)

Is this true? Do such mergers and acquisitions generate innovation necessary for long term growth? Or is this deal a disaster in the making?

This case study will examine the drivers behind such mergers and acquisitions as well examine the benefits and pitfalls to pharmaceutical companies. Finally, a commentary will be provided on whether this is a viable strategy for sustainable growth.

## Company Profile – Bristol-Myers Squibb

1989 marked a key date in Bristol-Myers Squibb history. It signified the inception of the company through the merger of two American pharmaceutical companies, Bristol-Myers and E.R. Squibb & Sons. (Bristol-Myers Squibb, 2019)

Dr Edward Squibb, a military surgeon was certainly ahead of the times. He recognized an immediate need for high quality medicines and began manufacturing them out of a humble brownstone building in Brooklyn, New York. Dr Squibb's ethos was also shared by Hamilton College graduates William Bristol and John Myers who in 1887 purchased the down-and-out Clinton Pharmaceuticals Company. (Bristol-Myers Squibb, 2019)

Fast-forward many decades later, the company has transformed from humble beginnings to a global bio-pharmaceutical company. Today, Bristol-Myers Squibb is ranked among the top ten pharmaceutical companies in the world following growth in 2018.

**(Exhibit A)** In fact, the company's year-end revenue was valued at $22.6 billion dollars, driven by strong sales of the immuno-therapy drug Opdivo and Eliquis, an anticoagulant.

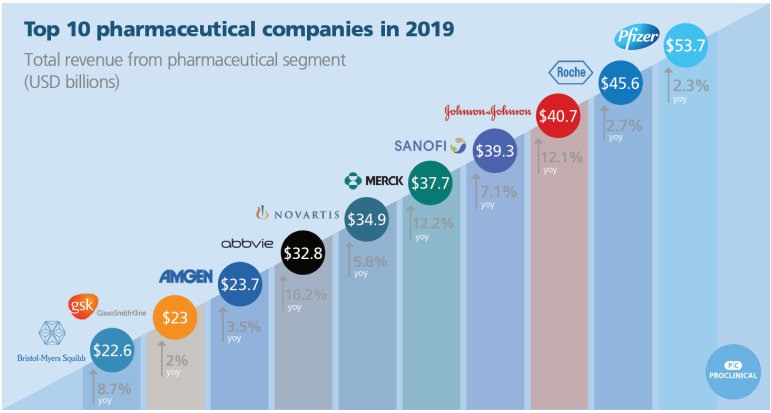


*Exhibit A. Top 10 pharmaceutical companies in 2019 by revenue. Ellis, M. (2019, March 20). Who are the top 10 pharmaceutical companies in the world? (2019) [Digital image]. Retrieved April 08, 2019, from https://www.proclinical.com/blogs/2019-3/the-top-10-pharmaceutical-companies-in-the-world-2019*

Bristol-Myers Squibb or BMS for short, focuses its R & D efforts on four key disease areas. This includes oncology, cardiovascular, immuno-science, and fibrosis. This narrow focus is in stark contrast to the company's early beginnings when it was churning out blockbuster drugs such as Plavix (anti-coagulant) and Abilify (anti-depressant) among others. (Bristol-Myers Squibb, 2019)

A key factor in BMS's success is the strategic approaches undertaken by the company. In 2007, the company made the decision to fully transition to a bio-pharmaceutical company focusing on the aforementioned niche markets. (2007 BMS Annual Report) Prior to this, the company's business model was a vertical fully integrated pharmaceutical company model.

## The Traditional Pharmaceutical Business Model or the "Big is Better!" Strategy

Why would a successful pharmaceutical company like Bristol Myers Squibb consider altering their business model? For most businesses, this is a risky gamble but often times, a necessary course of action.

Early on, pharmaceutical companies adopted the conventional strategy of creating blockbuster drugs. These were single products or a minority of products that generated large revenue streams of over $1 billion annually. (Exhibit B)

To develop a blockbuster drug however, it would take at least a decade and a price tag of $1 billion dollars to successfully bring the drug to market. (Franco & Kaitin, 2002)

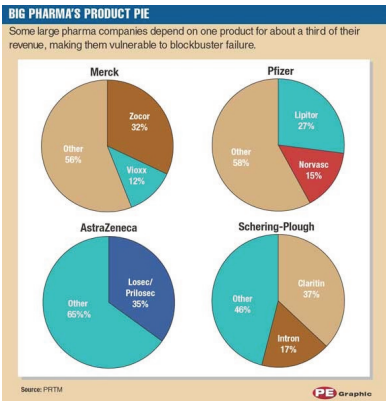


*Exhibit B. Franco, R., & Kaitin, K. (2002, November 01). Beyond the Blockbuster [Big Pharma's Product Pie]. Retrieved April 08, 2019, from http://www.pharmexec.com/beyond-blockbuster*

The high costs associated with developing these products stem largely from the company's operational model. Big Pharma companies are heavily invested with drug discovery, synthesis, clinical research and development, regulatory work and scale-up. Additionally, sales and marketing also play a large role in delivering the product to the public.

This type of model is termed as a fully integrated pharma company model or "FIPCO".

Although initially heralded as the gold standard of business models, a shift in market trends demanded a need for change. These trends include but are not limited to patent expiry, research and development productivity, and regulation standards.

## A SWOT analysis of the FIPCO model

### I. Strengths of the FIPCO business model

Or, in the words of Jerry Maguire, "Show me the money!".

A key strength of this business model are the good cash-flow streams which are 'recession resistant' and provide constant dividends keeping shareholders satisfied. (Lowe, 2014) (Berman, 2018)

There are several reasons for these positive cash-flow streams. Firstly, a direct consequence of exclusive patent rights means that big pharma companies can strong arm consumers to pay hefty prices for their blockbuster drugs.

Secondly, an aggressive sales team coupled with marketing strategies reinforce the product's brand. Interestingly, the target audience for these marketing campaigns is most often health care professionals, rather than consumers themselves. As seen on the right, around $3 billion was spent marketing to consumers and $24 billion spent towards physicians. (PEW Prescription Project, 2013)

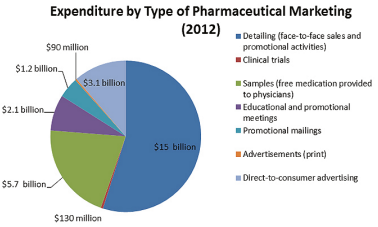


*Exhibit C. How Does the Pharmaceutical Industry Market its Drugs and How Much Does It Spend? [Cegedim Strategic Data, 2012 U.S. Pharmaceutical Company Promotion Spending.]. (2013). Retrieved April 07, 2019, from https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients*

Finally, big pharma companies have a strong global presence compared with smaller biotechnology firms. In accordance with the FIPCO model, pharma companies possess large manufacturing plants, laboratories and corporate offices distributed across the globe. Having this global presence also allows big pharma to build on their expertise concerning international regulations for clinical trials and product manufacture to name a few. (Gilbert et al., 2003) Big pharma companies retain a competitive edge over other small companies due to the scale of these commercialization operations.

## II. Weaknesses of the FIPCO business model

As highlighted above, big pharma's cash flow depends on revenue generated from one or two blockbuster drugs. This becomes a troubling issue when the patent for the blockbuster drug expires. What results then is a 'patent cliff' or a significant drop in revenue when the product goes off patent. (Song & Han, 2016)


*Exhibit D. US Pharmacist. Drug Patent Expirations and the "Patent Cliff". 2012;37(6) (Generic supp.):12-20. June 20, 2012. Retrieved April 07, 2019, from https://www.optum.com/resources/library/bio-technology-drug-revolution-part1.html*

To offset this loss of revenue, big pharma companies begin investing R & D efforts to generate a drug pipeline. This approach fails however, as big pharma companies cannot discover blockbuster drugs fast enough.

To make matters worse for investors, the return on investment (ROI) is a meager 5% and this return is only achieved over a significant period of time. (Bingham, 2006) Analysts estimate at least a forty-year cycle of investment and return as profits generated from blockbuster drug sales are re-directed towards R & D efforts for other pipeline drugs. Admittedly there is a great deal of risk to the potential investor due to high failure rates which are second nature to big pharma companies. (Bingham, 2006)

Secondly, technological developments with the advent of the genomics era have ushered in a need for personalized medicines rather than a one-size-fits-all approach. Lastly, regulatory bodies within the healthcare industry and social pressures from patients and insurance agencies alike also serve to drive competition between the expensive brand-name drugs and cheaper generic drugs.

**III. Threats to this business model**

The entry of generic companies on the playing field significantly impact revenue for big pharma companies. In fact, the largest wave of blockbuster patent expirations in 2010 led to significant revenue losses for big pharma companies. A look a Bristol-Myers Squibb 2012 annual report illustrates how the loss of exclusivity over Plavix resulted in a loss of $3.6 billion dollars. (Exhibit E)

**Highlights**

The following table is a summary of our financial highlights:

| Dollars in Millions, except per share data | Year Ended December 31, 2012 | 2011 | 2010 |
|---|---|---|---|
| Net Sales | $ 17,621 | $ 21,244 | $ 19,484 |
| Total Expenses | 15,281 | 14,263 | 13,413 |
| Earnings before Income Taxes | 2,340 | 6,981 | 6,071 |
| Provision for/(Benefit from) Income Taxes | (161) | 1,721 | 1,558 |
| *Effective tax/(benefit) rate* | (6.9)% | 24.7 % | 25.7 % |
| | | | |
| Net Earnings Attributable to BMS | | | |
| GAAP | 1,960 | 3,709 | 3,102 |
| Non-GAAP | 3,364 | 3,921 | 3,735 |
| | | | |
| Diluted Earnings Per Share | | | |
| GAAP | 1.16 | 2.16 | 1.79 |
| Non-GAAP | 1.99 | 2.28 | 2.16 |
| | | | |
| Cash, Cash Equivalents and Marketable Securities | 6,352 | 11,642 | 9,982 |

Our non-GAAP financial measures, including non-GAAP earnings and related EPS information, are adjusted to exclude specified items which represent certain costs, expenses, gains and losses and other items impacting the comparability of financial results. For a detailed listing of all specified items and further information and reconciliations of non-GAAP financial measures see "—Non-GAAP Financial Measures" below.

*Exhibit E. Squibb, B. M. (n.d.). 2012 Annual Report. [End of year financial highlights]. Retrieved March 11, 2019, from http://www.annualreports.com/HostedData/AnnualReportArchive/b/NYSE_BMY_2012.pdf*

Additionally, while big pharma companies such as BMS do have pipeline drugs in the making, stringent regulatory barriers limit the approval process for these drugs. Hence, although R & D spending has increased, the drug approval rate has decreased significantly.

**IV. Opportunities for developing new business models**

The famous American motivational speaker, Zig Ziglar has been quoted as saying "Try to look at your weakness and convert it into your strength. That's a success".

This same fundamental concept can be applied to big pharma business models as well.

Patent loss has led several big pharma companies to develop

innovative strategies for achieving new revenue streams. These can either be product centered  or business model centered, the latter of which is many times neglected.

The key question here then is what are these sources of innovation and how can big pharma companies use innovation to improve R & D productivity?

## Learning by example – Innovation exists in biotechnology business models

Henry Chesbrough of Harvard Business School in 2003 proposed innovation as being key to the success of businesses. This trend in terms of innovative technologies forms the very hallmark of biotechnology companies. In fact, the source of this innovation stems from the close relationships between biotech and academia through which many technologies are born. (De Rubertis et al., 2009)

The advent of emerging technologies has triggered a shift in terms of the type of blockbuster drugs now being produced. Currently, 12% of the global clinic pipeline are cell-based and gene therapies. Biologics which comprise 5% of the global clinic pipeline are another exciting therapeutic, distinct in terms of their manufacturing processes. (McKinsey & Company, 2017) (Exhibit F)

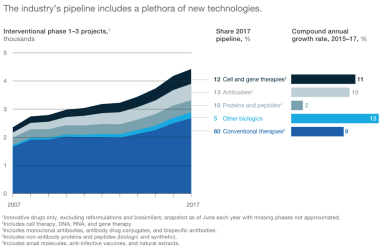


*Exhibit F. McKinsey & Company. (2017). R & D in the age of 'agile'. [The industry's pipeline includes a plethora of new technologies.]. Retrieved April 9, 2019, from https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/r-and-d-in-the-age-of-agile*

In this case, recombinant DNA technology is used to manufacture these large molecules. This strongly contrasts with the big pharmaceutical companies that focus on conventional small molecule drug therapies produced via chemical synthesis.

> **"The economic environment for small biotech companies has been difficult for the past three to four years and doesn't appear to be improving significantly."**

Another key advantage here is that there are no 'generic' forms for biologics. However, in 2009, the US Congress passed a 'bio-similar' law which is the generic equivalent for biologics. Despite this, there is no clear regulatory FDA framework for approving these bio-similars making it difficult for competing companies to replicate biologics.

With such innovative products and technologies, a steady stream of revenue is required to fund the intensive research and development involved. In fact, for many developed countries such as the US and Canada, this has been difficult owing to periods of

recession. In 2008, biotech companies were only able to raise 16.5 billion dollars – a decline of 45% compared with 2007. (PricewaterhouseCoopers, 2010)

Edward Lanphier, founder of Sangamo BioSciences whose company is developing a platform technology to treat HIV/AIDS has stated, "The economic environment for small biotech companies has been difficult for the past three to four years and doesn't appear to be improving significantly". (Drug Development Technology, 2012)

For this reason, many biotech firms look to form strategic alliances with big pharma companies for growth. (Exhibit G) There are various types of strategic alliances that can be adopted including partnerships, mergers, acquisitions and so forth.

2019 heralded one of the largest mergers in the big pharma industry – that of the biotech giant Celgene and Bristol-Myers Squibb.

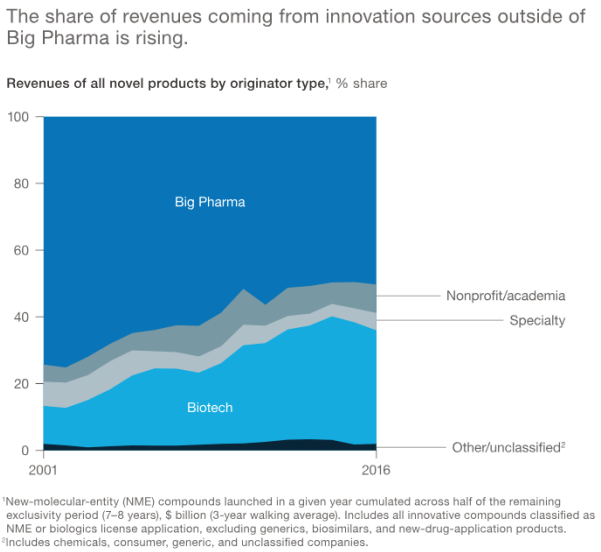


*Exhibit G. M. (n.d.). What's behind the pharmaceutical sectors push for M & A push [The share of revenues coming from innovation sources outside of Big Pharma is rising.]. Retrieved April 9, 2019, from https://www.mckinsey.com/business-functions/strategy-and-corporate-finance/our-insights/whats-behind-the-pharmaceutical-sectors-m-and-a-push*

## Bristol-Myers Squibb and Celgene sign a merger

On January 3rd, 2019, BMS and Celgene entered into a mega-merger having an equity value of $74 billion dollars. The terms of this agreement provide Celgene shareholders with one Bristol Myers Squibb's share and $50 cash for each Celgene share. The shareholders

would also receive one tradeable contingent value right for each share of Celgene. This would only apply however if the Celgene's pipeline drugs ozanimod, liso-cel (JCAR017), and bb2121 receive FDA approval by December 21st, 2020 for the first two and March 31st 2021 for bb2121. (Campbell, 2019)

There are several key drivers for strategic alliances such as these. The 2017 Tax Cuts and Jobs Act in the US allowed for a reduction of the corporate tax rate from 35% to 21% making mergers and acquisitions attractive in the US. Not surprisingly, 2018 proved to be the year for mergers and acquisitions. Historically, analysts state that such mergers and acquisitions are what have shaped the pharmaceutical landscape. (Exhibit H)

Secondly, the higher costs of bringing a new drug to market are another driver behind such deals. In 2017, the average cost (adjusted for risks) was $2.6 billion dollars compared with $1.2 billion dollars in 2010. The reason behind this is the high cost of failure associated with phase 3 clinical trials – success rates are usually between 10 and 12%. Thirdly, regulatory standards for complex diseases such as cancer are very stringent. In 2017, only 18% of drugs in big pharma pipelines succeeded in coming on the market. Another positive for mega-mergers such as these are the shareholder value created and profits generated for the acquiring company.

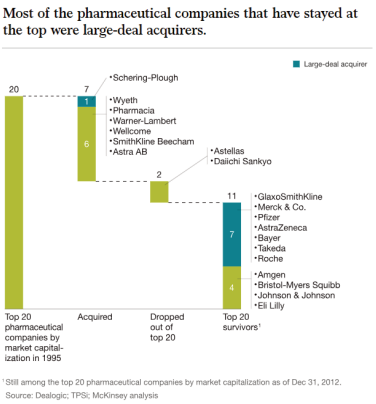


*Exhibit H. M. (2012, December 31). Why pharma megamergers work. [Most of the pharmaceutical companies that have stayed at the top were large-deal acquirers.]. Retrieved March 27, 2019, from https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/why-pharma-megamergers-work*

So, Big Pharma does indeed have the necessary cash to burn. Therefore, companies such as BMS can afford to pick and choose who they wish to form a strategic alliance with.

Why then would Bristol-Myers Squibb choose to merge with Celgene?

## Celgene – A biotech powerhouse

Celgene is a large American biotechnology company which specializes in innovative therapies for cancer as well as immune-inflammatory diseases. The company took root in 1986 when founders David Stirling and Sol Barer teamed up at the Celanese Corporation. Celgene began as a spinoff company and eventually transitioned to an independent biotechnology company. (Celgene, 2019)

The company enjoyed its first taste of success in 2003 following the launch of 'Thalomid' which was initially used to treat a side effect of leprosy. In 2006, Celgene obtained US regulatory approval to use Thalomid as a treatment for multiple myeloma as well. (Celgene, 2019)

The company continued to grow and expand its product line through the acquisition of minor biotech companies thereby cementing its position as a top producer of innovative cancer-based therapeutics. The company's relatively recent acquisition of Juno Therapeutics has allowed them to focus on CART based therapies. This would enable them to become a leader in immune-based therapies. (Celgene, 2019)

With so many smaller biotech companies under its belt, Celgene gained quite the reputation for being a savvy deal-maker. What is attractive about the company is its corporate culture. The biotech

giant does not dictate terms in these agreements rather accommodates its partners needs as well. This is observed through the variety of deals struck ranging from strategic equity investments to structured acquisitions. In lieu of this, the company is very attractive to young biotech companies with an entrepreneurial mind-set. (The Boston Consulting Group, 2014) (Exhibit I)

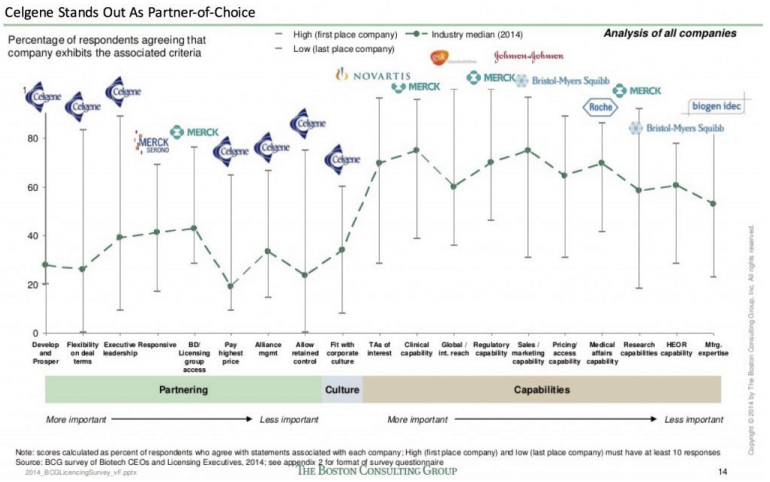


*Exhibit I. BCG survey of Biotech CEOs and Licensing Executives. The Boston Consulting Group. [Celgene stands out as a partner of choice.]. (2014). Retrieved March 15, 2019.*

Celgene's luck ran out however in 2014 when it purchased the rights to an experimental drug GED-301 which was supposed to be a blockbuster drug to treat Crohn's disease. In 2017, Celgene announced the drug had failed phase three trials. Immediately following this, Celgene's stocks plummeted. (Campbell, 2017) To add to this tale of woe, Celgene would soon be facing a patent cliff of its

own following the loss of exclusivity to its blockbuster drug Revlimid. The company was also running into significant debt as observed through its debt to equity ratio. This decline was attributed to the company's recent acquisition of Receptos.

Celgene emerged as an attractive prospect for BMS owing to its oncology pipeline drugs. Celgene's product portfolio proved to be complementary to BMS's key research areas as well. Hence for BMS, the deal would mean an expansion of pipeline drugs (specifically oncology) to offset stiff competition from Merck's product Keytruda.

A merger such as this appears to be a match made in heaven. However there are a few who are opposed to this marriage – namely BMS shareholders.

## Trouble in Paradise – BMS Shareholders are not happy

Bristol-Myers Squibb shareholders have openly voiced their dissatisfaction for the deal at hand. Firstly, the merger would mean that Bristol Myer Squibb assumes Celgene's $32 billion dollar debt. This is a sizeable increase from BMS's outstanding obligations of $7.3 billion dollars. (LaVito & Lovelace Jr. 2019)

BMS's largest shareholders Wellington, Dodge and Cox, and Starboard Value have stated that BMS would be accepting far too much of a risk; furthermore, BMS shareholders seem to be getting the short end of the stick as the merger undervalues BMS stock price. Secondly, shareholders have argued that Celgene has a poor track record of delivering on its promises.

On a positive note, although there is a significant of debt absorbed by the acquiring partner, this is not always a bad thing. In fact, such

mergers may lead to cost optimization strategies and improve R & D productivity.

## Are mergers the right approach for big pharma and biotech?

In conclusion, the remaining question that still needs to be addressed is, can mergers indeed generate innovation?

Mergers can be mutually beneficial. For Big Pharma, mergers may provide the big break these companies require to diversify their drug product pipeline. Secondly, the biotech industry cannot solely rely on investors to keep their firms afloat, eventually, they will be driven into such mergers and acquisitions to keep investors satisfied. (Warner, 2004) It is important however to note that mergers can occur between large biotech firms but is not as common as pharmaceutical mergers.

A butterfly effect resulting from these mergers is the job loss impacting scientists involved in R & D projects. Between 2002 to 2012, around 300,000 jobs were impacted by merger and acquisitions in the pharmaceutical industry. (Biospace, 2016) For employees that do survive the merger, there is the additional hassle of adapting to a new corporate environment. Big pharma is more conservative, whereas biotech may be considered more 'hip' and 'individualistic' and lacking the bureaucracy present in big pharma. (Biospace, 2016)

In the long run, however, critics argue that mergers and acquisitions may not be a sustainable means for big pharma to generate growth. Another consequence of mergers besides job loss is that certain R & D projects may be dropped by the acquiring company as part of cost-cutting strategies. Lastly, mergers and acquisitions

may remove competitors from the market landscape which removes health competition and reduces innovation. (Lo, 2015)

## The future of this deal is uncertain

April 12th, 2019 is set to be the date that Bristol-Myers Squibb shareholders cast their vote on whether or not to go through with this deal. Should the deal not go through, there would be significant penalties incurred by Bristol-Myers Squibb including $2.2 billion dollars in termination fees and additional $40 million dollars to compensate Celgene's expenses for this deal. On the one hand, should BMS win this merger, they could still lose out $15 billion dollars if the drug pipeline does not get approved.

Could this marriage be on the rocks? Only time will tell.

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# 43. What went wrong with Theranos?

**What went wrong with Theranos?**

Neil Jurkiewicz Winter 2019

In 2004 a second-year Chemical Engineering student at Stanford University decided that continuing her education would no longer be useful for her. She believed that the extra two years would only hold her back from her entrepreneurial dream as it held back her idol Steve Jobs(1). This student, Elizabeth Holmes even had a step up on her idol as she came from a wealthy family, her father was a former Vice President at Enron and her mother was a Congressional Committee staffer(1). Still, Holmes worked hard throughout high school and college, she learned Mandarin in high school and worked at a graduate level lab in her first year at Stanford. Holmes was destined for an incredible future which started with her first company Theranos in 2004. Theranos would eventually become an immense biotechnology company in Silicon Valley and famous for potentially changing the medical world. However, there is a reason that did not happen, and this starts with Holmes herself.

*Elizabeth Holmes pictured here in 2015(1)*

Theranos began based on a simple idea, Holmes wanted to create equipment that would eliminate needles from drawing blood and be replaced by a blood prick. This technology would be able to analyze over 100 tests all within minutes at a local Walmart or Walgreens(2). This would decrease wait times for patients for vital information and revolutionize health care all over the world. Through the years Theranos would slowly progress into a billion-dollar company and make Holmes a hero in the medical community and celebrity everywhere else. By 2014 Theranos would be evaluated at $9 billion dollars and have an all-star cast of a board of directors containing 2 former secretary of states and 2 united states senators which gave Theranos even more fame and credibility(1). Even though everything on the outside looked amazing for Theranos, on the inside there was a lot of trouble and ineptitude within the organization. What everyone thought was amazing an amazing company was actually terrible business practices built on lies that would eventually catch up to Theranos.

**The Start**

There were many problems with the management of Theranos which started out at the beginning. The majority of the start-up biotechnology companies will have leadership that have Ph.D.'s as seen with Amgen and George Rathmann in the 1980s or Walter

Gilbert of Biogen(3)(4). Theranos, even though its product was a medical technology company had its founder drop out after her second year in chemical engineering. Holmes was still considered a very intelligent person, but it could be a bit ignorant to change the medical technology landscape but not have the same amount of knowledge as someone that may have spent years attaining their Ph.D.'s or Master of Engineering. She also did not have any medical technology Ph.D.'s that she trusted in her management that could give her intelligent advice(1). She was a very bright student that had many ideas, however, a professor she worked with had rejected some of her ideas for not being technologically possible(1), which was an unfortunate foreshadowing of Theranos technology.

**Problems Begin**

It didn't take long for problems to occur after Theranos was incorporated in 2004. In 2006 Henry Mosley, the chief financial officer of Theranos noticed that employees were unhappy after a demonstration of their technology, Edison which analyzed blood samples, to the pharmaceutical company Novartis. When Mosley questioned his staff, he found out that they were unhappy because they had to pre-record the demonstration and lie to Novartis because Theranos's technology was often faulty and wouldn't work. Mosley was distraught as he also realized he had never seen any evidence of their technology working and that he had inflated future revenues due to his confidence in Holmes's idea(5). When he confronted Holmes about the problem, she fired him for not being a "team player." The big problem with this was that the technology would never work as it was nearly impossible. One of the big problems that never was solved for Theranos was the equipment needed a specific volume, and since Holmes was set on using a blood prick they would have to dilute the blood, which would skew the data on analysis(6). Another problem with the amount of blood drawn itself was the composition of the blood taken from a finger prick would not have a common concentration like what would be found if taken from a

vein. This would lead to varying concertation of molecules like lipids and proteins after each sample is taken, which would distort the data. Since blood taken from a finger prick is also considered bodily fluid it would mean that it would also need FDA approval for each test that Theranos said it needed(6). Theranos never got the FDA approval for these tests, only one test for detection of the Herpes infection. There were many problems with the lab practices itself as the FDA had warned Theranos with problems like a record of acceptable suppliers or that the device did not meet any expectations that it was stated in 2015(6). The majority of Theranos employee were not aware of the impossibility of Holmes idea and those that did were inspired by Holmes that their hard work would eventually pay off. However, it never would.

**The Question of Morality**

One of the worst things Holmes did at Theranos was using Theranos Edison, which produced inaccurate results in real life trials. This occurred when a major drug company made a deal with Theranos in 2008 to test its technology for a study on stage 3 and 4 cancer patients(7). Holmes told her employees that the results wouldn't impact the patients but there a few who knew that it was a lie. Ana Arriola, a product designer from Apple who was one of Theranos first recruits and Adam Vollmer a mechanical engineer confronted Holmes about this issue. They were concerned about the false results that would be given to the oncology patients in this trial and wanted to cancel the plan. All Holmes said to them was to follow suit with the company or resign, they both resigned in 2008. It got even worse in 2015 when the technology was estimated to be have been used on over 176,000 people (8). Their testing would misdiagnose patients by diagnosing them with an illness they did not actually have or not actually diagnose them at all. This would prompt the patients to completely change their lifestyles or would possibly not even be aware that they needed a lifestyle change in the first place.

**Bad Management**

There were also problems with the management at Theranos as seen with the firing of Mosley, but also with the hiring of Sunny Balwani (9). Balwani met Holmes before she went to Stanford when he was 37 and she was 18 in 2002. By 2005 Balwani and Holmes were living together and by 2009 Balwani joined Theranos as the chief operating officer. One of the major problems with this was that Balwani did not have any training in medical or biological science. Balwani was in also in a relationship with Holmes but it was not disclosed to investors or employees (10). His inexperience in biological science showed itself to the top researchers at the company as he was seen to be clueless in meetings especially as a top executive (10). Balwani also had a huge problem with a lot of the employees by yelling orders and continuing to humiliate if they did not follow his commands (9). Balwani also fired people so often that it became a common phrase in the company that "Sunny disappeared him." This created a toxic work environment for Theranos with an underqualified boss barking orders and high temper firings of competent people which caused a high turnover rate.

Another big problem found in Theranos was with the board of directors. It was a star-studded cast filled with many important and recognizable names that brought a lot of attention to Theranos like George Schultz and Henry Kissinger, two former secretaries of states(1). However, the majority of the board in 2014 may have had experience in politics or military but very few had any knowledge of medical technology. This would have allowed Holmes to persuade and convince the board to what she wanted as they did not have the knowledge in that field to question Holmes. Also if there were problems with the technology the board would not understand the severity and Holmes would pass the problem off as not a big deal. She was able to do this as she was always described having a charismatic personality that first attracted the elite board members(1). There

are also rumors that her booming deep voice is faked on purpose to garner more respect from her peers(10). With such an amazing company and reputation it dazzled many investors that were lining up to be to give Holmes money. The company even has an amazing story of an incredibly smart female CEO who wants to help save the world. This leads to a fear of missing out or FOMO to investors in silicon valley according to a one of Theranos former board of directors Avie Tevanian(7).

There was also a lot of problems with the lower level employees as many had described the company management as a "South American dictatorship or a drug cartel."(10) Holmes would constantly micromanage the employees that created distrust between the staff and herself. Holmes also isolated the majority of her employees to limit the communication about their tasks, which she defended by stating it was to keep trade secrets. However, it was more likely to ensure that other employees don't piece together the failure of their technology. This along with Sunny Belwani also berating the employees when he himself had very little knowledge of anything Theranos was doing led to a toxic work environment. This in case gave Theranos a high-turnover rate as many employees saw their intelligent partners quit or be fired if left a lot of the employees insecure.

**The Downfall**

In the end, Elizabeth Holmes biggest mistake was her desire to be like Steve Jobs which was something she could never accomplish. Jobs knew when he was in over his head and hired CEO's with previous experience, Holmes hired Sunny Balwani who had none(11). Jobs also had Steve Wozniak who was a gifted computer engineer that Jobs had highly respected, Holmes did not have anyone with such expertise that she trusted at Theranos(11). Finally, Jobs had visions for things that were challenging but not impossible. There was already a prototype for the Mac II made by Wozniak. To

miniaturize the iPod Jobs had a supplier and manufactures at hand. While what Holmes was doing was decreasing the size of current technology over a hundredfold which would be made from technology that had not been even invented yet(11). Holmes was in over her head at Theranos which led to bad decisions that would eventually lead to the downfall of Theranos.

*Balwani (left) and Holmes (right) during their 2017 deposition with the Securities and Exchange Commission. (7)*

Theranos's crimes were discovered by Wall Street Journal writer John Carreyou who was able to expose Holmes fraud(12). Holmes and Balwani were eventually charged and removed as CEO and COO and are currently awaiting trials for the future(13). What the world can learn from Holmes is that faking it until you make it for such a long time. Eventually, all the lies and deception will catch up.

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# 44. Ablexis LCC

Individual Case Study- ablexis

# 45. Aleafia Health Inc.: A Novel Approach in Medical Cannabis

**By Fatemeh Ameli**

## Introduction

Cannabis or marijuana, one of the oldest documented medicines in history, is prepared from a plant belonging to the Cannabaceae family and the *Cannabis sativa* species which encompasses 545 chemical compounds. Amongst more than 70 psychoactive compounds of cannabis called "cannabinoids", Delta 9-tetrahydrocannabinol (delta 9-THC) is the main active component with psychoactive and analgesic effects. In addition, Cannabidiol (CBD) and cannabinol are two other important constituents found in Cannabis [1]. The 2004 Canadian Addiction Survey, which surveyed 13,909 Canadians aged 15 and older, found that 44.5% reported using cannabis at least once in their lives and 14.1% reported using it during the 12 months before the survey [2]. Furthermore, approximately 4% of Canadians over the age of 15 (1 million persons) report consumption of cannabis in the previous 12 months prior to the survey for treating their self-defined diseases. According to the 2012 Canadian Alcohol and Drug Use Monitoring Survey which interviewed 27,767,855 Canadian residents aged 15 years and older, approximately 1.6% of Canadians (approximately 420,000 persons) used marijuana for medicinal purposes [3].

Medical Cannabis is conditionally permitted to be used for therapeutic purposes in some countries including Canada. Medical marijuana is cannabis and cannabinoids which are prescribed by physicians for therapeutic purposes. The 'Medical Marihuana Access Regulations' (MMAR) was established in Canada in 2001 by the (Liberal) federal government. MMAR defined an authorized medical marijuana user as someone confirmed by the physician to be suffering from a severe/chronic medical disease. Such individuals can obtain their required medical cannabis directly from Health Canada, grow it or obtain it from determined suppliers. (Medical Marijuana programs: Implications for cannabis control policy – Observations from Canada)[4]

According to literature, lack of evidence on safety and efficacy of cannabis is the main obstacle to physicians' therapeutic decisions [5]. Although studies have reported in favor of the efficacy of Cannabis in chronic pain, the debate about the usefulness and safety of marijuana has remained unresolved. Despite the potential advantages of using marijuana in the management of pain, it has also shown a number of harmful and potential disadvantages [6].

Given the uncertainties regarding the use of medical cannabis for treatment purposes and the existing gap in the literature, Aleafia Health Inc. was established to resolve the conflicts through a systematic approach including well-networked clinics, advanced cultivation and distribution facilities, evidence-based research, and qualified education.

## About Aleafia

Julian Fantino established the Aleafia Total Health Network in Vaughan, Ontario in 2016. He was the Chief of Toronto Police Service, as well as a Member of Parliament and the Minister of Veterans

Affairs before leading this company [7]. Aleafia, as a vertically integrated national company, focuses on cannabis cultivation in addition to providing health care services and cannabis research and development. The Aleafia Inc., as a distinguished company, has a health clinic run by qualified health care professionals which provides health care services to patients suffering from chronic pain and disabling diseases. This corporation, as a federally licensed producer and vendor of cannabis, aims to produce 98,000 kg of dried cannabis annually as of 2019 [7].

As a well-networked company, Aleafia takes a holistic view of healthcare, treating patients with cannabis as a pharmaceutical product. What has made it distinct is that it uses an interrelated model of medical services. Using a patient-centered, interdisciplinary approach, it focuses on how early intervention leads to successful treatment rather than only considering rehabilitation after an injury [8]. Aleafia Health now possesses and runs the largest physician-led referral medical cannabis clinic network in Canada. It has 40 clinics across Canada providing cannabis services by assessing and monitoring the most appropriate prescribed cannabis for patients.These clinics benefits from specialized doctors and qualified health care providers, specifically trained to evaluate if patients are fit to use medical cannabis, recommend appropriate doses and follow treatment progress over the time.

Aleafia team contains former government and law enforcement leaders, as well as successful growers and entrepreneurs. They started with friends and family funding and now are harvesting cannabis for medical and recreational use. Although this company is a newcomer, it has made a great progress over the past 18 months [7]. In Feb 2019, the Toronto Stock Exchange (TSX) selected Aleafia as one of the top 50 performing companies of the year based on share price, market capital, and liquidity [9,10]. The market capitalization of Aleafia has had a drastic rise from $26-million to $226-million during the year of 2018. This company has various plans for expanding

337,000 sq. ft. of the facility to increase 38,000 kg of cannabis cultivation annually. Construction work on this facility is nearing completion soon [7,19].

As the largest cannabis clinic network in Canada, Aleafia can collect a large amount of data and provide patients with the best cannabis care. This fact contributes to customer loyalty and has led to a 7.62% increase in market capital. It is noteworthy to mention that Aleafia's shares tripled in just three weeks last year (see Exhibit 1)[11,12,19]. Aleafia intends to invest on substantial opportunities including cannabis production, health care services, cannabis education and research on consumer experience to internationally expand its market [7]. In the following sections these 4 major strengths of this company will be evaluated.

## Cannabis Cultivation

In terms of the indoor facility, the Aleafia site has a 7,000 sq. ft. hydroponic facility in Port Perry located on Aleafia Health's farmland. In Oct 2018, Aleafia has started launching the outdoor expansion. Beside the operational Port Perry indoor cultivation facility, there is a 30-acre land which has a capacity of growing 60,000 kg of cannabis. Note that this land has obtained local regulatory approval. This outdoor cultivation site can minimize capital investments and operating costs. The company has planned to start the first harvesting in the upcoming summer. It also has the capability of creating 80 to 100 more job opportunities. To respect corporate social responsibility, Aleafia hires workforce from the local areas [7,12,13].

Aleafia plans to enhance its capacity in producing cannabis by the end of 2019. In July 2018, this company has started building a 160,000 sq. ft. automatic Greenhouse in Niagara. This greenhouse, as one of

the most advanced facilities in Canada, has a well-equipped irrigation and automatic moving container bench system. This system can produce one of the lowest costs and highest quality medication for patients. The phase one of this project is completed and ready to operate [7,12,13].

## Medical Cannabis Healthcare Services

On December 22, 2017, Aleafia Inc, announced that it has started a business partnership with Canabo Medical Inc. According to this agreement, Aleafia acquired 22 medical cannabis clinics across Canada, with more than 30,000 patients. What makes this company distinct from others is that it has the largest medical cannabis database in the world with R&D activities. These facilities allow Aleafia to concentrate on 17.4 million treatable conditions across Canada and provide suitable context for innovative research, insurance, and well-being services [14]. Canabo Medical Clinic, as a part of Aleafia Health Inc., is keen on providing medical cannabis care to Canadians all over the Canada through using distribution facility as well as conducting cannabis related research. The experimental knowledge and proven evidence about the effectiveness of medical cannabis use for treating different health conditions, driven from available data, can help inform cannabis prescription with confidence. This issue can also assist physicians to avoid making clinical decisions based on trial and error. New patients are provided with learning sessions and appropriate consultation to ensure that they are undertaking the most efficient treatment which fulfills their needs [15].

On December 19, 2018 Aleafia Health Inc. and Emblem Corp. signed an agreement under which Aleafia obtains all issued and outstanding common shares in an all-share transaction related to Emblem valuing

around $173.2 million.16 This acquisition can lead to the following outcomes: 1) It will make the largest medical cannabis clinic network in Canada by including 40 medical clinics and education centers providing health services to 60,000 patients. Furthermore, this will allow Aleafia to take an advantage of the extraction and product innovation offered by Emblem to sell medical cannabis directly to patients. 2) Aleafia patients can access the Emblem's unique and profitable products such as capsules, oils and oral sprays as well as the high-quality customer service and e-Commerce system. 3) Aleafia can leverage Emblem's Health Canada License to accelerate the process of producing medical cannabis products [16,17,18].

## Medical Cannabis Research

Aleafia's product innovation center is located on a 25000 sq. ft. campus. This center extracts different products such as oil, tinctures, sprays, and gel caps. The expansion of phase Ⅱ, including the formulation and analytical laboratories, is in progress right now [7]. Aleafia campus labs try to enhance the scientific knowledge regarding the benefits of using medical cannabis by organizing "Big Data" to affect patients' health. Their mission is to supply the best health care professionals, knowledgeable doctors and patient support. These services are based on the data evoked through comprehensive research, advanced strategies and the most recent industry findings. Numerous historical data provided by Canabo medical clinic along with the new cannabis products produced in Aleafia campus lab can enhance the efficiency of the products at the highest level [7]. These efforts are made to provide evidence-based information regarding medical cannabis products and the best approaches for treating opioid dependence and chronic diseases

such as chronic pain, sleep disorders (e.g. insomnia) and mental health problems (e.g. anxiety, and eating disorders) [37].

The results of a recent study conducted by Aleafia indicated that 45% of patients stopped using Benzodiazepines after being treat with medical cannabis. Since in 2017 the global market value for prescribing sedative drugs and opioids has been $2B and $23B respectively. Aleafia's recent result can be considered as a good opportunity for medical cannabis companies to look at the cannabis as a potential substitute [20,21].

## Medical Cannabis Education

In November 2018, Aleafia Health signed an international agreement with D2L (Desire2Learn) Corporation and launched global cannabis education platform with it. Educational program is taking advantage from Aleafia's experience and professional expertise regarding medical cannabis. This opportunity can provide knowledgeable and practical content used in persuasive and interactive educational materials for training different communities across the world. The available intellectual property such as huge patient data bases as well as D2L's leadership are also used in the cloud-based learning programs. According to Aleafia's chief medical officer Dr. Michael Verbora, "Our education and online learning platform will grow cannabis awareness and understanding across all sectors". He also mentions that "Our new LMS platform will ensure patients receive better care while providing medical professionals with a data-driven approach to diagnosing and treating chronic illnesses with medical cannabis" [7,22].

## The Challenge of Medical Cannabis Distribution

Despite all of the above-mentioned advantages, Aleafia has no direct sale to provincial distributors [11]. To address these limitations, it has recently made two agreements, including a supply agreement and an investment agreement with the Canntrust and CannaPacific companies respectively.

On January 14, 2019, Aleafia Health Inc. sold two cannabis crops to CannTrust Holdings Inc., the top "Licensed Producer of the Year" who received the 2018 Canadian Cannabis Awards. This agreement was the first deal that required Aleafia to supply 15,000 kg cannabis in 2019 [23]. According to Aleafia's chief executive officer (CEO), Geoffrey Benic, "The continued strategic agreement between Aleafia and CannTrust has provided measurable benefit to both companies, allowing Aleafia to rapidly accelerate the execution of its business plan"[24,25]. According to this contract, CannTrust has a right of first refusal to Aleafia's products. The contract with CannTrust is the only recreational market access of Aleafia. CannTrust can, but is not forced, to buy Aleafia's cannabis.

It seems that, based on a ratio of enterprise value-to-production capacity, Aleafia was offered a reasonable price in comparison with other companies; however, based on a ratio of enterprise value-to-supply agreements, the offered price was comparatively cheap. Since the profit is shared with CannTrust, Aleafia's enterprise value-to-supply agreements probably receive less revenue compared to other competitors that have access to provincial distributors to sell their products directly. The two crops sold out to CannTrust were harvested at an indoor Port Perry cultivation facility. They will supply high-quality cannabis for CannTrust which has an ever- growing number of patients (more than 58,000 registered customers) using this drug, and also for its four recreational brands including liiv, Synr.g, Xscape and Peak Leaf [24,25].

Furthermore, on Jan 18, 2019, Aleafia Health Inc. signed an investment agreement with CannaPacific as a licensed medical cannabis corporation in Australia. Through this agreement, Aleafia obtained 10% of the ordinary shares of CannaPacific. This agreement provided Aleafia with shortcut access to the Asia market via available trade contracts made in this area [26,27].

## Aleafia's Financial Results

As of September 30, 2018, the company has earned CA$ 22.8 million, a 2.071% increase over their earnings in December 2017. The company is trading at 32x forward revenues, which is significantly higher than most cannabis producers. According to the financial statements, 49% of the total amount of assets includes intangible assets and goodwill, which can be a negative point from an investor's perspective (see Exhibit 2) [12,28].

It is expected that Aleafia Health Inc. will become one of the most important competitors in the cannabis industry, because of its capacity in producing approximately 15,000 kg. of cannabis in 2019, and its target capacity of 60,000 kg. Despite the advantages mentioned above, some market experts believe that this company should not currently be considered as a real opportunity for investors, and that the market is counting on its future developments [11].

On the other side, according to the evidence synthesized in this company based on research studies, investors may consider the cannabis-based treatments offered by Aleafia Health as an enormous market opportunity. More importantly, the studies conducted on opioid treatment in Aleafia are suggesting great evidence of opioid dependence. This fact can help inform the importance of cannabis as a potential substitute with a high margin market, as compared to

opioids and sedative drugs which have a high global market value [12,28].

The revenue of Aleafia increased from a very small amount in 2017 to CA$ 2.97 million over a period of 9 months, ending in September 2018, which is very interesting for investors. Consultation services and research are two important factors which have had a key role in this income increase (see Exhibit 3). In this period, the expenditures remained almost stable, as in the same period in 2017. In the same duration, the net losses were reduced from CA$ -8.8 million to CA$ -6.5 million. Although Aleafia still needs to take a lot of steps to reach the break-even point, this net loss reduction is appreciated by investors. A supply agreement signed with CannTrust is expected to significantly enhance the earning of Aleafia in 2019 [12,19].

It seems that Aleafia Health Inc. has a very stable financial status and its cash flow is almost good. It is valuable that no financial debt was reported on the balance sheet untill September 30, 2018. In terms of the equity structure, investors should know that using available warrants may contribute to share price depreciation [28]. It is of great importance for investors to realize that cannabis is a young industry and the inherent risk of investment obtained from stock market volatility should be considered to be the main concern of investors; however, among different stocks in the OTC Markets, the stock of Aleafia Inc. should not experience dramatic volatility [12,19].

## SWOT:

In the following sections, the potential strengths, weaknesses, threats, and opportunities of Aleafia will be examined from different perspectives.

## Strengths:

- Aleafia, as a vertically integrated national company, probably ensures systematic control over its supply chain through focusing on a multifunctional approach including cannabis cultivation, cannabis research, and education, as well as providing cannabis- related health services. This fact helps Aleafia minimize operational costs and optimize the quality control over the supply chain.
- It contains the largest network of medical cannabis clinics and user's database in Canada. This fact gives Aleafia the chance to be the world leader in providing physicians with an innovative method of cannabis health and wellness care based on data, research, and experience. These efforts are aimed at developing evidence-based treatment methods and products.
- Although Aleafia has some famous major competitors, from the gem seekers' perspective, being less famous may provide a good opportunity for investors. Indeed, growth investing seeks companies that are growing well and are less known about by investors [12].

## Weaknesses:

- Experienced and outstanding companies would be Aleafia's competitors. For instance, Canopy Growth Corporation as the largest cannabis company in Canada, having strong collaborations with different companies in Brazil, Australia, Germany, and Colombia. In addition, Aurora Cannabis (ACB) exports cannabis to different countries, and has a current capacity of producing 150,000 kg.
- Aleafia, as a federally licensed producer and vendor of cannabis,

has no direct sale to provincial distributors.
- Shortage of liquidity is also another concern. Aleafia's financial records indicate that approximately half of their total amount of assets are intangible assets and goodwill [12].

## Opportunities:

- Canada is the first G7 country to legalize recreational cannabis. This has led to a high market size of around CA$22.6 billion [29].
- The international medical cannabis market is anticipated to reach 455.8 billion by 2025 [30].
- The ever-growing market of new cannabis products, including edibles, beverages, oils, and beauty & skin care products, brings profitability to the cannabis industry.
- Research findings obtained by Aleafia show that treating with medical cannabis can limit the use of sedative drugs and opioids, creating less of a market for these alternatives [21].

## Threats:

- From a health research perspective, there is no strong evidence regarding the efficacy of medical cannabis. Therefore, insurance companies are not interested in covering medical cannabis prescriptions [5]. Furthermore, the fear of cannabis dependence and its documented adverse events are the other challenges that should be taken into consideration [31].
- From a socio/cultural perspective, although medical marijuana is legal in Canada, some individuals suffering from pain may resist a trial of cannabis due to the associated stigma [32].

Although public opinion regarding cannabis has changed, medical cannabis users still experience a certain amount of stigma, especially from authorities. Medical cannabis users are usually exposed to different levels of disapproval from their friends and relatives, leading them to avoid disclosure of use [33]. These concerns can be attributed to the societal stigmatization of cannabis.

- From a political perspective, a) the Access to Cannabis for Medical Purposes Regulations (ACMPR) allows patients to grow their own plants or to have a designated person grow the plants, b) a change in government in Canada may affect the current cannabis related rules [4,34].
- From a financial perspective, since cannabis is still federally illegal in the United States, there are some limitations on the number of institutional investors. Hence, the big American investment companies may not be able to invest in this industry [35].

## Questions Moving Forward:

Aleafia is engaging with different challenges which can impact its market negatively. To address these challenges, the CEO needs to evaluate the following alternatives and make an optimum decision.

Due to the shortage of tangible assets, Geoffrey Benic needs to find an appropriate answer to this question: "What is the best way for Aleafia to enhance its cash flow?" Other questions that should be considered include:

- Since the acquisition strategy with Emblem has increased the liquidity and capital market [17,18], does another partnership agreement with other international or national companies have

the same result?
- Since Aleafia has the largest medical cannabis user's database, can capitalizing on this data source generate revenue for its business?
- How can Aleafia provide researchers, policy makers, and academia with its rigorous data and evidence?
- Would establishing a pre-sale agreement with distributors help Aleafia enhance its cash position?

In terms of market expansion:

- Emblem Inc. has a partnership with a German medical wholesaler named Acnos Pharma Inc. [16], and it is also likely that cannabis will become legalized in Europe. If so, is it a suitable time for Aleafia to explore more international opportunities through Europe's market, a population of approximately 82 million?
- Given the recent agreement signed with CannaPacific Inc. in Australia, is there any possibility for Aleafia to access the Asia – Pacific market?
- Would different kinds of partnership agreements, like acquisition or joint venture, help Aleafia expand its market in South America? Can collaboration with CannTrust facilitate Aleafia's presence in Brazil and Colombia's market?
- Where should Aleafia go from here?
- Aleafia can focus on product development via Emblem's modern product innovation center [16]. According to the differentiation strategy, is it beneficial for Aleafia to develop various cannabis products such as beverages, edibles, and concentrates for both medical and recreational markets?
- It is noteworthy to mention that, on Sep 20, 2018, Aleafia started a joint medical cannabis study with the Cronos group Inc. to modify the treatment of insomnia and sleep disorders [36]. Can

Aleafia promote medical cannabis as an alternative to prescription sedatives? Would medical cannabis be considered as a substitute for opioids used by professional athletes?

In terms of social and cultural limitations:

- Can Aleafia leverage its extensive knowledge of the cannabis patient's experience, and its professional expertise, to clarify public opinion and minimize stigma regarding cannabis use?
- As a part of business model differentiation, holding educational workshops and courses not only can educate practitioners, but also can build trust between Aleafia and health care providers. To overcome the related health concerns among physicians and insurance companies, does it make sense for Aleafia to provide learning sessions and continuous consultations to assure them about the efficiency of treatment and products?

Aleafia has a plan to produce a target value of 98000 kg cannabis in 2019; however, it has no direct sale to provincial distributors.

- Does it make sense for this company to increase its bargaining power by making new supply agreements with distributors alongside Canntrust?
- Emblem Inc. has the opportunity to supply cannabis to different provinces in Canada through connecting to medical distributors like Shoppers Drug Mart and retail distributors such as Fire & Flower and Starbuds [17]. Under such circumstances, can Emblem's approval facilitate Aleafia's national distribution platform?

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**Appendix:**


*Exhibit 1: Aleafia’s stock volatility during 200 days in 2018, Source: https://www.profitconfidential.com/stock/aleafia-health-inc-stock/otcmkts-aleaf-stock-found-footing-rise/*

| | Note | September 30, 2018 | December 31, 2017 |
|---|---|---|---|
| | | $ | $ |
| **ASSETS** | | | |
| **CURRENT** | | | |
| Cash | 15 | 22,820,979 | 1,057,231 |
| Accounts receivable | 15 | 1,150,138 | 123,979 |
| Prepaid expenses | | 307,202 | 15,162 |
| Biological assets | 13 | 908,907 | - |
| Other current assets | | 1,156 | - |
| | | 25,188,382 | 1,196,372 |
| Property, plant and equipment | 7 | 13,094,719 | 1,636,430 |
| Intangible assets | 5,6,8 | 22,956,409 | 10,048,000 |
| Goodwill | 5,6 | 14,970,835 | 5,064,288 |
| **TOTAL ASSETS** | | **76,210,345** | **17,945,090** |

Exhibit 2: Aleafia's list of assets in 2018, Source: https://seekingalpha.com/article/4245626-aleafia-expecting-total-capacity-60000-kg-overvalued

| | Three months ended September 30, 2018 | Three months ended September 30, 2017 | Nine months ended September 30, 2018 | Nine months ended September 30, 2017 |
|---|---|---|---|---|
| **REVENUE** | $ | $ | $ | $ |
| Consultation services | 423,685 | 400 | 1,008,747 | 400 |
| Research revenue | 612,224 | - | 1,247,634 | - |
| Sale of Cannabis | 429,146 | - | 429,146 | - |
| Other revenue | 174,910 | - | 286,697 | - |
| | 1,639,965 | 400 | 2,972,224 | 400 |
| **COST OF SALES** | | | | |
| Doctor Commissions | 336,286 | - | 767,030 | - |
| Cost of goods sold | - | - | 513 | - |
| **GROSS PROFIT BEFORE FAIR VALUE ADJUSTMENT** | 1,303,679 | 400 | 2,204,681 | 400 |
| Unrealized gain on fair value of biological assets | 908,907 | - | 908,907 | - |
| **GROSS PROFIT** | 2,212,586 | 400 | 3,113,588 | 400 |
| **EXPENSES** | | | | |
| Wages and benefits | 864,315 | 164,401 | 2,361,849 | 405,249 |
| Advertising and promotion | 181,047 | 332 | 356,996 | 49,698 |
| Investor Relations | 112,266 | - | 214,980 | - |
| Business Advisory Fees including share based fees | 1,051,702 | - | 1,473,176 | - |
| Amortization | 1,104,035 | 16,063 | 1,385,170 | 19,456 |
| Professional and legal | 282,184 | 16,965 | 569,423 | 17,895 |
| Office, supplies and services | 151,104 | 21,315 | 321,534 | 46,596 |
| Rent and facility | 232,430 | 14,420 | 526,760 | 50,261 |
| Supply and Maintenance | 28,041 | - | 121,419 | - |
| Share-based payments | 1,457,476 | 121,675 | 2,072,401 | 8,204,706 |
| Exchange and transfer agent fees | 86,882 | - | 139,791 | - |
| Travel and entertainment | 56,403 | 14,626 | 145,118 | 24,535 |
| | 5,607,885 | 369,797 | 9,688,617 | 8,818,396 |
| NET LOSS AND COMPREHENSIVE LOSS FOR THE PERIOD | (3,395,299) | (369,397) | (6,575,029) | (8,817,996) |
| LOSS PER SHARE – Basic and diluted | (0.025) | (0.009) | (0.062) | (0.308) |
| Weighted Average Common Shares Outstanding | 135,989,842 | 42,010,000 | 106,139,213 | 28,618,059 |

*Exhibit 3: Aleafia's income statement reported in the last quarterly, Source: https://seekingalpha.com/article/4245626-aleafia-expecting-total-capacity-60000-kg-overvalued*

# 46. Helix: Stocking the Shelves in their Genetic Testing App Store

**By: Tyler Boulanger**
**April 9th, 2019**

Mankind's knowledge of the human genome and its effects on health, behaviour, physical attributes and much more is constantly expanding. Each year there is a hot new product on the market that provides consumers with more information about their genetic makeup. From 23andMe to Ancestry DNA, several of these services have entered the mainstream and built public knowledge on genetic testing. These direct-to-consumer (DTC) genetic tests are putting an infinite amount of information into the hands of consumers and, naturally, many of these consumers want to try them all. Each product advertises its own unique approach to genotype analysis and it would seem like the information from one would supplement or overlap with the information from another. However, the lack of coordination between organizations is making it difficult for consumers to fully jump on board. Varying testing and analysis method have led to varying results between companies. The requirement to order a new genetic test for each company creates a price tag that is unaffordable to most. This also makes it difficult for startup companies to compete with the more popular entities, as consumers are put in a situation where they need to choose just one genetic test provider.

This was likely the situation that James Lu, a student

of chemical engineering and medicine, found himself in when he co-founded Helix in 2015. Helix provides a solution to the issue of needing to pay for a new genetic test with each test provider, acting as an "app store" platform where customers can pay for only one genetic test and have the results applied to a wide range of genetic tests. James was very interested in the vast landscape of information available from genetics, stating "DNA plays a role in every part of our lives, and we're just starting to use this information to make better decisions in our life and discover new things about ourselves" (Lu, 2016). In creating Helix, Lu hoped to make this information more accessible to everyone, believing that learning about how to make lifestyle changes to better their health and wellness is every patient's right. He stated, "We're really trying to focus on the 99 percent of people that have never had access to this kind of testing, but of course we want it to be responsible access" (Molteni, 2018).

As Helix grew to include a combination of well-known and startup partners from across the United States, the company's business model seemed to be working well in their home country. Lu and his team faced many questions about the future direction of Helix and if they could truly compete with the market's giants like 23andMe or Ancestry DNA. As an organization that only served the United States, international expansion seemed to be the only way to keep up. That process is costly though and required partnerships with genomics apps from around the world. And so, Lu and his team were left to consider what international growth would entail and how to create the right strategy to advance. Would they ever be able to take on 23andMe's research and resources, or should they just stick to being the solution in niche markets? Are there alternative revenue sources that could be used to fund this next step? Or would there need to be an exit strategy in place in case they can't compete? These decisions were looming as Helix's leadership tried to enjoy the success and growth of their company.

## THE BIRTH AND GROWTH OF HELIX

Helix was created in August 2015 by co-founders James Lu, Justin Kao, Scott Burke (Ramsey, 2016). The company is based in San Francisco, where technology businesses are made to thrive in Silicon Valley. It also runs its sequencing lab in San Diego; it is one of the largest CLIA- (Clinical Laboratory Improvement Amendments) and CAP- (College of American Pathologists) accredited Next Generation Sequencing laboratories in the world (Helix, 2016a). Only the United States are currently served by Helix, though some of the apps they are partnered with operate internationally independent of Helix. Robin Thurston, who created MapMyFitness and acted as CEO until the service was acquired by Under Armour, was brought in as CEO of Helix in 2016. Thurston joined the team because he was interested in going back to a startup after years at an established company. He wanted to make genomic data both fun and accessible to the average consumer (Ramsey, 2016). Helix's leadership was confident that Thurston can help Helix advance as DTC genetic testing enters the mainstream.

Helix claimed they had a simple but powerful mission: "to empower every person to improve their life through DNA" (Helix, 2016b). They did this by creating a standardized platform for performing a wide range of genomic analyses using only one genetic test. In essence, Helix is an app store that connects customers to both established and startup apps that they are partnered with. This way, Helix can provide their customers with a broad collection of services and partners no longer need to perform the genetic testing themselves. Helix's motivation for creating the platform was centred around some of the issues they saw with the DTC genomic testing services available. Mainly, the inconvenience of needing to get sequenced for each testing service was of concern (Lu et al., 2019).

They wanted to relieve this financial and administrative burden and administrative concern from consumers. The lack of incentives for companies to share data is theorized as the main cause of this burden; sharing large amounts of individual genomic data could create a myriad of issues relating to data privacy (Lu et al., 2019). By creating a centralized platform for DTC genetic testing, this concern can be mitigated by Helix.

Helix is responsible for shipping their own DNA collection kits to and from customers, sequencing the DNA, securely storing the sequencing data, and distributing relevant data to partners when customers want to use their service. They collaborate with high-quality partners who create on-demand products that use customer's DNA in interesting ways. The analysis from these products is involved in a variety of personal areas including health, fitness, nutrition, lifestyle, genealogy, and inherited traits. At launch in 2017, Helix had 20 products available to their customers (Ross, 2019). By 2019, Helix expanded to offer 35 products from 20 partner companies and continues to add more (Business Wire, 2018). These partners included established health care institutions and innovative app developers, providing both profound insights and discoveries that are just for fun. Helix evaluates each partner and product, making sure they meet the requirements of the company's Scientific Evidence Evaluation process. This ensures the underlying scientific concepts and claims of each partner product are logical and substantiated. On Helix's store, products are divided into four categories: entertainment, wellness, health, and ancestry (*Exhibit 1*).

## HELIX'S TECHNOLOGIES

In January 2019, Helix published patents on their platform

technology in the US and worldwide; the patent applications themselves are still pending. The title of the patent is "Genomic services platform supporting multiple application providers," outlining the concept of a network of genomic services as well as the pipeline from testing, to bioinformatics processing, to third-party apps, to consumers (Lu et al., 2019). The patent includes a series of diagrams that illustrate the possible variations of how Helix's platform will be executed, including *Exhibit 2*. Helix's pipeline essentially involves sending a DNA sampling kit to users, collecting those samples, sequencing them, and storing that data. Consumers then buy a product from an app partnered with the Helix store, Helix provisions only the data required to perform the genomic analysis of that specific product, and the partner analyzes the data and distributes the final results to the customer (Ross, 2019). Any companies with a good idea for a genomic analysis service but not the capacity to develop an end-to-end system that includes sequencing can be assisted by Helix's model.

Software aside, sequencing technologies play a large role in Helix's future success. While it cost US $10,000 to sequence a megabase (one million bases) of DNA in 2001, it now only costs about a cent (National Human Genome Research Institute, 2018). This emergence in technology has made the process much more affordable to genetic testing companies and, therefore, their customers. It was facilitated by the development of Next Generation Sequencing, which provides more efficient, automated, and high-throughput DNA sequencing and allows for lower labor and reagent costs (Mordor Intelligence, 2018). As DNA sequencing technologies continue to improve, the costs of DTC genetic tests will only get lower. In most DTC genetic testing, polymerase chain reaction is used on consumer DNA samples, usually isolated from a salivary sample, to amplify the DNA of genes being analyzed for the test (Biotech Primer, 2018). A Next Generation sequencing microarray is

then performed on this amplified DNA to determine which version of the gene the individual has for each of the hundreds or thousands of genes being tested. If you've used a DTC genetic test in the past, it is likely it was done using a microarray (Dunaway, 2018). While microarrays focus on specific areas of the genome that are theorized to be of importance, whole genome sequencing (WGS) and whole exome sequencing (WES) are far more comprehensive techniques that sequence the entire genome and protein-coding regions, respectively. However, these techniques are still far too costly to be used for a DTC genetic test and give large amounts of information that is difficult to sort through (Dunaway, 2018).

Where Helix gained a clear advantage over its competitors' techniques was in the creation of their own proprietary assay called Exome+. With Exome+, each of a customer's 20,000 protein-coding genes can be sequenced. It also sequences other information-rich regions of the genome identified by the Helix team, including mitochondrial DNA, making the test more robust than common microarrays or WESs (Dunaway, 2018). Helix claims that its exome sequencing is done at a clinical grade, allowing for the accuracy and quality of results that would be expected of a clinical test (Dunaway, 2018). Illumina, who assisted in the creation of Exome+, also states that the test yields 100 times more data than any test commonly used by other consumer-focused companies (Ross, 2019). With such a broad collection of data, Helix is able to apply this information across the products of any of their customers. This is the main reason that Helix customers only need to have their DNA sample once when using many apps, as the information produced by other consumer genetic tests is likely specifically applicable to their own analysis techniques. There is little information available on what makes Exome+ able to complete more comprehensive genetic testing at a competitive price, but the technique gives Helix a clear competitive advantage by producing superior data without breaking the bank.

## WORKING WITH ILLUMINA

As a company heavily focused on sequencing, it is certainly advantageous to be strongly backed by Illumina, their largest shareholder (Robbins, 2016). Illumina is a global leader in sequencing and array-based technologies, serving customers in a broad range of markets (Helix, 2016a). They mainly focus on research and clinical settings, but hoped to conquer the consumer market when they joined forces with Helix in 2015. At launch Illumina was a significant investor, contributing much of their Series A funding. As of November 2018, Illumina owned 50% of the outstanding shares, and therefore voting equity, in Helix (Ross, 2019). They also held a consolidated variable interest entity (VIE), giving them controlling interest that is not based on the majority of voting rights. As more investors have joined Helix, Illumina's shares have become more diluted, resulting in decreased income from Helix since 2016 (*Exhibit* 3). Much of the funding from Illumina contributes to Helix's research and development (R&D); and selling, general and administrative expenses (SG&A) (*Exhibit* 4). Illumina wanted originally wanted to partner with Helix to pursue the development and commercialization of a consumer genomics "marketplace" (Ross, 2019). They, like Helix, thought this was an effective way to affordably provide customers with unprecedented amounts of genetic information through third-party partners. Their end goal is that, through Helix, an ecosystem is created where a wide range of genetic testing apps are able to coexist and succeed.

Having connections to Illumina paid dividends to Helix early on, as they had access to their world-class equipment and received assistance in developing Exome+ and their own lab. However, Illumina's large presence in San Diego has allowed other genomics companies to make use of their services and equipment as well (Fikes,

2018). Human Longevity, Synthetic Genomics, and Edico Genomics are just some of the companies that have been able to flourish due in part to their proximity to Illumina. Perhaps the most impactful way Illumina helps genomics companies succeed is through the Illumina Accelerator, which is run in partnership with Helix. Both Illumina and Helix hope this will play a major role in creating the innovation ecosystem for the consumer genomics industry that they are striving for. As part of the accelerator, experts from Helix work with startups to innovate and develop their product with the ideal outcome of eventually being able to put that product in the Helix store. The available Helix experts have a wide range of specialties, from Next Generation Sequencing to software design to business development. This can help the startups overcome barriers including cost pressures, regulatory and data security requirements, and continually evolving sequencing technologies (Business Wire, 2017). With the accelerator, Helix is not only finding innovative partners to work with, but helping foster them themselves.

## EXAMPLES OF HELIX'S DIVERSE PARTNERS

With Helix's partnerships being formed through a variety sources, it is easy to recognize the broad range of potential for genomic applications when looking further into two very different products they offer: GeneGuide and Dot One. GeneGuide was created by Mayo Clinic, a well-known medical centre focused on education and research. Mayo Clinic is also an investor in Helix. Partnering with a well-known third-party organization can add reliability and higher reputation to genetic health tests, compared to the ambiguous standards of a consumer-based company such as 23andMe. The GeneGuide app provides users with insights into the implications that their genetics have on their health and educates

users about genetics and how to interpret genomic data (*Exhibit* 5). Physicians affiliated with Mayo Clinic can even recommend the service to patients. Additionally, physicians are encouraged to share their genetic reports with their health care providers for informed decision-making (Gallagher, 2018).

Contrasting with this clinical-grade testing from an established company is the startup company Dot One, who create personalized designs based on your genetic code. Founded by Iona Inglesby during her time at University, Dot One uses this DNA information provided by helix to create a variety of items; including socks, tee shirts, scarfs and tote bags; that feature colourations and patterns unique to the user (Inglesby, 2018) (*Exhibit* 6). Inglesby had a passion for fusing science with art and loved that Scottish families often patterned material that could be passed down generations. This led her to the idea for Dot One, which was initially given a 3/10 grade from a course evaluator at her university. After starting to work with Helix, entirely new customer channels in the US opened up for Dot One through assistance in simplifying their business model. Whether a partner is an established organization or an entrepreneur with humble beginnings, Helix has been able to both cut costs and increase market access for them.

## FUNDING & REVENUE

Before they were able to create their world-class sequencing lab, Helix needed funding to bring their idea to life. On August 15, 2015, Helix secured US $100 million in Series A financing from their founding investors, allowing them to launch the company. These investors included Illumina, Mayo Clinic, and LaunchCapital. After years of development, Helix then received US $200 million in Series B Financing in preparation for their initial release of the service to

consumers later that year. Illumina contributed about half of that funding while other major contributors included: Temasek, Sutter Hill Ventures, DFJ Growth, Warburg Pincus, and Kleiner Perkins (Business Wire, 2018). The law firm Cooley advised on both financings (Fikes, 2018).

As of now, Helix has two main sources of revenue. The first is through the sale of their DNA testing kits. Customers can either purchase Helix's DNA Discovery Kit (US $80), which involves no third-party organizations and gives broad, basic information about the user's genetics, or purchase one of the partner products in Helix's store, which will come with Helix's DNA kit. Prices for the partner products are highly variable, but once the testing kit is completed once it does not need to be completed again. It is unclear how much of the price of a product goes to Helix and how much goes to the partner when the testing kit is included, but this is certainly Helix's main way of getting revenue directly from consumers.

The other source of generating revenue is through selling users' data to companies conducting research on genomics. Much like at other DTC genetic testing companies, these transactions tend to bring large amounts amount of revenue in at one time. However, Helix takes a much more secure, controlled approach to this process. Helix user data is only sold to companies partnering with them through products; these companies have been thoroughly evaluated by Helix to ensure their data is being properly used in research. Because data is sold to partners, data will only be shared for users who use that partner's product and have consented to their data being studied. For example, genomic data is sold to National Geographic for research used in their app Geno 2.0. This contrasts with 23andMe, who recently sold all of their user data to GlaxoSmithKline for US $300 million (Brodwin, 2018). The amount of revenue gained by Helix from selling user data has not been publicly disclosed.

## DTC GENETIC TESTING MARKET

DTC genetic testing is a rapidly-growing industry; this growth sets the stage for a swift increase in partnerships with innovative genomic analysis products for Helix in the near future. Genetic testing in general is well established as being profitable, being valued at over $7.8 billion US in 2017 (Mordor Intelligence, 2018). DTC genetic tests, however, have just recently begun to appear as a rapidly growing and profitable market, largely due to the decrease in sequencing costs as technology advances (*Exhibit* 7). The DTC genetic testing market was valued at $117.1 million US in 2017 (Credence Research, 2018), and has been projected to reach $611.2 million US by 2026, with a compound annual growth rate (CAGR) estimated at 19.4% (Credence Research, 2018). North America leads the market with over 45% of the market share; much of the market's value is owed to sharing genome bank data, a trend that is expected to continue throughout the foreseeable future (Credence Research, 2018). With the number of consumers interested in partaking in consumer genomics increasing every year (*Exhibit* 8) and genetic data being of great importance in solving many public health concerns, the DTC genetic testing market looks to surely continue growing.

## CHALLENGES AHEAD

Going forward, there still exists the concern that consumers feel pressure to choose between Helix and other prominent competitors such as 23andMe or Ancestry DNA, as Exome+ is not applicable to those companies' analyses. Competing with these companies, who currently hold a much larger portion of the market than Helix, is the main challenge ahead. One major contributing

factor to Helix's smaller customer segment is their confinement to the United States, as those other services are available globally. Although North America is the largest market for DTC genetic testing, expansion into the worldwide market is an opportunity that is yet to be taken advantage of. But what would international expansion for Helix require? Certainly, regulations on genetic testing are very different around the world. The costs of transporting biological samples internationally and the differences in technological norms are barriers as well. It is possible that Helix could take advantage of worldwide diversity by forming partnerships with genomics companies all over the world, but what kind of expenses would this create? Finding the right approach to international expansion will be key to competing with the larger DTC genetic testing companies.

Additionally, Helix needs to consider what their strategy would be if competition between the large companies results in a polarized market, where customers are split between different tests and the lack of consistency between them causes a rift in consumers' images of DTC genetic testing. Although competition is healthy, would working together create a more accessible, consistent product for everyone? Although the market is clearly growing, should an exit or acquisition plan be made just in case customers dry up or the above effects of competition come to fruition? Whether it is a partnership with other large companies to pool their resources and lower costs for all; or being acquired fully by Illumina or another large genomics company, there are several possible approaches.

Overall, many questions remain about what approach Helix's leadership should take as they look to scale up and compete with the industry's giants.

# Exhibits

**EXHIBIT 1**

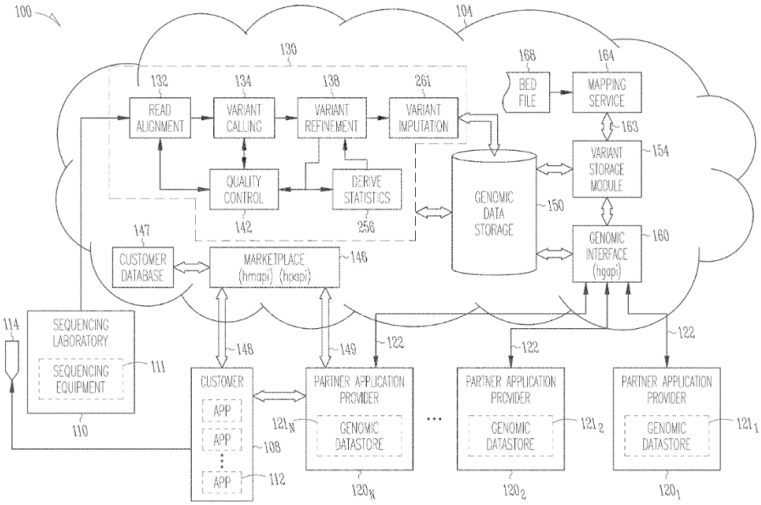
**CATEGORIES OF HELIX STORE PRODUCTS**


Source: https://www.helix.com/pages/store

**EXHIBIT 2**

**PATENT DIAGRAM OF HELIX PLATFORM CONCEPT**

"a high-level architectural view of a system including a genomic services platform in accordance with the disclosure"



Source: United States patent No. US20190026641A1: Genomic services platform supporting multiple application providers

**EXHIBIT 3**

**ILLUMINA'S NON-GAAP INCOME STATEMENT AFTER 2018 FISCAL YEAR**

Shows the decrease in their revenue from Helix since 2016 because of the dilution of their shares, especially as more investors entered during Series B funding in 2018

| | 2016 | | | | | 2017 | | | | | 2018 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (in millions, except per share amounts and %) (a) | Q1 16 | Q2 16 | Q3 16 | Q4 16 | FY 16 | Q1 17 | Q2 17 | Q3 17 | Q4 17 | FY 17 | Q1 18 | Q2 18 | Q3 18 | Q4 18 | FY 18 |
| Revenue | $571.8 | $600.1 | $607.1 | $619.3 | $2,398.4 | $596.2 | $662.4 | $714.0 | $777.7 | $2,752.3 | $782.0 | $830.3 | $853.4 | $866.8 | $3,332.5 |
| Gross profit | 407.4 | 434.3 | 437.1 | 430.4 | 1,709.3 | 397.2 | 443.7 | 491.3 | 551.4 | 1,883.5 | 546.1 | 583.5 | 606.6 | 599.2 | 2,335.4 |
| Research and development expense | 123.9 | 124.5 | 125.8 | 129.9 | 504.1 | 139.5 | 130.4 | 133.7 | 135.0 | 538.6 | 136.7 | 150.7 | 158.7 | 175.9 | 622.0 |
| Selling, general and administrative expense | 147.1 | 146.4 | 137.1 | 144.9 | 575.3 | 153.2 | 166.6 | 165.9 | 172.2 | 658.0 | 179.0 | 196.7 | 196.9 | 212.8 | 785.4 |
| Income from operations | 136.6 | 163.4 | 174.2 | 155.6 | 629.8 | 104.5 | 146.6 | 191.6 | 244.1 | 686.8 | 230.4 | 236.1 | 251.0 | 210.6 | 928.1 |
| Consolidated net income | 103.2 | 123.2 | 132.1 | 110.2 | 468.7 | 81.4 | 113.4 | 152.3 | 201.9 | 549.0 | 203.3 | 203.0 | 215.6 | 184.3 | 806.2 |
| Net loss attributable to noncontrolling interests | 2.4 | 4.0 | 12.0 | 16.2 | 34.6 | 12.8 | 7.9 | 10.9 | 10.2 | 41.8 | 10.7 | 9.5 | 11.2 | 12.5 | 43.9 |
| Net income attributable to Illumina stockholders | 105.5 | 127.2 | 144.1 | 126.4 | 503.2 | 94.2 | 121.3 | 163.3 | 212.1 | 590.8 | 214.0 | 212.5 | 226.8 | 196.8 | 850.1 |
| Diluted EPS attributable to Illumina stockholders | 0.71 | 0.86 | 0.97 | 0.85 | 3.33 | 0.64 | 0.82 | 1.11 | 1.44 | 4.00 | 1.45 | 1.43 | 1.52 | 1.32 | 5.72 |
| Helix and GRAIL dilution (benefit) | 0.06 | 0.08 | 0.07 | 0.08 | 0.36 | 0.07 | 0.05 | 0.07 | 0.06 | 0.25 | (0.04) | 0.03 | 0.05 | 0.05 | 0.09 |
| Tax rate | 25.5% | 25.7% | 24.6% | 28.5% | 26.1% | 24.4% | 25.1% | 21.6% | 18.0% | 21.5% | 12.9% | 15.9% | 17.3% | 16.3% | 15.6% |

*All amounts in tables are rounded to the nearest one hundred thousands, except as otherwise noted. As a result, certain amounts may not recalculate using the rounded amounts provided.*

*(a) 2016 non-GAAP results have been restated to include stock-based compensation in order to conform to current period presentation.*

Source: Illumina: Source Book January 2019

**EXHIBIT 4**

**STATEMENT IN ILLUMINA'S FINANCIAL STATEMENT FOR THE 2018 FISCAL YEAR**

Illumina describes the inclusion of Helix's R&D and SG&A expenses in their own expenses

Research and development (R&D) expenses for fiscal 2018 were $623 million compared to $546 million in the prior year. Excluding restructuring charges, non-GAAP R&D expenses as a percentage of revenue were 18.7%, including 0.9% attributable to Helix. This compares to 19.6% in the prior year period, including 1.0% attributable to Helix and GRAIL.

Selling, general and administrative (SG&A) expenses for fiscal 2018 were $794 million compared to $674 million in the prior year period. Excluding restructuring charges, amortization of acquired intangible assets, and acquisition related expense, non-GAAP SG&A expenses as a percentage of revenue were 23.6%, including 1.3% attributable to Helix. This compares to 23.9% in the prior year period, including 1.7% attributable to Helix and GRAIL.

Source: Press Release: Illumina Reports Financial Results for Fourth Quarter and Fiscal Year 2018

**EXHIBIT 5**

**IMAGE OF GENEGUIDE PRODUCT**

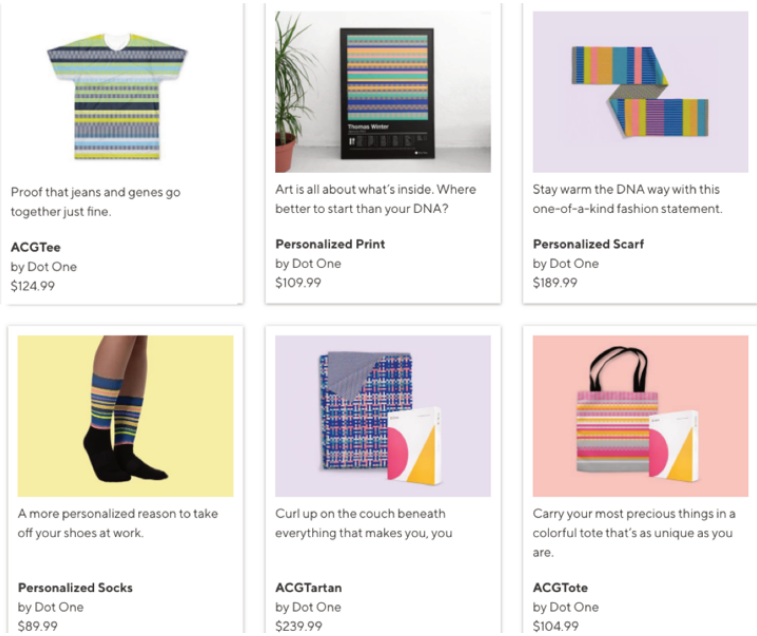
Illustrates components of GeneGuide's products, including the DNA sampling kit from Helix (left) and genetic education tools on desktop (middle) and mobile (right) apps


Source: https://newsnetwork.mayoclinic.org

**EXHIBIT 6**

**DOT ONE PRODUCT SELECTION**

Image of the options available from Dot One on Helix's store

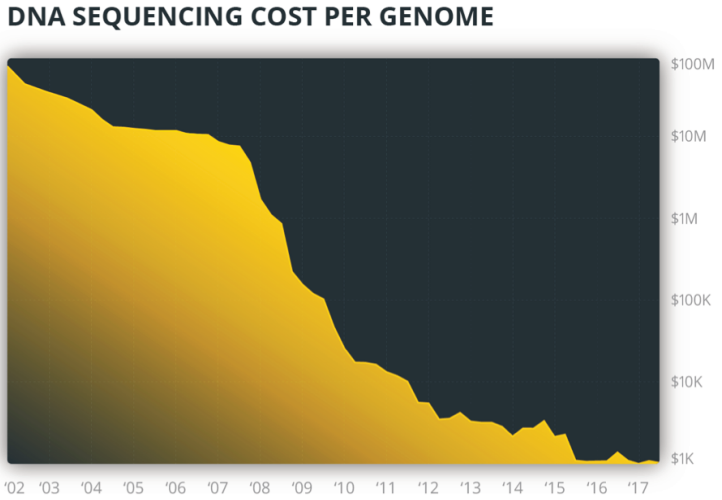



Source: https://www.helix.com/collections/entertainment

**EXHIBIT 7**

**DNA SEQUENCING COST FROM 2002 TO 2017**

Graph illustrating the decrease in sequencing cost per genome over time



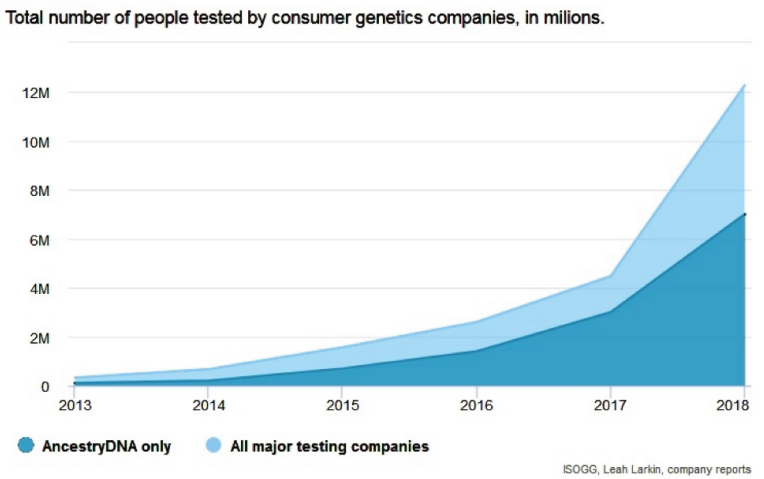

Source: https://cointelegraph.com/news/lifes-code-blockchain-and-the-future-of-genomics

***EXHIBIT 8***

**CONSUMERS OF DTC GENETIC TESTING FROM 2013 TO 2018.**

Graph illustrating the increase in genetic testing amongst worldwide consumers since 2013 (a) and chart showing their growth rates by year. Values in chart are in millions ("All" and "Ancestry" columns) and growth rate per year ("All Rate" and "Ancestry Rate" columns. The year 2017 has been referred to by many as "the year consumer genetics blew up", but this graph makes it clear there was also a large increase in 2015.

a)




b)

| Year | All | Ancestry | All Rate | Ancestry Rate |
|---|---|---|---|---|
| 2013 | 0.33 | 0.11 | - | - |
| 2014 | 0.675 | 0.2 | 2.05 | 1.82 |
| 2015 | 1.57 | 0.7 | 2.33 | 3.50 |
| 2016 | 2.6 | 1.4 | 1.66 | 2.00 |
| 2017 | 4.475 | 3 | 1.72 | 2.14 |
| 2018 | 12.275 | 7 | 2.74 | 2.33 |

Source: http://www.the-burgenland-bunch.org/Newsletter/Newsletter285.htm

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# 47. Medtronic: PETA and Public Pushback

**Medtronic: PETA and Public Pushback**

**By: Cameron Parry**

**BIOT*6610 Individual Case Report**

In the spring of 2005, the world's largest medical device producer, Medtronic, received proposals from the animal rights organization PETA in an effort to minimize the company's use of animals in their medical device testing. Unlike their battles with other companies, PETA was unable to propose that Medtronic completely eliminate the use of animals in testing because there are government regulations that require medical devices undergo a certain amount of animal testing prior to any clinical trials on humans. No clear agreement was made between the two sides, and in 2008 PETA filed another proposal to Medtronic, this time in an attempt to stop the medical device giant from outsourcing its animal testing to countries such as China, which have less stringent animal welfare laws. This, once again, resulted in no concrete agreement. Finally, in 2010 PETA filed another resolution proposal for Medtronic to stop performing tests on live animals, including the insertion of medical devices. Medtronic refused this proposal, and PETA withdrew their resolution proposal. However, the reputation of Medtronic took quite a hit in the eyes of many, especially those who support PETA and their initiatives. Being able to come to resolutions with PETA, along with getting out front on other public relation issues, may be in Medtronic's best interest to repair its reputation in the eyes of the public.

**MEDTRONIC**

Medtronic PLC is a medical device company founded in 1949 by a man named Earl Bakken, originally as a medical device repair shop. Through his business, he met a man named Dr. C. Walton Lillehei, a doctor at the University of Minnesota who was one of the pioneers of open-heart surgery. Lillehei approached Bakken in 1957 after a power outage caused the death of one of his pacemaker-dependent patients and asked Bakken if he had any potential solutions. Bakken, who considered himself quite innovative, ended up developing the first ever battery-powered artificial external pacemaker, which would turn out to be the first revolutionary product developed by Medtronic. Nowadays, Medtronic continues to be operational out of Minneapolis, Minnesota; however, for legal and taxing purposes, their headquarters are stationed in Dublin, Ireland.

Throughout its history, Medtronic has gone through multiple acquisitions, expanding its expertise and product line to grow on an international level. This was best represented by the 2014 purchase of Covidien for $42.9 billion, the largest medical device acquisition ever, which expanded Medtronic's portfolio immensely and has helped continue their excellence across a wide variety of areas. This range of product areas include pacemakers, spinal implants, neuromodulators, as well as having an entire division dedicated to producing high-quality surgical devices. This continued expansion has been reflected by the company's financial success, with Medtronic having a 2018 revenue of $29.95 billion USD. As a company, they have stood by their original mission statement that proclaims they aim:

To contribute to human welfare through application of biomedical engineering to alleviate pain, restore health, and extend life.

**PETA**

People for the Ethical Treatment of Animals (PETA) is a non-profit animal rights organization founded in 1980 and is located in Norfolk,

Virginia. As a whole, PETA has approximately 400 employees and nearly 6.5 million supporters worldwide, generating just under $50 million in revenue in 2017. The organization is famously known for standing up to a multitude of companies, organizations, and governments who they feel are not maintaining or practicing a high standard of animal welfare, whether it be through law, experimentation, or any form of animal cruelty. However, many followers and advocators of PETA feel as though the company doesn't go far enough in their efforts and that their resolution proposals should be much more extreme than they are. Many times, people believe PETA proposes deals for the sake of making deals, rather than attempting to make significant change with their partners.

PETA is known to be very vocal in the public sphere, taking stances on an array of animal rights issues. Some of the areas where PETA directs a great deal of time and effort towards include pet rights (euthanasia, neutering, outdoor pets, etc.), clothing, wildlife conservation, and scientific/industrial testing on animals. Quite often, PETA employees will become shareholders in companies that have some animal rights issues, simply to be able to build relationships with the companies in hopes of coming to some sort of resolution. However, some feel that this may look bad on PETA if they have employees who are shareholders in companies with poor animal rights values that choose not to come to agreements with PETA.

**MEDTRONIC VERSUS PETA**

The battle between Medtronic and PETA began in 2005 when PETA proposed that the medical device giant implement an initiative that they called "Give the Animals 5", where a company replaces five crude or cruel animal experiments with other scientifically-validated, non-animal experiments. This initiative was not meant to eradicate any misbehaviour or poor practices within a company, rather it was seen as a way for companies to start moving in the right direction.

Although, PETA withdrew their proposal to Medtronic, claiming that they were having advanced discussions with Medtronic to develop a partnership that would last beyond a simple initiative.

However, this partnership did not go as well as PETA had anticipated, claiming that Medtronic refused to make significant strides regarding their animal testing practices. This lead to PETA filing another shareholder resolution with Medtronic in 2008, calling for them to stop their outsourcing of experimentation to China where their animal rights laws are almost non-existent. This seemed to have some real negative blowback onto Medtronic in the public's eyes, as PETA made numerous appearances in the press calling out Medtronic, while at the same time essentially giving other companies doing similar things a heads-up that PETA would not turn a blind eye simply because a company moves its testing halfway across the world. Once again, PETA withdrew its shareholders resolution based on the advice given by PETA scientists and advisors, stating that Medtronic would comply with their wishes.

Not surprisingly, Medtronic seemed to sweep their PETA discussions under the rug by not following up or making any substantial progress on significant issues. With these previous resolution proposals not leading to any change, PETA once again went after Medtronic, this time filing a shareholder proposal that Medtronic stop using live animals for experimentation and demonstration for sales purposes. Finally, Medtronic agreed to some terms with PETA, stating that they would being performing feasibility tests to determine whether or not they are able to stop using live animals to test their devices. PETA seemed to be satisfied with this and withdrew the shareholder proposal again. However, the results of Medtronic's feasibility tests were not what PETA hoped, and Medtronic claimed that they would be unable to confirm the safety of their devices without being able to test them on animals first, and

that they will continue to use live animals until other solutions come along.

**CONCLUSIONS**

The five year battle with PETA overall gave Medtronic an extraordinarily large amount of bad press, causing many people to question whether or not it should be acceptable to put the needs of humans above the welfare of living animals. Medtronic spent close to five year skirting around the issues that PETA brought to light, rather than coming forward and making definitive statements in the early going. By finally doing the feasibility tests in 2010, Medtronic was able to save face by claiming they aren't just using animals for their own convenience and benefit, but rather it is for the safety of humans. Although their public battles seem to have calmed down, PETA remains active in their attempt to make progress with Medtronic.

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# 48. ROAD SALT ADDICTION

By: Andrea Campos

***Please note, although problems, information and names mentioned below are real, the story serving as the case scenario is fictional.***

**"There's really no change," ….. "The challenge with salt is it's pretty much invisible. You put it down and it disappears. The more people that are aware there's an environmental impact, the more people will think twice before demanding that level of service from their local store or municipality. Their behaviour impacts the health of the watershed. (Simon, 2017)"**

**Bill Thompson – Integrated watershed management manager**

**Lake Simcoe Region Conservation Authority**

**Barrie, ON. Apr 27, 2017**

Temperatures were finally going up. This was a relief for most Canadians living in southern Ontario who had experienced severe weather this winter too many times for their liking. However, for Mike Walters – Chief Administrative Office for the Lake Simcoe region Conservation authority, this change in the weather could only mean one thing. He soon would need to face once more Craig Morton, the city of Barrie roads manager. This was a meeting he was not particularly eager to have, as it felt repetitive. It was almost like adéjà-vuof winning the battle but losing the war. Once again, the leadership team of the city of Barrie would get together to discuss and approve both budget and purchases for the annual "Winter road maintenance" program.

In the last years, during this meeting, the group had listened to Mike and his team's presentation about the worrisome salinization indicators for the lake and its tributaries, and the potentially devastating consequences this situation could generate if immediate measures were not taken. Year after year, election after election, since the first scientific report was presented (Minister of Public Works and Government Service, 2001), leaders of the region – among them Barrie, Orillia and Infield mayors, had accepted the information. Yes, they were concerned; yes, they understood the problem. Each of them had asked their work units to develop policies to reduce road salts use. Yes, they were on the conservation authority's side. However, Mike and his team could not help but think that what was being done was not enough. Although the amount of road salt per-determined area was slowly decreasing, the truth was that the chloride concentration in the Lake Simcoe watershed was annually increasing around 0.7 milligrams per litre since 1971 (Simon, 2017) (Lake Simcoe Region Conservation Authority , 2016). Effects on the local fauna and flora started to be seen, as the presence of the zebra mussels – invasive marine species (Lake Simcoe Region

Conservation Authority, 2012 ), and negative impacts on insect populations at the lake's tributaries.

Why were implemented actions not working? What should be done then? What points were the first ones to be addressed in the plan for upcoming winters? Would quick adjustments here and there help? Alternatively, would this be the scenario to propose a complete overhaul of the program and go for radical measures?

## *ROAD SALT USE*

It is estimated that around 60 million metric tons of rock salt were employed worldwide in 2016. Main consumption was seen in North America and Europe, and at a much lower level in Asia and South America (Breining, 2017 ). In the United States, salt use on roads to melt ice and snow first started in 1940, using only 150 kilograms per year. Nowadays, US utilization of road salts is around 18 Million metric tons per year (Exhibit 1:), in 26 states – some using much more than others depending on winter severity.

The volume Canada uses varies from year to year depending on winter severity and frequency of major storms (Russell, 2017)., but the numbers in the last decade have been around five million tons per year (Summers & Valleau, 2019 )Toronto spends about 10 million dollars annually in about 140,000 tons (City of Toronto, n.d.), and the city of Montreal follows closely with around 130,000 tons per year. At the Simcoe county the use is calculated to be near to 46,000 tons per year, including in this volume what is used by the county plus what the province uses on highways in the area (Adams, 2019).

Aside from the constant increase in consumption as volume per year statistics show, it is also a lucrative mining business. Multinational companies like Cargill are leaders in the industry (Whitehouse, 2018 ). Due to the extreme weather experienced in

the last decade, municipalities were forced to over-forecast their budget's allowance for winter road maintenance. This increased demand made prices go up. Just in December 2018 prices in Canada were between CAD 140 and CAD 160 /ton, a significant rise from the previous year, when the price was between CAD 90 and CAD 110 /ton (Tumilty, 2018). Moreover, these prices were only for contracted volumes. If municipalities were forced to buy additional volumes outside the contracted ones, it became a seller's game, and price per ton could be twice as much, depending on product availability.

## *NORTH AMERICA VS. EUROPE, WHY THE DISPARITY?*

Europe uses about 8 million tons per year. The size of the land and the snowfall amount is comparable to that one in North America; however, when comparing the areas strongly impacted by winter, Europe has twice the population of North America. So why does North America use three times as much salt? Several reasons need to be considered. First, in Europe public transportation is prioritized over private vehicles. Thus, de-icing efforts are focused on clearing the railways and pathways that the majority of the population employs for mobility. In North America, it is the standard for each household to own several vehicles with one or two passengers per vehicle. Also, although municipalities like Barrie had made an effort to reduce the rate of use per squared area, the rapid population growth and physical expansion of cities seen in North America, has required the construction of new roads, and hence, the addition of new square footage that will need to be clean. Therefore, efforts to reduce total volume used are offset when cities grow, and new roads are added (Simon, Busy year pushes Barrie's winter maintenance work more than $900K over budget, 2018).

Environmental regulations are stricter in the European Union, as the organism has established official limits to be met when applying salt to roads (MaxiSALT, 2017). In North America, because conditions and winter severity are different for each location, policies are more a recommendation, a guidance that federal governments hope the local ones will translate and adjust to the particularities of their area.

Also, in North America, society became spoiled. Keeping the roads clear "for business as usual" functioning for economic reasons, became the standard, and individual's expectations grew accordingly, not only for the main centres of activity but for all neighbourhoods' roads and sidewalks.

A common misconception is that for it to work the salt needs to be "rocky", in other words, "the more salt, the safer (Simon, Busy year pushes Barrie's winter maintenance work more than $900K over budget, 2018)". The truth is that it is the sodium chloride molecule mixed in solution with the water molecules what makes it chemically happen. So, the more and the sooner the salt molecule is dispersed in water, the better. Apparently for some people, a community's safety is more related to the ice and snow melting concept than to looking for some mechanisms to increase traction. This, on top of the apathy against the time and energy-consuming good old shovelling is about.

Last but not least, there is the fear North American public feels regarding the slip & fall laws (Russell, 2017). For business owners, the potential liability is always around, and with the average settlement usually costing over $100,000 US per case, over-salting represents a cheaper way to minimize the risks.

Lately, a new factor has come into play, with climate change and global warming, more frequent and/or severe storms are now being seen in areas with no precedent, which triggers panic. Southern states in the US have now to include winter road management programs as an item, and not surprisingly, have a higher chance to overreact, due to their unfamiliarity with managing winter conditions.

## *WHY ROAD SALT IS USED*

Road salts are used to secure mobility throughout the winter season. Salts help to melt ice and snow at a much faster pace than the natural one. It works because the Sodium Chloride lowers the water's freezing point – which prevents accumulation, and thus, ice formation. The ions from the sodium chloride charged atoms squeeze in between the water molecules pushing them away, melting the forming ice into a liquid phase. This reaction is known technically as the freezing point depression.

Additionally, rock salt also provides some level of traction. It is a safety measure, statistics have shown that traffic accidents are reduced by 85% in general, and 93% decrease in accidents right after de-icing. In 2014 a study from the American Highway Users Alliance concluded that clear roads are the most crucial factor for winter driving, even more than visibility (Mohn, 2014).

However, it also allows mobility to continue doing business as usual at a relative "low cost", which is valued in millions of dollars as economy and society keep functioning normally (Plumer, 2015). In areas like Lake Simcoe where tourism represents a vital portion of the economic activities, safety for their visitors is prioritized to keep the region attractive, with good intentions but ignoring the potential consequences in the long run (Kelly, Findlay, & Weathers, 2019).

## *WHAT IS ROAD SALT*

Road salt, also known as "rock salt" is course, ungrounded table salt. It is the same molecule – NaCl, 40% sodium and 60 % chloride ( NH Department of Environmental Services, 2017). It is mined, with vast reserves in Michigan, Kansas, Ohio in the US (Plumer, 2015); or it

can be dried from salty water bodies, as it is done in South America and Asia.

When looking at the components, chemically speaking, the Sodium element has a strong ionic charge that can affect its surrounding area due to ion exchange. Chloride as an element is highly soluble and mobile, and there is not a protocol to separate it from water once it gets in solution with it.

Aside from the two main ones, usually an anticaking agent, like Ferrocyanide, is added by producers, so the product does not become hard stone when humidity is high. Finally, because of its natural origins from mines, it is not unusual for road salts to contain a small percentage of impurities, and many of these turn out to be heavy metals. These other components could represent up to 5% of the salt composition ( NH Department of Environmental Services, 2017).

## *THE NEGATIVE EFFECTS*

Once salt dissolves, the sodium and chloride elements make it separately to the environment, in the runoff from rain, melting snow and ice and storm drains (Exhibit 2). Most of the road salt used every season finds its way back to nature and affects soil, sediments, water streams and groundwater bodies (Kelly, Findlay, & Weathers, 2019). While normal chloride levels in natural water bodies are between 1 to 10 mg/L, during winter and spring levels could surpass 800 mg/L ( NH Department of Environmental Services, 2017). At this rate, by 2050 salt concentration maximum limit for aquatic life and drinkable water will be exceeded (Summers & Valleau, 2019 ). Measurements were taken at the Orillia side of the Simcoe Lake in June of 2014 and the result of 46.3 mg/litre was alarming when compared to the 29.8 mg/litre measured back in 2000 (Adams, 2019)(Exhibit 3).

Chloride is highly persistent and cannot be filtered by soil, so it freely continues on its way to waterways. There is no protocol to remove it from water, so chloride permanently stays in solution and accumulates. Proof of how easy waterways are contaminated is one of the conclusions from the US Geological Survey: chloride levels were 84% higher in urban streams during winter time (Plumer, 2015). Sodium as a free element can alter the soil chemistry, causing an imbalance in the nutrients that are retained or released from the soil to the adjacent water bodies, thus changing the ecosystems' dynamics. Anticaking agents like ferrocyanide can release toxic cyanide ions once exposed to sunlight. Furthermore, toxic heavy metals contained as regular impurities included lead, chromium and cadmium ( NH Department of Environmental Services, 2017).

There are hidden costs attributed to road salt use. Just the corrosion damage to infrastructure and vehicles in the US is estimated to be over $16 billion/year (Plumer, 2015) ( NH Department of Environmental Services, 2017). Also, it is important to note that road salts do not always work, as it is no longer effective when temperatures go below -10oC. In those cases, it is necessary to use other salts that are more expensive and equally harmful like calcium chloride or magnesium chloride (Plumer, 2015)(Exhibit 4). This last one is around three times the cost of the common road salt (Russell, 2017).

Some practices improve the salt efficacy, like mixing it with sand, which acts as an effective abrasive until temperature drops below -18oC. Nevertheless, sand and other aggregates employed also have adverse effects, like much higher clean-up costs once the season is over (Russell, 2017).

Pre-salting before the storms helps as the layer underneath the snow prevents ice from forming and sticking to the roads. For this practice to have a significant impact, it is necessary to start from an accurate forecast, that provides a very close estimate for the time

a storm will begin at. If precise, this practice could reduce salt use between forty-one and seventy-five percent.

Since almost half of the road salt is spread by the local governments and private entities, and not by the federal or provincial authorities, education has become another strategy to decrease salt use (Russell, 2017). Parking lots and residential areas do not have guidelines or protocols, and along with roads, are the most significant contributors of road salt application (Exhibit 5). Governments like Barrie's continue to make an effort providing training and certifying contractors (Simon, Busy year pushes Barrie's winter maintenance work more than $900K over budget, 2018).

## *EFFECTS ON WILDLIFE*

In general, the entire ecosystem in a waterbody can be affected by salt accumulation, which usually happens at the bottom of it. A dead zone is created due to the lack of natural water turnover. This last is driven by the water temperature – which is affected by salt concentration. If there is less circulation of water, there is no aeration and levels of oxygenation fall (Kelly, Findlay, & Weathers, 2019).

Aquatic species living in these water bodies are among the most affected organisms due to road salt abuse. Fish, insects, amphibians and invertebrates could see their food sources compromised because of the chemical imbalance of their habitat, and consequently disturb their ability to thrive. This impacts their survival chances as well as their growth and reproduction cycles ( NH Department of Environmental Services, 2017).

High chloride levels are particularly harmful to amphibians, as it affects their skin permeability and fluids exchange thru it. Also, sex reversals due to high concentrations of road salts have been seen

in frog populations (Canadian Wildlife Health Cooperative regional centre., 2018).

Adjacent vegetation to roads is also impacted. Foliage and grass suffer osmotic imbalance once the salt from vehicles splashes and reaches them. Symptoms are very similar to those experienced during draught season: dehydration, foliar and root damage, and poor germination and flowering ability ( NH Department of Environmental Services, 2017).

An additional problem is that it increases the road kill events incidence, as salts adhered roads and vehicles attract wildlife like moose and elks interested on an easy way to suffice their natural need for salts (Plumer, 2015). Bird populations are affected as well, when they mistake the rocks for seeds and other foods, causing toxicosis and damaging tract intestinal tissue ( NH Department of Environmental Services, 2017).

In general, biodiversity is affected as only species tolerant to the high concentration of Sodium and Chloride would be able to survive. Even worse, these might not be necessarily robust local populations. Instead, this inhospitable environment could be the invitation for invasive species to take the opportunity and colonize areas where local ones were defeated. Soil fertility and permeability are altered, as high sodium concentrations cause nutrient depletion and eventually erosion ( NH Department of Environmental Services, 2017).

## *EFFECTS ON HUMANS & SOCIETY*

A portion of the population was probably not interested in prioritizing the effects on wildlife and environment over the road safety benefits the use of salts had shown in several studies. However, they might have changed their mind when they saw that what was at risk was their community. General population, worried about their

health and trying to lower their sodium intake, were at risk of seen their drinking water sources compromised. Incidentally, this situation could be potentially fatal for patients forced to follow strict low-sodium diets. High sodium intake increases the chances of stroke, hypertension, cardiovascular and kidney disease ( NH Department of Environmental Services, 2017).

For animal lovers and pet owners, road salt poses two risks. First, pets could accidentally eat the crystals directly or consume them by linking their paws or drinking water from the street. Either way, road salt acts as a poison causing symptoms like drooling, vomiting, disorientation and even cardiac arrest or death. Second, pets 'paws are exposed to this salt, what could eventually turn into painful cracks, irritation and infection ( NH Department of Environmental Services, 2017).

Sodium chloride is highly corrosive and increases water conductivity. This damages metal structures, including vehicles and public infrastructures like bridges and concrete buildings. Rebar corrosion has been pointed out as one of the causes for the damages in the Champlain bridge in Montreal and the Gardiner Expressway in Toronto (Hopper, 2018).

## *OTHER ALTERNATIVES*

Beet juice, a waste product from sugar beet processing, is being already used in both Canada and the US, thanks to its competitive cost and multiple benefits. If applied before snowfall, not only keeps salt effect down to -30oC but also make it will stick to the road surface; and a thin layer of beet juice itself prevents ice from attaching to the surfaceof the road (Russell, 2017). Also, it has been claimed that beet juice naturally has anti-corrosive properties (American Physiological Society, 2018).

Cheese and pickle brines are being used in Wisconsin, where they are readily available by-products from local dairies. Still, the reason why they work is that they naturally have chloride as one of its components. So, their use does not really prevent chloride contamination, but at least contributes to the circular economy, when otherwise these brines would have been considered waste. The utilization of Garlic Salt as a de-icer happened more like a happy accident when a local spice factory in Iowa found in 2009 a surplus of 18,000 pounds. It was donated to the city, that used it to treat local roads that winter, giving its streets a garlicky aroma (Russell, 2017).

The main positive aspect of these alternative solutions is the fact that they are all biodegradable by-products. Although these materials would be considered waste from industrial processes, there is still an associated cost, as formula needs to be adjusted so they can be used as de-icers. Although more expensive than regular road salt, these brines are less toxic and less corrosive. However, they do not replace salt entirely, only reduce the amount required and help it to stick to the ground (instead of being quickly washed off from the roads)

Nonetheless, there are some challenges associated that need to be kept in mind when considering the employment of these agro-sourced de-icers. First, there are some issues related to public perception, like the smells that emanate from them once applied on to the roads. For example, it has been said the beet juice smells like old coffee or soy sauce.

Another potential issue is if they are cost-competitive. Organic liquids are difficult to store and can only be used in customized spraying vehicles, which adds up to the final price. In most cases, when going with one of these products, municipal equipment would need to be retrofitted, or new purchases would be necessary. So, is it budget-wise to make such an expense? Should municipalities temporarily commit to cheaper, short-term alternatives, in hopes of buying some time to wait for researchers to come up with a definitive solution? The above needs to be considered on top of the additional

costs generated when these "natural" products require a formulation adjustment in order to be usable as a de-icer.

Maybe the most negative secondary effect of implementing these biodegradable alternatives is the risk of adding carbohydrates and protein to water bodies (Kelly, Findlay, & Weathers, 2019). Uncontrolled addition of organic material could stimulate fermentation and affect the local ecosystem equilibrium.

Beet juice as a de-icer is considered one of the eco-friendliest options currently available. Unfortunately, a recent study revealed that it could be harmful to certain freshwater aquatic species. Mayflies nymphs have been pointed as an organism that can indicate pollution levels, and a study conducted by York University demonstrated that they retained higher salt levels in their bloodstream when exposed to beet juice de-icing agent (American Physiological Society, 2018). This was the possible ecause for nymphs in this study to retain more fluid and potentially have organ functions compromised. Additional studies will be required to determine if a high concentration of potassium usually present in beet juice de-icers is the culprit. The main lesson here is that a product cannot be labelled as absolutely environmentally friendly, most likely not all probable positive and negative interactions with the surrounding environment can be foreseen.

## *ecoTRACTION*™

A promising Canadian alternative came to light back in 2008, as a sales pitch in the Dragon's Den show. EcoTractionTMis a volcanic-based material that can absorb more than 50% of its volume (Earth Innovations Inc., 2012). The resulting structure is entrenched on the ice surface and produces a sandpaper effect. Manufacturers claim

for it to be the only genuinely eco-friendly alternative. Even better, the claim is extremely cost-competitive, being 40% cheaper when compared to sand and 600% cheaper vs. other de-icers. Its technical properties make it highly efficient, providing better traction than salt, allowing it to work event at temperatures close to -50oC and with an impressive yield – one cup for a 144 square feet area.

So why hasn't EcoTractionTMbeen declared as the definitive solution? For several reasons. First, this is a zeolite mineral, with an undefined molecular structure. So far only a few mines have been identified to produce this particular grade. Also, only one company – Earth Innovation has exclusive distribution rights in North America. Thus, do governments want to depend on one material with limited suppliers and sources? Besides, consumers are somehow confused by its mechanism of action: it is not a de-icer; thus, it will not melt ice or snow. The way it works is by creating a non-slippery surface, offering maximum traction.

## *PATH FORWARD*

The scientific community is trying to find an alternative solution (Plumer, 2015). One by itself might not be the definitive answer to replace once and for all the use of road salts. Does a combination of technical approaches offer a solution in the medium term? Maybe…

For example, Professor Xianming Shi at Washington State University is currently working on developing smart road surfaces that could trigger action only when ice is detected on the pavement. His team is also working on smart snowplows that could respond with customized solutions depending on the weather conditions. A solution with much potential, in the long run, is the invention of

solar-powered highways that could absorb heat from the pavement and at the same time could generate electricity to melt ice and snow, and have a potential surplus to be used as a clean electricity source for surrounding buildings. Very promising options, but not for the short term, and also highly costly when compared to the current methods.

## *CONCLUSION*

There are several alternatives currently available for road salt, and none of them is the coveted solution to the problem. Making a decision has turned into a balancing act for regional and local governments and environmental authorities. It is not as simple as condemning the use of road salts, since there are some benefits recognized to their use. What should be prioritized and to what degree? Public safety and winter mobility? Local economies and regional budgets? Is there a reliable estimate for environmental costs, benefits and damages associated to each of these options? What would be the most effective approach?

# EXHIBITS

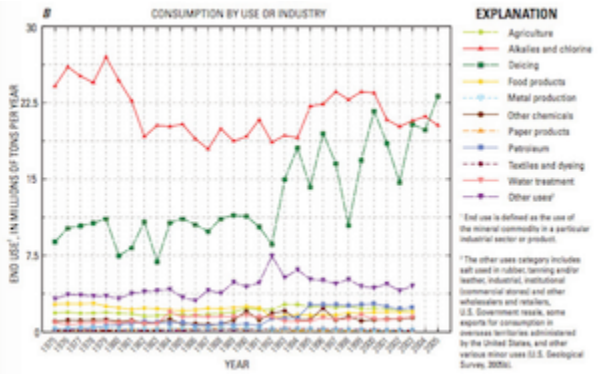


*Exhibit 1: Salt consumption in the US by use or industry from 1975 to 2005 (U.S. Geological Survey) (Plumer, 2015).*

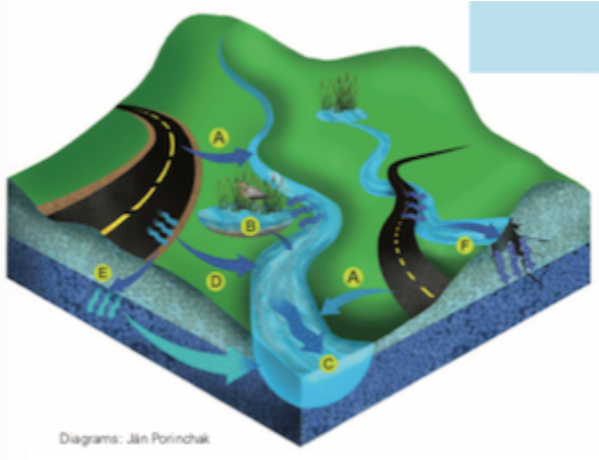


*Exhibit 2: Pathways by which road salts find their way to the environment: (A) seasonal streams, (B) ponds and wetlands, (C) rivers, (D) soil, (E) groundwater, (F) road fractures (Kelly, Findlay, & Weathers, 2019).*

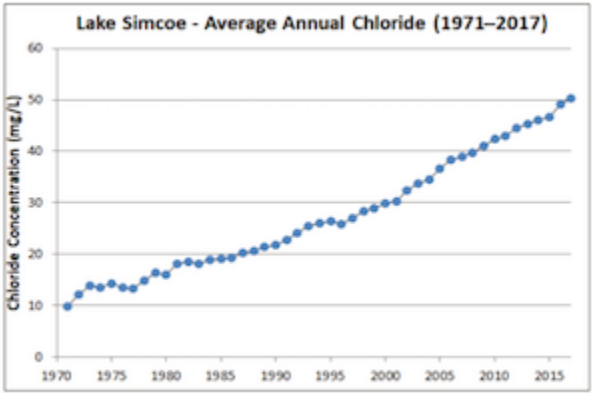


*Exhibit 3: Chloride concentration in Lake Simcoe (Lake Simcoe Region Conservation Authority , 2016).*

| Product | Relative Direct Cost | Effective Lower Limit (degrees F) | Corrosive? | Aquatic Toxicity | Other Environmental Impacts |
|---|---|---|---|---|---|
| Road Salt or Rock Salt | Low | 15 | Yes | Moderate | Roadside tree damage |
| Potassium Chloride | Moderate | 12 | Yes | High | Potassium fertilization |
| Magnesium Chloride | Moderate | 5 | Yes | High | Magnesium addition to soil |
| Calcium Chloride | Moderate | -25 | Very | Moderate | Calcium addition to soil |
| CMA - Calcium Magnesium Acetate | High | -17 | No | Indirect | Decreased aquatic oxygen |
| Potassium Acetate | High | -15 | No | Indirect | Decreased aquatic oxygen |
| Sand | Low | | No | Indirect | Sedimentation |

*Exhibit 4: Comparison of different chemical products currently available as an alternative for Sodium Chloride (Kelly, Findlay, & Weathers, 2019).*

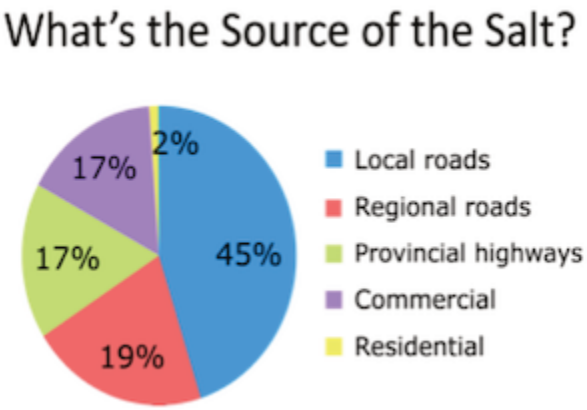


*Exhibit 5: Distribution of road salt application by source (Lake Simcoe Region Conservation Authority , 2016).*

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