

A STRATEGIC ANALYSIS OF POTENTIAL NEW MARKET OPPORTUNITIES FOR PLATFORM X OF FIRM Y

by

Sanja Tarailo

B.Sc. Integrated Life Sciences, University of British Columbia, 2005

PROJECT SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

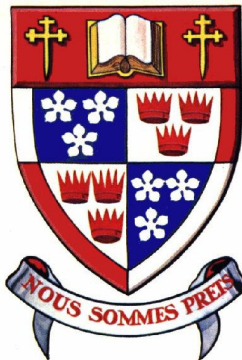
MASTER OF BUSINESS ADMINISTRATION

In the Faculty
of
Business Administration

© Sanja Tarailo

SIMON FRASER UNIVERSITY

Summer 2010



All rights reserved. However, in accordance with the *Copyright Act of Canada*, this work may be reproduced, without authorization, under the conditions for *Fair Dealing*. Therefore, limited reproduction of this work for the purposes of private study, research, criticism, review and news reporting is likely to be in accordance with the law, particularly if cited appropriately.

Approval

Name: Sanja Tarailo

Degree: Master of Business Administration

Title of Project: A STRATEGIC ANALYSIS OF POTENTIAL NEW
MARKET OPPORTUNITIES FOR PLATFORM X
OF FIRM Y

Supervisory Committee:

Dr. Aidan Vining
Senior Supervisor
CNABS Professor of Business and Government Relations

Dr. Rick Colbourne
Second Reader
Executive Director, Learning Strategies Group; Adjunct
Professor

Date Approved:



FACULTY OF BUSINESS ADMINISTRATION

Partial Copyright License

I hereby grant to Simon Fraser Faculty of Business the right to lend my thesis, project or extended essay[s] (title[s] below) to users of the Simon Fraser University Faculty of Business Library, and to make partial or single copies only for such users or in response to a request from the library of any other university, or other educational institution, on its own behalf or for one of its users.

I further grant permission to Simon Fraser University Faculty of Business to keep or make a digital copy for posting to a faculty website. I agree that SFU may, without changing the content, translate if technically possible, my thesis/project or extended essays to any medium or format for the purpose of preservation of the digital work.

I further agree that permission for multiple copying of this work for scholarly purposes may be granted by me or the Associate Dean of Graduate Programs, Faculty of Business. It is understood that copying, publication or public performance of this work for financial gain shall not be allowed without my written permission.

While licensing SFU to permit the above uses, I retain full copyright in my thesis, project or extended essays, including the right to change the work for subsequent purposes, including editing and publishing the work in whole or in part, and licensing other parties as I may desire.

Title of Thesis/Project/Extended Essays:

A Strategic Analysis of Potential New Market Opportunities for Platform X of Firm Y

Author's name

and signature: Sanja Tarailo

Date signed: _____

Abstract

Firm Y is a biopharmaceutical firm specializing in the newly emerging business sector of RNAi Therapeutics. Firm Y is one of a few firms aspiring to bring this potential new class of human therapeutics to the market. Currently, the firm has a well-established RNAi therapeutics delivery platform, manufacturing capabilities, a stream of strategic partnerships, and development stage products in its pipeline. Firm Y wants to expand its product pipeline to give it a sustainable competitive advantage in RNAi therapeutics and ensure long-term success in its strategy to develop important new human therapeutics.

The purpose of this strategic analysis is to identify new market opportunities for Firm Y for expansion of its product pipeline. The analysis is based on the company's core competency of RNAi product delivery to the liver using its proprietary platform, PLATFORM X. First, analyses were conducted on the external industry environment and Firm Y's internal capabilities and situation. Second, new market opportunities were identified and assessed. Third, a number of criteria were used to conduct a comprehensive evaluation of potential new markets for Firm Y. This evaluation was based on scientific and business feasibility specific to Firm Y.

The results of this strategic analysis indicate that Firm Y should expand its product pipeline in a liver diseases area. The analysis further suggests that the expansion should be in the area of infectious diseases. The opportunities of interest for Firm Y within the liver diseases are Hepatitis B and Hepatitis C. The analysis also indicates Hepatocellular Carcinoma as a good next opportunity. Overall, with expansion of its product pipeline, Firm Y will show long-term growth potential for its shareholders and provide increased confidence in its ability to continue as a successful firm.

Dedication

To My Dearest Parents!

My Words Can Never Express Your Unconditional Love And Support. Thank You!

To My Dearest Sister!

Acknowledgements

Thanks To:

All the wonderful faculty and staff at the SFU Segal Graduate School of Business, the 2008 MOT MBA Cohort, Ann Rose, Phil Hieter, MSFHR, Ivana Vranić, Anne Laird, Sharon Hummel, Melissa McCrae, Michelle Sloper, Sharan Girn, Anjali Bal, Viren Thaker, Kevin McLeod, Gordon Elder, Bruce Schmidt, Colleen Collins, Ian McCarthy, Gervase Bushe, Malcolm Kendall and many more!

Thanks To:

Firm Y and its management team for giving me the opportunity to work on this project.

Special Thanks To:

Nana Collett for her knowledge and support provided throughout this project.

Dr. Aidan Vining and Dr. Rick Colbourne for their help and support throughout this project.

Very special thanks to my supervisor Dr. Aidan Vining. This project could have not been completed without your extensive patience, guidance and mentorship. Aidan, your tremendous help will always be remembered and greatly appreciated! Thank You!!!

Table of Contents

Approval.....	ii
Abstract	iv
Dedication	v
Acknowledgements	vi
Table of Contents	vii
List of Figures	x
List of Tables.....	xi
Glossary.....	xii
Chapter 1: INTRODUCTION	1
1.1 Purpose of the Analysis.....	1
1.2 Outline of the Analysis.....	2
Chapter 2: AN ANALYSIS OF FIRM Y’S EXTERNAL ENVIRONMENT	3
2.1 An Introduction to Firm Y’s External Environment	3
2.2 The Industry Group: An Analysis of the Global Pharmaceutical, Biotechnology and Life Sciences (GPBLS) Industry.....	3
2.3 The Biotechnology Sector: An Important Source of Innovation	5
2.4 The Changing Biotechnology Business Models	7
2.4.1 An Introduction to Changing Business Models	7
2.4.2 Product Business Model.....	9
2.4.3 Platform Business Model	10
2.4.4 Hybrid Business Model.....	10
2.4.5 Vertical Integration Business Model.....	11
2.4.6 Adding Value via Partnerships.....	11
2.4.7 Summary: From Business Models to the Value Chain	12
2.5 The Value Chain: The Drug Development Process (DDP).....	13
2.5.1 An Introduction to the Drug Development Process	13
2.5.2 Regulatory Aspects of the Drug Development Process	13
2.5.3 Main Stages in the DDP	14
2.5.4 A Closer Look: A Product’s Journey from Research to Development to Market.....	15
2.5.5 Summary: From the DDP to a New Class of Therapeutics.....	18
2.6 RNAi Therapeutics: A Potential New Class of Therapeutics	19
2.6.1 An Introduction to RNAi Therapeutics.....	19
2.6.2 Different Classes of Human Therapeutics	19
2.6.3 A Definition of the Industry Sector in Which Firm Y Specializes	20
2.6.4 An Overview of the RNAi Therapeutics Sector.....	20
2.6.5 An Analysis of the Potential of RNAi Therapeutics	21
2.6.6 Competitive Landscape of the RNAi Therapeutics Sector	24

2.6.7	RNAi Therapeutics Sector Competitive Analysis.....	29
2.6.8	The RNAi Therapeutics Sector Shows Great Promise.....	33
2.7	Summary: From the External Environment to Firm Y	33
Chapter 3: AN INTERNAL ANALYSIS OF FIRM Y		34
3.1	An Introduction to Firm Y	34
3.2	Firm Y's Organizational Capabilities	34
3.2.1	Firm Y's Resources.....	34
3.2.2	Firm Y's Capabilities	37
3.3	Summary: Firm Y Has Solid Organizational Capabilities	37
Chapter 4: FIRM Y NEEDS NEW PRODUCTS IN ITS PIPELINE TO SHOWCASE LONG TERM GROWTH POTENTIAL.....		38
Chapter 5: THE APPROACH TO THE IDENTIFICATION AND EVALUATION OF NEW MARKET OPPORTUNITIES FOR FIRM Y		40
5.1	An Introduction to the Identification of New Product Opportunities for PLATFORM X	40
5.2	The Scope: Identification of New Indications for PLATFORM X.....	40
5.3	The Methodology: From Genes to Potential Indications for PLATFORM X	41
5.4	Summary: From Identification to Analysis of Potential Identifications for PLATFORM X	45
Chapter 6: A COMMERCIAL POTENTIAL ANALYSIS OF NEWLY IDENTIFIED INDICATIONS FOR FIRM Y		46
6.1	Introduction: Business Feasibility of New Market Opportunities.....	46
6.2	The Liver Diseases Group: HBV/Liver Fibrosis/Hepatocellular Carcinoma (HCC).....	47
6.2.1	An Introduction to Liver Diseases	47
6.2.2	Healthcare Costs for Liver Diseases in the US	49
6.2.3	Hepatitis B (HBV)	50
6.2.4	Liver Fibrosis	53
6.2.5	Liver Cancer and Hepatocellular Carcinoma (HCC)	54
6.3	The Liver-Associated Group: Diabetes/Cardiovascular Diseases (Metabolic Syndrome).....	59
6.3.1	Metabolic Syndrome in Relation to Diabetes and CVDs.....	59
6.3.2	Diabetes.....	59
6.3.3	Cardiovascular Diseases (CVDs).....	61
6.4	Summary: From A Commercial Potential to Strategic Options for Firm Y	63
Chapter 7: A COMPREHENSIVE EVALUATION OF THE STRATEGIC OPTIONS FOR FIRM Y		65
7.1.1	The First Strategic Option: Focus on the Current Product Pipeline.....	65
7.1.2	The Second Strategic Option: Expanding the Product Pipeline by Focusing on the Liver Diseases Group	65
7.1.3	The Third Strategic Option: Expanding the Product Pipeline by Focusing on the Liver-Associated Group	68
7.1.4	The Fourth Strategic Option: Searching Beyond the Liver.....	71
7.2	An Evaluation of Firm Y's Strategic Options	71

7.2.1	A Summary of the Results of the Evaluation of Potential New Markets for Firm Y	73
Chapter 8: RECOMMENDATIONS FOR FIRM Y.....		75
8.1	Moving Forward With the Second Strategic Option.....	75
8.2	Benefits of Focusing on the Liver Diseases Group.....	75
8.2.1	Diversification of Risk With New Products.....	75
8.2.2	In Line With the Current Partnerships	76
8.2.3	Starting With HBV.....	76
8.2.4	Summary: The Second Strategic Option is a Good Fit for Firm Y.....	77
8.2.5	Challenges and Risks Moving Forward With Liver Diseases.....	78
8.3	General Recommendations Moving Forward	79
BIBLIOGRAPHY		81

List of Figures

Figure 1: Business Models and Supply Chain	9
Figure 2: The Standard Drug Development Process (DDP) in the US	14
Figure 3: The Competitive Analysis of the RNAi Therapeutics Sector.....	30
Figure 4: Liver Disease Progression from Inflammation to Liver Failure.....	47

List of Tables

Table 1: Evidence for RNAi therapeutics Proof-of-Concept	24
Table 2: A List of Scientific Feasibility Criteria	41
Table 3: A List of Business Feasibility Criteria	43
Table 4: A List of Corporate Criteria Specific for Firm Y	44
Table 5: A Summary of Treatments for Chronic HBV Infection.....	51
Table 6: HCC Profile Identified in a 15 Year Long Study in the US.....	56
Table 7: Prevalence, Incidence and Mortality of Major CVDs.....	62
Table 8: A Comprehensive Evaluation of Strategic Options for Firm Y	72

Glossary

DNA – stands for deoxyribonucleic acid; it is a molecule that makes up genes; it consists of nucleotides

EFFICACY – refers to the therapeutic effect of medicines in treating the intended disease

EFFECTIVENESS – a term referring to both safety and efficacy of the therapeutics

GENE – hereditary unit that consists of nucleic acids that can be DNA or RNA; it is part of a genome, organism's hereditary material

NUCLEIC ACIDS – molecules made of nucleotides

NUCLEOTIDE – building blocks of DNA and RNA; there are five of them: three common to both DNA and RNA (adenine – A, cytosine - C and guanine – G) and one specific to DNA (thymine – T), and one specific to RNA (uracil – U)

OLIGONUCLEOTIDE – a short nucleic acid molecule consisting of twenty or less nucleotides; oligonucleotides form basis for RNAi therapeutics

RNA – stands for ribonucleic acid; a biological molecule crucial for the protein synthesis; it consists of nucleotides

RNAi therapeutics – for this analysis refers to a potential class of human therapeutics

RNAi Therapeutics – refers to the RNAi Therapeutics sector within the biotechnology sector

SAFETY – how safe therapeutics is for patients

siRNA – small interfering RNA, a one type of oligonucleotides, it is approximately twenty nucleotides in length; it is a specific sequence corresponding to a target gene; results in triggering a mechanism to “silence” specific gene that results in no or reduced amount of protein made

Chapter 1: INTRODUCTION

1.1 Purpose of the Analysis

Firm Y is a biopharmaceutical firm that specializes in the delivery and development of ribonucleic acid interference (RNAi) therapeutics. Firm Y has two lines of business: (1) RNAi delivery technology, and (2) product development. PLATFORM X is a leading delivery technology to deliver RNAi therapeutics to specific target sites within the body. Currently, Firm Y has a couple of development stage products in the product pipeline. Firm Y is publicly traded on the TSX.

Firm Y has numerous collaborations with leading pharmaceutical firms. These collaborations allow it to maximize the potential of PLATFORM X. Firm Y's partnering goal is to help its collaborators develop successful product candidates that utilize the PLATFORM X. This line of business has allowed Firm Y to generate revenues that cover its operational costs and allow it to pursue its own drug development program.

In order to grow and succeed in returning value to its shareholders, Firm Y would like to expand its internal product pipeline. The firm needs to identify new market opportunities in order to find the most profitable opportunities that build on its current core competencies. The purpose of this strategic analysis is to identify and evaluate new market opportunities for Firm Y. Recommendations for the best new market opportunities will be provided, considering the firm's capabilities and potential future strategies for PLATFORM X.

1.2 Outline of the Analysis

To reach a final set of recommendations on the strategic market opportunities for Firm Y, first, I analyze the external environment in which Firm Y operates. Second, I analyze the organizational capabilities of Firm Y. Third, I describe the approach and methodology that led to identification of new potential markets for this analysis. Fourth, I provide information and analysis concerning the newly identified market opportunities specific to Firm Y. Finally, I conclude with a complete evaluation of potential new markets and a set of recommendations for Firm Y.

Chapter 2: AN ANALYSIS OF FIRM Y'S EXTERNAL ENVIRONMENT

2.1 An Introduction to Firm Y's External Environment

In this chapter, I analyze the external environment in which Firm Y operates. I start with a broader industry group that consists of the Global Pharmaceuticals, Biotechnology and related Life Sciences industry (Datamonitor, 2010a). I narrow in on the biotechnology sector within the broader industry group. Next, I look at the business models and supply chain relevant to Firm Y. First, I discuss the emerging business models of the firms within Firm Y's competitive environment. Second, I discuss Firm Y's value chain, the drug development process (DDP). Then I focus on a specific sector within Biotechnology, RNAi Therapeutics. This sector is still embryonic and shows great promise for providing breakthroughs for treatment of human disease. Firm Y specializes in this sector. For the RNAi Therapeutics sector, I use the ``Five Forces Model`` (Porter, 2008) to analyze the competitive landscape.

2.2 The Industry Group: An Analysis of the Global Pharmaceutical, Biotechnology and Life Sciences (GPBLS) Industry

In this section, I analyze the broader industry group using the Datamonitor definition. The industry group includes the Global Pharmaceuticals, Biotechnology and Life Sciences industry (Datamonitor, 2010a). From now on, I refer to it as "the industry group".

The definition of each market within the industry group is defined according to the Datamonitor report. The industry consists of three markets. The pharmaceuticals market includes only therapeutic drugs for human use (Datamonitor, 2010a). The biotechnology market includes

both medical and non-medical biotechnology products developed, manufactured or marketed by biotechnology firms (Datamonitor, 2010a). The life and sciences market is limited to firms providing tools and services to the pharmaceuticals and biotechnology markets (Datamonitor, 2010).

While the industry group faced uncertain times during the 2008 to 2010 global financial crisis, it still was able to grow (Datamonitor, 2010a). In 2009, the industry generated revenue of US \$1,071.1 billion representing a growth rate of 5.3% (Datamonitor, 2010a). By 2014, the revenue for the industry group is expected to reach US \$1,402.4 billion (Datamonitor, 2010a).

The Americas region leads the geographic market share with 50.5% while Europe has 20.7%, Asia-Pacific 18.2%, and the rest of the world represents 5.7% of the market share (Datamonitor, 2010a). Pfizer is the leading firm with 4.7% market share followed by Roche with 4.2%, Sanofi-Aventis with 3.8% and Novartis with 3.6% (Datamonitor, 2010a).

The pharmaceuticals market segment represents 75.7%, biotechnology 22.7% and the life science tools and services 1.7% of the total industry group (Datamonitor, 2010a). The competitive landscape can be summarized as follows: buyer power for the industry group is moderate, the threat of substitutes is low, supplier power is moderate, the threat of entry is moderate, and rivalry is moderate (Datamonitor, 2010a).

The industry group spends heavily on research and development (R&D). Once a drug is successfully developed and brought to market, profits for the firm can be high. The pharmaceuticals market is very profitable, with a 17% profit margin (Datamonitor, 2010a). However, biotechnology's innovative R&D capabilities are becoming more important to the large pharmaceutical (Big Pharma) firms and their pipelines. These pharmaceutical firms are turning to biotechnology and to emerging biopharmaceutical firms for innovative new technologies and approaches to novel therapies. In the next section, I analyze the global Biotechnology sector.

2.3 The Biotechnology Sector: An Important Source of Innovation

The biotechnology market refers to the products arising from the biotechnology research. One useful definition of the biotechnology industry is that it “is the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge and biotechnology products and services” (IBIS World, 2010, pg.3).

The biotechnology industry is now approximately thirty years old. In 2009, the estimated revenue for the global biotechnology industry was US \$200.9 billion representing a growth rate of 5.3% (Datamonitor, 2010b). The biotechnology sector revenue accounts for approximately 20% of the revenue of the industry group reported above. The growth rate of the biotechnology sector is currently the same as the broader industry group. However, by 2014, revenue for this sector is expected to reach US \$318.4 billion (Datamonitor, 2010b). Compared to 2009, this is an increase of 58.5% (Datamonitor, 2010b) and is significantly higher than the estimated 31% for the broader industry group.

There are several reasons for this higher growth rate. First, the biotechnology sector is mature and growing. Firms that spent years developing products are finally becoming profitable. Second, biotechnology products in the therapeutics sector have potential for a longer period of exclusivity for patent protection (Trusheim, 2010). As such, they can be more profitable for a longer time. Third, the field of bio-generics is still in its infancy. Big Pharma is currently struggling with competition from generics. In 2000, generics had 49% of the pharmaceutical market share. In 2009, generics had 74% of the market share (PhRMA, 2010). As such, generics represent a significant threat to Big Pharma’s revenues and profits.

Overall, the biotechnology sector is very innovative, especially when it comes to specific diseases. The biotechnology sector focuses on addressing areas of high-unmet needs such as orphan diseases, which also meet the needs of Big Pharma to fill their diminishing pipelines. Big Pharma's strategy is to invest in these biotechnology firms as a supplement or replacement to in-house R&D. As a result, there is an increasing trend of partnerships, mergers and/or acquisitions between Big Pharma and biotechnology firms.

For the biotechnology sector, the Americas region represents a 48.4% market share, Asia-Pacific 26.4% and Europe 25.2% (Datamonitor, 2010b). Datamonitor lists Merck KGaA, Novartis AG, Pfizer Inc. and Astra Zeneca PLC as the leading firms in these markets. However, that all of these firms are Big Pharma suggests that biotechnology-based products are a significant part of the Big Pharma investments in the biotechnology sector. Consequently, the biotechnology sector can be considered well established and growing.

However, the IBIS World report on the Global Biotechnology Industry reports on "true" leading biotechnology firms. What is meant by "true" is that these firms started as biotechnology firms and were pioneers that helped establish the biotechnology sector. In 2010, the market share distribution of these major biotechnology players is: (1) Amgen Inc. with 9.5%, (2) Genentech, Inc. with 9.0%, (3) Syngenta AG with 5.5%, (4) Merck KGaA with 4.5%, (5) Monsanto Firm with 4.5%, (6) Genzyme Corporation with 2%, and (7) Biogen Idec Inc. with 2% (IBIS World, 2010).

The market segmentation for the global biotechnology industry is divided into five categories. The medical/healthcare category has 66.2% of the market share, service provider 13.9%, food and agriculture 11.5%, environment and industrial processing 4.2%, and technology service 4.1% (Datamonitor, 2010b). Note that the medical/healthcare sector identified as most relevant to Firm Y leads the market share.

For the global biotechnology industry, the competitive landscape can be summarized as follows: buyer power is moderate, the threat of substitutes is moderate, supplier power is moderate, the threat of entry is low, and rivalry is moderate (Datamonitor, 2010b). However, as the global biotechnology industry includes markets not relevant to Firm Y, such as the food and agriculture market segment, the analysis that follows will focus exclusively on the RNAi Therapeutics sector specific to Firm Y.

Overall, the biotechnology industry has two key characteristics: (1) the need for a strong intellectual property (IP) to ensure firm survival; and (2) very strict government regulations for the development, manufacturing and marketing of products. These two key characteristics influence the entry and rivalry within the biotechnology sector relevant to Firm Y.

2.4 The Changing Biotechnology Business Models

2.4.1 An Introduction to Changing Business Models

A business model serves a firm as a basis of how to generate revenues and profits (Grant, 2008). However, a firm still needs a strategy of how it will create (develop), deliver (make revenues and profits) and capture (sustainable competitive advantage) value proposed in the business model (Grant, 2008). This strategy allows the firm to prosper and to display a long-term growth potential while creating value for its shareholders.

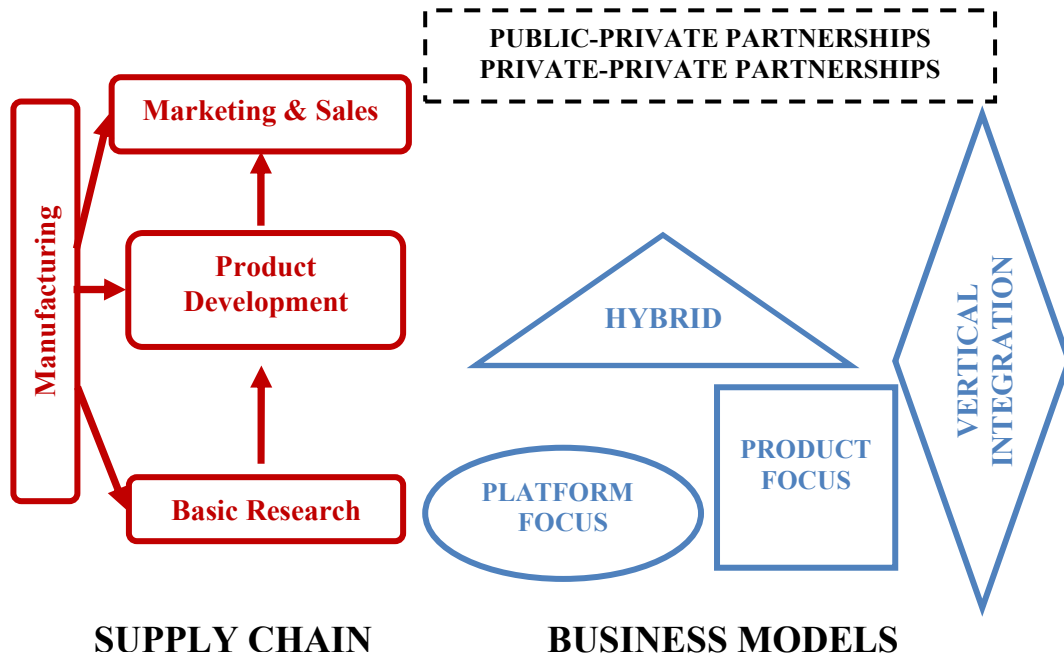
Today, advances in science and technology create novel therapeutic approaches. They also create new opportunities for existing and emerging firms. Hence, the changing landscape calls for more flexible and adaptable business models, in which for example, firms are more creative at reducing fixed costs by adopting different business models to enhance profits while creating additional value for the firm and its shareholders.

The changing landscape is important for Big Pharma and biotechnology firms. In particular, the biotechnology sector is in need of more flexible and creative business models. First, biotechnology firms that only develop therapeutics, remain unprofitable for most of their lifecycle. The reason for this is a long and costly drug development process (DDP). It takes many years to bring a product to the market, and many products never make it to the market. Hence, it takes years of investment to develop such therapeutics before any revenues or profits are made. The scarcity of investments, especially during the global financial crisis made it difficult for biotechnology firms to raise the needed capital.

Second, the biotechnology sector is a high-risk and has a high-failure rate. Big Pharma can afford to have numerous products in its pipeline, leading to more diversified portfolios. In addition, it increases the chance that some products will survive and make it to the market. These successful products are expected to offset the cost of products that fail. However, a small biotechnology firm with limited resources and capabilities often starts with only one product in its pipeline. This is a very high-risk proposition as the firm can either make it with that one product, or cease to exist. Hence, the call for new business models in the biotechnology sector. Current business models are more flexible and variable. There are more service and tool firms emerging as well that, for example, attempt to create value from scientific and technological advances in fields such as bioinformatics.

For the purpose of this analysis, I discuss different business models relevant to Firm Y and its external environment. Figure 1 is adapted from and based on information from Konde (2009). Figure 1 shows the business models and how they fit within the supply chain.

Figure 1: Business Models and Supply Chain



Source: Adapted from Figure 1 in Konde (2009).

The supply chain is simplified for the purpose of this analysis. It is based on the value chain of the drug development process (DDP) that consists of basic research, product development, manufacturing, and marketing and sales. There are four different business models: (1) Platform, (2) Product, (3) Hybrid and (4) Vertical (Konde, 2009). Next, I describe each of these business models.

2.4.2 Product Business Model

The product business model of biotechnology firms focuses on developing a product. For example, a vaccine or a cancer drug is developed. Many firms in the early days of the biotechnology industry started with this type of business model. However, due to the high-risk, high-failure rate, high costs and complexities of therapeutic product development, many firms failed with this model. Only a few firms like Amgen managed to survive. Therefore, this business model required a change. The main focus of the change was to reduce fixed costs as much as

possible. One strategy was the formation of more public-private partnerships. This allowed firms to utilize the resources and capabilities of the public institutions like universities for the basic research stage in the supply chain. The second strategy was to remain virtual as long as possible. This approach allowed firms to make minimal infrastructure investments. Hence, many activities would be out-sourced to focus on advancing the product to the next stage of the development rather than building an organization.

2.4.3 Platform Business Model

Some biotechnology firms develop a strong technology platform around which they build IP and patents, and then out-licence this technology to other biotechnology firms and Big Pharma. As a result, these firms are able to generate revenues at an early stage of the firm. There are different options with the platform business model as well. For example, the emergence of bioinformatics led to new commercial opportunities for tools or service type firms. Other platform firms resemble Firm Y. They develop drug delivery technologies for different types of therapeutics.

2.4.4 Hybrid Business Model

The hybrid business model is a combination of product and platform business models. In the hybrid model, firms usually use proprietary technology platform to generate revenues to offset costs of their operations. This revenue allows firms to invest in R&D at an early stage to improve their proprietary platform. Alternatively, it allows firms to enter a new line of business and start developing other products. Overall, the firm generates revenue while improving its current technology and developing a new line of products. Firm Y utilizes this business model.

In utilizing this hybrid model, firms avoid the dependency on limited external financing options, and, therefore, have less liability and are more liquid. The hybrid business model is becoming more important in the biotechnology sector as it prevents the high-failure rate problem

of the product business models, and allows firms to generate revenues early on to support the high R&D costs of drug development.

2.4.5 Vertical Integration Business Model

Fully Integrated Biotechnology Company (FIBCO) is a business model that encompasses full vertical integration along the supply chain. A few major biotechnology firms like Amgen are FIBCO. Big Pharma firms are vertically integrated as well. Firms like Novartis, Pfizer, and Merck have organizational capabilities to take the drug from the discovery stage to the market. However, due to sector's fast changing landscape, the vertical business model is changing as well. Big Pharma is turning to emerging markets such as BRIC (Brazil, Russia, India and China) countries to out-source some aspects of their business. In addition, Big Pharma and FIBCO invest in emerging, new product, platform and hybrid biotechnology firms to enable them to add innovative products developed by the biotechnology sector to their portfolios. This further increases the industry trend of early stage partnerships, mergers and acquisitions.

2.4.6 Adding Value via Partnerships

Partnerships are important strategic choice of many firms: emerging biotechnology firms, FIBCO and Big Pharma. Newly emerging firms can adopt the strategy of specializing in one area of the supply chain in order to build value for a future acquisition or merger. In addition, scientific and technological advances add to the changing trends for partnerships. Advances in molecular biology and genetics encourage firms to build more collaborative research partnerships early on with public institutions such as universities. These collaborations can lead to validated gene targets as potential future therapeutics for a disease. As a result, the private and public efforts are maximized. Firms save costs of the early research stage of the DDP while public funds and research aid the development of better therapeutics for patients.

Partnerships also create value between private companies. A product development firm can strategically assess which products to add to its pipeline. This creates value and attractiveness of that firm for a potential future buyer. For example, a firm developing a product finds a Big Pharma or another biotechnology firm as a potential partner. As a result, this leads to either an acquisition or a merger, co-development of the product, or assistance with commercialization of the product. All these partnership options serve the purpose of benefiting both firms and their shareholders.

2.4.7 Summary: From Business Models to the Value Chain

As the competitive landscape changes, so do business models. Firms are not only innovative with their scientific and technological platforms and products, but with their business models as well. The adaptability of the firm to its internal and external environment is vital for its survival. This is especially important in an IP driven and highly complex and regulated industry such as biotechnology. The fast changing competitive landscape stimulated the emergence of more flexible and adaptable business models such as the product, platform, hybrid of the product-platform and integrated business models.

In addition, through participating in out-sourcing, mergers and acquisitions, the industry is shifting towards more global and collaborative public and private partnerships in established and emerging economies. Even though the human therapeutics sector is challenging and complex, it is driven by passion for research to improve human lives. In the next section, I look at this challenging and long process of bringing a human therapeutics from the lab to the market.

2.5 The Value Chain: The Drug Development Process (DDP)

2.5.1 An Introduction to the Drug Development Process

In this section, I describe the value chain of the Drug Development Process (DDP). The regulation and complexity is justifiable, because the industry is dealing with human lives and health. While the main stages in the process have remained constant over time, the process is becoming more complex and costly as advancements in science and technology arise. In the next sections, I describe the regulatory body that oversees the DDP, and then I outline each stage of the DDP process to conclude with a brief note on current complexities and costs.

2.5.2 Regulatory Aspects of the Drug Development Process

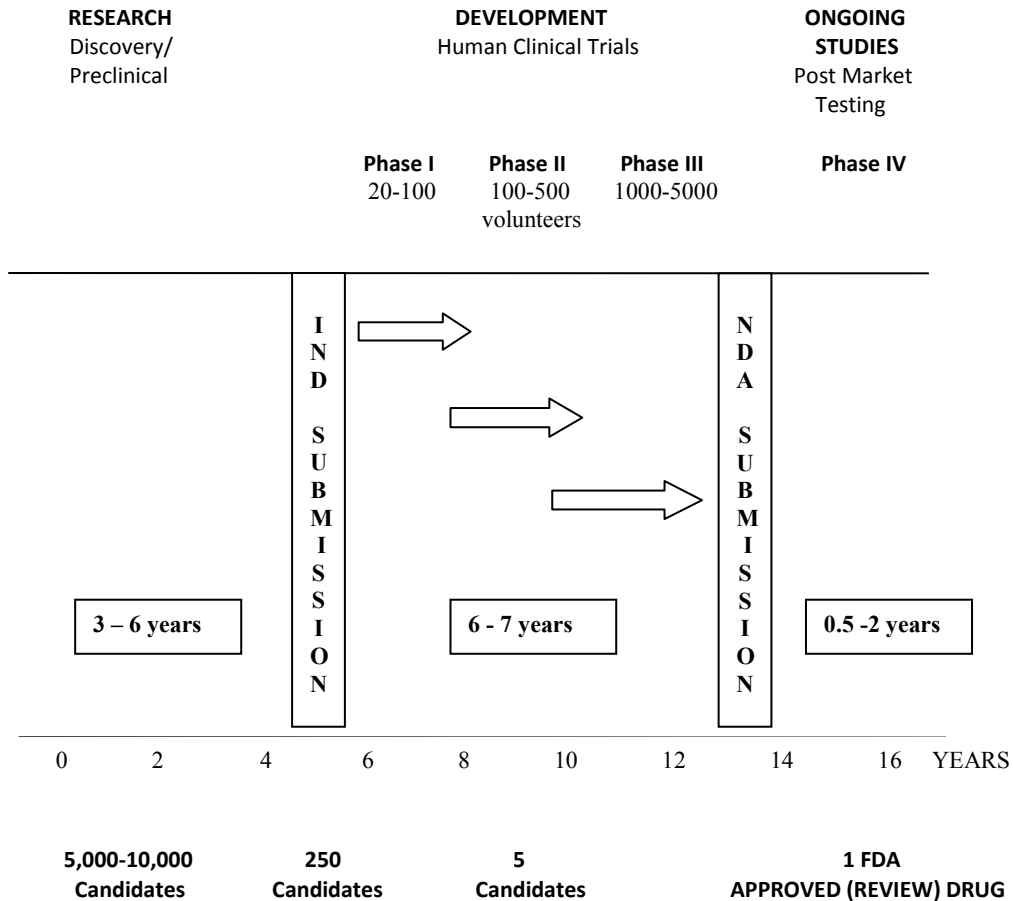
Which regulatory bodies oversee this highly regulated industry? In Canada, it is Health Canada. In the United States, it is the Food and Drug Administration (FDA). In Europe, it is the European Medicines Agency (EMA) and the National Health Authorities in EU countries (Mancini, 2010). As we are in era of globalization and consolidation, the regulatory environment is no different. There is a need for harmonization to make it easier for firms to obtain approvals in more than one country. There is such an initiative to harmonize the regulatory process in the US, EU and Japan called The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (Mancini, 2010).

Overall, the main goal of regulatory bodies is to ensure safety, efficacy, and quality of the new therapeutic products in order to ensure improvement and protection of public health (Mancini, 2010). For the purpose of this analysis, I refer to stages typical for the DDP under the US FDA.

2.5.3 Main Stages in the DDP

There are three main stages in the DDP. Figure 2 shows these different phases of the DDP.

Figure 2: The Standard Drug Development Process (DDP) in the US



Source: Adapted from MedicineandBiotech (2004) and based on information from PhRMA report (2010).

The first is a research stage. It progresses to a development stage through the submission and approval of an Investigational New Drug (IND) document to the US FDA. The development stage consists of three human clinical trials on the drug. Once these trials are completed, a New

Drug Application (NDA) document is submitted, reviewed and approved by the FDA. The third stage is the market entry and commercialization of the drug. Once the drug is on the market, there might be phase IV clinical trials to conduct post-approval surveys. In the next sections, I describe each stage in more detail.

2.5.4 A Closer Look: A Product's Journey from Research to Development to Market

2.5.4.1 The Research Stage

The Research stage takes from three to six years to complete. A discovery stage starts with understanding a disease and looking for a potential target. In the case of a small molecule drug, this stage starts with 5,000 to 10,000 candidate compounds (PhRMA, 2010). In the research stage, there are fewer candidates, which progress to preclinical studies in animals to ensure safety. At the end of this stage, the IND is filed, and when approved, a Phase I clinical trial can be initiated. As Figure 2 depicts, at this stage there are approximately 250 candidates in a pipeline.

2.5.4.2 The Development Stage

The Development stage consists of three human clinical trials: Phase I, Phase II and Phase III. These are described in more detail in the following sections.

2.5.4.2.1 Phase I Clinical Trials

Next is the development stage that starts with the Phase I human clinical trials once the IND is approved by the FDA. In Phase I, the trial usually has 20 to 100 healthy volunteers and the safety of the drug is extensively tested. The trial might take a year or longer to complete (PhRMA, 2010). Safety is tested by administering high doses of the drug so that toxicities and

safety ranges are fully explored (Tomke, 1998). However, this phase does not typically provide information on the efficacy of the drug.

2.5.4.2.2 Phase II Clinical Trials

Phase II clinical trials are designed to test the efficacy of the drug. Efficacy is determined by testing how well the drug treats the disease for which it is being developed. The Phase II clinical trials consist of 100 to 500 volunteers (PhRMA, 2010). These trials are usually “blinded” and utilize controls. This means that a portion of the patients is taking placebo and the doctors themselves do not know which patients receive placebo and which do not (Tomke, 1998). This phase usually takes about two years.

2.5.4.2.3 Phase III Clinical Trials

Phase III clinical trials are larger versions of the Phase II clinical trials. They test for extended safety and efficacy of the drug in treating the intended disease. The Phase III clinical trials are the most expensive. They typically involve from 1,000 to 5,000 volunteer patients (PhRMA, 2010). Usually, the Phase III clinical trials are international. Once the Phase III clinical trial is complete, the NDA application and the FDA Review and Approval process begins. This phase takes up to three years.

2.5.4.3 The Ongoing Studies Stage: Phase IV

The NDA approval by the FDA means that the drug can enter the market. Once the drug is on the market, the collection of effectiveness data for the drug continues. Phase IV is focused on evaluating the overall safety and efficacy of the drug on a global scale with a wide range of people. This global testing is difficult to achieve even with the well-designed Phase III trials. In addition, some trials are only conducted in the US.

2.5.4.4 Meetings With the FDA

Throughout the DDP, firms are encouraged to have regular meetings with the FDA. The purpose of these meetings is to review the process and design of clinical trials. This ensures that FDA requirements are met. In addition, the DDP has a high-failure rate. There are many instances of drugs failing in the Phase III trials. For this reason, an interactive approach with the FDA can be very beneficial to the firm for a couple of reasons. First, it can result in an early stop of drug development to save the unnecessary costs to the firm if the drug is unlikely to be approved. Second, it can add to a successful approval and market entry of the drug. The meeting with the FDA might be particularly important when a new class of therapeutics is being developed. This is the case with the RNAi Therapeutics sector in which Firm Y operates.

2.5.4.5 The Current Situation With the Drug Development Process (DDP)

We are in an era of technological advancements in which we expect processes to become faster and more profitable for the firm. In addition, we expect a better quality of products, especially if these products are related to human health. However, the opposite seems to be true for the DDP that is becoming more complicated and costly resulting in more pressure on the industry. In 1979, for example, the cost of developing a new drug was estimated US \$100 million, in 2000, it was US \$800 million, and, in 2005, it was US \$1.3 billion (PhRMA, 2010). These estimates also include the cost of developing products that failed to reach the market.

The main drivers of the cost and complexity of trials seem to be advancements in science and technology. Even though these advancements are useful, they generate deeper understandings of the safety and efficacy of drugs (PhRMA, 2010). In addition, the development of biologics is more complex than small molecule drugs that previously dominated pharmaceutical markets. As such, larger and more complicated clinical trials are needed for the drug to move to the next stage (PhRMA, 2010).

In terms of R&D expenditures, the PhRMA 2010 document reports the distribution by each phase of drug development. This data is based on the 2008 statistics and is generated from the twenty-nine member firms of the PhRMA. According to the report, the highest spending occurs in two of the stages: 27% of spending is allocated to the Pre-human/Preclinical stage and 32.5% for Phase III clinical trials (PhRMA, 2010). The rest of the R&D cost is distributed as follows: 8.2% for Phase I, 12.9% for Phase II, 4.7% for the approval stage, and 14.4% for Phase IV (PhRMA, 2010).

The two most expensive stages are justifiable for the following reasons. The Pre-human/Preclinical phase is very important. A firm is screening a potential drug in which it will continue to invest. The potential drug has to be extensively tested in animals before it is approved for humans. The Phase III clinical trials are expected to be the most expensive because they are the largest. They also take the longest time to be completed.

2.5.5 Summary: From the DDP to a New Class of Therapeutics

The DDP process is complex and costly. There are many regulations and stages in the process. The success rate of drugs moving from the discovery stage to the market is still low. The process is getting more complex and costly with the evolving scientific and technological advances. This is due to both the process and the newly emerging therapeutic opportunities. Previously, most of the drugs were chemical in nature. These drugs are termed small molecule drugs. However, the establishment and evolution of the biotechnology sector led to new therapeutic opportunities. These biotechnology products might be more difficult to take through the regulatory process for two reasons. First, the regulatory processes might not be in place yet. Second, they might be more complex to validate due to the manufacturing process, and clinical safety and efficacy. However, these products potentially have better therapeutic effects in treating disease. One example of a newly emerging class of potential therapeutics is the sector termed RNAi Therapeutics.

2.6 RNAi Therapeutics: A Potential New Class of Therapeutics

2.6.1 An Introduction to RNAi Therapeutics

In the next sections, I describe the specific sector in which Firm Y operates. First, I discuss different classes of human therapeutics. This leads me to a definition of the sector in which Firm Y specializes. Second, I analyze the competitive landscape of this newly emerging sector, RNAi Therapeutics.

2.6.2 Different Classes of Human Therapeutics

New scientific and technological advancements not only give rise to new markets, but also to a new terminology. In addition, until these are well established, defining industries involving new entities can be challenging (Trusheim et al., 2010). This leads to a lack of harmonization and consistency on the use of terminology related to the biotechnology, pharmaceutical and biopharmaceutical industries (Rader, 2005a). Biopharmaceuticals is defined as biotechnology-derived pharmaceuticals (Rader, 2005a). Firm Y is a biopharmaceutical firm. Broadly, human therapeutics can be divided into drugs and biopharmaceuticals. There is a basic difference between the two. Drugs are manufactured chemically involving small molecules and other needed chemical substances, and, hence, are considered non-biological (Rader, 2005a). On the other hand, biopharmaceuticals are manufactured with biotechnology techniques and involve complex biological molecules, and, thereby are considered biological (Rader, 2005a). In addition, biologics often cannot be taken orally and must be injected or infused by healthcare providers (Trusheim et al., 2010). Overall, they differ in pricing, general adoption, regulations, and how they are made available to patients (Trusheim et al, 2010). For the purpose of this analysis, I divide biopharmaceuticals into two major groups: biologics and RNAi therapeutics. Next, I discuss and define the RNAi Therapeutics sector.

2.6.3 A Definition of the Industry Sector in Which Firm Y Specializes

RNAi therapeutics collectively refers to all the nucleic acid-based therapeutics, and includes DNA and RNA-based therapeutics. A type of nucleic acids used in the field of RNAi therapeutics is termed oligonucleotides, which are shorter nucleic acids approximately twenty nucleotides in length. For this analysis, RNAi therapeutics includes small interfering RNA (siRNA), microRNA (miRNA) and antisense oligonucleotide-based therapeutics. Different firms develop different types of the oligonucleotide-based therapeutics. I will consider all of these to be part of the RNAi Therapeutics sector.

2.6.4 An Overview of the RNAi Therapeutics Sector

In this section, I analyze competitive landscape. RNAi therapeutics brings a new hope and approach to treating many human diseases. The RNAi sector is about ten years old (Haussecker, 2008). The RNAi mechanism was discovered in a small nematode *Caenorhabditis elegans* (Fire et al., 1998). The RNAi is a mechanism for “silencing” a gene of interest that causes a disease. Unlike gene therapy, RNAi therapeutics does not try to “repair” the defective or mutated gene on a DNA level; it “silences” the target gene by preventing the protein production of that gene (Fire et al., 1998; Bumcrot et al., 2006). Hence, in a very simplified way, if there is no production of a defective protein, there will be no disease. The oligonucleotide used to silence a gene of interest needs to be delivered to cells of a target tissue or organ. This delivery can be carried out by technology platforms such as Firm Y’s PLATFORM X. The RNAi Therapeutics sector is still embryonic and the vision of commercialized and widely used RNAi therapeutics has not yet been realized.

2.6.5 An Analysis of the Potential of RNAi Therapeutics

2.6.5.1 Distinguishing Factors of RNAi Therapeutics

Since its discovery, the RNAi mechanism has been used as a tool in many genomic screens (Haussecker, 2008; Reidhaar-Olson & Vornlocher, 2008). The RNAi mechanism has helped identify potential therapeutic targets, which are genes believed to be involved in different diseases. Now, RNAi has a potential to become a new class of therapeutics (Haussecker, 2008; Bumcrot et al., 2006). RNAi therapeutics can be developed to target those same genes to cure diseases. There are several key benefits of RNAi therapeutics compared to traditional small molecule drugs and biologics.

First, RNAi therapeutics starts at the root of a disease, the gene. Therefore, it silences the production of a protein at the RNA level and not the protein level, as is the case with many current therapeutics. As such, RNAi therapeutics has the potential to treat diseases with a higher efficacy.

Second, the RNAi mechanism is very specific and effective. If an RNAi therapeutic is delivered to the target site, it can be highly selective and potent. The high selectivity translates into higher safety, and high potency translates into higher efficacy in the clinical trials. Overall, a disease can be treated with higher effectiveness.

Third, RNAi therapeutics has the opportunity to broaden the scope of possible disease targets to include those thought to be “undruggable” by other conventional methods (Haussecker, 2008; Melnikova, 2007; Bumcrot et al., 2006; Rossi, 2007).

Fourth, RNAi therapeutics falls in between small molecules and biologics. They can combine the best of both of these classes. They can be chemically manipulated and easy to synthesize. In addition, they are affordable to manufacture, and target identification and optimization is fast compared to other conventional methods (Bumcrot et al., 2006). For RNAi

therapeutics, the target identification and optimization process is estimated to take weeks rather than years (De Fougerolles et al., 2007). This step alone can significantly reduce costs and time for the drug development. As I mentioned previously, 27% of the DDP cost is spent on the Pre-human / Preclinical research stage of the DDP.

Overall, RNAi therapeutics has a great potential to fill the current gap in human therapeutics. It has a potential to treat the disease at the gene level, not the protein level like current conventional therapeutics. In addition, this emerging sector is quickly gaining some needed regulatory experience. The FDA has already reviewed about fifty different protocols and INDs. In addition, more than 10,000 patients in clinical trials have experienced treatment with oligonucleotides (Schaffer, 2010).

2.6.5.2 The Potential Risks of RNAi Therapeutics

There are risks and limitations with RNAi therapeutics. First, many genetic diseases cannot be treated by RNAi therapeutics. One example is when a mutation in a gene causes a loss of function of that gene. As a result, there is no protein made. In these cases, there is no gene product to silence or treat. For these types of diseases, RNAi therapeutics cannot be developed.

Second, the RNAi mechanism is a naturally occurring biological process in the host. As such, there are potential safety risks to the host. RNAi therapeutics competes with the host's biological process, or RNAi machinery, to use it to silence the target gene. This approach to utilizing host's natural biological process makes it analogous to viral infections. It can potentially overwhelm the host's natural biological processes resulting in safety implications and side effects to the host (Rossi, 2007).

2.6.5.2.1 The Limiting Step: The Importance of Delivery in RNAi Therapeutics

The most important aspect of RNAi therapeutics is delivery. There was an attempt to develop RNAi therapeutics without a delivery system. However, the fact that oligonucleotides are not stable in blood serum prompted the need for effective delivery technologies. In fact, specific (safe) and potent (efficacious) delivery technologies to the target organs, tissues and eventually cells are considered the most limiting step for RNAi therapeutics (Reidhaar-Olson & Vornlocher, 2008; Melnikova, 2007, Bumcrot et al., 2006; Haussecker, 2008).

2.6.5.2.2 Potential Applications of RNAi Therapeutics

There are two different routes of administration of RNAi therapeutics. Direct RNAi delivery refers to a local administration of RNAi therapeutics. Systemic RNAi delivery refers to intravenous delivery of RNAi therapeutics. Firm Y's PLATFORM X is a systemic RNAi delivery technology. Considering that the RNAi field is embryonic, the advancements in the field have been quite rapid. Proof-of-concept for RNAi therapeutics has been shown for several organs and indications. Table 1 integrates most of this evidence. It includes the type of administration, organs and indications.

Table 1: Evidence for RNAi therapeutics Proof-of-Concept

DIRECT RNAi (LOCAL DELIVERY)	
ORGAN	DISEASE
Lung	RSV (respiratory syncytial virus), Flu, SARS
Eye	AMD (wet age related macular degeneration)
Nervous system	Encephalitis, West Nile virus, Neuropathic pain, ALS (Amyotrophic Lateral Sclerosis, also known as Lou Gehrig's Disease), Spinocerebral ataxia, Huntington disease, Depression
Tumour	Adenocarcinoma, Prostate, Human papillomavirus, Glioblastoma
Digestive system	Irritable bowel disease
Vagina	HSV (herpes simplex virus)
SYSTEMIC RNAi (INTRAVENOUS DELIVERY)	
ORGAN	DISEASE
Lung	Influenza
Tumour	
Liver	Hypercholesterolemia, HBV and HCV
Joint	Rheumatoid arthritis

Source: Adapted from information in Bumcrot et al. (2006).

In addition, RNAi therapeutics, similar to biologics, can potentially treat more than one condition. Currently, there are only two RNAi therapeutics on the market. The first is fomivirsen (Vitravene), which is an antisense oligonucleotide-based RNAi therapeutic. It was developed to treat cytomegalovirus retinitis (a condition related to eye) in patients with AIDS (Melnikova, 2007). The second is pegaptanib, also known as Macugen developed by OSI Pharmaceuticals and Pfizer for wet age-related macular degeneration (AMD) (Melnikova, 2007). However, both drugs have not performed as well as expected. RNAi therapeutics from other nucleic acid classes, for example siRNAs, are still waiting to reach the market. However, the two therapeutics on the market demonstrate the great potential of this sector. In addition, there are many more in the research and clinical development stages.

2.6.6 Competitive Landscape of the RNAi Therapeutics Sector

In this section, I look at the major firms within the RNAi Therapeutics sector. I analyze Firm A, Firm B, Firm C, Firm D, and Firm E. These five firms, along with Firm Y, are probably the most advanced players within this young sector. These firms develop siRNA, miRNA or

antisense oligonucleotide-based RNAi therapeutics. There are new emerging firms with delivery platform, RNAi therapeutics or both that have not been considered or included in this analysis.

Firm A and Firm C are the two leading firms within the RNAi Therapeutics sector. Firm A has strong IP, a robust product pipeline and the aspiration of becoming the first fully integrated RNAi therapeutics firm. Firm C has probably the second strongest position within this sector, with a robust product pipeline.

All these firms have the hybrid business model. These firms have either delivery or target discovery technology as their platform. In addition, these firms develop diagnostic tests and/or RNAi therapeutics as their products. They all follow a trend very specific to the RNAi Therapeutics sector, with a stream of both public-private and private-private partnerships. A number of Big Pharma firms have either partnerships or in-house development related to RNAi therapeutics. An example is the Merck-Sirna acquisition. Big Pharma's strong presence this early on in the process indicates its strong interest and belief in this sector.

2.6.6.1 Firm A

2.6.6.1.1 Overview

Firm A's corporate strategy is to lead the RNAi Therapeutics sector. The firm's goal is to become a fully integrated biopharmaceutical firm (Firm A, 2008). Firm A has a leading position in the IP related to RNAi therapeutics.

2.6.6.1.2 Delivery Focus

Firm A understands the importance of a delivery system in the RNAi Therapeutics sector. Hence, the firm focuses on developing delivery technology for siRNA-based RNAi therapeutics. Their current success includes gene silencing of more than twenty-five disease targets, in more than five tissues, and in six species, including humans (Firm A, 2008).

2.6.6.1.3 Product Pipeline Focus

Firm A has a diverse and robust product pipeline. It has twenty-two products in its pipeline: two in Phase II, four in Phase I, six in the preclinical development stage and ten in the discovery/research stage (Firm A, 2008). Firm A's pipeline consists of its own products and those developed through collaborative, partnered, co-developed and joint venture partnerships.

2.6.6.2 Firm B

2.6.6.2.1 Overview

Firm B is a public biotechnology firm. The firm has a hybrid business model with a technology platform and an RNAi therapeutics pipeline. The focus of the firm is to develop treatments for autoimmune diseases, cancer, infectious diseases, and neurological disorders (Firm B, 2007). However, their products are in the early stage of R&D. Firm B has many partnership and is involved in various market segments from the RNAi research agents to target validation, drug development and disease modelling (Firm B, 2007).

2.6.6.2.2 Delivery Focus

Firm B is using its patented technology DNA directed RNA interference for the development of its products. DNA is delivered to a cell, which then triggers production of corresponding siRNA that triggers the RNAi mechanism. Hence, it starts with the DNA rather than RNA, as is case with siRNAs.

2.6.6.2.3 Product Pipeline Focus

Firm B is focusing on HIV/AIDS, Hepatitis B and lung cancer where all the projects are in collaboration with various partners (Firm B, 2007). The firm is developing two products for HIV. The first HIV/AIDS RNAi therapeutics is in clinical trials. The second product is expected to enter clinical trials soon.

2.6.6.3 Firm C

2.6.6.3.1 Overview

Firm C specializes in antisense oligonucleotide-based therapeutics. The firm has a hybrid business model with a proprietary drug discovery platform and a product pipeline. The firm specializes in discovering a range of potential therapeutics, more than they can develop themselves (Firm C, 2010). They hold a strong IP portfolio with more than fifteen hundred patents worldwide (Firm C, 2010). The firm out-licenses its products to partners in later development stages. These partners complete the drug development process and commercialization stage. In addition, the firm generates revenues through its platform. Firm C also has a number of partnerships.

2.6.6.3.2 Discovery Focus

Firm C has an antisense drug discovery platform. It focuses on many organs and tissues, including spleen, liver, kidney, bone marrow and fat cells (Firm C, 2010).

2.6.6.3.3 Product Pipeline Focus

Firm C has a robust product pipeline targeting a number of indications. The firm specializes in the early drug discovery and development. Firm C focuses on five major indication groups: cardiovascular (five products), metabolic (four products), neurodegenerative diseases (two products), inflammation (three products) and cancer (four products) (Firm C, 2010). The firm also has six other products unrelated to these major indications (Firm C, 2010).

The cardiovascular group has one product in Phase III, two products in Phase I, and two products in the preclinical stage. The metabolic group has one product in Phase II, one product in Phase I and two products in the preclinical stage. The cancer group has one product in Phase III, one product in Phase II and two products in the preclinical stage. The neurodegenerative group has one product in Phase I and one product in the preclinical stage. The inflammation group has

three products in Phase II. The group termed others has one product approved, one in Phase II, two in Phase I, and one in the preclinical stage.

2.6.6.4 Firm D

Firm D is a firm focused on the miRNAs oligonucleotide-based RNAi therapeutics. Firm D also has a hybrid business model: it has a proprietary discovery platform and a product pipeline. Their proprietary discovery platform combines informatics and high-throughput biological approaches to identify miRNAs (Firm D, 2008). Firm D specializes in two lines of products: diagnostic tests and the miRNA-based RNAi therapeutics. Firm D currently focuses on using miRNAs as biomarkers to develop diagnostic tests for cancer and for women's health indications. In 2009, Firm D commercialized three diagnostic tests (Firm D, 2008). Currently, the firm has three more products in the pipeline. In addition, Firm D is focusing on miRNA-based therapeutics for liver cancer. The firm has a number of partnerships.

2.6.6.5 Firm E

2.6.6.5.1 Overview

Firm E has a hybrid business mode. The firm has a discovery platform, a delivery platform, an RNAi therapeutics product pipeline and a number of partnerships. In addition, the firm holds a strong IP portfolio with two hundred issued and worldwide patent applications (Firm E, 2010).

2.6.6.5.2 Delivery Focus

Firm E has two types of delivery platforms: (1) lipid and (2) polymer-based delivery platforms. The lipid delivery platform systemically delivers therapeutics to the liver, endothelium, and other tissues (Firm E, 2010). The polymer delivery platform can systemically reach any disease target (Firm E, 2010).

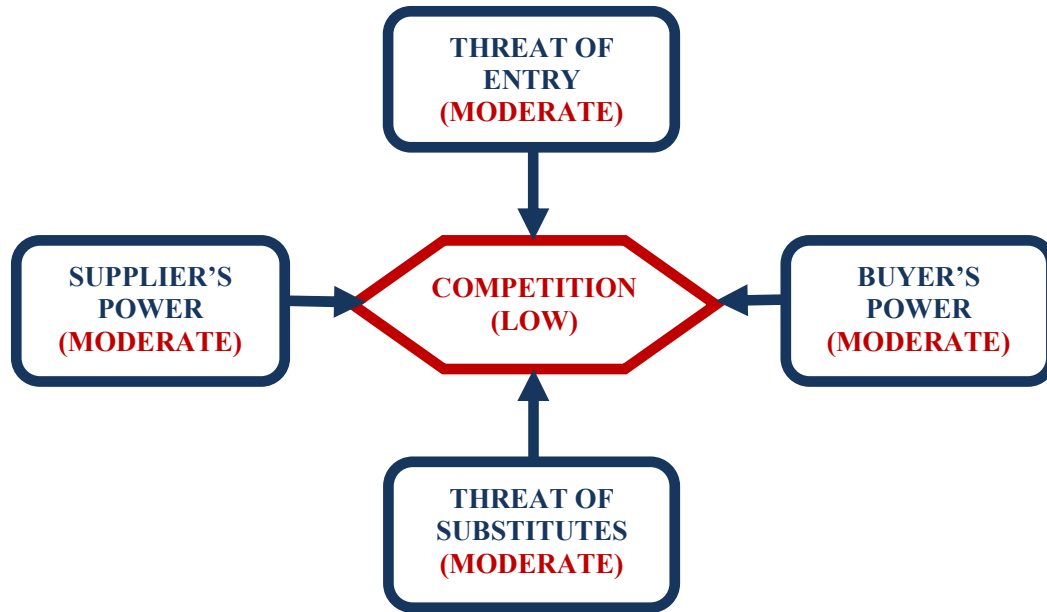
2.6.6.5.3 Product Pipeline Focus

Firm E has six different products in their pipeline. The firm is developing four internal products and three with partners. One product developed internally is in the clinical stage and three are in the preclinical stage. All three products developed with partners are in the clinical stage.

2.6.7 RNAi Therapeutics Sector Competitive Analysis

In this section, I use the “Five Forces Model” (Porter, 2008) to analyze the competitive landscape of the emerging RNAi Therapeutics sector. Because this sector is embryonic, the analysis is based on the limited information available. The analysis considers the six major players in the sector. However, there are a number of emerging firms not included in this analysis. In addition, the role of partnerships and Big Pharma is considered as well. Figure 3 depicts a summary of the analysis. Next, I briefly address each of the five forces.

Figure 3: The Competitive Analysis of the RNAi Therapeutics Sector



Source: Adapted from Porter (2008).

The main focus of this analysis is on human therapeutics. As previously identified, I classified these as small molecules, biologics, and RNAi therapeutics. As such, key buyers considered for the analysis are healthcare providers and drug retailers. The substitutes are conventional human therapeutics. I consider discovery and delivery platforms as suppliers. Therefore, firms like Firm Y that have manufacturing capabilities are also suppliers.

2.6.7.1 Buyer Power is Moderate

Currently, there are only two nucleic-acid based RNAi therapeutics on the market. As such, I analyze the bargaining power of buyers from the potential perspective of RNAi therapeutics. Therefore, the bargaining power of healthcare providers and drug retailers is moderate. This is due to many conventional therapeutic options currently available on the market. The buyer's bargaining power increases when generics and bio-generics are available as a treatment.

However, RNAi therapeutics is a novel class of therapeutics that has the potential to treat the targeted indications with superiority over other available treatments. If this is the case, the bargaining power shifts to the firm. The firm will be able to charge premium price for superior RNAi therapeutics. The bargaining power of the firm increases if RNAi therapeutics also addresses the unmet medical needs. Overall, buyer power is moderate.

2.6.7.2 The Threat of Substitutes is Moderate

The threat of substitutes is moderate overall. This is based on couple of factors. A first factor is the number of other human therapeutics available. This factor makes the threat of substitutes high. This is due to many small molecules and biologics already available on the market and in development. In addition, many of these products are available over the counter. Hence, a prescription is not needed for these treatments. In addition, many of these treatments are orally available. As such, an oral formulation of the RNAi therapeutics will be beneficial in the future. It could increase the value and application of RNAi therapeutics. Furthermore, the presence of generics and bio-generics further increases the threat of substitutes.

The second factor is based on the potential of RNAi therapeutics. Novelty of RNAi therapeutics makes the threat of substitutes low. This factor applies if firms focus on a target considered “undruggable” by other conventional means. In addition, firms need to develop RNAi therapeutics that treats high-unmet medical need with high effectiveness. In such instances, the threat of substitutes to this RNAi therapeutics is low. This is due to superior performance of these therapeutics where there is no other or a limited number of substitutes available for them. Overall, the threat of substitutes is moderate.

2.6.7.3 Supplier Power is Moderate

The bargaining power of suppliers is currently moderate. However, as the sector matures, I expect the bargaining power of supplier to increase, especially as more RNAi therapeutics reach the market. Firms that have capabilities and the IP to manufacture RNAi therapeutics will have a high bargaining power. This is mainly due to delivery aspect of this sector. In a sense, the delivery platform is the complementary asset of RNAi therapeutics. The IP and significance of product-platforms will shift the power to firms that have capabilities in both. Hence, since one cannot go without the other, the manufacturing process of producing both is important. Overall, supplier power is moderate.

2.6.7.4 The Threat of Entry is Moderate

Currently, the barrier to entry is moderate. Even though there are only few firms in this sector, including Firm A, Firm C, and Firm E, they hold a significant barrier in this sector due to their IP power. As this industry sector matures, barriers to entry will increase. If new firms choose to enter, they will have to go through firms holding the IP in order to develop RNAi therapeutics. However, knowledge about other potential oligonucleotides might lead to new opportunities. The current IP barriers might not apply to these new opportunities. As such, it is possible that more start-up firms will emerge with these new opportunities. The latest example is efforts with the miRNA oligonucleotide-based RNAi therapeutics. The delivery aspect of RNAi Therapeutics sector further raises the entry barrier. Overall, the threat of entry is moderate.

2.6.7.5 The Competition is Low

The competition is low for now. I am basing this analysis only on firms in the RNAi Therapeutics sector. As such, there are only few firms currently operating in this sector. In addition, there are not many RNAi therapeutics in the market and in development. However,

there is emerging competition. As the sector matures, competition is to intensify. Future advances in RNAi therapeutics will intensify rivalry. Overall, the rivalry is low.

2.6.8 The RNAi Therapeutics Sector Shows Great Promise

The RNAi Therapeutics sector is embryonic; however, it is rapidly growing. There are some key success factors important for this sector. RNAi therapeutics has the potential to be very specific, hence safe, potent, and efficacious in treating a disease. As such, it can bring great benefits to patients.

In addition, RNAi therapeutics needs an effective delivery platform. This platform will bring RNAi therapeutics to its target site. The more specific delivery is to the intended target, the better the overall effectiveness (safety and efficacy) of the treatment. As such, synergy between delivery (where to) and RNAi therapeutics (for what) is very important.

Public and private partnerships are important in the RNAi Therapeutics sector. Many Big Pharma firms such as Pfizer, Novartis, Roche, Merck, and Astra Zeneca are investing in this sector. In addition, during the global financial crisis, some of the most strategic financial deals signed were around the RNAi Therapeutics sector (Melnikova, 2007). This indicates Big Pharma's belief in the future of the sector. Furthermore, FDA experience will increase as more RNAi therapeutics enters clinical trials. This will move the sector forward.

2.7 Summary: From the External Environment to Firm Y

The previous sections provide the analysis of the external environment in which Firm Y operates. Overall, the RNAi Therapeutics sector is rapidly evolving and showing great promise for the future of human therapeutics. Firm Y is endeavouring to lead in this sector. In the next chapter, I move from the external environment analysis to the internal analysis of Firm Y where I assess its organizational capabilities.

Chapter 3: AN INTERNAL ANALYSIS OF FIRM Y

3.1 An Introduction to Firm Y

Firm Y is a publicly traded biopharmaceutical firm focusing on the development of novel RNAi therapeutics. These therapeutics are delivered to the target site via PLATFORM X, Firm Y's leading delivery platform. Firm Y supports its product development pipeline with revenues earned from its partnerships. It does so by: (1) out-licensing its technology to its partners and (2) by manufacturing products that use PLATFORM X technology for its partners.

3.2 Firm Y's Organizational Capabilities

In the next sections, I examine Firm Y's organizational resources and capabilities (Grant, 2008). For resources, I look at tangible and intangible resources. Then I discuss the capabilities of Firm Y that give the firm its competitive advantage in the RNAi Therapeutics sector.

3.2.1 Firm Y's Resources

Currently, Firm Y has a leading delivery platform with solid IP and a product development pipeline that is expected to grow. The current corporate strategy has two goals: (1) the development of the firm's product pipeline and (2) nurturing of the firm's partnerships (Firm Y, 2009).

3.2.1.1 Firm Y's Tangible Resources

Despite the recent economic recession, Firm Y has continued to grow. Firm Y's business model is a hybrid one. In terms of the supply chain, it has PLATFORM X delivery technology, manufacturing capabilities, and its own products in the development pipeline. Firm Y has a

worldwide licence to a number of gene targets via its agreements with one of the RNAi therapeutics sector's leaders (Firm Y, 2009). With these licences Firm Y can discover, develop, and commercialize several other potential RNAi therapeutics.

Firm Y has considerable infrastructure. It has R&D and manufacturing capabilities in-house. Firm Y is wisely using its internal capabilities by generating revenues via manufacturing agreements and out-licensing its delivery PLATFORM X technology. This revenue allows Firm Y to grow by developing its own line of products. Firm Y focuses on developing its products and evidence of this is Firm Y's increase in the R&D expenditure throughout the three years. In 2007, Firm Y spent less than ten million US dollars on the R&D, almost doubling in 2008 and in 2009 (Firm Y, 2009). In addition, Firm Y is incrementally improving its PLATFORM X technology with the aim to develop a more potent second generation PLATFORM X with a potential broader use.

In 2007, 2008 and 2009 Firm Y's revenue was in the ten to fifteen million US dollars range (Firm Y, 2009). Overall, shareholder's equity more than doubled from 2007 (Firm Y, 2009). Next, I look at Firm Y's intangible resources.

3.2.1.2 Firm Y's Intangible Resources

Intangible resources are very important in the biotechnology industry. Firm's value in the biotechnology sector is heavily based on its IP. Firm Y has solid IP. Its intangible resources include PLATFORM X, the current product pipeline, and a stream of strategic partnerships. Next, I address each of these in some detail.

3.2.1.2.1 Firm Y's Delivery Platform: the PLATFORM X

Delivery platforms are key to a successful development and a broad application of RNAi therapeutics. As such, superior delivery platform in the RNAi Therapeutics sector can bring a significant competitive advantage to the firm.

Importantly, Firm Y's organizational capabilities are built around its delivery platform. The firm generates revenues and future growth through PLATFORM X. PLATFORM X is a systemic delivery platform widely recognized within the RNAi Therapeutics sector. It delivers RNAi therapeutics to the target site via intravenous administration. PLATFORM X's current expertise is delivery to one or more organs (Firm Y, 2009).

3.2.1.2.2 Firm Y's Product Pipeline

Firm Y's product candidates are the siRNA class of RNAi therapeutics. In addition to its own products, Firm Y is involved in a number of other product development projects via its partners. One product is involved in hypercholesterolemia, a condition also known as high or "bad" cholesterol, and it is Firm Y's leading product candidate. This product is expected to enter Phase I/II clinical trials by the end of 2010 (Firm Y, 2009). The second product is the firm's oncology candidate that is expected to enter Phase I clinical trial by the end of 2010 (Firm Y, 2009).

3.2.1.2.3 Firm Y's Stream of Partnerships

Firm Y follows the RNAi Therapeutics sector trend. It has a number of important partnerships that have allowed it to build its organizational capabilities. In 2009, Firm Y earned close to fifteen million US dollars through these partnerships (Firm Y, 2009).

Firm Y has both types of partnerships: public-private and private-private partnerships. It has a number of important and diversified licence and collaborative research partnerships. Some of these are with Big Pharma, smaller biotechnology firms, and with government and research institutions.

3.2.1.3 Firm Y's Human Resources

Firm Y has less than hundred employees and its management team consists of less than five executives (Firm Y, 2009). Currently, Firm Y is recruiting in R&D and manufacturing staff

(Firm Y, 2010). The expansion of the R&D team is in areas of infectious diseases and oncology. The firm's core capabilities are in R&D, manufacturing, and forming strategic partnerships. Next, I address these core capabilities.

3.2.2 Firm Y's Capabilities

Firm Y has three core capabilities that give rise to the firm's competitive advantage: (1) PLATFORM X delivery technology, (2) in-house manufacturing, and (3) strategic stream of partnerships. PLATFORM X gives Firm Y the opportunity to build diverse partnerships. These partnerships lead to the need to combine PLATFORM X with Firm Y's manufacturing capabilities in order to generate revenues. In addition, these partnerships result in Firm Y's ability to pursue its own product pipeline and ensure further growth and vertical integration of the firm.

3.3 Summary: Firm Y Has Solid Organizational Capabilities

The internal analysis of Firm Y indicates that the firm has solid organizational capabilities. The firm's strategy and organizational capabilities, along with the industry's key success factors, should lead to a strong competitive advantage of the firm within its industry (Grant, 2008). As such, Firm Y's organizational capabilities and its strategy should provide it with a strong competitive advantage within the RNAi Therapeutics sector. In the next section, I analyze Firm Y's current competitive advantage. In addition, I assess Firm Y's potential to further maximize its organizational capabilities to ensure sustainable competitive advantage within the RNAi Therapeutics sector.

Chapter 4: FIRM Y NEEDS NEW PRODUCTS IN ITS PIPELINE TO SHOWCASE LONG TERM GROWTH POTENTIAL

The internal analysis demonstrates that Firm Y has solid organizational capabilities that provide Firm Y with a competitive advantage within the RNAi Therapeutics sector. As such, Firm Y is one of few firms that lead this sector. However, is Firm Y fully utilizing its organizational capabilities? It has a great delivery platform needed for the RNAi Therapeutics sector and manufacturing capabilities. In addition, Firm Y follows the sector's trend in having a diverse partnership portfolio.

Unlike Firm A, Firm C, and Firm E, Firm Y does not have a robust IP portfolio. In addition, the firm has only few products in its pipeline despite all the partnerships. This is not sufficient for the biotechnology industry, which has a high-failure product development rate. As such, the failure of any of Firm Y's products in clinical trials would significantly devalue the firm. Therefore, if a firm in the biotechnology industry has the means to expand its product pipeline, it should do so. In addition, the RNAi Therapeutics sector is still in its infancy and RNAi therapeutics still needs to be commercially validated. Therefore, the high-risk, high-failure rate for the industry is higher for the RNAi Therapeutics sector.

Hence, Firm Y should minimize its risk by having more products in its pipeline. This brings me back to the question: is Firm Y fully utilizing its organizational capabilities? Considering the firm's resources, Firm Y still has the right to a number of targets via its worldwide licence agreements. Therefore, Firm Y should identify new market opportunities to expand its current product pipeline. However, new market opportunities should be considered against Firm Y's core competencies.

In the next sections, I identify new market opportunities for Firm Y based on PLATFORM X's ability to deliver RNAi therapeutics to the liver. Then, I further analyze these new market opportunities according to: (1) Firm Y's external environment, (2) Firm Y's organizational capabilities, and (3) the competitive environment for each indication. I conclude this analysis with an evaluation of the identified market opportunities. In addition, I provide strategic recommendations to Firm Y.

Chapter 5: THE APPROACH TO THE IDENTIFICATION AND EVALUATION OF NEW MARKET OPPORTUNITIES FOR FIRM Y

5.1 An Introduction to the Identification of New Product Opportunities for PLATFORM X

The external and internal analysis shows that Firm Y needs to expand its product pipeline. As such, the purpose of this chapter is to describe methodology I used to identify and assess new market opportunities. These are based on PLATFORM X's competency to deliver oligonucleotides to specific organs. In addition, I include the evaluation criteria used for the overall evaluation and recommendations for Firm Y.

5.2 The Scope: Identification of New Indications for PLATFORM X

The overall goal for Firm Y is to identify new target opportunities for the expansion of its current product development pipeline to treat one or more new indications. To leverage on PLATFORM X's core competency, I focus on finding indications related to diseases that have potential gene targets in the liver that are eligible for treatment with RNAi therapeutics. First, I identified new opportunities based on scientific feasibility criteria listed in Table 2. Second, I assess the shortlisted group according to business feasibility criteria listed in Table 3. Third, I consider each identified opportunity relative to the firm based on the criteria listed in Table 4. I conclude with the comprehensive evaluation of each strategic opportunity to make recommendations for Firm Y.

5.3 The Methodology: From Genes to Potential Indications for PLATFORM X

The approach taken to identify a number of potential indications was broad. The Internet was used as a primary research tool. The basis for the search was the potential to use the RNAi mechanism to treat a disease with focus on liver gene targets. The selection criteria for the evaluation of opportunities are based on scientific and business feasibility specific to Firm Y.

First, the identified opportunities were assessed based on the scientific feasibility criteria listed in Table 2.

Table 2: A List of Scientific Feasibility Criteria

EVALUATION CRITERIA	DESCRIPTION OF EACH CRITERION
ELIGIBLE FOR RNAi	<ul style="list-style-type: none"> ❖ Is the indication eligible for RNAi therapeutics? ❖ Is there a gene to be silenced? ❖ What is the likeliness that disease will be treated with high effectiveness? ❖ Will treatment with RNAi therapeutics address the targeted indication/target site?
PROOF-OF-CONCEPT EVIDENCE	<ul style="list-style-type: none"> ❖ How well are potential targets validated preclinically? ❖ What about already available treatments?
FOCUSED GENE TARGET	<ul style="list-style-type: none"> ❖ Is the indication complex where it might involve many genes?
LIVER SPECIFICITY	<ul style="list-style-type: none"> ❖ Where is the potential target expressed? ❖ Is the target only expressed in the liver?
NOTE	<ul style="list-style-type: none"> ❖ These are based on limited data obtained for this analysis. ❖ Some of the criteria were developed in collaboration with Firm Y's R&D team.

The most important criterion was for the disease to have genetic basis in order to make it eligible for RNAi therapeutics. The initial research resulted in the following list of indications: (1) diabetes with three related sub-indications (Type 2 diabetes, non-alcoholic fatty liver disease, and metabolic syndrome), (2) liver cancer, (3) cardiovascular diseases with three sub-indications (dyslipidemia, atherosclerosis and Budd-Chiari syndrome), (4) Alagille syndrome, and (5)

Hepatitis B. After consultation and input from the R&D team at Firm Y, two more indications were considered: hemochromatosis and liver fibrosis.

The list was shortened mainly based on consultation with the R&D team. The remaining indications are: (1) Hepatitis B (HBV), (2) liver fibrosis, (3) liver cancer, (4) diabetes, and (5) cardiovascular diseases (CVDs). In addition, metabolic syndrome is considered in relation to diabetes and CVDs. For the purpose of this analysis, I classified the main indications into two groups. These are based on: (1) interconnectedness of indications related to each other, and (2) group's liver specificity. I refer to these two groups as the liver diseases group and the "liver-associated" group.

The liver diseases group consists of HBV, liver fibrosis, and liver cancer (HCC). This group is liver specific since the indications are classified as diseases specifically affecting the liver. The "liver-associated" group consists of diabetes, cardiovascular diseases (CVDs), and related metabolic syndrome. This group is less specific to the liver since these diseases also affect other organs. However, these indications have potential gene targets, which can be silenced in the liver. As such, these diseases show potential for treatment with RNAi therapeutics delivered to the liver. Therefore, for the purpose of this analysis I refer to this group as the "liver-associated" group.

Second, each group was assessed based on its commercial potential according to the business feasibility criteria listed in Table 3. In the next chapter, I analyze these shortlisted indications as new market opportunities. The evaluation criteria for the commercial potential of the indications are based on, and limited to, the data collected for this analysis.

Table 3: A List of Business Feasibility Criteria

EVALUATION CRITERIA	DESCRIPTION OF EACH CRITERION
MARKET POTENTIAL	❖ Based on prevalence, incidence and mortality rate.
UNMET MEDICAL NEED	❖ Estimated from the data collected; also partially incorporates route of administration.
COMPETITIVE LANDSCAPE	❖ Includes brief overview of products on the market and in development, as well as in the RNAi therapeutics sector. ❖ Mainly based on the number of products in the clinical trials studies.
FDA EXPERIENCE WITH RNAi THERAPEUTICS	❖ Mainly based on the current evidence of the FDA's experience with RNAi therapeutics.
NOTE	❖ These are based on limited data obtained for this analysis. ❖ Most of the criteria were suggested by Firm Y's management.

Third, I made a list of evaluation criteria for Firm Y in order to integrate all of the information obtained and analysis conducted. These evaluation criteria are listed in Table 4 and are mainly based on the external and internal analysis. This adds to the overall evaluation of strategic options and recommendations for Firm Y.

Table 4: A List of Corporate Criteria Specific for Firm Y

EVALUATION CRITERIA	DESCRIPTION OF EACH CRITERION
CORPORATE PIPELINE GROWTH (DIFFERENTIATION)	<ul style="list-style-type: none"> ❖ Will new targets bring focused differentiation in line with corporate goals and Firm Y’s organizational capabilities? ❖ Will overall value and growth potential of Firm Y be higher? ❖ Will shareholder’s value be higher?
SYNERGY WITH PLATFORM X	<ul style="list-style-type: none"> ❖ How specific is the medical condition to the liver? ❖ More liver specific the better it is to avoid off-target effects. This adds synergy with PLATFORM X
SYNERGY WITH CURRENT PRODUCTS	<ul style="list-style-type: none"> ❖ Will new targets benefit and work synergistically to some extent with the current pipeline? ❖ Can Firm Y’s current product development capabilities be transferred to a new line of potential targets and products?
PARTNERSHIP SYNERGY (CURRENT)	<ul style="list-style-type: none"> ❖ Will new targets / market opportunities create synergy with Firm Y’s current R&D and manufacturing partnerships?
PARTNERSHIP SYNERGY (FUTURE)	<ul style="list-style-type: none"> ❖ Will new market opportunities create future partnership opportunities?
EXIT/INTEGRATION (STRATEGY)	<ul style="list-style-type: none"> ❖ Will new targets / market opportunities create value for Firm Y and its shareholders in terms of potential exit strategy? ❖ For acquisition, will Firm Y have higher overall valuation in terms of tangible and intangible assets? ❖ Or, will Firm Y as a result achieve further forward integration in the value chain? ❖ Will this add value to Firm Y in terms of Big Pharma and the RNAi Therapeutics sector in which it competes and operates?
NOTE	<ul style="list-style-type: none"> ❖ These are based on limited data obtained for this analysis

Rationale for these criteria is that Firm Y needs to have necessary organizational capabilities in order to excel in developing RNAi therapeutics for newly identified indications. This strategy will further maximize the potential for the Firm Y to succeed in developing such treatments to create value for itself and its shareholders. For example, some indications might have a larger market size like CVDs. However, is pursuing CVDs the best strategic option for Firm Y? Would this be in line with its organizational capabilities and corporate strategy? This comprehensive strategic approach to evaluating new market opportunities can maximize Firm Y’s ability to develop superior treatments for the identified indications providing Firm Y with the competitive advantage over other treatments intended for the same indications.

5.4 Summary: From Identification to Analysis of Potential Identifications for PLATFORM X

The research led to a number of potential indications for Firm Y's PLATFORM X technology. The initial list was shortened mainly based on input from Firm Y's R&D team. The new list includes two main groups of indications. The next chapter provides information and analysis needed to integrate the external, internal and new market opportunities assessment suitable for Firm Y according to the three main evaluation categories presented in this chapter. This leads to the overall evaluation of strategic options and final recommendations for Firm Y.

Chapter 6: A COMMERCIAL POTENTIAL ANALYSIS OF NEWLY IDENTIFIED INDICATIONS FOR FIRM Y

6.1 Introduction: Business Feasibility of New Market Opportunities

The sections in this chapter present business feasibility data for each indication within the two groups. The two groups are: (1) liver diseases, and (2) liver-associated diseases. The liver diseases group consists of Hepatitis B (HBV), liver fibrosis, and liver cancer. The liver-associated group consists of diabetes, CVDs, and related metabolic syndrome. However, due to time and resources, data on some of the indications is limited. For example, the competitive landscape and unmet medical needs for diabetes and CVDs is difficult to assess.

The chapter sections include an overview of each indication, its market size, current and future standard of care, unmet medical needs, and competitive landscape. The focus is on the North American market, in particular the United States. The competitive landscape estimates used for this analysis are based on open clinical trial studies from the ClinicalTrials website. The number of new products in development might be overestimated due to enrolment in multiple clinical trials.

6.2 The Liver Diseases Group: HBV/Liver Fibrosis/Hepatocellular Carcinoma (HCC)

6.2.1 An Introduction to Liver Diseases

Liver is the largest and one of the most important organs in the human body. Hepatitis viruses and other chemicals cause liver diseases. In addition, there are adult and paediatric liver diseases. Treatments are limited and there is a need for new ones.

There are several stages in the progression of liver disease as shown in Figure 4. The progression from a healthy liver to liver failure is quite consistent. Moreover, liver diseases have a wide range of symptoms from ones that are undetectable to those that can result in death (American Liver Foundation, 2007).

Figure 4: Liver Disease Progression from Inflammation to Liver Failure



Source: Adapted based on information from the American Liver Foundation website (2007).

6.2.1.1 There is Time for Regeneration

A liver disease starts with inflammation of the liver (American Liver Foundation, 2007). This is usually caused by two factors: (1) the body is fighting an infection, or (2) the liver is healing itself due to its regenerative capabilities. One of the problems in detecting the disease is that the liver is an internal organ. As such, a patient may not feel the inflammation, and will not be diagnosed and treated. Thus, the inflammation might continue to cause more damage and can progress to liver fibrosis (American Liver Foundation, 2007).

Fibrosis refers to scarring of the liver. An untreated inflammation of the liver leads to scarring that can keep blood from flowing through the liver (American Liver Foundation, 2007). If diagnosed and treated on time, the liver can regenerate to a healthy state, and if not, further scarring of the liver can lead to cirrhosis.

Cirrhosis, if left undiagnosed and untreated, will cause permanent liver scarring. In some patients, cirrhosis leads to cancer. At this stage, patients are likely to have symptoms resulting in a higher chance that patients will seek medical help. Cirrhosis and HBV are considered leading risk factors for primary liver cancer (American Liver Foundation, 2007).

In liver cancer patients, the main goal is to preserve as much of the remaining healthy liver as possible. Undiagnosed and untreated liver cirrhosis or liver cancer leads to liver failure. At this stage, most of the liver is not functioning. This is life threatening to a patient where the last option for the patient is liver transplantation.

6.2.1.2 A Summary of Liver Diseases

Early diagnosis and treatment is very important to treating liver diseases. There is a high chance of liver failure if liver disease progresses to cirrhosis and cancer. At this stage, treatment options are very limited and liver transplantation might be the only option. As a result, there is a need for novel approaches for diagnosis, treatment, and prevention of liver diseases using molecular and genetic advancements to develop new products (Blum, 2007). Thus, there is an opportunity for RNAi therapeutics, and more specifically, for Firm Y.

6.2.2 Healthcare Costs for Liver Diseases in the US

The US National Institute of Health (NIH) website lists 1477 open clinical trial studies related to liver diseases (ClinicalTrials, 2010). Liver diseases have a significant impact on the US healthcare system. In the next section, I address the healthcare costs of liver diseases in the US, as well as, the increasing incidence of liver diseases due to the aging population and Baby Boomers.

Liver disease is the twelfth most common cause of death in the US (Davis & Roberts, 2010). The prevention and/or monitoring of the hepatitis infections can be important for progression and management of liver diseases. This is because Hepatitis B (HBV), Hepatitis C (HCV) and fatty liver diseases are more common in Baby Boomers. As a result, liver cancer is expected to be more prevalent in the future (Davis & Roberts, 2010). The Baby Boomers group in the US refers to 78 million seniors born between 1946 and 1964 (Davis & Roberts, 2010). In addition, life expectancy has increased from 68 years to an estimated 80 years of age. As such, chronic diseases represent a major trend in the future. It is estimated that 70% of chronic diseases are responsible for deaths and 80% of health care costs in the US (Davis & Roberts, 2010). These costs are mainly due to emergency visits and hospitalization. Hence, these costs might be reduced with effective treatments.

Overall, the impact of liver diseases on the US healthcare system is considerable. There are many risk factors associated with progression of liver diseases that are preventable. One example is alcohol intake. It is estimated that 45% liver disease mortality in the US is linked to alcohol consumption (Davis & Roberts, 2010). However, there are other high-risk factors more difficult to manage such as hepatitis infections, in particular Hepatitis B (HBV) and Hepatitis C (HCV). These might be good therapeutic targets important for both the acute and chronic prevention and overall progression of liver diseases.

HBV and HCV have significant health and cost implications. Their effective prevention and monitoring can improve human health and reduce healthcare costs. This is important for the aging population with a longer life span. The aging population will become a global challenge and significant burden to already saturated healthcare systems around the world. Emphasis on early diagnosis and prevention is important. For further analysis, I look at the liver diseases group. This group includes HBV, liver fibrosis, and liver cancer (HCC). I start with HBV, continue with liver fibrosis and conclude with liver cancer.

6.2.3 Hepatitis B (HBV)

Hepatitis refers to inflammation of the liver mainly caused by viruses. There are A, B, C, D and E classes of hepatitis virus. Types A, B and C are the most common in the US (CDC, 2009). The severity of HBV infection depends on whether the infection is acute or chronic. If acute, symptoms are mild and last several weeks while chronic symptoms can progress to liver failure (CDC, 2010).

6.2.3.1 Market Size

In the US, there are between 800,000 and 1.4 million people with chronic HBV infection, and globally there are an estimated 350 million people with chronic HBV (CDC, 2009). In the US, the prevalence in the general population is considered to be around 1%. In populations, such as native Alaskans or Asians, the prevalence is estimated to be 5-15% (Carey, 2009). There is clear evidence that HBV is a precursor to other liver conditions. In at least 40% of patients, infection with HBV will lead to either HCC or liver failure (CDC, 2009). In 2007, 43,000 people in the US were newly infected with HBV. The infection rate is the highest among adults between ages 25-44 (CDC, 2009). An estimated 620,000 people worldwide die from diseases related to infections with HBV (CDC, 2009).

6.2.3.2 Current Standard of Care

Currently, there is a prophylactic vaccine available for HBV. Since its wide adoption among both children and adults, the incidence of acute infection in the US has dropped dramatically (Blum, 2010). The vaccine has been available since 1982 and it took 18 years to implement it in 135 countries (Bosch, 2004). It is 95% effective against infection and its chronic consequences (WHO, 2010).

Chronic HBV remains a global health concern and there are few antiviral therapies available. However, developing a guideline for their use is challenging. In the US, the majority of patients infected with HBV are not taking these antivirals (Davis & Roberts, 2010). Currently, there are two classes of approved therapies. Table 5 depicts a summary of treatments for HBV.

Table 5: A Summary of Treatments for Chronic HBV Infection

NUCLEOSIDE ANALOGUES (antivirals)		
Name	Frequency of Treatment (oral)	Duration
Lamivudine (Zeffix®)	daily	long-term
Telbivudine (Sebivo®)	daily	long-term
Entecavir (Baraclude®)	daily	long-term
NUCLEOTIDE ANALOGUES (antivirals)		
Name	Frequency of Treatment (oral)	Duration
Adefovir dipivoxil (Hepsera®)	daily	long-term
Tenofovir disoproxil fumarate (Viread®)	daily	long-term
INTERFERON α		
Name	Frequency of Treatment	Duration
Standard interferon α -2a (Roferon®)	3x/week	4-6 months
Standard interferon α -2b (Intron A®)	3x/week	4-6 months
Pegylated interferon α -2a (Pegasys®)	1x/week	48 weeks

Source: Adapted from information in Hepatology clinical textbook in Chapter 9 (2010).

The first class is interferon α -based therapies that can address both viral replication and host's immune response (Bömmel et al., 2010). The second class is antiviral nucleoside/nucleotide analogues. This class inhibits HBV DNA replication (Bömmel et al., 2010). While the number of approved treatments is increasing, the application of these therapies remains problematic. For example, interferon α -based therapies are not recommended for long-term treatments. This is due to tolerability and side effects (Bömmel et al., 2010). Antiviral nucleoside/nucleotide analogues are better tolerated and can be prescribed for longer use. However, the problem with viral therapies is that viruses mutate at high rates. As such, possible resistance of the virus to the therapies might jeopardize the efficacy of these treatments. The best approach involves early detection and effective treatment with what is available (Bömmel et al., 2010).

6.2.3.3 Competitive Landscape

The US National Institute of Health (NIH) website lists 298 open clinical trial studies related to HBV (ClinicalTrials, 2010). In terms of RNAi therapeutics, Firm B is working on HBV. Their product is in the early stage of development. Overall, the competition for HBV is low.

6.2.3.4 Unmet Medical Needs and Future Trends

Incidence of HBV will continue to decline because of standardization of the HBV vaccine (Davis & Roberts, 2010). However, there is a need for therapies for HBV even with the available vaccine. Chronic infections prevalent in current generations will persist for some time. Hence, the next stage is treatment of chronic HBV. The main aim of chronic HBV therapy is to reduce the future impact it has on liver disease progression from inflammation to liver failure and hepatocellular carcinoma (HCC) (Davis & Roberts, 2010).

6.2.4 Liver Fibrosis

Liver fibrosis can progress from mild liver inflammation to liver failure if not treated. Many underlying conditions such as hepatitis infection, alcohol abuse, dietary component and others can contribute to liver fibrosis. Some studies show that liver fibrosis can be the cause of non-alcoholic steatohepatitis (NASH) (Bataller & Brenner, 2005). NASH is a component of metabolic syndrome that is characterized by obesity, Type 2 diabetes mellitus, and dyslipidemia (Bataller & Brenner, 2005). This further proves that liver fibrosis is a disease of many underlying conditions. As such, I mention it briefly in context of the liver disease group. Hence, RNAi therapeutics for liver fibrosis would benefit treatments for the liver.

6.2.4.1 Market Size

Prevalence and incidence statistics for liver fibrosis are difficult to find because it is not a well defined indication. A recent study using FibroTest predicts the prevalence of advanced fibrosis to be 2.8% in the general population that is forty years of age or older (Poynard et al., 2010).

6.2.4.2 Current Standard of Care

There is no standard treatment for liver fibrosis. If it leads to liver failure, patients undergo liver transplantation. In many patients with HCV, infection will recur and repeated liver transplantation is required (Bataller & Brenner, 2005). Diagnosis, treatment, and monitoring progress of the disease are difficult. Biopsy is the standard of care for diagnosis of liver fibrosis. Hence, there is a real need for non-invasive methods. Many non-invasive biomarker tests are in development with the FibroTest and Fibroscan being the most validated (Bataller & Brenner, 2005). Future diagnostic advancements will lead to better and earlier diagnosis. The goal is to eliminate the need for biopsy. Overall, there is potential for RNAi therapeutics to be used as an

antifibrotic therapy. The ideal therapeutic needs to be liver-specific, safe, well tolerated, and efficacious (Bataller & Brenner, 2005).

6.2.4.3 Competitive Landscape

The US National Institute of Health (NIH) website lists 195 open clinical trial studies related to liver fibrosis (ClinicalTrials, 2010). Due to the nature of liver fibrosis, most trials include other indications, for example, HCV, heart failure, obesity, metabolic syndrome, and insulin resistance. In terms of RNAi therapeutics, Firm C is developing a drug for fibrosis that is in Phase II. Overall, the competition for liver fibrosis is low.

6.2.5 Liver Cancer and Hepatocellular Carcinoma (HCC)

Primary liver cancer refers to cancer that starts in hepatocytes. There are four different types of liver cancer: Hepatocellular Carcinoma (HCC), Cholangiocarcinoma, Hepatoblastoma and Angiosarcoma, or hemangiosarcoma (MayoClinic, 2010). HCC is the most common type of liver cancer and the focus of this analysis. HCC affects both children and adults. HCC is different from other cancers in that 80% of patients have two diseases: cirrhosis and cancer (Carr, 2004). In addition, there is a gender preference in the estimated 80% of patients who also suffer from cirrhosis. Those patients show a range of three to one, and up to nine to one, male predominance of disease compared to women (Carr, 2004). HCC is a whole organ disease in which metastasis is rare or absent. This is because patients die from liver failure before the metastasis can happen. Overall, HCC is specific and a good target for PLATFORM X.

6.2.5.1 Market Size

There are several important facts about HCC. First, it is the third leading cause of cancer mortality worldwide (Altekruse et al., 2009). Second, it primarily affects elderly patients with liver fibrosis or cirrhosis (Gary & Roberts, 2010). In addition, there is evidence that patients infected with HCV and HBV will progress to HCC. The incubation period is long, however. It

can take anywhere from two to four decades for a disease to progress from inflammation to HCC (Carr, 2004). Third, mathematical models have predicted that prevalence of HCC due to HCV is expected to increase to 2020 and possibly beyond (Davis et al., 2003). Further evidence shows a link between HBV, HCV and HCC. 75% to 80% of primary liver cancers in patients are correlated with chronic infection with HCV (in 25% to 30%) or with HBV (in 50% to 55%) (Bosch et al., 2005). Even though HCV and HBV are on decline, HCC is on the increase in the US.

Worldwide prevalence of liver cancer is estimated to be 564,000 (398,000 in men and 166,000 in women) people per year (Bosch et al., 2004). Overall, liver cancer accounted for 5.6% of all tumours: 7.5% in men and 3.5% in women. In high-risk countries, the onset of HCC is from age 20 to 50.

Liver cancer has a very high mortality rate. As such, incidence and mortality are assumed to be equal. Both frequency and mortality are on the increase in the US (Hoofnagle, 2004; Bosch, 2005). This might be due to the aging population and higher life expectancy trend. In addition, incidence of HCC is on the rise in North America, Central Europe, Japan, Australia, and the United Kingdom (Bosch, 2004). The 15-year study of the HCC profile in the US reported by Carr is summarized in Table 6.

Table 6: HCC Profile Identified in a 15 Year Long Study in the US

NUMBER OF PATIENTS	❖ 1700
HCC CHARACTERISTIC	❖ 75% had bilobar cancer ❖ 72% had portal vein thrombosis ❖ 65% had 3 or more tumor masses
OTHER CONDITIONS	❖ 30% HCV infection ❖ 20% infected with HBV ❖ 28% alcohol-associated cirrhosis ❖ 20% no identifiable underlying liver disease
GENDER PREFERENCE	❖ 2.5:1 male predominance ratio
AGE	❖ average 56 years; range: 6 months to 92 years
SUB-GROUP	❖ 20% found ineligible for treatment; median survival: 3 months

Source: Adapted from information reported by Carr (2004).

Risk factors associated with the development of liver cancers are gender, age, chronic infection with HCV and HBV, cirrhosis, certain inherited diseases, diabetes, exposure to dietary aflatoxins, obesity, and alcoholism (MayoClinic, 2010, Bosch et al., 2004). A recent study also assessed that HCC has a significant impact on the US healthcare system where the annual cost of HCC was estimated to be US \$454.9 million with each patient costing US \$32,907 (Lang et al., 2009). An estimated 82.9% of this cost is due to health care and 10.8% to lost productivity (Lang et al., 2009).

6.2.5.2 Current Standard of Care

There are three ways of diagnosing liver cancer: (1) blood tests, (2) imaging tests with ultrasound, including CT, MRI, chest X-ray, and bone scan, and (3) biopsy (MayoClinic, 2010). Biopsy is the standard of care. However, the liver is already scarred in HCC. As such, biopsy is considered even more invasive and risky as it might lead to bleeding, bruising, and infection (MayoClinic, 2010). Hence, better non-invasive diagnostic tools are needed.

Cancer is a complex disease, and HCC is no different. In fact, cirrhosis potentially makes HCC worse than other cancers. Current treatments for HCC are very limited. The mortality rate is high due to late diagnosis and even if patients are diagnosed, there is a lack of standardized

guidelines for monitoring. However, non-invasive biomarker tests should improve diagnosing, monitoring, and treatment of HCC.

Current treatments include surgery and chemotherapy (Carr, 2004). Surgery includes either the removal of a part of the liver or liver transplantation. Chemotherapy is very limited and more harmful than useful due to cirrhosis. Drugs in current use are doxorubicin (Adriamycin) and cisplatin, and a newer promising treatment is liver hepatic artery chemoembolization (TACE) that is considered a new benchmark for future treatment (Carr, 2004). The approach is to inject chemotherapy drugs directly into the liver so that it is more efficacious and has less negative impact on the already fragile liver. New treatments include angiogenesis inhibitors, such as Sorafenib (Nexavar), which adopt a more targeted approach (Lang et al., 2008). Sorafenib achieves improvement for patients, but only for a few months. The combination of surgery/transplantation and chemotherapy/TACE is likely to be most beneficial to patients. This is due to targeting both cirrhosis and the tumours of HCC.

6.2.5.3 Unmet Medical Need

HCC is a very serious disease and current treatment options are highly invasive, costly, not beneficial to the patient, and as a result are not meeting the medical needs. Chemotherapy is largely ineffective and toxic to the already scarred livers (Hoofnagle, 2004; Carr, 2004), and therefore, better therapies for treating cirrhosis are needed. Liver transplantation is invasive, yet it is not very beneficial for many patients. Especially in HCV patients, the cancer recurs and as such, the liver transplantation might have to be repeated. In addition, an estimated 50% of patients with HCC do not pass eligibility criteria for transplantation, and are not treated (Carr, 2004).

6.2.5.4 Competitive Landscape

The US National Institute of Health (NIH) website lists 574 open clinical trial studies related to liver cancer (ClinicalTrials, 2010). In terms of RNAi therapeutics, Firm A has a liver cancer drug in Phase I. Firm D is testing several liver cancer targets in collaboration with other firms. For HCC, the US National Institute of Health (NIH) website lists 274 open clinical trial studies (ClinicalTrials, 2010). Overall, the competition for HCC is low to medium.

6.2.5.5 Future Standard of Care

In general, prevention, early detection, and more targeted therapies are needed (Hoofnagle, 2004). With 50% of patients remaining untreated there is a high need for non-invasive or minimally invasive diagnostic tools and therapies. Hence, RNAi therapeutics could be an important non-toxic approach to treating HCC based on molecular pathways and genes. In addition, non-invasive diagnostic and prognostic biomarker tests are emerging and will be significant in the future because they can accelerate early detection and reduce the need for invasive biopsy. As such, these diagnostic advancements can lead to faster clinical trials and possibly accelerated FDA approvals where patient recruitment and monitoring will be easier.

6.3 The Liver-Associated Group: Diabetes/Cardiovascular Diseases (Metabolic Syndrome)

6.3.1 Metabolic Syndrome in Relation to Diabetes and CVDs

Metabolic syndrome represents a common combination of conditions and risk factors that can lead to diabetes and cardiovascular diseases (CVDs) (MedlinePlus, 2010). The research of potential targets for this analysis also identified a correlation between metabolic syndrome, diabetes, and CVDs. For the purpose of this analysis, I grouped these three indications. Next, I analyze diabetes and CVDs in more detail. Metabolic syndrome is a condition linking the two.

6.3.2 Diabetes

Diabetes mellitus, commonly known as diabetes, represents a group of diseases the hallmark of which is high glucose levels. This is due to the body's inability to produce or use a hormone called insulin (CDC, 2009). Pancreatic beta cells are the only cells in the body that produce insulin to regulate blood glucose levels. While diabetes, if not prevented or treated, can lead to death, many lifestyle related risk factors are preventable. There are four different categories of diabetes: Type 1, Type 2, gestational, and others.

Type 1 diabetes is a serious condition in which the patient's immune system attacks pancreatic beta cells where patients cannot produce insulin. Type 1 diabetes accounts for approximately 5-10% of all diabetes (CDC, 2009). Type 1 diabetes risk factors are autoimmune, genetic, and environmental. Type 2 diabetes accounts for 90-95% of all the diagnosed diabetes (CDC, 2009). While patients with Type 2 diabetes produce insulin, their bodies are not utilizing it properly, and as such, this can lead to chronic insulin resistance. If chronic diabetes is not treated, it can have serious implications for a patient. However, Type 2 diabetes is highly

preventable. Patients can prevent or improve their condition by lowering the risk factors related to their lifestyle. Some of the risk factors are obesity, physical inactivity, and age. Another type of diabetes is gestational diabetes caused by glucose intolerance that occurs during pregnancy (CDC, 2009). The fourth category results from genetic conditions and it accounts for an estimated 1-5% of diagnosed diabetes (CDC, 2009). For diabetes-associated complications, control of blood glucose, pressure and lipids, is important. This correlation and connectedness led me to analyze and evaluate diabetes/cardiovascular diseases (CVDs)/metabolic syndrome as a group.

6.3.2.1 Market Size

The worldwide prevalence of diabetes for all-age groups was estimated to rise from 171 million (2.8%) in 2000 to 366 million (4.4%) in 2030 (Wild et al., 2004). In 2007, prevalence in the US was higher than the global estimate. In the US, 23.6 million (7.8%) people of all ages have diabetes. Of these, 17.9 million are diagnosed and 5.7 million are undiagnosed (CDC, 2009).

In 2007 in the US, 1.6 million people twenty years and older were newly diagnosed with diabetes 50% of which are in the 40-59 age group (CDC, 2009). The mortality rate is difficult to obtain because many people are undiagnosed since it is a disease with underlying conditions. Therefore, these statistics may be underestimated. In 2005, death certificates indicated that diabetes contributed to 233,619 deaths. As such, diabetes was the seventh leading cause of death in the US in 2006 (CDC, 2009). In 2007, US \$174 billion was spent on diabetes. Direct medical costs were US \$116 billion and indirect costs were US \$58 billion (CDC, 2009).

6.3.2.2 Competitive Landscape

The US National Institute of Health (NIH) website lists 2027 open clinical trial studies related to diabetes (ClinicalTrials, 2010). For metabolic syndrome, there are 648 open clinical

trial studies listed (ClinicalTrials, 2010). For Type 2 diabetes, there are 967 open clinical trial studies listed (ClinicalTrials, 2010). There are many treatments already on the market and others are in development. These include all types of human therapeutics: small molecules, biologics, and emerging RNAi therapeutics. However, most of the treatments available are oral. The majority (57%) of adults diagnosed with diabetes take only oral medications, 13% both insulin and oral medications, 14% only insulin and 16% take no medications (CDC, 2009).

In terms of RNAi therapeutics, there are several products in development. This indicates higher competition and potential application of RNAi therapeutics in treating diabetes. Firm A has a product for diabetic macular edema in Phase II via its partnered program. In addition, there are several other products in the discovery and development stage. Firm C has four products in their pipeline for Type 2 diabetes: one is in Phase II, one in Phase I and two in the preclinical stage. Firm E has one product in the clinical stage for diabetic macular edema. Overall, the competition for diabetes is high.

6.3.3 Cardiovascular Diseases (CVDs)

Cardiovascular diseases are a group of conditions affecting heart and blood vessels. There are many cardiovascular diseases (CVDs). These are widely known as heart attacks and strokes. They are often acute and caused by fatty deposits or blood clots that block the blood flow to the heart (CDC, 2009). Research for this analysis led to a number of potential gene targets related to CVDs.

6.3.3.1 Market Size

In 2004, an estimated 17.1 million people died from CVDs worldwide (Rosamond et al., 2007). This represented 29% of all global deaths making CVDs the number one killer. In the US, CVDs affect one in three American adults. In 2004, the estimated prevalence was 79.4 million and mortality was 875 thousand (Rosamond et al., 2007). The majority of these deaths were due

to coronary heart diseases (7.2 million) and strokes (5.7 million) (Rosamond et al., 2007). Many Americans have more than one type of CVDs where an estimated half of those who have them are 65 years or older (Rosamond et al., 2007). Since the disease targets elderly, prevalence is expected to rise in the future due to the aging population trend. Table 7 summarizes prevalence, incidence and mortality of four major categories of CVDs.

Table 7: Prevalence, Incidence and Mortality of Major CVDs

DISEASE	PREVALENCE	INCIDENCE	MORTALITY
Total Cardiovascular Diseases (CVDs)	79.4 million	-	871.5 thousand
Coronary Heart Disease (CHD)	15.8 million	1.2 million	452.3 thousand
Stroke	5.7 million	700.0 thousand	150.1 thousand
High Blood Pressure (HBP)	72.0 million		54.2 thousand
Heart Failure (HF)	5.2 million		57.7 thousand

Source: Adapted from information in Heart and Stroke Statistics Report (2007)

There are many underlying risk factors contributing to CVDs. Some of these are tobacco, high blood cholesterol, lack of exercise, obesity, diabetes mellitus, renal disease, chronic kidney disease, nutrition, and metabolic syndrome (Rosamond et al., 2007). In 2007, the estimated costs for CVDs in the US were US \$431.8 billion (Rosamond et al., 2007). In 2004, cancer costs were estimated US \$190 billion and in 1999 HIV costs were estimated US \$28.9 billion (Rosamond et al., 2007). Hence, CVDs have the highest economic costs.

6.3.3.2 Competitive Landscape

The US National Institute of Health (NIH) website lists 5920 open clinical trial studies related to CVDs (ClinicalTrials, 2010). For dyslipidemia there are 233 open clinical trial studies and there are 295 open clinical trial studies for atherosclerosis (ClinicalTrials, 2010). In terms of RNAi therapeutics, Firm C has five CVD products in development: one is in Phase III, two in

Phase I and two in the preclinical stage. While Firm Y's product shows great potential, there are many drugs in development and on the market resulting in high competition. Overall, the competition for CVDs is high.

6.4 Summary: From A Commercial Potential to Strategic Options for Firm Y

In this chapter, I assessed a commercial potential of newly identified market opportunities for Firm Y based on the business feasibility criteria. This data adds to the final comprehensive evaluation of the strategic options for Firm Y that emerged from this analysis. The evaluation of the strategic alternatives is partially based on Vining and Meredith metachoice evaluation method (2000). These strategic options for Firm Y are:

- (1) First strategic option is status quo. Firm Y should focus only on its current products and should not expand its product pipeline.
- (2) Second strategic option is for Firm Y to focus on the liver specific group. Therefore, Firm Y should focus on expanding its product pipeline in the direction of the liver diseases group that consists of HBV, liver fibrosis and liver cancer (HCC).
- (3) Third strategic option is for Firm Y to focus on a broader group related to the liver. Therefore, Firm Y should focus on expanding its product pipeline in the direction of liver-associated group that consists of diabetes, CVDs and metabolic syndrome.
- (4) Fourth strategic option is to look for targets not specific to the liver.

In the next chapter, I analyze these strategic alternatives for Firm Y. The overall comprehensive evaluation of the strategic options is based on the integration of all the criteria listed in chapter five to ensure suitability for Firm Y. These are: (1) scientific feasibility criteria listed in Table 2, (2) business feasibility criteria listed in Table 3, and (3) corporate criteria

specific to Firm Y listed in Table 4. The overall comprehensive evaluation leads to the set of recommendations for Firm Y.

Chapter 7: A COMPREHENSIVE EVALUATION OF THE STRATEGIC OPTIONS FOR FIRM Y

In this chapter, I start with the strategic options including the summaries of each indication opportunity, and conclude with the overall evaluation that leads to the set of recommendations for which strategic option Firm Y should pursue and why.

7.1.1 The First Strategic Option: Focus on the Current Product Pipeline

The first strategic option implies status quo. As a result, Firm Y would focus on development of its current products. As such, it would choose not to exercise its option to expand its product pipeline. This option would put a high-risk on Firm Y because of the high-risk, high-failure rate of the DDP. Therefore, failure or underperformance of any of its current products in the pipeline could devalue the firm. As such, the first strategic option is high-risk. Overall, it would not result in Firm Y's long-term sustainable growth and competitive advantage within the industry. However, it might be a viable option if Firm Y plans to exit via merger or acquisition in the near future. As such, the available target worldwide licence agreements would be considered as intangible assets adding value to the potential buyer firm.

7.1.2 The Second Strategic Option: Expanding the Product Pipeline by Focusing on the Liver Diseases Group

The second strategic option is the liver specific group of diseases that includes HBV, liver fibrosis, and liver cancer, more specifically HCC. In the next sections, I include a brief summary of each of the indication opportunities within the group. I follow with the evaluation of

the second strategic option as an opportunity for Firm Y based on all the criteria: scientific, business, and corporate. The evaluation scores are listed in Table 8.

7.1.2.1 A Summary of Hepatitis B for Firm Y

Overall, HBV shows a good potential for Firm Y. It is liver specific. There are examples of potential effective treatment strategies using siRNAs in the preclinical studies to treat viral infections. Only Firm B is currently working on RNAi therapeutics for HBV. However, the product is in the early stage and as such, the FDA experience with the HBV RNAi therapeutics might be limited. However, Firm Y already has experience with infectious diseases. In addition, HBV has only four genes that significantly reduce the number of potential targets for identification and target validation stage in the DDP. However, due to the nature of viral infections, RNAi therapeutics for HBV would have to include more than one target. This is to ensure complete halting of viral replication. As such, efficacy of treatment could be increased. However, the cost of treatment might be higher. In addition, future resistance of the virus to RNAi therapeutics can be problematic in terms of the long-term efficacy of the treatment. The fact that an effective vaccine is available represents a strategic limitation for Firm Y. However, chronic HBV presents a problem since not many drugs are in development, and those that are on the market are not very effective.

7.1.2.2 A Summary of Liver Fibrosis for Firm Y

Overall, liver fibrosis shows a medium potential for Firm Y. It is liver specific. There are examples of effective treatment strategies in the preclinical and clinical studies using RNAi therapeutics. Hence, the FDA is already familiar with the process. However, that the indication is not very specific and occurs due to many underlying conditions can be a disadvantage for several reasons. First, target identification and optimization might be too complex for Firm Y with its limited resources. Second, patient recruitment for clinical trials might be challenging. Third,

safety and efficacy might be more difficult to prove due to many underlying conditions. Fourth, the need of biopsy for diagnosis could be limiting. Fifth, the fact that the indication is not well defined makes it difficult to assess market and commercial potential. On the other hand, the broadness of liver fibrosis can lead to a wider application and use of therapeutics for more than one indication.

7.1.2.3 A Summary of HCC for Firm Y

Overall, HCC shows a good potential for Firm Y. It is liver specific. The complexity of the disease adds to the difficulty in assessing market and commercial potential. However, there is a significant unmet medical need where RNAi therapeutics can make a real difference. Clinical trials might be difficult due to diagnosis and progress monitoring of patients. However, non-toxic potential of RNAi therapeutics might lead to accelerated FDA approvals if treatment shows significant benefit to the patients compared to the limited treatments currently available. In addition, RNAi therapeutics could be used for other liver diseases. Firm A and Firm D are developing RNAi therapeutics for liver cancer. Hence, the FDA is already familiar with the process.

7.1.2.4 An Evaluation of the Second Strategic Option

In terms of scientific criteria, the second strategic group is highly eligible for RNAi therapeutics where there is a low to moderate body of evidence for the effective treatment strategies in the preclinical and clinical studies. The research for this analysis identified lower, but more focused potential gene targets. The liver specificity is high for this strategic option.

In terms of business criteria, the market size might be smaller for this group; however, RNAi therapeutics has an opportunity to address a real unmet medical need compared to current conventional methods. As such, Firm Y has a real potential to capture a larger size of this smaller market, where if treatments are highly effective Firm Y can charge premium prices for these

RNAi therapeutics. In addition, the commercial aspect increases based on the lower competition present in this group. Currently, RNAi therapeutics in development are less advanced, however, the FDA is somewhat familiar with RNAi therapeutics for this group of indications.

In terms of corporate criteria, the second strategic option would add to the differentiation of Firm Y's pipeline by expanding into infectious diseases. In addition, it is suitable for PLATFORM X's liver specific capabilities where focus on this group of indications has a higher potential to achieve the synergy of target-PLATFORM X product development. The synergy refers to a specific delivery of the product to the target site. This is very important in the RNAi Therapeutics sector. As such, products that have this target-delivery platform synergy would give rise to RNAi therapeutics that treats intended indication with higher effectiveness. Therefore, the second strategic option gives Firm Y the opportunity to develop expertise in the liver related diseases. This strategic approach can lead to achieving a sustainable competitive advantage based on PLATFORM X's capabilities. This group might have less synergy with current Firm Y's products; however, it is better suited for current and future partnership and exit/integration opportunities for Firm Y.

7.1.3 The Third Strategic Option: Expanding the Product Pipeline by Focusing on the Liver-Associated Group

The third strategic option is the liver-associated group of diseases that includes diabetes, CVDs, and related metabolic syndrome. In addition, this group has a wide range of risk factors. Most of these are common to the indications within the group. Some of them are genetic, lifestyle related, or environmental. However, many of these risk factors are preventable with healthier lifestyles. In the next sections, I include a brief summary of each of the indication opportunities within the group. I follow with the evaluation of the third strategic option as an opportunity for Firm Y based on all the criteria: scientific, business and corporate. The evaluation scores are listed in Table 8.

7.1.3.1 A Summary of Diabetes for Firm Y

Overall, diabetes shows a low to medium potential for Firm Y. Diabetes is not liver specific. There are examples of effective treatment strategies in the preclinical and clinical studies using RNAi therapeutics. As such, the FDA is familiar with RNAi therapeutics related to diabetes. The potential product might be applicable to treating more than one condition. There are quite a few potential targets. However, the high number of potential targets might be costly and difficult to identify, optimize, and validate. Diabetes is an indication of many underlying conditions and it is highly preventable. The competition for diabetes is high and many medications are oral. Firm Y's RNAi therapeutics would have to be superior to current treatments with high potential to treating the unmet medical need. It might be too difficult to make a difference on the already saturated market. However, in-depth analysis on the gene level is needed to assess current gaps in treatments and if there is potential for RNAi therapeutics, and more importantly for Firm Y. However, that is beyond the scope of this project.

7.1.3.2 A Summary of Cardiovascular Diseases for Firm Y

Overall, CVDs show a low to medium potential for Firm Y. CVDs are not liver specific. There are examples of effective treatment strategies in the preclinical and clinical studies using RNAi therapeutics. As such, the FDA is familiar with RNAi therapeutics in regards to CVDs. There are quite a few potential targets. In fact, the highest number of potential targets identified for this analysis was for the CVDs. However, finding, optimizing, and validating these targets might be costly and difficult. CVDs are diseases of many underlying conditions and are highly preventable. The competition is even higher than for diabetes where there are many medications already available and in development. As such, Firm Y's RNAi therapeutics product would have to have higher effectiveness and treat the disease better than current treatments. As for diabetes, a more detailed unmet medical need based on gene analysis still needs to be conducted in order to

assess why current medications are not addressing this need. However, that is beyond the scope of this project.

7.1.3.3 An Evaluation of the Third Strategic Option

In terms of scientific criteria, the third strategic group is moderately eligible for RNAi therapeutics, but there is a moderate body of evidence for the effective treatment strategies in the preclinical and clinical studies. The research for this analysis identified more, but less focused potential gene targets. The liver specificity is low for this strategic option.

In terms of business criteria, the market size might be larger for this group; however, RNAi therapeutics might have a lower opportunity to address a real unmet medical need compared to current conventional methods. As such, Firm Y might not have the potential to capture a larger size of this larger market. In addition, the commercial aspect for this group decreases based on the high competition present in this group. Currently, RNAi therapeutics in development is more advanced, hence, the FDA is familiar with RNAi therapeutics for this group of indications.

In terms of corporate criteria, the third strategic option would not add to Firm Y's pipeline differentiation. In addition, it is less suitable for PLATFORM X's liver specific capabilities where focus on this group of indications has a lower potential to achieve the synergy of target-PLATFORM X product development. This group has higher synergy with current Firm Y's products. This is an advantage because Firm Y has in-house knowledge in this area. However, a disadvantage is that moving further in this direction would result in a less diversified product portfolio. This group is considered a worse fit for current and future partnership and exit/integration opportunities for Firm Y.

7.1.4 The Fourth Strategic Option: Searching Beyond the Liver

The fourth strategic option considers targets in tissues or organs other than the liver. This option would explore PLATFORM Xs delivery capability to other organs. However, that is beyond the scope of this project. As such, I do not consider the fourth strategic option in this analysis.

7.2 An Evaluation of Firm Y's Strategic Options

In this section, I present the results in Table 8. The table shows all the strategic options, evaluation criteria and scores based on the overall integrated analyses conducted so far for this project.

Table 8: A Comprehensive Evaluation of Strategic Options for Firm Y

GOALS (EVALUATION CRITERIA)	FIRST STRATEGIC OPTION	SECOND STRATEGIC OPTION	THIRD STRATEGIC OPTION
SCORING (1-5) 1 is the lowest 5 is the highest	NO NEW PRODUCTS	LIVER DISEASES GROUP	LIVER-ASSOCIATED GROUP
SCIENTIFIC FEASIBILITY			
ELIGIBLE FOR RNAi	1	4	3
PROOF-OF-CONCEPT EVIDENCE	1	3	4
FOCUSED GENE TARGET	1	3	2
LIVER SPECIFICITY	1	4	3
BUSINESS FEASIBILITY			
MARKET POTENTIAL	1	4	3
UNMET MEDICAL NEED	1	4	2
COMPETITIVE LANDSCAPE	1	4	2
FDA EXPERIENCE WITH RNAi THERAPEUTICS	1	3	4
CORPORATE ATTRACTIVENESS			
CORPORATE PIPELINE GROWTH (DIFFERENTIATION)	1	4	2
SYNERGY WITH PLATFORM X	2	4	3
SYNERGY WITH CURRENT PRODUCTS	1	3	4
PARTNERSHIP SYNERGY (CURRENT)	2	4	3
PARTNERSHIP SYNERGY (FUTURE)	2	4	3
EXIT/INTEGRATION (STRATEGY)	2	4	3
TOTAL SCORE	18	52	41
TOTAL POSSIBLE SCORE	70	70	70

The scoring scheme for the evaluation criteria is from one to five. One is the lowest and five is the highest. Hence, the higher the overall score, the better the standing of each of the strategic options for Firm Y. For the first strategic option, I assigned one for the first two categories, because these were not applicable to the first strategic option as it assumes that Firm Y would not expand its product pipeline. In addition, it is worth briefly discussing the scoring rationale for criterion number three (focused gene target) and number five (market potential).

For the number three criterion, the lower the score the more difficult it is to identify the target. The number of potential targets is also important. First, many targets get a lower score.

Second, targets not related to the liver get a lower score. For example, HBV has a higher score because it has four genes and, as such, a lower number of potential targets, and is liver specific.

For number five criterion, I based the scores on the potential to capture market share. It is not based on market size. I consider the potential effectiveness of the treatment developed by Firm Y. As such, for the liver diseases group there are not many treatments on the market and those that are available are not meeting the medical need. In addition, majority of these treatments are not oral. In addition, I considered Firm Y's organizational capabilities. Would Firm Y be able to excel in treating this indication? If yes, I assumed that Firm Y would have a higher chance to capture a larger market share of a smaller market. In contrast, the liver-associated group already has various treatments on the market and many of these are oral treatments. Hence, Firm Y would have to compete against intense competition with its intravenously administered products. However, the competitive landscape of the second strategic group is quite complex and requires resources for a deeper analysis. Thus, the evaluation, analysis, and scores are based on limited data and resources available for this project.

7.2.1 A Summary of the Results of the Evaluation of Potential New Markets for Firm Y

Table 8 shows results for the comprehensive evaluation of strategic options for Firm Y. The second strategic option focusing on liver diseases has the highest overall score of 52/70. In addition, it has the highest score for each section. The score in the scientific feasibility section is 14/20, 15/20 in the business feasibility section, and 23/30 in the firm's attractiveness section. To summarize, this is because the second strategic option: (1) is specific to the liver, (2) has high unmet medical needs, and (3) has synergy potential with Firm Y's overall organizational capabilities mainly PLATFORM X's capabilities and the firm's partnerships.

The third strategic option with focus on liver-associated diseases has the overall score of 41/70. The score in the scientific feasibility section is 12/20, 11/20 in the business feasibility section, and 18/30 in the firm's attractiveness section. To summarize, this is because the third strategic option: (1) is less specific to the liver, (2) has high competition and high preventability, and (3) is lacking synergy potential and attractiveness for Firm Y's overall organizational capabilities mainly PLATFORM X's capabilities and the firm's partnerships. In the next chapter, I provide Firm Y with the final set of recommendations.

Chapter 8: RECOMMENDATIONS FOR FIRM Y

8.1 Moving Forward With the Second Strategic Option

Previous chapters evaluated and assessed the four strategic options based on research and analyses conducted. The second strategic option has the highest score. This indicates two conclusions: (1) Firm Y should expand its product pipeline and (2) it should do so strategically in the direction of the liver diseases group. This is due to PLATFORM X's core competency to deliver to the liver. For the purpose of this analysis, the liver diseases group includes HBV, liver fibrosis, and liver cancer (HCC) indications. In addition, I recommend Firm Y focuses on infectious diseases, specifically HBV, first and then later expands into HCC since the expansion should be based on Firm Y's organizational capabilities and corporate strategy. This approach will allow Firm Y to grow while sustaining its competitive advantage within the RNAi Therapeutics sector. In the next section, I highlight potential benefits for pursuing this strategic option.

8.2 Benefits of Focusing on the Liver Diseases Group

8.2.1 Diversification of Risk With New Products

Adding new products to Firm Y's current product pipeline will diversify the risk of potential future product failures. The firm is preparing to advance its first product to the planned Phase I/II clinical trials where safety and efficacy will be tested. This is an important stage in the development of the drug. This product has already been pulled once from Phase I trials in order to test it using an improved formulation of PLATFORM X. However, there is a risk that the product will not hold to anticipated efficacy. This can devalue the overall potential of the

product. In addition, Firm Y's second product is preparing for Phase I trial. These are important milestones for the product development of the firm. As such, this is an appropriate time to start advancing new products into the pipeline. These new products would diversify the risk and show a long-term growth potential of the firm.

8.2.2 In Line With the Current Partnerships

First, Firm Y's recent partnership will add significant value to having more products in its pipeline. It is the multi-year target validation agreement with a Big Pharma firm. Firm Y will further gain important knowledge and capabilities in target validation so that it can identify and validate targets internally for its own products.

Second, the two recent accomplishments of Firm Y will add to the synergy with the second strategic option. Firm Y published collaborative results showing successful elimination of one of the viruses in monkeys (Firm Y, 2009). In continuation to this success, Firm Y signed a contract to develop RNAi therapeutics against one of these viruses (Firm Y, 2009). This is significant for Firm Y since it further expands its product development capabilities into viral infections as well. Thus, Firm Y has experience with products related to "bad" cholesterol, hence CVDs, solid tumours, and infectious diseases. This development is in-line with the second strategic option where Firm Y can transfer this knowledge into developing its own antiviral product.

8.2.3 Starting With HBV

Based on this analysis, I recommend Firm Y pursues HBV for its future product development. However, there are some risks and challenges. First, target identification will depend on Firm Y's license agreements with its partner where Firm Y would have to choose targets in which its partner is not interested. Second, due to nature of viral infections, Firm Y will have to target more than one gene of the virus, and as such, might have to use more than one

target per indication. Furthermore, there might be a problem related to future viral resistance. Nonetheless, there is a benefit to starting with HBV since it has four genes in its genome, where costs associated with identification and validation of targets can be lower. In addition, Firm Y has experience in the area of viral infections.

Targeting liver diseases group can have a good synergy with PLATFORM X's core competency. This potentially results in the development of safer and more efficacious RNAi therapeutics treating the disease at its core target organ, the liver. Furthermore, Firm Y can look into combinatorial approaches that would target both viral and cellular genes. However, safety is a concern because targeting too many genes could trigger an important biological process in the host. This would result in side effects and less safe treatments.

8.2.4 Summary: The Second Strategic Option is a Good Fit for Firm Y

The second strategic option gives Firm Y a potential of targeting a niche market within the broad liver diseases. It has a real potential to address the high-unmet medical need. Firm Y has in-house experience within the infectious diseases and oncology sectors, thus HBV and HCC are a good fit. Another compelling commercial aspect is that treatments for HCC are limited. There is relatively low competition both in the RNAi Therapeutics sector and overall. In addition, depending on firm's exit strategy, the HBV/liver fibrosis/HCC focus has a potential to give Firm Y competitive advantage over other firms. Movement towards infectious diseases and HCC would make Firm Y a great candidate for a merger or acquisition with other sector leaders or a Big Pharma firm which are not developing products for this group of indications.

8.2.5 Challenges and Risks Moving Forward With Liver Diseases

8.2.5.1 Method Limitations

It should be noted that this analysis and recommendations for new market opportunities are based on limited data and resources. As such, Firm Y needs to conduct further analysis. First, Firm Y should obtain deeper analysis of each indication on a gene level, and assess RNAi therapeutics potential and gaps in available treatments. This is especially important for the liver-associated group. There are many therapeutics on the market and in development, and yet, diabetes and CVDs are leading causes of death. For the purpose of this analysis, I put considerable weight on the fact that many risk factors for the liver-associated group are preventable. However, as mentioned, the strategic group should be further analysed in terms of gene targets. Is there a gene to target by RNAi therapeutics that cannot be targeted with other conventional methods, but can meet current unmet medical needs? And if so, does Firm Y have organizational capabilities to develop such RNAi therapeutics? Furthermore, each indication needs to be analyzed based on internal data of Firm Y, and specifically, its estimated costs of drug development and manufacturing.

Another risk is the grouping of indications presented in this analysis. Firm Y can further diversify its portfolio and choose to explore targets in both groups. As such, it might choose to develop products for both HBV and Type 2 diabetes. However, further analysis is needed to assess this alternative option.

8.2.5.2 Recommendation Risks

The primary risk is the fact that the liver diseases group poses limitations due to agreements Firm Y has with its partners. Another risk is that, even though it is important to have a diversified portfolio, for some firms this is not feasible. Firm Y needs to assess internally its ability to expand its pipeline. Also, it should assess how many indications it should pursue at

once. As such, Firm Y needs to address questions relevant to its other operations and the potential impact of the product pipeline expansion. Moreover, due to its knowledge in CVDs via its first product, Firm Y might choose to expand in that direction instead of diversifying into infectious diseases.

8.3 General Recommendations Moving Forward

PLATFORM X gives Firm Y competitive advantage within the RNAi Therapeutics sector. This is evident by its important partnerships gained via out-licensing of PLATFORM X. However, Firm Y should broaden the scope of PLATFORM X's delivery capability beyond the liver, enabling it to develop products for more indications and to gain new partnerships. In addition, PLATFORM X's broader application beyond the liver would give it a potential to become a delivery standard platform within the RNAi Therapeutics sector.

The research conducted for this analysis indicates further opportunities for Firm Y in the RNAi Therapeutics sector. These are:

- ❖ PLATFORM X can carry nucleic acids other than siRNAs. Firm Y can consider emerging opportunities for other nucleic acids, such as miRNAs. These can be explored as: (1) new product opportunities and (2) potential new partnerships, which can lead to future revenues for Firm Y.
- ❖ Firm Y's manufacturing capabilities cannot be underestimated. Manufacturing can be pursued beyond the product development stage of RNAi therapeutics that use PLATFORM X. As such, Firm Y should be the main manufacturer for PLATFORM X products when they reach the market. Thus, broader manufacturing capabilities can add value to Firm Y in the future.
- ❖ Firm Y should look for more opportunities and have a greater involvement within the local biotechnology community. Firm Y can apply for smaller collaborative research government grants. This would allow the firm to leverage on local expertise in areas of cancer, infectious diseases, cardiovascular diseases, and diabetes. Furthermore, these collaborations can lead to accelerated potential target identification and validation for future products.

Firm Y has the needed organizational capabilities to excel in the RNAi Therapeutics sector. Analysis for this study shows that Firm Y should add new products to its product

development pipeline to showcase long-term growth potential to its shareholders. In addition, this analysis indicates that strategic expansion should be in the area of liver specific diseases in order to capitalize on PLATFORM X's core competencies. Firm Y has great delivery system PLATFORM X, products in its product portfolio, streamline of important partnerships, and manufacturing capabilities. However, to enter new indication markets Firm Y has to ensure that it has systems in place necessary for the expansion of its product pipeline. This business strategy, in-line with the corporate strategy, will ensure controlled expansion to a more diversified product portfolio. As a result, Firm Y will continue to build value for itself and its shareholders. Overall, the RNAi Therapeutics is a promising and exciting sector in which Firm Y has an important role.

BIBLIOGRAPHY

- Firm A. (2008). *About Firm A, Programs and Pipeline*. Retrieved June 27, 2010, from Firm A website
- Altekruse et al. (2009). Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *Journal of Clinical Oncology*, 27, 1485-1491. doi: 10.1200/JCO.2008.20.7753
- American Liver Foundation (2007, September 28). *The Progression of Liver Disease*. Retrieved from <http://www.procto-med.com/progression-of-liver-disease/>
- Barazani et al. (2007). Chronic viral hepatitis and hepatocellular carcinoma. *World Journal of Surgical Oncology*, 31, 1243–1248. doi: 10.1186/1477-7819-3-27
- Bataller, R., & Brenner, A.D. (2005). Liver fibrosis. *The Journal of Clinical Investigation*, 115, 209-218. doi: 10.1172/JCI200524282
- Fire et al. (1998). Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature*, 391, 744-745. doi:10.1038/35888
- Firm B. (2007). *Welcome to Firm B Limited, Technology*. Retrieved June 27, 2010, from Firm B website
- Blum, H.E. (2007). Molecular therapy and prevention of liver diseases. *Advances in Medical Sciences*, 52, 29-36. Retrieved from http://www.advms.pl/?q=system/files/3_52Blum.pdf
- Bömmel et al. (2010). *Hepatology clinical textbook: Chapter 9: Standard of care for hepatitis B virus infection* (2nd ed.). Retrieved from <http://www.hepatologytextbook.com/>
- Bosch, F.X. (2004). Primary Liver Cancer: Worldwide Incidence and Trends. *Gastroenterology*, 127, S5-S16. doi: 10.1053/j.gastro.2004.09.011
- Bumcrot et al. (2006). RNAi therapeutics: a potential new class of pharmaceutical drugs. *Nature Chemical Biology*, 2 (12), 711-719. doi: 10.1038/nchembio839
- Carey, W.D. (2009). The prevalence and natural history of hepatitis B in the 21st century. *Cleveland Clinical Journal of Medicine*, 76, S2–S5. doi: 10.3949/ccjm.76.s3.01
- Carr, BI. (2004). Hepatocellular Carcinoma: Current Management and Future Trends. *Gastroenterology*, 127(5), S218-224. doi:10.1053/j.gastro.2004.09.036
- Centers for Disease Control and Prevention (CDC). (2009). *National Diabetes Fact Sheet, 2007*. Retrieved from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf
- Centers for Disease Control and Prevention (CDC). (2009, June). *Hepatitis B FAQ's for Health Professionals*. Retrieved from <http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview>

- ClinicalTrials. (2010). Atherosclerosis/Open Studies. Retrieved on August 1, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Cardiovascular Diseases/Open Studies. Retrieved on August 1, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Diabetes/Open Studies. Retrieved on August 1, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Dyslipidemia/Open Studies. Retrieved on August 1, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Hepatitis B/Open Studies. Retrieved on August 5, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Hepatocellular Carcinoma/Open Studies. Retrieved on August 1, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Liver Diseases/Open Studies. Retrieved on August 5, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Liver Fibrosis/Open Studies. Retrieved on August 5, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- ClinicalTrials. (2010). Metabolic syndrome/Open Studies. Retrieved on August 1, 2010, from <http://clinicaltrials.gov/ct2/results/refine>
- Datamonitor. (2010a, March). *Global Pharmaceuticals, Biotechnology & Life Sciences: Industry Profile*, 1-37. 0199-2357.
- Datamonitor. (2010b, May). *Global Biotechnology: Industry Profile*, 1-35. 0199-0695.
- Davis et al. (2003). Projecting future complications of chronic hepatitis C in the United States. *Liver Transplantation*, 9, 331-338. doi: 10.1053/jlts.2003.50073
- Davis, G.L. and Roberts W.L. (2010). The Healthcare Burden Imposed by Liver Disease in Aging Baby Boomers. *Current Gastroenterology Reports*, 12, 1-6. doi 10.1007/s11894-009-0087-1
- De Fougères et al. (2007). Interfering with disease: a progress report on siRNA based therapeutics. *Nature Reviews: Drug Discovery*, 6, 443-453. doi:10.1038/nrd2310
- Grant, R.M. (2008). *Contemporary Strategy Analysis* (6th ed.). Oxford, UK: Blackwell Publishing.
- Haussecker, D. (2008). The Business of RNAi Therapeutics. *Human Gene Therapy*, 19, 451-462. doi: 10.1089/hum.2008.007
- Hoofnagle, J.H. (2004). Hepatocellular Carcinoma: Summary and Recommendations *Gastroenterology*, 127, S319-S323. doi:10.1053/j.gastro.2004.09.047

- IBIS World. (2010, February). *Global Biotechnology: IBIS World Industry Report*, 1-52. L6724-GL.
- Firm C. (2010). *About Firm C, Technology, Drugs in Development*. Retrieved June 27, 2010, from Firm C website
- Konde, V. (2009). Biotechnology business models: An Indian perspective. *Journal of Commercial Biotechnology*, 15(3), 215-226. doi:10.1057/jcb.2008.52
- Lang et al. (2009). The burden of illness associated with hepatocellular carcinoma in the United States. *Journal of Hepatology*, 89-99. doi:10.1016/j.jhep.2008.07.029
- Mancini, A. D. J. (2010). Regulatory Affairs for the Biotech Executive Course Notes. Management of Technology MBA. Simon Fraser University.
- MayoClinic. (2010). *Liver cancer*. Retrieved on July 16, from <http://www.mayoclinic.com/health/liver-cancer/DS00399>
- MedicineandBiotech. (2004). *FDA Approves Rituxan*. Retrieved from <http://www.medicineandbiotech.com/gpage3.html>
- MedlinePlus. (2010). Metabolic Syndrome. Retrieved on July 13, 2010 from <http://www.nlm.nih.gov/medlineplus/metabolicsyndrome.html>
- Melnikova, I. (2007). RNA-based therapies. *Nature Publishing Group*, 6, 863-864. doi:10.1038/nrd2443
- PhRMA. (2010). *Pharmaceutical Industry Profile*. Retrieved from http://www.phrma.org/sites/phrma.org/files/attachments/Profile_2010_FINAL.pdf
- Porter, M.E. (2008, January). The Five Competitive Forces That Shape Strategy. *Harvard Business Review*, 78-93. R0801E.
- Poynard et al. (2010) Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest). *BMC Gastroenterology*, 10:40. doi: 10.1186/1471-230x-10-40
- Rader, R.A. (2005a). What is Biopharmaceutical? Part 1: (Bio) Technology–Based Definitions. *Bioexecutive International*, 60-65. Retrieved from http://www.biopharma.com/bioexecutive_article_pt1.pdf
- Rader, R.A. (2005b). What is Biopharmaceutical? Part 2: Company and Industry Definitions. *Bioexecutive International*, 42-49. Retrieved from http://www.biopharma.com/bioexecutive_article_pt2.pdf
- Reidhaar-Olson, J. & Vornlocher, H.P. (2008). Delivering RNAi Therapeutics. *Drug Discovery and Development*, 22-25.
- Rosamond et al. (2007). *Heart Disease and Stroke Statistics-2007 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee*. Retrieved on July 21, 2010, from circ.ahajournals.org

- Firm D. (2008). *Products, Pipeline, Technology*. Retrieved June 27, 2010, from Firm D website
- Rossi, J.J & Aagaard, Lars. (2007). RNAi Therapeutics: Principles, prospects and challenges. *Advanced Drug Delivery Reviews*, 59, 75-86. doi: 10.1016/j.addr.2007.03.05
- Rossi, J.J & Castanotto, D. (2009). The promises and pitfalls of RNA-interference based therapeutics. *Nature Review*, 457, 426-433. doi:10.1038/nature07758
- Shaffer, C. (2010). Getting Closer to Market. *Drug Discovery and Development*. 28-31.
- Firm E. (2010). *Therapeutic Platform, Pipeline*. Retrieved June 27, 2010, from Firm E website
- Firm Y. (2009). *Firm Y's 2009 Annual report*. Retrieved from [http://www. Firm Ypharm.com/files/Files_2010/Annual_Report_2009.pdf](http://www.FirmYpharm.com/files/Files_2010/Annual_Report_2009.pdf)
- Tomke, S & Nimgade A. (1998). *Note on New Drug Development in the United States*. Harvard Business School, 1-7. Harvard Business School Publishing, Boston.9-698-028.
- Trusheim et al. (2010). Characterizing Markets for Biopharmaceutical Innovations: Do Biologics Differ from Small Molecules? *Forum for Health Economics & Policy*, 13(1), 1-43. doi: 10.2202/1558-9544.1200
- Vining, A & Meredith, L. (2000). Metachoice for Strategic Analysis. *European Management Journal*, 16 (8), 605-618. doi:10.1016/S0263-2373(00)00053-0
- Wild et al. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(10), 1047-1053. doi: 10.2337/diacare.27.5.1047
- World Health Organization (WHO). (2010). *Hepatitis B*. Retrieved from <http://www.who.int/mediacentre/factsheets/fs204/en/>