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ABSTRACT

Pharmaceutical drug development is a costly and risky venture characterized by low clinical success rates. The neurodegenerative disease market segment has the highest drug development costs and the lowest clinical success rate of any therapeutic disease area. Small biotechnology companies that specialize in the neurodegenerative disease market must carefully select the appropriate disease indications to pursue.

This study examines the neurodegenerative disease market and analyzes the attractiveness of drug development in four key market indications. The purpose of this study is to identify the most economically viable neurodegenerative disease indication for a small biotechnology company to pursue.

Recommendations are made based on a risk adjusted net present value analysis that assesses the drug development risks, costs, and potential value of each disease indication.

Keywords: Biotechnology; Drug Development; Neurodegeneration; Risk; NPV

Subject Terms: Masters of Business Administration; Biotechnology Management; MOT
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# TABLE OF CONTENTS

Approval ......................................................................................................................... ii
Abstract.......................................................................................................................... iii
Acknowledgements .........................................................................................................iv
Table of Contents ...........................................................................................................v
List of Figures ................................................................................................................ viii
List of Tables ................................................................................................................ ix
Glossary .......................................................................................................................... x

1: Introduction ................................................................................................................. 11
  1.1 Overview of the Pharmaceutical Biotechnology Industry ..................................... 11
  1.2 Pharmaceutical Biotechnology Value Chain ......................................................... 11
  1.3 The High Risk of Drug Development .................................................................... 13
  1.4 The Purpose of This Analysis .............................................................................. 15

2: Overview of the Neurodegenerative Disease Market .............................................. 17
  2.1 Market Background ............................................................................................. 17
  2.2 Market Size .......................................................................................................... 17
  2.3 Major Competitors .............................................................................................. 18
  2.4 Market Drivers ..................................................................................................... 19
    2.4.1 The Aging Population ................................................................................... 19
    2.4.2 Largely Unmet Treatment Needs ................................................................. 19
    2.4.3 Advances in Innovation .............................................................................. 19
  2.5 Market Limiters .................................................................................................... 20
    2.5.1 Low Clinical Success Rates ......................................................................... 20
    2.5.2 High Cost of Drug Development ................................................................ 20
    2.5.3 Difficult to Diagnose CNS Diseases ............................................................ 21

3: Overview of Company X .............................................................................................. 23
  3.1 Company Background .......................................................................................... 23
  3.2 Corporate structure ............................................................................................. 23
  3.3 Business Strategy ................................................................................................. 24
  3.4 Technology Platform ........................................................................................... 24
    3.4.1 Neurodegeneration and Neuroprotection ..................................................... 24
  3.5 Product Pipeline .................................................................................................. 25
  3.6 Financials .............................................................................................................. 25
# 6: Discussion and Recommendations

6.1 First Recommended Disease Indication – Schizophrenia

6.1.1 Advantages to Pursuing the Schizophrenia Indication

6.1.2 Disadvantages to Pursuing the Schizophrenia Indication

6.2 Second Recommended Disease Indication – Diabetic Neuropathy

6.2.1 Advantages to Pursuing the Diabetic Neuropathy Indication

6.2.2 Disadvantages of Pursuing the Diabetic Neuropathy Indication

6.3 The Third Recommended Disease Indication – Chemotherapy-Induced Neuropathy

6.3.1 Advantages to Pursuing the Chemotherapy-Induced Neuropathy Indication

6.3.2 Disadvantages of Pursuing the Chemotherapy-Induced Neuropathy Indication

6.4 The Fourth Recommended Disease Indication – Parkinson’s disease

6.4.1 Advantages to Pursuing the Parkinson’s disease Indication

6.4.2 Disadvantages to Pursuing the Parkinson’s disease Indication

6.5 Summary of Recommendations

## Appendices

- Appendix 1 Diabetic Neuropathy rNPV
- Appendix 2 Chemotherapy-Induced Neuropathy rNPV
- Appendix 3 Schizophrenia rNPV
- Appendix 4 Parkinson’s disease rNPV

## Reference List
LIST OF FIGURES

Figure 1  Biotechnology and Pharmaceutical Value Chain .............................................. 13
Figure 2  Drug Development Cycle ................................................................................. 15
LIST OF TABLES

Table 1  rNPV Analysis Parameters .................................................. 82
Table 2  rNPV Analysis Results ..................................................... 84
GLOSSARY

Biotechnology  The application of biological techniques such as recombinant DNA and cell fusion to product research and development.

Burn Rate  A measure of how fast a company uses financial resources. Denotes negative cash flow.

Clinical Trials  Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people.

Discount Cash Flow  A valuation method used to estimate the attractiveness of an investment opportunity. DCF analysis uses future free cash flow projections and discounts them to arrive at a present value.

Drug Pipeline  All the compounds in clinical or preclinical testing for a biotechnology or pharmaceutical firm(s).

Endpoint  In a research trial, a clinical endpoint refers to a disease, symptom, or sign that constitutes one of the target outcomes of the trial.

Net Present Value  The present value of an investment's future net cash flows minus the initial investment.

Neurodegeneration  The progressive loss of structure or function of neurons, including death of neurons.

Neuropathy  Disease, inflammation or damage to the peripheral nerves, which connect to the spinal cord and brain, or central nervous system.

Value Chain  A connected series of organizations, resources, and knowledge streams involved in the creation and delivery of value to end customers.
1: INTRODUCTION

1.1 Overview of the Pharmaceutical Biotechnology Industry

The biotechnology industry began 31 years ago when a young microbiologist, Herb Boyer, and a venture capitalist, Bob Swanson teamed up to form the world’s first modern biotech company, Genentech. Since then, the biotechnology industry has grown substantially, creating hundreds of drug therapies and vaccines including treatments for cancer, diabetes, HIV/AIDS and other autoimmune disorders. Incidentally, Genentech has become the world’s most valued biotechnology company with a market capitalization of over $85 billion US. According to Ernest & Young, there are now over 4000 public and private biotechnology companies worldwide contributing to over $73 billion in revenues in 2006. However, the revenue figures are misleading and do not accurately indicate the profitability of the industry. In 2006, the biotechnology industry suffered a net loss of over $4 billion US. In reality, only a small percentage of the 4000 companies worldwide generate a profit. In fact, the top two-biotech giants, Amgen and Genentech, dominate the industry’s profits, each generating over $2 billion US in net profits in 2006. (Ernest & Young, 2007)

1.2 Pharmaceutical Biotechnology Value Chain

Companies range from small start-ups with a handful of employees to the fully integrated biotech giants (referred to as FIBCOs) such as Genentech and Amgen who have workforces that number in the tens of thousands. Refer to figure 1. However, the
majority of biotech companies are primarily research and development (R&D) focused and lack downstream capabilities such as manufacturing, sales and marketing. As shown in figure 1, some biotech companies focus heavily on research indicated by a large R and a little d. These companies only focus on target identification and validation. Other small biotech firms may concentrate more heavily on clinical development, indicated in figure 1 with a small r and large D. These companies focus on identifying and developing lead drug candidates through the clinical development phases. In fact, many biotechnology companies do not have upstream capabilities either, as they choose to in-license technologies from other research firms. Very few biotechnology companies have the capabilities to develop a drug from the target identification stage through clinical trials and eventually to the market. The primary reason for limiting capabilities is to keep the company’s expenditures, known as burn rate, as low as possible. Most biotechnology companies have limited financial resources and thus are very economical in their spending.

Biotech companies generally collaborate with larger pharmaceuticals in late stages of clinical development to bring a drug to market. In return, the biotech company usually receives financing to complete clinical trials, milestone payments and a percentage of the sales that the drug generates. Currently, lacklustre internal innovation coupled with patent expiration is forcing large pharmaceutical companies such as Pfizer and Johnson and Johnson to seek alliances with smaller biotech companies to replenish their pipeline and technology platforms. As financing for the biotechnology sector steadily increases, small biotech firms are beginning to move towards building their own commercialization capabilities thus enabling those companies to control the entire drug
development process. This strategy reduces the reliance on partnerships with larger pharmaceutical companies and allows the company to receive higher product revenues.

Figure 1  Biotechnology and Pharmaceutical Value Chain

1.3 The High Risk of Drug Development

Drug development is a costly and time-consuming venture. Estimates indicate that the average cost of developing a drug is now over $800 million US (Tufts, 2004). The highly regulated process requires 10 – 15 years of development from drug discovery to drug approval and commercialization. The odds of a drug moving through the entire process are 1 in 10,000 (Burrill, 2006). Refer to figure 2.

A drug candidate undergoes extensive clinical testing before being submitted to the appropriate regulatory bodies, such as the Federal Drug Administration (FDA) in the
US and Health Canada (HC) in Canada, for clearance to market and sell the product. The clinical testing usually consists of three phases: Phase I (20-100 individuals) is testing on a small healthy control group; Phase II (100-500 individuals) is testing on a small group of ailing patients for drug efficacy; in Phase III (1000-5000 individuals) the drug is administered to a large group of patients to verify the safety, efficacy, and optimum dosing regimens. A drug must pass the first clinical trial phase before it can be evaluated in a phase II trial, and phase II trial must be passed before initiation of a phase III trial. After the drug has passed through the clinical trial stages, the sponsor company files a New Drug Application (NDA) or a Biologic License Application (BLA) with the FDA, which makes the final approval decision. As shown in figure 2, phase I and II clinical trials can last 6.5 years, while phase III trials and the approval phase can last up to 7 years and 1.5 years respectively.

Many biotech companies have high burn rates and often do not observe any revenues for many years after inception. Failures at any phase of the regulatory process can be disastrous for a company often leading to liquidation or bankruptcy. Therefore, it is essential that a biotechnology company is able to select a disease indication that best suits its current scientific and economic capabilities. The biotechnology industry can be classified as high risk, high reward. If a company is successful, the profit margins on drug sales can be very lucrative often in the range of 70-90%, however, the hurdles to success are quite prevalent and numerous.
1.4 The Purpose of This Analysis

This study examines drug development in the neurodegenerative disease market segment by analyzing the market and key clinical development risks of four neurodegenerative disease indications: Diabetic neuropathy, chemotherapy-induced neuropathy, Parkinson’s disease, and schizophrenia. The study further analyzes the economic value of each disease indication using a risk adjusted net present value analysis and recommendations are provided to a small biotechnology company, known as Company X, as to which disease indication market the company should pursue.

Company X specializes in developing drug therapies for neurodegenerative diseases. The company’s lead drug candidate has the potential to effectively treat the four disease indications examined in this study therefore it is essential for Company X to
select the most suitable indication to pursue based on its current resources. This study only focuses on the U.S. market as it is the initial market that Company X will pursue.
2: OVERVIEW OF THE NEURODEGENERATIVE DISEASE MARKET

2.1 Market Background

Neurodegenerative diseases are central nervous system disorders caused by a deterioration of the neurons. Neurons are responsible for processing and transmitting cellular signals and are core components of the central nervous system. Neurodegeneration often leads to disabilities such as difficulty with movements, difficulty processing information and loss of cognition, pain, memory loss and dementia. Slow progression and a late onset of symptoms are characteristics of neurodegenerative diseases. Several of the more prominent diseases include Alzheimer’s disease, Multiple Sclerosis, Huntington’s disease, Parkinson’s disease, Schizophrenia and Neuropathy. Neurodegenerative diseases can also result from stroke, heat stress, head and spinal cord trauma, surgery and neurotoxins. In addition, diseases such as diabetes, HIV, and herpes zoster are common causes of neurodegeneration and neuropathic pain.

No effective treatments on the market stop the progression of neurodegeneration. Current treatments aim to alleviate the symptoms of individuals with neurodegenerative diseases. However, research efforts have increased in the past several years to discover a drug that is capable of modifying disease progression.

2.2 Market Size

According to a report published by IMS Health (IMS 2005), the worldwide market value for neurodegenerative diseases will reach $18 million US in product
revenues in 2007. This value increased from $16 million US in 2006 and $14.5 million US in 2005. In 2005, Alzheimer’s drugs accounted for $4 billion US, while Parkinson’s, Multiple Sclerosis and Neuropathies totalled $2.8 billion, $5.1 billion, and $2.5 billion respectively. The projected growth of the neuropathic pain market is $5.5 billion US by the year 2010. Drug products on the market that have shown neuroprotective effects had a value of $5.1 billion US in 2005. The estimated growth of the overall neurodegeneration disease market is over 12% per year. A global market report published by Arrowhead Publishers estimates that there are over 22 million individuals worldwide affected by neurodegenerative disorders (Arrowhead, 2007). The World Health Organization (WHO) predicts that neurodegenerative disorders will overtake cancer to become the second leading cause of death next to cardiovascular disease (WHO, 2007).

2.3 Major Competitors

Currently, there are over 500 companies’ worldwide conducting research and development in the central nervous system therapeutic area. Roughly 150 of these companies specialize in the neurodegenerative disease market (Pharmalicensing, 2007). The market for neurodegenerative disease drugs is currently dominated by large pharmaceutical companies such Pfizer, Novartis, Biogen Idec, Eli Lilly and Johnson & Johnson. However, mainly small and medium sized biotechnology and specialty companies are investing heavily in potential new neuroprotective agents. Due to the high drug development costs of neurodegenerative and central nervous system drugs, it is common practice for small research companies to partner or license out their drug candidates to large pharmaceutical firms.
The major competitors and leading drugs in each disease indication will be examined in detail in the following sections.

2.4 Market Drivers

Several key factors drive the growth of the neurodegenerative disease market; the ageing population, largely unmet treatment needs, and advances in treatment technologies.

2.4.1 The Aging Population

In the industrialized world, the population of individuals over the age of 65 is increasing substantially. It is estimated that by the year 2050, the 65 years old and over demographic will have doubled (Lansbury, 2004). The aging of the large “baby boomer” demographic and increasing life expectancy are the primary causes of the increase. The incidence rate of neurodegenerative diseases is highest among elderly individuals.

2.4.2 Largely Unmet Treatment Needs

No existing treatments on the market prevent the progression of neurodegenerative diseases. The negative symptoms of neurodegenerative diseases often have high impacts on the quality of life of the individuals affected. Market approval of a disease-modifying drug in any of neurodegenerative disease indications would potentially be a blockbuster drug and would garner huge financial returns.

2.4.3 Advances in Innovation

As the number of biotechnology and pharmaceutical companies conducting research on neurodegenerative diseases increase; so do the advances in drug discovery.
An improving understanding of the pathology of disease leads to new discoveries and potential drug targets. In addition, new treatment options such as gene therapy are beginning to emerge.

2.5 Market Limiters

The market size for neurodegenerative diseases will continue to increase and will be limited only by any discoveries that can cure the disease. However, several factors affect the development of suitable drug candidates for neurodegenerative diseases. These factors include; low clinical success rates, high cost of drug development, and difficulty in diagnosing the diseases.

2.5.1 Low Clinical Success Rates

A report from Tufts Center for the Study of Drug Development (2005) indicated that central nervous system (CNS) drug candidates entering clinical development have a 7% probability of reaching the marketplace. The industry average across all other therapeutic areas is 15%. Reasons for the low clinical success rate include the complexity of the brain, a propensity for CNS drugs to cause side effects, a difficulty in drugs passing through the blood-brain barrier, and a lack of validated biomarkers that can inform whether the drug is reaching the brain in sufficient concentrations to modulate the desired CNS target.

2.5.2 High Cost of Drug Development

Central nervous system drugs cost on average $527 million US to develop and to bring the drug to market compared to $375 million US for analgesic/anaesthetic drugs and an industry average of $466 million for all drugs (Tufts, 2004). These figures reflect
total out of pocket and time costs. Tufts also factored in phase attrition rates and clinical approval success rates. These figures exclude non-clinical research and development costs such as cost of capital. Slow progression of CNS diseases contributes to the high cost of development. Longer clinical trial evaluation times increase development and time costs. A CNS drug requires an average clinical phase time of 92 months compared to the industry average of 72 months for all drugs. In addition, the efficacy of CNS drug candidates is often difficult to assess. Clinical endpoints are not well defined and often subjective to patient, administrator, and physician bias. For many CNS diseases, there is no standard assessment tool or efficacy test. Efficacy evaluation becomes expensive and time consuming.

2.5.3 Difficult to Diagnose CNS Diseases

Neurodegenerative disease and central nervous system disorders on a whole are often misdiagnosed or not diagnosed at all. According to post-mortem pathological studies, physicians misdiagnose greater than 15% of cases of Alzheimer’s and Parkinson’s disease in the clinic (Lansbury, 2004). Diagnostic and assessment tools are insufficient to diagnose many CNS diseases. For example, definitive diagnosis of Alzheimer’s disease can only occur upon autopsy of the brain. Advances in neuroimaging techniques are likely to strengthen diagnosis capabilities in the future. Moreover, preclinical phases of CNS disorders are often long. By the time that an individual shows symptoms, a substantial amount of neuron degeneration has already occurred. In many instances of Parkinson’s patients, greater than 70% loss of the nigral dopaminergic neurons has already occurred when diagnosed with the disease. Existing
diagnostic tools do not enable the detection of pre-symptomatic loss of neurons in a clinical setting.
3: OVERVIEW OF COMPANY X

3.1 Company Background

Company X, founded in 2001, is a small biotechnology company developing neuroprotective drug therapies that may be applicable to several neurodegenerative disorders such as Alzheimer’s disease, mild cognitive impairment, traumatic brain injury, stroke, coronary artery bypass graft surgery, and neuropathy. Company X, based out of Canada, is traded publicly on the Toronto Stock Exchange (TSX).

3.2 Corporate structure

Company X is a small clinical stage biotechnology company that employs less than 20 staff members at their head office. The staff consists of a strong executive team that includes the President and Chief Executive Officer, the Chief Financial Officer, the Chief Scientific Officer, the Vice President of Drug Development, the Vice President of Clinical Operations, and the Clinical Development and Regulatory Affairs Advisor. In August of 2007, Company X appointed a Vice President of Business Development to join the executive team. In addition to the executive team, there is a Director of Corporate Development and a Manager of Investor Relations. In addition, a Board of Directors and a Scientific Advisory board consisting of seven and ten members respectively support Company X.

In addition to the head office in Canada, Company X also has research and development facilities overseas.
3.3 Business Strategy

Company X has positioned itself as an early to mid stage biotechnology company that does not have the resources to manufacture, commercialize or distribute a drug product. The company is pursuing central nervous systems markets of unmet medical need, specifically targeting neurodegenerative disorders. Company X’s current strategy is to develop a drug candidate through the first several stages of clinical development and then seek partnership opportunities to bring the drug to market. The partnership strategy allows the company to reduce development costs and decrease risk in the overall development process. In addition to seeking out licensing, co-development and partnership deals with large biotechnology and pharmaceutical firms, Company X also seeks in-licensing opportunities and acquisitions to complement and bolster their existing technology platform.

3.4 Technology Platform

Company X is developing a class of compounds that protects neurons against the effects of neurodegenerative diseases.

3.4.1 Neurodegeneration and Neuroprotection

Neurons are the core component of the brain and central nervous system. Neurons are responsible for processing and transmitting information that result in all complex human behaviours including vision, speech, motor skills, memory and consciousness. In all humans, neurons undergo a process called apoptosis or programmed cell death. This is a normal and necessary process for proper functioning of the nervous system. The process triggers neurodegeneration. The neuron begins to
degrade and eventually leads to cell death. Neurodegenerative diseases, stroke, traumatic brain injury and exposure to chemical and biological neurotoxins cause abnormal cell death thus leading to symptoms such as memory loss, psychosis, decrease in motor functioning, and slurred speech.

The intention of neuroprotective drugs is to block cell death pathways and protect neurons from disease processes and neurotoxins. Neuronal cell death involves common molecular pathways and mechanisms across different disease and brain injuries. Studies have shown that neuroprotection occurs naturally in response to assault and injury due to the production of neurotrophic factors that promote cell growth, rather than death. However, in disease states, these factors are inadequate and unable to prevent degeneration of the neuron.

3.5 Product Pipeline

Company X currently has two drugs in clinical development and an additional three drugs in the pre-clinical development phase. The company does not have any FDA approved drugs on the market.

3.6 Financials

In 2006, Company X reported a net loss of $9,184,051 CAD compared to a net loss of $5,549,367 CAD in 2005. A net loss is typical of small biotechnology companies that do not have an approved drug on the market. The primary reason for the increase in net loss is the increase in research and development spending and the increase in personnel requirements to support the increased R&D activities. R&D expenditures totalled $6,721,548 CAD in 2006 versus $4,975,629 CAD in 2005. In the first three
quarters of 2007, Company X has accumulated a net loss of $8,612,351 CAD. This translates into an average monthly burn rate of $956,927 CAD.

Due to external financing, Company X is in a strong financial position to complete three phase II clinical trials as well as its other milestones through the first half of 2008.
4: ANALYSIS OF NEURODEGENERATIVE DISEASE INDICATIONS

This chapter consists of a detailed description and analysis of the four disease indications that Company X is considering for drug development; diabetic neuropathy, chemotherapy induced neuropathy, Parkinson’s disease and schizophrenia. Company X’s lead drug candidate has the potential to treat any of the four neurodegenerative disease indications. The analysis will examine market sizes, leading drug treatments, clinical trials, and potential drug therapies on the horizon for each disease indication.

4.1 Neuropathy Overview

Neuropathy is a disorder that affects the peripheral nervous system that consists of motor, sensory and autonomic nerves. The disorder describes damage to the nerves thus hindering or eliminating information transfer from the brain and spinal cord to muscles, skin and internal organs. Neuropathies can affect a single nerve, mononeuropathy, or multiple nerves polyneuropathy. Neuropathy is a common disorder that affects approximately 20 million Americans. (The Neuropathy Association, 2007)

Approximately 30% of neuropathies are idiopathic or of unknown cause. Diabetes is a primary contributor to neuropathy, accounting for 30% of all cases. (The Neuropathy Association, 2007) Toxins such as chemotherapeutic agents, physical injury to nerves, tumours, autoimmune responses affecting nerve tissue, nutritional deficiencies, alcoholism, vascular disorders, herpes zoster infection, HIV/AIDS and genetic mutations are all possible causes of neuropathy.
Over 100 types of neuropathy identified have their own unique set of symptoms, pattern of development, and prognoses that are dependent on the type of nerve affected (NINDS, 2007). Symptoms may include temporary numbness, tingling, pricking sensations, sensitivity to touch, and/or muscle weakness. More extreme symptoms include burning pain, muscle wasting, paralysis, organ dysfunction and/or gland dysfunction. Symptoms generally first occur in the feet and eventually spread to the legs and hands. In acute neuropathies such as Guillain-Barre syndrome, symptoms appear suddenly, progress rapidly, and resolve slowly as nerves heal. In chronic forms such as diabetic neuropathy, symptoms are subtle at initiation and progress slowly. Neuropathies are seldom fatal.

There is no cure for most forms of neuropathy. Treatments are generally directed at managing the underlying condition causing the neuropathy and relieving the symptoms to improve quality of life. Pain relievers (acetaminophen, aspirin), Anti-seizure medications (gabapentin, carbamazepine), Lidocaine patches, Tricyclic antidepressants (amitriptyline, paroxetine), Opioid analgesics (codeine, oxycodone) and Cannabinoids (marijuana) are common medications used to treat pain symptoms (Mayo Clinic, 2005). Therapies such as Transcutaneous Electrical Nerve Stimulation, Biofeedback, Acupuncture, Hypnosis and relaxation techniques also alleviate pain symptoms. Current investigation of treatments using nerve growth factors and gene therapy to regenerate peripheral nerves could prove effective for treating the disorder in the future. However, research in this field is lagging far behind other neurological disorders with similar ranges of disability. The U.S. National Institutes of Health (NIH) spent $29 million in 2005 on peripheral neuropathy research. The NIH expenditure for multiple sclerosis and
epilepsy is approximately 200 times greater than neuropathy on a per-patient ratio (The Neuropathy Association, 2007).

This analysis will primarily focus on the two forms of neuropathy that Company X is interested in pursuing, diabetic neuropathy and chemotherapy induced neuropathy with additional emphasis on breast cancer treatment as the initial chemotherapy market. The causes, symptoms, market sizes, current treatments, and clinical trials will be examined with the goal of differentiating each type of neuropathy.

### 4.2 Diabetic Neuropathy

Diabetic Neuropathy is a degeneration of peripheral nerves associated with type 1 and type 2 diabetes mellitus. Individuals afflicted with diabetes commonly develop temporary or permanent damage to nerve tissues, which often results in pain, tingling or weakness in their limbs; classified as sensorimotor peripheral neuropathy, which is the most common type of diabetic neuropathy. Autonomic neuropathy, which affects nerves associated with organ systems, is also a common form of diabetic neuropathy.

The exact cause of diabetic neuropathy is not known, however researchers believe that hyperglycemia is the primary risk factor (Medscape, 2004). Elevated glucose levels have shown to cause micro vascular disease, advanced glycated proteins, activation of protein kinase C, and the activation of the enzyme aldose reductase, which can all lead to the progression of diabetic neuropathy. Smoking and alcohol consumption are also risk factors associated with diabetic neuropathy.
4.2.1 Prevalence

The prevalence of diabetic neuropathy is difficult to estimate because the criteria for diagnosis vary across the world. Many diabetes sufferers are unaware that neuropathy is a common occurrence associated with the disease. A study by Schwarz Pharma estimates there are 11 million diabetics with neuropathy worldwide (Nicolas, 2006). The American Diabetes Association estimates that 3.5 million Americans experience pain caused by diabetic neuropathy. In the United States, 20.8 million individuals are afflicted with diabetes. However, estimates indicate that diagnosis occurs in only 14.6 million cases while the other 6.2 million individuals are unaware that they have the disease (American Diabetes Association, 2007). The prevalence of neuropathy can range from 5% in diabetes sufferers under the age of twenty to 100% in diabetes sufferers over the age of 60 (Kelkar, 2005). A common estimation of prevalence is 30% of all diabetes patients have symptomatic diabetic neuropathy. (Sherman, 2007) The incidence is 2% of the general population. Cardiovascular Biotherapeutics estimates that over 800,000 diabetics receive treatment annually for neuropathy in the United States (Cardiovascular Biotherapeutics, 2007). In 2005, diagnosis of 1.5 million new cases of diabetes occurred. Estimates indicate that neuropathy is present in 7.5% of patients at the time of diabetes diagnosis (Quan, 2006). This equates to 112,500 patients diagnosed in 2005 with neuropathy at the onset of the disease.

4.2.2 Symptoms

The symptoms associated with diabetic neuropathy can vary significantly based on the type of neuropathy. Symptoms are generally more intense and prominent amongst patients that have been afflicted with diabetes for longer durations. On average,
observation of symptoms occurs 10 to 20 years after the diagnosis of diabetes in the individual (NIH, 2007). In late stages of neuropathy, symptoms of pain may subside, as sensation is lost to the affected area often leading to severe tissue damage because pain is no longer an indication of injury. This is a primary factor leading to foot and leg amputations.

Patients with sensorimotor neuropathy most often report symptoms of altered sensation in the feet and hands. The most common symptoms include the following:

- **Dysesthetic Pain**: burning sensations, skin tingling, allodynia (painful sensation upon contact with items that would not normally hurt), and hyperalgesia (elevated response to painful stimuli).

- **Paresthetic Pain**: sensation of pins and needles, electric shock like sensation, numbness and aching, knifelike pain, and sensation like feet in ice water. (Sherman, 2007)

Patients with autonomic neuropathy may display a different set of symptoms that generally associate with vital organ systems such as gastrointestinal, cardiovascular and excretory.

- **Gastrointestinal neuropathy**: dysphasia, abdominal pain, nausea/vomiting, diarrhoea, and constipation

- **Cardiovascular neuropathy**: sinus tachycardia, orthostatic hypotension, sinus arrhythmia, and decreased heart variability to response to deep breathing

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1 Pain caused by an impairment to sensitivity especially touch. Source: National Institute of Health
2 Pain caused by a sensation of prickling, tingling or creeping on the skin. Source: National Institute of Health
• **Excretory neuropathy**: poor urinary system, feeling of incomplete bladder emptying, and straining to void (Sherman, 2007).

### 4.2.3 Treatments

A study conducted by Adam Gordois and colleagues estimated that the annual cost of treating diabetic neuropathy in the United States is between $4.6 and $13.7 billion dollars in 2001 (Gordois, 2003). This accounted for up to 27% of the direct medical costs of treating diabetes.

The treatment of diabetic neuropathy can be classified into three areas; disease prevention, symptom management, and disease modifying (Duby et al, 2004). The simplest method to disease prevention is intensified glycemic control. This can dramatically reduce the complications associated with diabetes such as neuropathy.

Treatments for symptom management are the most commonly prescribed pharmaceutical therapies for diabetic neuropathy. However, these medications are only moderately effective and can cause unwanted side effects. Often, prescription of medications for treating diabetic neuropathy is on an off-label\(^3\) basis. The US Food and Drug Administration only approved several drugs for treating neuropathy caused by diabetes, duloxetine and pregabalin.

In cases of acute diabetic neuropathy, physicians often prescribe mild analgesics such as acetaminophen and non-steroidal anti-inflammatories such as ibuprofen. When symptoms are more severe, prescription of the following drug classes often occurs. The

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\(^3\) An approved drug legally prescribed for a purpose for which it has not been specifically approved. Source: Merriam-Webster’s Dictionary, 2007.
type of drug prescribed is typically varied and is dependant on the patient’s symptoms and tolerance to the drug.

4.2.3.1 Tri-cyclic Antidepressants (TCA)

TCA’s are the most investigated class of medications for treatment of diabetic neuropathy. (Duby et. al, 2004) Prescription of these drugs is common as first line treatments and is generally safe and effective for decreasing painful symptoms at lower doses. The inhibition of the re-uptake of norepinephrine and serotonin allows for the analgesic effects of TCA’s. Side effects of TCA’s often include dry mouth, constipation, sedation and nightmares. Tri-cyclic antidepressants may also require up to a two month period to achieve the maximum benefits. The most commonly prescribed TCA’s are amitriptyline desipramine, imipramine, and clomipramine.

4.2.3.1.1 Amitriptyline (Elavil)

Amitriptyline, marketed and sold as Elavil by AstraZeneca is the most commonly prescribed tri-cyclic antidepressant. Sales of Elavil totalled $98.8 million US in 2006 (Njardarson Group, 2007). The drug is a monoamine oxidase inhibitor that dispenses in pill form. The targeted daily dosage for treating pain due to diabetes is 75-150m (Duby et. al, 2004). The dosage requirement is generally adjusted 10mg/day per week until the drug reaches maximum effectiveness. Sale of the drug occurs in 10mg, 25mg, 50mg, 75mg, 100mg and 150mg tablets at a retail cost of $0.12US per tablet across all dosage levels (Drugstore.com, 2007). A patient can be treated for $.12US per day which equates to roughly $3.60 medication costs per month. Side effects of this drug include dry mouth, sedation, dizziness, confusion and hypotension.
4.2.3.2 Selective serotonin and norepinephrine re-uptake inhibitors (SSNRI)

SSNRI’s are a group of anti-depressants prescribed for regulating depressive disorders and pain management associated with diabetic neuropathy. This group of drugs balances sustained levels of the two neurotransmitters, serotonin and norepinephrine. In general, SSNRI’s are more tolerable but are less effective than tri-cyclic antidepressants for the treatment of neuropathy (Duby et. al., 2004).

4.2.3.2.1 Duloxetine (Cymbalta)

Duloxetine is the most prescribed SSRNI. In 2004, it was the first drug approved by the FDA for the treatment of diabetic neuropathic pain (Wu, 2005). Eli Lilly markets the drug, in pill form, under the brand name Cymbalta. The targeted daily dosage for treating neuropathic pain is 60mg. Administration of the drug occurs once or twice daily (Quan, 2006). Common side effects include nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating.

In 2006, worldwide sales of Cymbalta reached $1.316 billion US. (Drugs.com, 2007) However, it is difficult to estimate how much of the sales are attributed to neuropathic pain prescriptions. Ben Greener of Datamonitor estimates that the total sales of duloxetine will reach $1 billion US by the 2015, not including prescriptions for depression and other indications. (Smith, 2006) The drug is sold in 20mg, 30mg and 60mg capsules at about $3.40 US, $3.70 US, and $3.80 per capsule respectively. Average monthly cost of using Cymbalta as a primary drug treatment is $114US. (Drugstore.com, 2007)
4.2.3.3 Anticonvulsants

Anticonvulsants are a class of drugs typically prescribed for the prevention of epileptic seizures. However, several anticonvulsants are effective in treating pain caused by diabetes. Gabapentin, carbamazepine, and lamotrigine are the most extensively studied drugs in this class. Anticonvulsants provide analgesic effects by blocking sodium and calcium channels, AMPA receptors or NMDA receptors. These channels and receptors have shown to be associated with pain regulation. (Todorovic, 2003)

4.2.3.3.1 Pregabalin (Lyrica)

Pregabalin is the only anticonvulsant approved for use by the FDA in treating diabetic neuropathy. The drug manufactured by Pfizer and sold under the brand name Lyrica, is a successor to a similar anticonvulsant, gabapentin. Both drugs utilize a similar mode of action; binding to and regulating calcium channels and decreasing the presynaptic release of neurotransmitters (e.g., substance P, glutamate) that are involved with pain sensation and transmission. (Pfizer, 2007) The recommended dosage of Lyrica is 150mg/day at initiation and scaled up to a maximum of 300mg/day. Administration of the drug occurs in three equal dosages over the course of the day. Patients ingest Lyrica in capsule form. Common side effects of Lyrica include dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and problems with concentration. (Pfizer, 2007)

In 2006, worldwide Lyrica sales topped $1 billion US making it one of Pfizer’s most successful drugs launched ever. (Smith, 2007) Ben Greener of Datamonitor estimates that sales of Lyrica will exceed $2 billion US by the year 2015. The drug sells in 25mg, 50 mg, 75 mg, 100 mg, 150 mg, 200mg, 225 mg, and 300 mg capsules.
Average cost per capsule is about $2 US. (Drugstore.com, 2007) Three equal doses of 100mg daily will equal about $6 per day in medication costs. Total monthly cost of treating diabetic neuropathy with Lyrica is roughly $180 US. (Thomas, 2006)

4.2.4 Clinical Trials

There are twenty-seven clinical trials in process and sixty-three clinical trials currently recruiting patients for diabetic neuropathy research. Using clinical trial data obtained from the FDA; the estimate of the treatment length of a phase IIa clinical trial for the treatment of diabetic neuropathy is 23 weeks with a range of 16 weeks to 30 weeks. The average number of patients in these trials was 87 with a range of 72 to 102. The average treatment length of a phase IIb clinical trial for the treatment of diabetic neuropathy is 24 weeks. The average patient enrolment is 290 with a range of 180 to 400 patients. The average treatment length of a clinical trial to evaluate a treatment for pain caused by diabetic neuropathy was substantially shorter. It is estimated that the average treatment time of a phase IIa trial to be 6 weeks. The average number of patients for these trials is 214 with a range of 200 to 228. The average treatment length of a phase IIb trial for pain treatment in diabetic neuropathy is 15 weeks with a range of 8 to 21 weeks. The average patient enrolment is 343 patients with a range of 320 to 360.

In phase III clinical trials for the treatment of diabetic neuropathy, there was insufficient data to calculate an average trial length. Only one trial indicated a period of 20 weeks. However, the average number of patients was 483 with a range of 400 patients to 550 patients.

The average treatment length of a phase III clinical trial to evaluate a treatment for pain associated with diabetic neuropathy was 14.5 weeks with a range of 12 weeks to
20 weeks. The average number of patients for the trials was 481 with a range of 208 patients to 760 patients.

4.2.5 Endpoint Tests

Study conductors use several common tests in the clinical trials to determine if the treatment met its clinical endpoints (the desired effect of the drug). Clinical trials that assess the ability of the drug to prevent progression of diabetic neuropathy often used Nerve Conduction Velocity tests. Drugs developed to treat pain associated with the disease undergo evaluation using several assessment scales such as the Verbal Pain Intensity Scale, the Visual Analogue Scale and the Likert Numeric Pain Intensity Scale.

4.2.5.1 Nerve Conduction Velocity Tests

Study conductors use this test to evaluate the speed of signals through a nerve to determine the level of nerve damage. They place electrodes on the skin over the nerve at various locations. Nerves are then stimulated using mild electrical impulses. Another electrode that is placed at a distance from the first records the electrical activity of the nerve. The time required for the electric impulse to travel from one electrode to other determines the speed of the nerve signals. (NIH, 2007)

4.2.5.2 Pain Intensity Scale

This is one of the most commonly used scales to measure pain intensity. The scale measures 10 cm in length and contains a bar labelled “no pain” at one end and a bar labelled “worst possible pain” at the other end of the scale. The test evaluator asks the patient to mark off where along the line of the scale their pain is. A measurement in centimetres of the distance from the “no pain” bar is recorded.
4.2.5.3 The Likert Pain Scale

The Likert scale is a numerical scale where 0 is no pain and 10 is the worst possible pain. The study conduct asks the patient to identify the number that is best associated with their level of pain. It is very similar to the Visual Analog Scale with the exception of the numerical rating. This is the most commonly used scale in a hospital setting. (Argoff, 2002)

4.2.6 Drug Pipeline

Treating the symptoms of diabetic neuropathy is the basis for the majority of drugs on the market. This indication only has two FDA approved drugs for treatment and both are for symptom management. Successful use of disease modifying agents that target the underlying pathologies to treat diabetic neuropathy is still absent. A prime example is Eli Lilly’s drug ruboxistaurin mesylate. The drug was highly touted as a novel approach to treat diabetic neuropathy. However, the drug did not show favourable phase III clinical trial results. The drug is currently undergoing testing for diabetic retinopathy. Currently, several disease modifying agents undergoing clinical trials show promise in treating the affliction.

4.2.6.1 SB-509

Sangamo Biosciences is developing a drug called SB-509 for the treatment of mild to moderate and moderate to severe diabetic peripheral sensory motor neuropathy. SB-509 is an injectable formulation of plasmid DNA that encodes a zinc finger peptide transcription factor that up-regulates the production of vascular endothelial growth factor (VEGF). (Sangamo, 2007) VEGF potentially improves the structure and function of
nerves by protecting and repairing the damage to nerves caused by diabetic neuropathy. Phase I studies showed the drug to be well tolerated after a single injection with few adverse side effects. In addition, three of twelve subjects showed recovered and improved nerve conduction velocity.

SB-509 is currently in two phase II clinical trials to determine the safety and efficacy of repeated doses of the drug. The first indication is mild to moderate diabetic neuropathy and the second is moderate to severe diabetic neuropathy. The first phase II study enrolled 102 patients and the second enrolled 45 patients. For each patient, Sangamo expects trials to require two months of initial screening, three months of treatment, and nine months for subject follow up. The patients will be assessed using nerve conduction velocity tests, visual analogue scale for pain intensity, and the total neuropathy score. Sangamo Biosciences expects completion of both trials by the end of 2007, and clinical data reported by the second half of 2008.

4.2.6.2 Ranirestat

Ranirestat is an aldose reductase inhibitor evaluated in clinical trials for the treatment of mild to moderate symptoms of diabetic neuropathy. Dainippon Pharmaceutical is developing the drug in Japan and Eisai is responsible for the marketing. Ranirestat suppresses the accumulation of sorbitol within the nerve cells. Hyperglycemia increases aldose reductase enzyme activity, which causes an increased conversion of glucose into sorbitol. Scientists hypothesize that the accumulation of sorbitol is responsible for nerve damage and decreased nerve conduction velocity in patients with diabetes. In phase II trials, Ranirestat reduced sorbitol levels by 65% to 84%. This
resulted in improvements in nerve conduction velocities. The study enrolled 94 patients for an initial treatment period of 12 weeks followed by a 48-week extension. (Bril, 2006)

Phase III studies of Ranirestat have recently been completed. The data from the trials has not been released. The study treated 500 enrolled patients for a period of one year. Patient evaluation using Nerve Conduction Velocity tests occurred on five separate occasions during the year (New York-Presbyterian, 2005).

4.2.7 Summary of Diabetic Neuropathy

Diabetic neuropathy is a neurodegenerative disorder that is caused by the onset of type 1 and type 2 diabetes mellitus. The primary symptoms include pain, tingling, and discomfort in the patient’s limbs, especially in the hands and feet. The disorder affects a large population of diabetes sufferers in the United States totalling 3.5 million. However, due to varying levels of symptomatic pain observed among those affected and difficulties diagnosing the disorder, only 800,000 individuals in the US are treated annually. There are no existing drug therapies that can prevent the progression of the disorder. Current treatment methods focus on treating the symptoms of the disorder. The top three drugs used to treat diabetic neuropathy had a combined market value of over $2.4 billion US in 2006. Clinical trials to evaluate potential drug candidates for this disorder are generally shorter than most other neurodegenerative disease indications. The primary endpoint for most studies is pain assessment which requires less time to evaluate. However, current endpoint testing methods for pain assessment are very simple and subjective to each individual and may be a cause for inaccurate results.
4.3 **Chemotherapy Induced Neuropathy**

Chemotherapy induced neuropathy describes degeneration or damage to nerves located in the peripheral nervous system caused by the use of chemotherapeutic agents in cancer treatment. Chemotherapeutic agents are widely used in the treatment of most forms of cancer. While chemotherapy can be a successful treatment option to prolong life, the drugs used are often toxic to the body thus leading to serious side effects such as neuropathy. This type of neuropathy can often be painful and can cause a dose-limiting affect on the chemotherapy treatment. Taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinorelbine) and platinum compounds (cisplatin, oxaliplatin) are the most common classes of therapeutic agents used in chemotherapy and have shown to cause neuropathy in the patient.

The mechanisms by which these drugs cause neuropathy are not well known. However, scientists hypothesize that neurotoxic chemicals damage nerve fibres by deactivating components required to maintain the metabolic needs of the axon. (Visovsky, 2005) Most of the chemotherapeutic agents cause damage to the core of the peripheral neuron however; the type of neuropathy varies with the agent used in the cancer treatment.

### 4.3.1 Prevalence

The number of patients affected with chemotherapy-induced neuropathy is dependant upon the drug used to treat the cancer and its dosage level. Estimates indicate that paclitaxel causes neuropathy in 60% of all prescribed patients. (Wampler, 2007) The incidence rate when using platinum compounds such as cisplatin and oxaliplatin to treat cancer can be as high as 74%. The incidence of neuropathy can also increase when
drugs are used in a combination therapy. For example, neuropathy occurs in about 45% - 50% of ovarian cancer patients receiving cisplatin alone. This percentage increases to 90% - 100% when cisplatin is used in conjunction with paclitaxel. (Valeant, 2007)

The American Cancer Society estimates that there will be 1,444,920 new cancer cases in the United States in 2007. Over 50% of these cases will receive chemotherapy as their primary treatment. (Rona, 2000) This equates to 722,460 patients that will receive chemotherapy in 2007. Based on the incidence estimates of the individual drugs, roughly 60% of the chemotherapy treated patients will encounter some form of neuropathy thus equalling 433,476 patients in the United States in the year 2007. Valeant Pharmaceuticals estimates that there are over 150,000 new cases of chemotherapy induced neuropathic pain per year in the US alone.

4.3.2 Symptoms

The symptoms of chemotherapy-induced neuropathy can vary depending on the chemotherapeutic agent used in the treatment. Vincristine, commonly used in treating non-Hodgkin’s lymphoma and Hodgkin’s lymphoma and can often cause severe peripheral neuropathy. The drug causes damage to the sensorimotor neurons that can lead to paresthesias\(^4\) followed by severe motor weakness if the treatment is prolonged. (Van den Bent, 2005) Pain is not a major symptom of using vincristine; however, the neurotoxicity often leads to dose limiting during treatment.

Physicians commonly use cisplatin for treating a wide variety of cancers including testicular, ovarian, bladder, lung and various forms of head and neck cancers.

\(^4\) An abnormal sensation of the skin such as numbness, tingling, pricking, burning, or creeping on the skin that has no objective cause. Source: Medicine.net, 2007
This drug affects the sensory nerve bodies and becomes symptomatic at cumulative dose levels of 420mg/m². (Van den Bent, 2005) The use of cisplatin commonly attributes to sensory loss and in some cases renders the patient in able to walk. Pain and temperature senses are only minimally affected. Unlike vincristine, cisplatin neurotoxicity requires a relatively long period to develop. Symptoms often do not occur until the end of treatment thus preventing timely discontinuation of treatment for patients that encounter neurotoxicity. The neurotoxicity caused by cisplatin is also dose limiting and often the effects are irreversible.

Physicians commonly use Paclitaxel for treating breast, lung, ovarian and various forms of head and neck cancers. Often, combination therapy uses paclitaxel and cisplatin in conjunction. In combination, neurotoxicity becomes amplified and often causes intense neuropathic pain. Paclitaxel neuropathy is dependent on the dose per cycle when used alone. Keeping the dose under 200mg/m² per cycle rarely leads to severe symptoms (Van den Bent, 2005) Signs and symptoms generally begin early after the start of treatment and tend to improve before the start of the next cycle. Dysesthesias⁵ and weakness can be profound with continued chemotherapy treatment and may prove disabling if there is no alteration of the treatment regimen.

4.3.3 Treatments

There are no current drug therapies approved by the FDA to treat chemotherapy-induced neuropathy. Chemotherapy dosing regimens often require alteration to alleviate the symptoms caused by the neurotoxic drugs. In addition, the use of antidepressants and

⁵ Subjective cutaneous sensations such as cold, warmth, tingling, pressure, etc. that are experienced spontaneously in the absence of stimulation. Source: Medical Dictionary Online, 2007
anticonvulsants has become the first line therapy for treating symptoms such as pain. Prescription of antidepressants such as amitriptyline and duloxetine are commonly. Gabapentin and pregabalin are the most prescribed anticonvulsants.

Prescription of the drug therapies occur at the onset of symptoms and continue for the entire duration of the treatment course. In some cases, patients will remain on the drug treatment for an extended period of time post chemotherapy as symptoms can often persist. On average, the course of a chemotherapy treatment will range between 3 to 6 months. During this period, a patient will undergo 4 to 8 cycles of chemotherapy that can vary from 1 to 4 weeks in duration per cycle. (Cancer Research UK, 2007)

The prescribed dosage of antidepressants and anticonvulsants are similar in treating chemotherapy-induced neuropathy as in diabetic neuropathy. Prescription of amitriptyline at 10-25mg nightly is the starting dose and increases to a dosage of 50-150mg nightly. The daily prescription of Duloxetine is 60mg. The starting dose of gabapentin ranges from 100-300mg daily with a maximum dosage of 3600mg per day. Prescription of pregabalin, a successor to gabapentin occurs in lower doses but is equally effective as gabapentin. The starting dose for pregabalin is 150mg daily and up to a maximum of 300mg per day. (Macdonald, 2006)

The diabetic neuropathy section provides a detailed description of the cost, side effects and mechanisms of action of these drugs.

4.3.4 Clinical Trials

There are currently 19 clinical trials recruiting patients for chemotherapy induced neuropathy treatments and nine ongoing studies. Using data provided by the FDA, the average phase IIa trial treatment length for chemotherapy-induced neuropathy was 13
weeks with a range of 8 weeks to 18 weeks for Johnson & Johnson’s neuroprotectant Procrit. On average, the studies enrol 87 patients in the trials with a range of 40 to 120 patients in Johnson & Johnson’s trial. Information was not available to calculate the duration and patient population of a phase IIb trial.

The average length of a phase III trial in the prevention of chemotherapy-induced neuropathy was 29 weeks with a range of 12 weeks to 48 weeks. The average enrolment of patients in these studies was 448. However, the Sanofi Aventis’ clinical trial that enrolled 900 patients dramatically skews the average. The average trial size excluding the Sanofi Aventis trial is 222 patients. The average length of a phase III trial in the treatment of symptoms of chemo-induced neuropathy is 15 weeks with a range of 10 weeks to 24 weeks. The average patient enrolment is 185 with a range of 100 patients to 400 patients.

A primary issue concerning the evaluation of drug compounds for treating chemotherapy-induced neuropathy is the high patient dropout rate in clinical trials. A study performed by R. F. Bell and colleagues examined 34 clinical trials that evaluated the efficacy of drug treatments associated with pain due to cancer. Twenty of the 34 trials consisted of patients who recently or currently receiving chemotherapy treatment. The average patient population of the trials was 55 patients with treatment duration of 14.7 days. The average dropout rate was 22.7%. The most common reason for dropout was adverse effects, followed by insufficient pain relief and deterioration due to disease progression. (Bell et. al., 2006)
4.3.5 Endpoint Tests

Study conductors use several common instruments to determine if the treatments have reached the intended clinical endpoints. One of the most common methods used to determine the level of nerve damage and nerve improvement are Nerve Conduction Velocity tests. These are the same tests used in diabetic neuropathy clinical trials. However, the most commonly used tests to determine neurotoxicity due to chemotherapeutic agents are the NCI-CTC, FACT/COG-Ntx, and the total neuropathy score.

4.3.5.1 NCI-CTC

The National Cancer Institute Common Toxicity Criteria is a widely accepted standardized scale for measuring the effects of neurotoxicity in chemotherapy patients. All National Cancer Institute sponsored clinical trials use these criteria as the evaluation method. The NCI sponsors more chemotherapy trials than any other research or drug development organization. The NCI-CTC scale is a questionnaire containing many possible symptoms that can indicate toxicity. The scale ranges from 0 (no effect) to 4 (severe effect) for each symptom. The overall toxicity of the drug is determined by calculating the total at the end of the questionnaire. (NCI, 2007)

4.3.5.2 FACT/COG-Ntx

The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity questionnaire is another widely used scaled to evaluate the symptoms and concerns associated with chemotherapy-induced neuropathy. Patients undergoing treatment for ovarian cancer with the chemotherapeutic agent Paclitaxel often receive
evaluations using this scale. The questionnaire consists of a series questions pertaining to the patient’s illness, which are answered using a rating scale of 0 (not at all) to 4 (very much). A similar scale called the Functional Assessment of Cancer Therapy – Taxane, assesses the toxicity caused by the taxane class of chemotherapeutic agents. (Oncology Nursing Society, 2007)

4.3.5.3 Total Neuropathy Score

Study conductors use The Total Neuropathy Score (TNS) to quantify the severity of chemotherapy-induced neuropathy. The TNS contains eight to ten variables such as sensory symptoms, motor symptoms, pin sensitivity and vibration sensitivity. These variables are ranked by patients on a scale of 0 (limited or slight) to 4 (disabling or severe). (Wampler, 2006)

4.3.6 Drug Pipeline

Research and development of drugs to treat chemotherapy-induced has been limited. Few pharmaceutical companies have targeted this indication for drug development. The National Cancer Institute has conducted the majority of the research. The number of clinical trials for drugs used to treat the symptoms chemotherapy-induced neuropathy still out numbers the drugs used to treat the underlying complication. There are only several drugs currently being developed that can be classified as potentially disease modifying.

4.3.6.1 Procrit

Procrit is glycoprotein that stimulates red blood cell production currently undergoing an evaluation for neuroprotective effects in patients with cancer who develop
chemotherapy-induced neuropathy. Johnson & Johnson is conducting the clinical trial that focuses on patients previously treated with a combination of taxanes and platinum based chemotherapeutic agents. The FDA has approved Procrit for the treatment of anaemia in patients with most types of cancer receiving chemotherapy.

Procrit potentially provides neuroprotection by inducing the erythropoietin-signalling pathway in neuronal cells thus inducing an insulin-like growth factor signalling pathway in the neuronal cells. The combination of pathway activities is though to produce a synergistic acute neuroprotective effect in the neuronal cells. (Murat, 2003)

Procrit is currently in phase II clinical trials. The trial is evaluating 120 patients for an 18-week period. Administrators will inject patients with doses ranging from 20,000 to 60,000 units. Evaluation of the clinical endpoints will occur using the NCI-CTC scale.

4.3.6.2 Xaliproden

Xaliproden is a neuroprotective 5-HT receptor agonist developed by Sanofi Aventis currently undergoing an evaluation for the treatment of chemotherapy-induced neuropathy. Current use of orally administered drug is for treating amyotrophic lateral sclerosis. The understanding of the mechanism of the drug is not complete but it hypothetically the drug may mimic the activity or stimulate the synthesis of endogenous neurotrophins thereby stimulating neuronal cell differentiation and proliferation in addition to inhibiting neuronal cell death. The neuroprotective effect involves the activation of MAP kinase pathways via stimulation of the 5-HT1A receptor. (Sanofi-Aventis, 2006)
A previous phase III clinical trial showed that xaliproden reduced the occurrence of severe sensory neuropathy associated with oxaliplatin based chemotherapy treatment. The results indicated that xaliproden reduced the risk of occurrence of grade 3 peripheral sensory neuropathy by 39% in oxaliplatin treated patients.

Xaliproden is currently in phase III clinical trials for the prevention of neurotoxicity caused by oxaliplatin. Sanofi-Aventis is currently recruiting nine hundred patients. The treatment phase is scheduled to last for 12 weeks and the clinical endpoints will be measured using the oxaliplatin specific scale for dose adjustment. Xaliproden is also undergoing an evaluation for the treatment of Alzheimer’s disease.

4.3.7 Chemotherapy Induced Neuropathy in Breast Cancer

Breast cancer is the most frequently diagnosed cancer amongst women. The American Cancer Society estimates that there will be 180,510 new cases of breast cancer in the United States in the year 2007. Estimates indicate that 40,910 individuals will die from the disease in 2007.

Treating breast cancer is dependent upon several factors including type of breast cancer, size of tumour, location of tumour, and stage of cancer progression. Treatment options include one or a combination of following; surgery, chemotherapy, hormone therapy or radiation therapy. Chemotherapy is widely used in the treatment of breast cancer. Almost all patients diagnosed with breast cancer will receive chemotherapy at some point in the treatment process. (Kolata, 2006) It is common to use chemotherapy before surgery to shrink a tumour (neoadjuvant therapy), post surgery to reduce the chance of the cancer spreading or coming back (adjuvant therapy) or as a primary treatment for cancer that has spread or come back.
In neoadjuvant and adjuvant therapy settings, a combination of drug therapies is often used. There are two broad categories of combination adjuvant treatments, CMF and anthracycline based chemotherapy. (Burstein, 2007) The CMF chemotherapy regimen consists of a combination of cyclophosphamide, methotrexate, and 5-fluorouracil. Anthracycline based chemotherapy regimens are slightly more effective in treating breast cancer and are the preferred means of treatment. There are several regimens of this type of therapy; AC chemotherapy—doxorubicin and cyclophosphamide, CAF or FAC chemotherapy—cyclophosphamide, doxorubicin, and 5-FU, CEF or FEC chemotherapy—cyclophosphamide, epirubicin, and 5-FU. Treatments usually combine taxanes (paclitaxel and docetaxel) with anthracycline based chemotherapy regimens and are some of the most effective drugs for treating breast cancer. Cancer treatment for women with node positive breast cancer routinely use paclitaxel (Taxol) and docetaxel (Taxotere) and is becoming increasingly popular in a form of adjuvant chemotherapy called dose-dense chemotherapy. (Burstein, 2007) Dose-dense chemotherapy is a method of giving anthracycline therapy in conjunction with taxanes in shorter intervals between cycles to increase the intensity of the treatment. The average treatment cycle lasts 21 days. The dose-dense treatment cycle condenses to 14 days. The course of adjuvant treatment generally requires between 4 and 8 cycles depending on the degree of cancer metastasis. The treatment lasts about 3 to 6 months.

Taxanes are effective drugs in treating metastatic breast cancer; however, this class of drugs is associated with causing neuropathy in patients. The neurological toxicity caused by paclitaxel and docetaxel can lead to numbness or tingling of the fingers and toes. Pain is also a common side effect and often causes a dose limiting
effect in the treatment. Estimates indicate that 60% of patients treated with paclitaxel will encounter neuropathy while 71% of patients treated with docetaxel will encounter the same. (Wampler, 2007)

4.3.8 Summary of Chemotherapy Induced Neuropathy

Chemotherapy induced neuropathy is a degeneration of neurons caused by the toxic effects of chemotherapeutic agents used in treating cancer patients. Patients generally feel intense pain during chemotherapy treatment often leading to dose-limiting. In essence, the dose of the chemotherapy agent is reduced thus decreasing the effectiveness of the treatment. Estimates indicated that 433,476 patients in the US will encounter chemotherapy induced neuropathy in 2007. Breast cancer patients will account for 108,306 of this number. Current treatments are the same for chemotherapy induced neuropathy as in diabetic neuropathy. Clinical trials for this disorder are also based on pain assessment but the patient population and duration of trials is often shorter than those of diabetic neuropathy. This is due to the smaller population base to draw from and the quick onset of symptoms. In addition, endpoint testing methods are more standardized for this type of neuropathy compared to diabetic neuropathy.

4.4 Parkinson's disease

Parkinson’s disease is a neural degenerative disease that affects the nerve cells in the part of the brain that controls muscle movements. (Mayo Clinic, 2007) This disease commonly impairs motor skills and speech. People with Parkinson’s disease often experience trembling, muscle rigidity, difficulty walking, slow movement, and in some cases loss of movement. Symptoms begin to appear later in life, generally after the age
of 60. The disease is progressive and symptoms become worse over time and can lead to severe disability.

Parkinson’s disease is primarily idiopathic or of unknown cause. However, researchers believe that genetics, the environment and certain medications play a factor in the progression of the disease. Degradation of the neurons located in substantia nigra is the primary cause of the symptoms of the disease. (Mayo Clinic, 2007) These cells are responsible for releasing dopamine, which transfers signals from the substantia nigra to the corpus striatum. These signals are responsible for making smooth controlled movements in the muscles. The loss of dopamine producing neurons is the main factor in the loss of motor skills and speech. People affected with Parkinson’s disease lose over half of all the neurons in the substantia nigra.

4.4.1 Prevalence

The Michael J. Fox foundation estimated that there are between 1 million and 1.5 million Americans affected with Parkinson’s disease. The number increases to 6 million worldwide and will approach 8.7 million by the year 2030. The prevalence of the disease is widespread and estimates indicate the disease to be present in 100 to 250 cases per 100,000 people in North America. (Zhang, 2005) Estimates of the incidence of disease are as high as 20.5 affected per 100,000 individuals in the United States. (Rajput, 1984) This figure correlates with an estimate performed by the American Association of Neurological Surgeons, which estimated 60,000 new cases of Parkinson’s disease per year in the US.
4.4.2 Symptoms

The symptoms of Parkinson’s disease can be mild at the onset. Slight trembling in the fingers, slowed speech, lack of energy, depression and trouble sleeping can be signs of early Parkinson’s disease. The symptoms often intensify, as the disease progresses and are often are quite visible. The major signs and symptoms of Parkinson’s disease include:

- **Tremor** – Mild tremors start in the fingers and hands and can eventually progress to the legs. The severity of the tremors often increases in times of stress and can disappear during sleep. Many people with Parkinson’s disease will not experience substantial disabling tremors.

- **Impaired Speech** – Many individuals with Parkinson’s disease will have impaired speech. Their voice often becomes monotone and soft causing difficulty in communicating with others.

- **Slowed Motion** – Parkinson’s disease often causes difficulty in walking with a regular gait. Individuals often stoop over in posture and shuffle their feet when walking. Leg muscles may freeze up and make it nearly impossible for an affected individual to resume normal routines.

- **Loss of Autonomic Actions** – In Parkinson’s disease, unconscious acts such as blinking, smiling, and arm swinging while walking, are diminished and in some instances completely lost. Some individuals will appear to have no expressions or a fixed stare.
• **Dementia** – In the late stages of Parkinson’s disease, a small number of individuals will experience dementia. This is symptom is characterized by slowed thought processes and the inability to concentrate.

4.4.3 Treatments

No FDA approved treatments exist that can cure Parkinson’s disease. Additionally, no drugs on the market prevent the progression of the disease. The most common treatments are medications used to alleviate the symptoms of the disease. In some cases, surgery such as deep brain stimulation; is used to help alleviate a patient’s symptoms if they do not respond to medication. The Parkinson’s disease foundation estimates that the total treatment cost of the disease is nearly $25 billion per year in the United States alone. This estimation includes direct and indirect costs such as medications, social security payments, and lost income from inability to work.

Medication costs per patient, per year are $2500 US. Surgery to treat Parkinson’s can cost up to $100,000 US. (Parkinson’s disease Foundation, 2006)

The use of several drug classes to treat Parkinson’s disease is common. The most common drug treatments are dopamine replacement therapies and dopamine agonists.

4.4.3.1 Dopamine Replacement Therapies

Dopamine replacement therapies are the most commonly used type of treatment for Parkinson’s disease. The primary dopamine replacement drug is levodopa. The use of levodopa has been around since the 1960s and is the “gold standard” in treating Parkinson’s disease. (Mayo Clinic, 2007) The drug approved by the FDA to treat the disease in 1970, was the first of its kind. The use of levodopa accounts for roughly 25%
of all Parkinson’s disease treatments. (Schwarz Pharma, 2007) Levodopa is a precursor to dopamine and when given to patient’s with Parkinson’s converts to dopamine in the brain through enzymatic activity. A major advantage to using this treatment is that it is capable of crossing the blood brain barrier. Dopamine cannot cross this threshold thus is not a direct treatment for the disease. Treatments often combine levodopa with carbidopa to slow enzyme breakdown of levodopa before it reaches the brain.

Levodopa/carbidopa significantly improves mobility in patients however; the drug also causes significant side effects. The efficacy of the treatment tends to weaken over long periods. The drug becomes unpredictable and can cause periods of involuntary movements, hallucinations and illusions. There are often periods of time when the drug is effective followed by periods of ineffectiveness which are referred to as “on time” and “off time” respectively. (Michael J. Fox Foundation, 2007)

4.4.3.2 Levodopa/Carbidopa (Sinemet)

Bristol Meyers Squibb markets and sells levodopa/carbidopa under the brand name Sinemet. In 2006, sales of Sinemet reached $66 million US. (Bristol Myers Squibb, 2007) Sinemet tablets are available in a 1 to 4 ratio of carbidopa to levodopa (SINEMET 25-100) as well as a 1 to 10 ratio (SINEMET 25-250 and SINEMET 10-100). The initial dose prescribed is one tablet of 25-100 Sinemet three times daily. Patients will less severe symptoms may be prescribed the 10-100 tablets. The dosage is scaled up on a daily basis by one tablet increments until the optimal dosage of eight total tablets per day is reached. (Rxlist, 2007) The retail cost of Sinemet ranges from $0.86 US to $1.00 US per 25-100 tablets. (Drugstore.com, 2007) Monthly treatment cost of using Sinemet could reach $240.
4.4.3.3 Dopamine Agonists

Dopamine agonists are a class of drugs that mimic the effects of dopamine in the brain. They cause neurons to react as if there were sufficient amounts of dopamine present. These drugs can be taken as adjunct therapy to levodopa/carbidopa or used on their own in early stage Parkinson's disease. Dopamine agonists such as bromocriptine (Parlodel), apomorphine (Apokyn), pramipexole (Mirapex) and ropinirole (Requip) are often prescribed first to patients to dull the symptoms of the disease. If these drugs do not show the desired effect, administration of levodopa/carbidopa follows. The side effects of dopamine agonists are similar to levodopa/carbidopa but are less likely to cause involuntary movements. Changes in behaviour such as compulsive gambling, hyper-sexuality and overeating are additional side effects to this class of drugs.

4.4.3.4 Pramipexole (Mirapex)

Pramipexole marketed and sold Boehringer Ingelheim under the brand name Mirapex is the world's top selling dopamine agonists. Net sales of Mirapex in 2006 reached 536 million euros which equates to roughly $741 million US. The drug commands a market share of 22%. (Boehringer Ingelheim, 2007) The sales figures are slightly misleading as Mirapex is also approved for treating restless leg syndrome. Since the approval of the drug to treat restless leg syndrome in 2006, sales have increased by 23%.

Initial prescribed dose of Mirapex is 0.375mg per day. Administration of the drug requires even distribution three times daily. The dosage scales up to a maximum of 4.5mg per day over a seven-week period. (RXlist, 2007) Mirapex sells in 0.125mg, 0.25mg, 0.50mg, 1.0mg and 1.5mg tablets. The price per tablet ranges from $1.91 US for
the 0.125mg tablet to $2.70 US for the 1.5mg tablet. (Drugstore.com, 2007) At the maximum dose of 4.5mg, the average daily treatment cost would be $8.10 US. Monthly costs could reach $243 US.

4.4.3.5 Rotigotine (Neupro)

Rotigotine developed by Schwarz Pharma is one of the newest dopamine agonists on the market. The drug sells under the brand name Neupro and received recent approved by the FDA for treating early stage Parkinson's disease. The official launch Neupro in the US occurred in July of 2007. The advantage of Neupro is that the transdermal patch releases the medication over a twenty-four hour period. Application of the patch occurs once daily and will be available in 2mg/24 hours, 4mg/24 hours and 6mg/24 hours doses. Sales of the drug in Europe reached 17 million euro in the first half of 2007, up 500% from the previous year. (UCB, 2007) The price of the patch is comparable to the existing orally administered drugs currently available to treat Parkinson's disease. Schwarz Pharma is currently awaiting approval from the FDA to use Neupro for advanced stage Parkinson's disease. The company predicts revenues for Neupro to reach $350 million US per year once the drug receives FDA approval.

4.4.4 Clinical Trials

There are currently 153 clinical trials for Parkinson's disease treatments recruiting patients. In addition, there are 63 ongoing clinical trials for the treatment of the disease. (FDA, 2007) Using data provided by the FDA, the calculated average length of a phase IIa clinical trial to evaluate the efficacy of Parkinson's disease treatments is 15 months with a range of 6 months to 18 months. The average number of patients enrolled in these
trials is 137 with a range of 40 patients to 150 patients. The average length of a phase IIb trial is 10 months with a range of 4 months to 14 months. The average patient population is 176 with a range of 120 to 244 patients.

The average calculated treatment period for phase III clinical trials is 15 months with a range of 3 months to 60 months. The average number of patients enrolled was 768 with a range of 133 to 1720. However, several extension studies to previous phase III trials that are evaluating the long-term safety and efficacy of the treatment on Parkinson’s disease. The average trial length of an extended term study is 24 months with a range of 4 months to 60 months. The average patient population is 1164 with a range of 900 to 1720 patients.

### 4.4.5 Endpoint Test

The most widely used method to test the progression of Parkinson’s disease in a clinical setting is the United Parkinson’s Disease rating scale (UPDRS). This scale is the standard test for the disease, largely eliminating the use of the Hoehn and Yahr Staging of Parkinson’s disease scale. Various Parkinson’s disease questionnaires and the patient’s own documentation of the disease in their diaries, often supplement the UPDRS.

#### 4.4.5.1 United Parkinson’s disease Rating Scale (UPDRS)

The UPDRS, developed in 1987 is now a well-established tool to measure and quantify the signs and symptoms of the disease. The comprehensive scale allows for overall measure of disability and individual subscale items. The UPDRS consists of four subscale headings; mentation, behaviour, and mood, activities of daily living, motor examination, and complications of therapy. (Teva Neuroscience, 2006) The scale
consists of forty-two questions that are graded from 0 (none, normal) to 4 (severe, persistent). Summing of the results from the questionnaire provide an overall value that determines the severity of the disease. The scale also includes two additional subsections that incorporate the Hoehn and Yahr Parkinson’s disease scale and the Schwab and England Activities of Daily Living Scale.

4.4.6 Drug Pipeline

Current treatment methods for Parkinson’s disease focus on increasing dopamine levels and/or activation of dopamine receptors in the brain. The greatest issue concerning these types of drugs is the progression of nerve degeneration. As nerves continue to deteriorate, dopamine drug therapies gradually become less effective. The search for drug therapies that may delay or prevent the pathologic progression has become a high priority for researchers. A discovery in this area of focus could lead to a potential blockbuster drug. Currently there are no therapies on the market proven to offer neuroprotection and slow the progression of the disease. However, several drugs in clinical development have shown neuroprotective qualities in treating Parkinson’s disease.

4.4.6.1 Rasagiline (Azilect)

Azilect, generic name Rasagiline, is a MAO-B inhibitor developed by Teva Pharmaceuticals. MAO-B inhibition blocks the breakdown of dopamine, which allows the signalling neurons to reabsorb the hormone for later use. The drug received approval by the FDA for the treatment of idiopathic Parkinson’s disease, both as monotherapy and
as adjunct therapy with levodopa. The drug was officially launched in the United States on July 31, 2006. Azilect is a once daily pill administered via oral ingestion.

Azilect has been associated with delays in disease progression in previous phase III clinical trials. Teva Pharmaceuticals is currently conducting a large-scale clinical trial of 1100 patients to examine the neuroprotective properties of the drug. (Teva, 2007) The trial will last 18 months and Teva expects to announce the in 2009.

4.4.6.2 PD-02

PD-02 is a creatine-based drug being developed by Avicena Group Inc. and is sponsored by the National Institute of Health. The basis for the drug candidate is on the company’s regulation of cellular energy processes technology platform. PD-02 is an ultra pure clinical form of creatine that thought to have neuroprotective properties including protection of dopaminergic cells. (Avicena, 2007) Studies have suggested that PD-02 can improve the function of mitochondria, which produce energy inside cells. In addition, it may also act as an antioxidant that prevents damage from compounds that are harmful to cells in the brain.

PD-02 exhibited promising phase II clinical trial results. The study evaluated the futility of the drug over predetermined thresholds for a 12-month period on 200 patients. After twelve months of daily treatment, investigators found that the rate of Parkinson’s disease progression was lower as measured by the UPDRS. The drug is also determined safe and well tolerated in patients.

Phase III trials to evaluate the efficacy of the drug were initiated in March of 2007. The five-year study will enrol over 1,720 patients. The National Institute of Neurological Disorders and Stroke (NINDS), a subdivision of the National Institute of
Health, are funding the study. The phase III PD-02 study is the largest study ever conducted in Parkinson’s disease research. It is also the largest NIH sponsored study ever conducted.

4.4.7 Summary of Parkinson’s disease

Parkinson’s disease is a neurodegenerative disorder that affects nerve cells in the brain that controls muscle movements. Symptoms include impaired motor skills and loss of speech. The disease is progressive and symptoms become worse over time, in many cases leading to severe debilitation. Estimates indicate that 1.5 million Americans are diagnosed and treated for the disease making it the largest market of the four disease indications in this study. There is no cure for Parkinson’s disease. Current treatments are focused on alleviating symptoms. The market value of the top three drugs used to treat this disease is over $1 billion US. The attractive potential market is offset by the cost of developing a drug for this indication. Parkinson’s disease has the longest clinical trial durations with the largest patient populations which contribute to the high costs. The lengthy clinical trials are due to the slow progression of the disease.

4.5 Schizophrenia

Schizophrenia is a chronic, severe and disabling disease of the brain. It is a mental disorder that can often cause affected individuals to hear voices that do not exist and have fears of people plotting against them. These symptoms can cause extreme fear and anxiety. People with Schizophrenia may make no sense when they speak, may sit still for many hours without movement or may look and act normal until they begin speaking about the thoughts they are having. The onset of the symptoms of the disease
can begin in the late teenage years and early twenties in men. In women, the occurrence of symptoms usually begins between the mid twenties to the early thirties. (NIMH, 2007)

A combination of genetic predisposition and environmental factors are primary attributes to the cause of Schizophrenia. The combination of the two results in a disruption in brain development during pregnancy and early childhood that can lead to alterations in the brain that make the individual more susceptible to the disease. (Glick, 2005) The exact cause of the disease is unknown; however, scientists have linked several genes to the development of schizophrenia. Researchers also implicate neurotransmitters in the development of the disease. Currently the most studied neurotransmitters are dopamine, serotonin, and glutamate. (Coconea, 2005)

4.5.1 Prevalence

Estimates indicate that over 1.1% of the world’s population will suffer schizophrenia over their lifetime. At any given time, as many as 51 million people worldwide suffer from schizophrenia. (NIMH, 2007) In the United States alone, 2.4 million individuals are afflicted with the disease. The National Institute of Mental Health also estimates that 70% of all schizophrenia sufferers will also show signs of cognitive impairment. The number of people diagnosed with schizophrenia in a year is 1 in 4000 individuals. In the United States, an estimated 100,000 individuals are diagnosed each year for the disease. 1.5 million Individuals worldwide are diagnosed with schizophrenia each year. However, according to the Diagnostic and Statistical Manual of Mental Disorders, 60% of all individuals with schizophrenia are unaware of being ill and are untreated. (Amador, 2006)
4.5.2 Symptoms

The symptoms of schizophrenia vary depending on the type and severity of the disease. Some individuals with schizophrenia may not have any appearance of being while others may display unusual behaviours such as wearing tin foil on their heads to prevent other individuals from reading their thoughts. The grouping of schizophrenia symptoms is often in clusters of positive symptoms, negative symptoms, cognitive symptoms and affective symptoms (Cooncea, 2005).

- **Positive symptoms**: hearing voices, suspiciousness, feeling under constant surveillance, delusions, and making up words that have no meaning.

- **Negative symptoms**: social withdrawal, difficulty expressing emotions, difficulty taking care of themselves, and inability to feel pleasure. These symptoms often cause severe impairment and may be mistaken for laziness.

- **Cognitive symptoms**: inability to process information about the environment around them, inability to remember simple tasks.

- **Affective symptoms**: predominately depression, which accounts for a high rate of suicide attempts.

The symptoms are the basis for diagnosing several types of schizophrenia. These include paranoid type, disorganized type, catatonic type, undifferentiated type and residual type (Cooncea, 2005).

4.5.2.1 Paranoid Type

Delusions and auditory hallucinations characterize this type of schizophrenia. Delusions are often about unfair persecution or being another person who is in most cases...
famous. Individuals display relatively normal intellectual functioning and expression of affect.

4.5.2.2 Disorganized Type

Disorganized speech and behaviour that is difficult to understand characterizes this type of schizophrenia. Laughing at the changing colour of a traffic light for no apparent reason is an example of this type of schizophrenia. The disorganized behaviour tends to disrupt normal activities such as dressing and preparing meals.

4.5.2.3 Catatonic Type

Odd patterns of movement characterize this type of schizophrenia. Individuals may remain immobile for extended periods or they may move all over the place. They may also not speak for hours or repeat everything another individual says.

4.5.2.4 Undifferentiated Type

Some of the symptoms seen in all other types of the disease characterize this type of schizophrenia. However, there are not enough symptoms from any single type to define it as a particular type of schizophrenia.

4.5.2.5 Residual Type

The family history of the disease characterizes this type of schizophrenia but the patient currently has no positive symptoms. It could identify a transition to a complete symptomatic episode or complete remission of the disease. (Cocceea, 2005)
4.5.3 Treatments

No current treatments available cure schizophrenia. The treatment of schizophrenia often requires a combination of patient care and medication depending on the severity of the disease. Often, individuals with early stage schizophrenia undergo treatment with medication and do not require additional care from family or trained professionals. However, if the symptoms of the disease become severe, patients are often cared for at home. In many cases, hospitalization is required when patients become psychotic and become a danger to themselves and others. A study conducted by Johnson and Johnson indicated the cost of treating schizophrenia in the United States is over $60 billion per year. This figure includes societal and family costs, medication costs, and hospitalization costs. The total translates into roughly $32,500 in annual direct and indirect costs per patient.

The basis of current drug therapies is on treating the symptoms of the disease. Schizophrenia is a chronic disorder that requires constant management and does not have a cure at this time. However, taking medications can significantly decrease the rate of recurrence of psychotic episodes. Most people with schizophrenia will need to take some type of medication for the rest of their lives. Drug selection is dependant upon each individual affected with the disease. Patients often interact closely with their physicians to determine which drug is the most effective for them in treating the disease. Close monitoring by the physician is necessary because most drug treatments for schizophrenia require several weeks to be effective and up to two months to reach maximum effectiveness. In addition, stopping drug treatments can have very adverse effects on the patient.
Antipsychotic drugs are the most widely used treatment for schizophrenia and prove to be effective in treating acute psychosis and reducing the risk of future psychotic episodes. Sales of antipsychotic drugs reached $18 billion US worldwide and $12 billion in the US alone. (Berenson, 2007) This class of drugs enables the patient to function better and have a higher quality of life. However, antipsychotic drugs have limited ability to treat the cognitive impairments caused by the disease. Currently there are no drugs approved for the treatment of cognitive impairment caused by schizophrenia.

4.5.3.1 Olanzapine (Zyprexa)

Olanzapine is the highest selling antipsychotic drug on the market. Eli Lilly markets and sells the drug under the brand name Zyprexa. In 2006, worldwide sales of Zyprexa reached $4.346 billion US. (Eli Lilly, 2007) The FDA approved the drug for treating schizophrenia and bipolar disorder. Olanzapine is a monoaminergic antagonist, which binds to receptors and prevents the reuptake of dopamine and serotonin. The initial dose of the drug is 5 to 10mg with a target dose of 10mg/day. The patient administers the drug orally in tablet form once daily. Zyprexa sells in 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg tablets. The retail price of Zyprexa ranges from $6.70 US per 2.5mg tablet to $23.33 US per 20mg tablet. (Drugstore.com, 2007) At the optimal dose of 10mg per day, the daily cost of treatment is about $13 US. Monthly treatment cost of using Zyprexa at the optimal dose can reach $400 US. Common side effects of Zyprexa include dizziness, dry mouth, constipation, weight gain, drowsiness and postural hypotension. (Eli Lilly, 2007)
4.5.3.2 Risperidone (Risperdal)

Risperidone was the second highest selling antipsychotic drug. Johnson & Johnson markets and sells the drug under the brand name Risperdal. Worldwide sales of Risperdal reached $4.184 billion US in 2006. (Johnson & Johnson, 2007) Risperdal is also a monoaminergic antagonist that prevents the reuptake of dopamine and serotonin. The drug received approval for treating schizophrenia, bipolar mania and irritability associated with autistic disorder in children. Risperdal is initially administered at 2mg/day. The oral administration of the drug can occur once or twice daily. Dosage increases at increments of 1 to 2 mg/day up to the recommended dosage of 4-8 mg/day. (RXlist.com, 2007) Risperdal is available in tablet form in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg doses. The drug is also available in an oral solution at 1 mg/ml concentration. The retail price per tablet ranges from $3.30 US for the 0.25 mg to $12.80 US for the 4 mg strength. (Drugstore.com, 2007) The daily cost of treating schizophrenia using Risperdal can be up to $25.60 US if the maximum dose of 8 mg is required. This would equate to a monthly cost of $768 US. Common side effects of Risperdal include insomnia, agitation, tremors, headache, nausea and constipation.

4.5.3.3 Quetiapine Fumarate (Seroquel)

Quetiapine fumarate is the third highest selling antipsychotic drug. AstraZeneca sells the drug under the brand name Seroquel. Sales of Seroquel reached $3.416 billion in 2006. (AstraZeneca, 2007) Seroquel is an antagonist at multiple neurotransmitter receptors in the brain including serotonin and dopamine. Similar to Zyprexa and Risperdal, Seroquel inhibits the reuptake of dopamine and serotonin. The drug has also received approval from the FDA for the treatment of schizophrenia and bipolar disorder.
The administration of Seroquel begins at 50 mg/day to start and then increases to an optimal dose of 300 mg/day by the fourth day of treatment. (RXlist, 2007) The maximum recommended dose is 400 mg/day. The oral administration of the tablet occurs before bed on a daily basis. Seroquel is available in 25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg tablets. The drug is also available in an extended release formulation. The retail price of Seroquel ranges from $2 US per 25 mg tablet to $11.70 US per 400 mg tablet. (Drugstore.com, 2007) At the optimal dose of 300 mg, the daily cost of treating schizophrenia is $8.90. The monthly treatment cost of using Seroquel is $267 US. Common side effects of Seroquel include dry mouth, uncontrolled movements, dizziness, drowsiness, sedation, weight gain, elevated blood sugar and even cases of diabetes. (AstraZeneca, 2007)

4.5.4 Clinical Trials

Currently there are three hundred clinical trials recruiting subjects for the study of Schizophrenia. An additional 87 clinical trials are ongoing. (FDA, 2007) Using data comprised from the FDA clinical trial database, the average treatment length of a phase IIa clinical trial for the evaluation of a drug candidate in the treatment of Schizophrenia is 9 weeks with a range of 2 weeks to 16 weeks. The average patient population of the trials is 134 with a range of 44 patients to 250 patients. The average length of a phase IIb clinical trial is 13 weeks with a range of 6 weeks to 24 weeks. The average patient population is 416 with a range of 250 to 700 patients. Sanofi-Aventis is currently conducting a 24-week study that is enrolling 700 patients to evaluate the efficacy of the drug AVE1625, a cannabinoid 1 antagonist, on cognitive impairment caused by Schizophrenia. This is the largest phase II clinical trial currently conducted.
The average treatment length of a phase III clinical trial to evaluate the efficacy of a drug in treating Schizophrenia is 13 weeks with a range of 6 weeks to 26 weeks. The average patient population is 345 with a range of 60 patients to 600 patients.

4.5.5 Endpoint Test

Researchers use several common methods in clinical trials to measure the severity and progression of Schizophrenia to determine if desired clinical endpoints are met. The measurement tools generally focus on two areas of study; cognitive functions and positive and negative symptoms of schizophrenia. The two most widely used measurement tools are The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCBB) and the Positive and Negative Symptoms Scale. (PANSS)

4.5.5.1 MATRICS Consensus Cognitive Battery

The National Institute of Mental Health developed the Matrics to help facilitate the development of psychopharmacological agents to improve cognition in schizophrenia. (Matrics Assessment, 2006) The Consensus Cognitive Battery is a product of this initiative. The MCCB is a standardized assessment tool that measures the level of cognition in individuals suffering from schizophrenia using ten cognitive performance tests in seven sub categories. The categories include speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition. (See appendix X) Clinicians administer the test to patients, who generally require an estimated time of 1 hour and 4 minutes to complete. Clinicians score and administer each test separately.
4.5.5.2 Positive and Negative Symptoms Scale (PANSS)

The PANSS is an assessment tool used to measure the symptom reduction of schizophrenia patients. It is widely used in the study of antipsychotic therapy. The scale measures both the positive symptoms of schizophrenia, which refer to the excess, or distortion of normal functions, and the negative symptoms, which refer to the diminution or loss of normal functions. (The PANSS Institute, 2007) The scale has seven positive symptom items, seven negative symptom items, and sixteen general psychopathology symptom items. Clinicians use an identical seven-point severity scale to score each item. The assessment tool provides a balanced representation of both positive and negative symptoms and how the symptoms interact with each other.

4.5.6 Drug Pipeline

The basis of current drug therapies in treating schizophrenia targets the alleviation of the symptoms of the disease. The treatment of schizophrenia has consisted primarily of conventional and atypical antipsychotic medications. Research is continuing in the area of antipsychotic therapies; however, advances in the study of the pathology of the disease have spurred the research and development of drug therapies to treat the underlying mechanisms of the disease.

4.5.6.1 Asenapine and Bifeprunox

Several potential blockbuster antipsychotic drug treatments have fared poorly in clinical trials. A study conducted by Datamonitor estimated that Organon drug asenapine for treating negative symptoms of schizophrenia would be the leading market entrant in terms of value by the year 2015. In addition, the report also estimated that Wyeth’s drug
bifeprunox would become the second highest new entrant in terms of value by 2015. (Datamonitor, 2006) Since the study was release both drugs have not received FDA approval. Organon is continuing with additional phase III trials to evaluate the efficacy of asenapine. The results of the first phase III trial were minimally positive in proving efficacy. As a result, Pfizer discontinued their collaboration with Organon for the commercialization of the drug citing the trial did not provide enough positive data for the FDA to approve the treatment. (Organon, 2006)

Wyeth filed a new drug application with the FDA for the drug bifeprunox in October of 2006. The FDA denied the application and returned it with a “not approvable” letter, citing that there was not enough test data demonstrating the drug’s effectiveness to merit approval. Wyeth is continuing with additional phase III trials and states that market entry of the drug, if approved, will be delayed until at least 2009. (Smith, 2007)

4.5.6.2 LY2140023

Eli Lilly’s antipsychotic drug candidate LY2140023 has shown promise in clinical trials. Unlike most antipsychotic treatments, LY2140023 does not target dopamine and serotonin receptors. Instead, the drug targets the metabotropic glutamate 2/3 (mGlu 2/3) receptor. (Wilkinson, 2007) LY2140023 works as a receptor agonist for the glutamate system to reduce the presynaptic release of the glutamate neurotransmitter. Eli Lilly considers the positive results of the drug to be a potential breakthrough in schizophrenia research. According to the company, the trial provides strong new evidence for the role of glutamate modulation in treating psychosis. The trial also shows mGlu2/3 receptor activation as a viable therapeutic approach to treat schizophrenia.
In phase II clinical trials of, 196 patients suffering from schizophrenia received oral administration of LY2140023. The study found the drug to be safe and well tolerated with patients showing significant improvements in positive and negative symptoms associated with the disease. Observation of the treatment revealed that drug did not cause the adverse effects typically associated with existing antipsychotic treatments such as increased prolactin elevations, extrapyramidal symptoms and weight gain. Ely Lilly is currently evaluating the most effective dosage required to elicit positive results and will soon be moving the drug candidate into phase III clinical trials.

4.5.7 Summary of Schizophrenia

Schizophrenia is a chronic, severe and disabling neurodegenerative disease. Symptoms can include psychosis, incoherent speech, and manic anxiety. The onset of symptoms can begin as early as the late teenage years and will continue to progress throughout the individual's life. In the US alone, 2.4 million individuals are afflicted with disease. However, only 40% of these individuals are treated equating to 960,000 patients. Similar to the other disease indications examined in this study, there is no cure for the disease and current treatments focus on alleviating the symptoms. Antipsychotic drugs currently dominate the schizophrenia market. The top three drugs in this class had a market value of nearly $12 billion US in 2006. This is attributable to the high treatment cost per patient which averages over $5000 per year. Schizophrenia has the highest potential market value of the indications examined in this study. Clinical trial costs are lower than those of Parkinson's disease and higher than both neuropathies. However, competition in this market is high due to the potentially lucrative market.
5: RISK ADJUSTED NET PRESENT VALUE ANALYSIS

This section of the report will calculate the financial value of each of the four neurodegenerative disease indications; diabetic neuropathy, chemotherapy induced neuropathy, schizophrenia, and Parkinson’s disease using a risk adjusted net present value methodology.

5.1 Introduction

A risk adjusted net present value (rNPV) analysis is utilized to evaluate the financial attractiveness of pursuing each of the four disease indications examined in this study. Net present value (NPV) is a common valuation tool used to analyze the profitability of an investment or project. It measures the present value of future discounted cash flows. A risk adjusted net present value analysis is specific design for valuing biotechnology investments. Unlike traditional NPV, rNPV accounts for the inherent risks that apply directly to the clinical development of drugs for pharmaceutical use.

The rNPV analysis is performed under the assumption that the company will incur 100% of the development costs and 100% of the financial return. It is important to note that this scenario is unlikely based on Company X’s business model. Company X is likely to partner the development of their drug candidate with a larger pharmaceutical organization and would receive a percentage of the sales revenue as a royalty payment. This rNPV analysis does not account for partnership and licensing structures due to their
high variability. The rNPV analysis will provide an estimate on the total market value of the drug candidates.

5.2 Background

Valuing biotechnology assets such as potential drug candidates can be a challenging task for biotech organizations. The high-risk nature of drug development coupled with strict regulatory bodies can make it difficult to assess the potential value of a new drug accurately. Analysts commonly utilize several valuation techniques but each has its deficiencies.

5.2.1 Discounted Cash Flow (DCF) and Net Present Value (NPV)

Discounted cash flow (DCF) and net present value (NPV) analysis are traditional valuation methodologies used in the industry. However, due to the uncertainties in drug development, these assessment tools may be an unreliable measure of biotech value. In traditional DCF analysis, the projected market value is discounted using a high discount rate (and often a discount rate that decreases over time). The high discount rate is meant to account for all the risks that the company faces, however, the difficulty lies in establishing the correct rate. When key risk drivers are not reasonably estimable, the DCF suffers as a reliable indicator of value. Discount rates tend to be arbitrary and therefore DCF analysis remains an unreliable measure of biotechnology assets.

5.2.2 Real Options Analysis

Real option analysis is another valuation method commonly used to calculate biotech value. A real options analysis assigns a value to the ability to pull back from a project in the event that the market is no longer attractive or attainable, a call option.
However, for many biotechnology companies, call options are not exercisable in practice. For example, it is unlikely for a small biotech company to pull the plug on a drug in a late stage clinical trial due to a revised market projection. The company would have already sunk millions of dollars in costs and many years into the clinical development of the drug. This would be detrimental to a company with limited financial resources and a slim product pipeline.

5.2.3 Advantages of rNPV

A risk adjusted net present value (rNPV) approach offers an improvement over the traditional valuation methods. Jeffrey Stewart of the Milken Institute designed the rNPV analysis. The valuation technique applies specific risks associated with clinical development of drug candidates. Risk adjusted NPV analysis incorporates clinical trial success rates into more traditional financial analysis to estimate the current values of biotechnology projects as the development of projects continue. Specifically, clinical trial success rates combine with traditional DCF methodology to establish a risk adjusted net present value for drug candidates. The rNPV method incorporates an increased number of biotechnology specific parameters over other valuation methodologies to provide a more accurate assessment of value.

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6 Jeffrey J. Stewart is President of Clinical Capital Group. The Clinical Capital Group prices biotech and pharmaceutical R&D for acquisition or investment. The Milken Institute is an independent economic think tank whose mission is to improve the lives and economic conditions of diverse populations in the U.S. and around the world by helping business and public policy leaders identify and implement innovative ideas for creating broad-based prosperity. We put research to work with the goal of revitalizing regions and finding new ways to generate capital for people with original ideas. Source: Milken Institute, 2007
5.3 Methodology and Parameters

To calculate rNPV, four general parameters are required; clinical success rates, projected costs, projected market, and the discount rate. Refer to table 1 for a detailed summary of the parameters used in the analysis.

5.3.1 Clinical Success Rates as Payoff Probabilities

All drug candidates with the intention of marketing and sale in the United States must undergo a strict regulatory evaluation set forth by the U.S. Food and Drug Administration (FDA). The FDA must approve the drug before a company can sell it as a pharmaceutical product. FDA approval hinges on a series of clinical trials, essentially experimenting with the drug on human subjects. Drug development consists of three clinical trial phases. In phase I (20-80 patients), healthy volunteers are given the drug to determine if it is toxic to humans. If the drug proves safe, then patients receive the drug in phase II trials to determine if it is efficacious in treating the targeted disease. Phase II trials generally consist of 100 to 300 patients. If the drug shows success in treating the disease, then phase III trials are initiated to further confirm the efficacy of the drug. Phase III trials are often longer in duration to enable monitoring of long-term side effects and are tested on a larger patient population, 1,000 to 5,000 patients.

The Tufts University Center for the Study of Drug Development periodically publishes average clinical success rates of drug trials. Average success rates (the chances of reaching the market eventually) for new drugs are about 20% for those that pass phase I trials, 30% for those that pass phase II, and 67% for phase III. (Stewart, 2002) These rates apply as the drug enters each clinical trial phase. In addition, only 81% of all new
drug candidates submitted through a New Drug Application (NDA) or a Biologics Licensing Application (BLA) receive FDA approval for market distribution.

For this rNPV analysis, the clinical success rates are further broken down by the therapeutic disease area. Central nervous system disorders such as Parkinson's and Schizophrenia have lower clinical success rate or 18%, 25%, and 61% for phase I, II, and III respectively. Company X intends to evaluate diabetic neuropathy and chemo-induced neuropathy in clinical trials using pain assessment tests to determine desired endpoints, therefore their clinical success rates will be compared to other drugs that have been developed for the treatment of pain. Pain therapies have much higher clinical success rates than CNS therapies. Average success rates are 25%, 38%, and 78% for phase I, II, and III respectively. (DiMasi, 2004) A rate of 81% will be applied to all four disease indications for the approval phase.

5.3.2 Projected Clinical Trial Costs

Several primary factors contribute to the cost of clinical trials. This analysis will use the average length of the trial, number of clinical trial patients and the average cost per patient of the trial to calculate the cost. Other factors that may contribute to the overall cost of the clinical trial such as administration fees, company overhead, and supporting animal studies will not be included in this evaluation. The average clinical phase of drug development for pain therapies is 61.8 months. Six months on phase I, 12 months on phase II and 27.6 months on phase III. The approval process requires an additional 15.6 months. The rNPV analysis will apply these clinical phase durations to calculate the clinical trial costs of diabetic neuropathy and chemo-induced neuropathy. Schizophrenia clinical phases require an average of 75.8 months to complete with an
additional 24 months for the approval phase. The duration of phase I, II, and III schizophrenia trials require 13.4, 26.58, and 35.82 months respectively. Parkinson’s disease has the longest clinical trial phase of all four indications. The average clinical phase duration for Parkinson’s lasts 105.6 months with an additional 24 months for the approval phase. The duration of phase I, II, and III Parkinson’s trials require 19.2, 37.2, and 49.2 months respectively to complete. The Tufts publication on clinical trial durations is the basis for the calculation of all clinical trial phase data.

The second variable used to calculate the cost of clinical trials is the number of patients in each trial. Analysis of current clinical trials listed in the FDA database in each indication allowed for the calculation of the average patient population. A standard patient population of 40 will be applied to each indication because research was not performed on phase I clinical trial data. Calculation of phase II data consists of taking the average number of patients of phase IIa and phase IIb clinical trials. The average number of patients was 279, 87, 275, and 156 for diabetic neuropathy, chemo-induced neuropath, schizophrenia, and Parkinson’s disease respectively. The average number of phase III patients was 481, 448, 345, and 768 for diabetic neuropathy, chemo-induced neuropath, schizophrenia, and Parkinson’s disease respectively.

The third variable is the average clinical trial cost per patient. A report from Next Generation Pharmaceutical published in 2005 indicated that the average clinical trial cost per patient was $5500, $6500, and $7600 US for phase I, II, III trials respectively. However, clinical costs tend to vary by therapeutic class therefore using cost data from Tufts, the average cost per patient was recalculated to be $4,428, $5,233, and $6,118 for phase I, II, and III clinical trials respectively in both diabetic neuropathy and chemo-
induced neuropathy. The average cost per patient is substantially higher for central nervous system disorders such as schizophrenia and Parkinson’s disease. The average per patient costs for these indications was recalculated to be $6,138, $7,254, and $8,482 US for phase I, II, and III clinical trials respectively.

5.3.3 The Projected Market Value

An important variable required for the rNPV analysis is the projected market value of the drug candidate. This analysis utilizes a bottom up approach to estimate the market value. Multiplying the treatable population by the estimated market penetration by the estimated annual treatment cost per patient provides the estimation for the market value.

The number of total patients diagnosed and treated annually in the United States provides the basis for the treatable population. The American Diabetes Association estimates that 3.5 million Americans experience pain caused by diabetic neuropathy, however only 800,000 patients are treated annually for the disorder. Estimates show that physicians diagnose 1.5 million new cases of diabetes each year thus equating to an annual growth rate of 7.2%. A 30% market penetration applies to this analysis for diabetic neuropathy. This penetration rate is attainable for drugs that offer novel therapeutic properties in the disease indication. Company X’s drug would be the first drug on the market that targets the underlying causes of the disease therefore it would be likely to become the market leader. The average yearly cost to treat diabetic neuropathy with the current leading therapies is $1,764 US. For this analysis, a 20% market premium applies to account for a higher willingness to pay for a leading treatment option. The annual revenue per patient used in this analysis is $2,116 US.
The market size for chemotherapy-induced neuropathy is equal to 433,476 patients per year in the US. However, for this study, the market is further defined to be chemotherapy-induced neuropathy in breast cancer patients that have been treated with the taxane class of chemotherapy agents. The American Cancer Society estimates that there will be 180,510 new cases of breast cancer in the US. The use of chemotherapy is as a treatment option is present in almost 100% of all breast cancer cases. (Kolata, 2006) The taxane class, in particular paclitaxel causes neuropathy in 60% of all chemotherapy treatments, which equates to 108,306 patients per year. The incidence rate of breast cancer has not increased over the past several years therefore there is no annual growth rate for this market. A 30% penetration rate also applies to the chemotherapy induced neuropathy market for this analysis. Chemotherapy patients typically undergo eight cycles of treatment, which lasts approximately six months, therefore Company X’s drug will be used over this six-month period. Current treatment options are the same for chemotherapy-induced neuropathy as for diabetic neuropathy therefore annual revenue per patient value of $1058 US will apply to this analysis. This equates to exactly half of the treatment per patient value of diabetic neuropathy to account for the six-month treatment term of chemotherapy patients.

The National Institute of Mental Health estimates that 2.4 million Americans have been diagnosed with schizophrenia. However, the Diagnostic and Statistical Manual of Mental Disorders estimates that only 40% of this population receives treatment for the disease thus equating to a market size of 960,000 patients. On average, 100,000 new individuals are diagnosed with the disease per year thus providing an annual market growth rate of 10.4%. A market penetration rate of 35% applies to the analysis for
schizophrenia. The higher rate is attributable to a high willingness to pay factor due to
the large effect of the disease on the patient’s quality of life. A novel treatment that
prevented the progression of the disease would surely become the market leader in this
disease segment. An application of a 20% market premium to the annual revenue per
patient of existing treatments equates to $6888 US per patient per year.

Parkinson’s disease has the largest number of patients treated annually and
therefore the largest market size of the four indications in this study. There are 1.5
million Americans diagnosed and treated for the disease. (Michael J. Fox Foundation,
2007) However, Parkinson’s disease has the lowest incidence rate. The American
Association of Neurological Surgeons estimates that only 60,000 new cases of the disease
are diagnosed annually in the US. This translates into an annual market growth rate of
4%. Similar to schizophrenia, Parkinson’s disease is very debilitating therefore there is a
high willingness to pay factor which allows for a market penetration rate of 35%. A
market premium for Company X’s drug would bring the annual per patient cost to $3478
US.

5.3.4 Additional rNPV Parameters

This rNPV analysis utilizes several additional parameters. A duration of 17 years
will be applied to all four indications for the period that the drug will remain under patent
protection. The rNPV analysis will only evaluate revenues up to the end of the 16th year.
The 17 year duration is taken directly form Company X’s 2006 annual report which states
that the company expects the useful life of a drug candidate to be between 15 and 17
years.
A standard two-year period applies to all indications for the time required to ramp up to peak market sales. The analysis also applies an additional 60% manufacturing and marketing offset cost. This figure was adapted from Uwe Reinhardt’s 2001 report, Perspectives on the Pharmaceutical Industry.

For this analysis, there is also an application of a $500,000 FDA fee and a $1,000,000 NDA/BLA preparation fee across all drug indications.

<table>
<thead>
<tr>
<th>Table 1  rNPV Analysis Parameters</th>
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<tbody>
<tr>
<td><strong>PHASE 1</strong></td>
</tr>
<tr>
<td>Duration (yrs)</td>
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<tr>
<td>-----------------------------------</td>
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<tr>
<td>Patients</td>
</tr>
<tr>
<td>Per Patient Cost ($US)</td>
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<tr>
<td>Likelihood of Reaching Revenue (%)</td>
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<tr>
<td><strong>PHASE 2</strong></td>
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<td>Per Patient Cost ($US)</td>
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<td>Likelihood of Reaching Revenue (%)</td>
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<td><strong>PHASE 3</strong></td>
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<td>Likelihood of Reaching Revenue (%)</td>
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<td><strong>APPROVAL PHASE</strong></td>
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<td>Duration (yrs)</td>
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<td>FDA Fees</td>
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<td>Likelihood of Reaching Revenue (%)</td>
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<td>Patient Population</td>
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<td>Annual Revenue per Patient ($US)</td>
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<td>Peak Market Penetration (%)</td>
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<td>Patient Population Growth Rate (% annual)</td>
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<td>Ramp to Market Peak</td>
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<td>Discount Rate (%)</td>
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<tr>
<td>Manufacturing and Marketing Offset (%)</td>
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<tr>
<td>Year Patent Protection and Revenues End</td>
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</table>
5.4 The Risk Adjustment Equation

Once the cost and revenue parameters have been determined, a risk adjustment equation is used to calculate the risk adjusted cash flows. The risk adjustment equation is:

\[
\tilde{r} V = \sum_{i=0}^{n} \frac{C_i R_0}{R_i (1 + r)^i}
\]

where \( rV \) is the risk-adjusted value, \( C_i \) is the cash flow at time \( i \), \( R0 \) is the current likelihood of reaching the final cash flow, \( R_i \) is the likelihood at time \( i \) of reaching the final cash flow, and \( R0 / R_i \) is the current likelihood (i.e., at time 0) of realizing the cash flow of time \( i \) (Stewart, 2002).

5.5 Discounting the Cash Flow

The second step of the analysis is to discount the risk-adjusted cash flow using a traditional discount cash flow methodology. The discounted cash flow of the risk-adjusted cash flow equals the risk adjusted net present value. The rNPV equation is:

\[
r_{NPV} = \sum_{i=0}^{n} \frac{C_i R_0}{(1 + r)^i R_i}
\]
Where $C_i$ is the cash flow at time $i$, $R_0$ is the current likelihood of reaching the final cash flow, $R_i$ is the likelihood at time $i$ of reaching the final cash flow, $R_0/R_i$ is the current likelihood (i.e., at time 0) of realizing the cash flow of time $i$, and $r$ is the discount rate. (Stewart, 2002)

Discount cash flow analysis requires selection of an appropriate discount factor. Even though the clinical trial risks are accounted for, a discount factor is still required to account for risks that are external to clinical development process. A common method for choosing an appropriate discount rate is to set the rate equal to the opportunity cost of capital. Analysts variously calculate the discount rate to be between 9% and 15%. (Stewart, 2002) This analysis will apply a discount rate of 15%. Applying the discount rate to the rNPV analysis then allows for the calculation of the economic value of the drug candidate. Refer to table 2 for a summary of the analysis results.

### 5.6 rNPV Analysis Results

<table>
<thead>
<tr>
<th>Disease Inication</th>
<th>rNPV Phase I ($1000's)</th>
<th>rNPV Phase II ($1000's)</th>
<th>rNPV Phase III ($1000's)</th>
<th>rNPV Peak ($1000's)</th>
<th>Peak Net Cash Flow ($1000's)</th>
<th>Total Net Cash Flow ($1000's)</th>
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<tbody>
<tr>
<td>Diabetic Neuropathy</td>
<td>225,523</td>
<td>398,085</td>
<td>954,298</td>
<td>2,282,959</td>
<td>576,380</td>
<td>4,135,310</td>
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<tr>
<td>Chemotherapy Induced Neuropathy</td>
<td>6,318</td>
<td>11,760</td>
<td>29,175</td>
<td>75,454</td>
<td>13,751</td>
<td>123,087</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>657,467</td>
<td>1,189,071</td>
<td>5,166,726</td>
<td>13,522,823</td>
<td>4,083,462</td>
<td>20,517,279</td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td>156,270</td>
<td>325,827</td>
<td>1,634,815</td>
<td>4,082,287</td>
<td>1,315,373</td>
<td>5,509,419</td>
</tr>
</tbody>
</table>

Table 2: rNPV Analysis Results
The rNPV analysis shows that the peak risk adjusted net present value for diabetic neuropathy to be $2,282,959,000 US. The rNPV’s at the completion of phases I, II, and III are $225,523,000, $398,085,000, and $954,298,000 respectively. The peak net sales revenue (cash flow) in a single year is $576,380,000 with total net sales revenue of $4,135,310,000 over the 16-year patent protection period.

The peak risk adjusted net present value of a chemotherapy induced neuropathy drug candidate is $75,454,000. The rNPV’s at the completion of phases I, II, and III are $6,318,000, $11,760,000, and $29,175,000 respectively. The peak net sales revenue (cash flow) in a single year is $13,751,000 with total net sales revenue of $123,087,000 over the 16-year patent protection period.

The peak risk adjusted net present value of a schizophrenia drug candidate is $13,522,823,000. The rNPV’s at the completion of phases I, II, and III are $657,467,000, $1,189,071,000, and $5,166,726,000 respectively. The peak net sales revenue (cash flow) in a single year is $4,083,462,000 with total net sales revenue of $20,517,279,000 over the 16-year patent protection period.

The peak risk adjusted net present value of a Parkinson’s disease drug candidate is $4,082,287,000. The rNPV’s at the completion of phases I, II, and III are $156,270,000, $325,827,000, and $1,634,815,000 respectively. The peak net sales revenue (cash flow) in a single year is $1,315,373,000 with total net sales revenue of $5,509,419,000 over the 16-year patent protection period. Refer to Appendix 1 to 4 for detailed rNPV results for each indication.
6: DISCUSSION AND RECOMMENDATIONS

This section of the report will rank the four-neurodegenerative disease indications in order from the most highly recommended indication for the Company X to pursue to the least recommended. In addition, this section discusses the advantages and disadvantages of pursuing each indication.

6.1 First Recommended Disease Indication – Schizophrenia

Schizophrenia is the most highly recommended disease indication to pursue for Company X. The rNPV analysis reveals that the economic value of this disease indication is by far the highest of the four indications in this study. A large market coupled with a wide recognition of the disease contributes to its high recommendation. However, drug development in this disease indication is more risky and the high economic value attracts many biotechnology and pharmaceutical companies aiming to enter the market.

6.1.1 Advantages to Pursuing the Schizophrenia Indication

6.1.1.1 Highest Economic Value

The rNPV analysis shows that a drug developed for schizophrenia has the highest economic value of the four indications. The peak rNPV is $13,522,823. The total risk adjusted net revenue of the drug equals $20,517,279,000 over the 16-year patent protection period. This value is by far the highest, nearly four times the net revenue of the second highest indication. The net revenue of Parkinson’s disease, the second highest
indication, is only $5,509,419,000. The high revenue of the schizophrenia indication is attributable to the high willingness-to-pay factor of affected individuals. Schizophrenia is highly debilitating disease therefore; patients are willing to pay large sums of money for treatment. Existing therapies cost a patient nearly $6000 per year compared to existing Parkinson’s treatments which cost about $3000 per year. A schizophrenia drug that can stop the progression of the disease would be the first of its kind and would surely become blockbuster drug.

6.1.1.2 Large Market

The market for schizophrenia drugs is large and growing at an enormous pace. The potential market is 960,000 individuals that receive proper diagnosis for the disease in the United States alone. This is the second highest patient population of the four disease indications, next to Parkinson’s disease, which has $1,500,000 diagnosed individuals. However, the schizophrenia market is growing faster than any other indication in this study. Estimates show that the diagnosed population is increasing by 100,000 individuals each year in the United States, translating into an annual growth rate of 10.4%, which is 3.2% higher than the growth rate for diabetic neuropathy, the second fastest growing indication.

6.1.1.3 Wide Recognition of the Disease

The wide recognition of schizophrenia as a disease can translate into greater opportunities for Company X. Company X is likely to out-license the drug or seek collaboration with large biotechnology and pharmaceutical firms to develop and market the drug in the late phases of development. A blockbuster drug in a widely recognized
disease indication such as schizophrenia is very attractive for large firms like Pfizer and Eli Lilly. Company X would have a greater chance of out-licensing the drug or partnering the development of the drug and due to the high demand, could negotiate greater financial returns.

A breakthrough in the treatment of a widely recognized disease can also help validate and bring name recognition to Company X, thus increasing their future drug development and partnership opportunities.

6.1.2 Disadvantages to Pursuing the Schizophrenia Indication

6.1.2.1 Moderate to High Drug Development Risks

Neurodegenerative diseases tend to have higher drug development risks compared to other therapeutic areas. As shown in the parameters section, the clinical success rates of a CNS drug receiving approval is 18%, 25%, and 61% after completion of phase I, II, and III respectively compared to 20%, 30%, and 67% for all other therapeutic areas combined. The duration of clinical trials is longer for CNS disorders, which translates into higher clinical development costs thus increasing the level of risk for small biotechnology companies.

6.1.2.2 Moderate to High Competition

An economically attractive market often coincides with a high level of competition. Currently there are over 400 clinical trials either ongoing or recruiting patients for studies related to schizophrenia. This is the highest amount compared to the other indications in this study. Several of the largest pharmaceutical companies in the world including Pfizer, Eli Lilly, AstraZeneca, Johnson & Johnson, Glaxo Smith Kline,
Wyeth, and Sanofi-Aventis are currently evaluating drug candidates in clinical trials for the treatment of schizophrenia.

6.2 Second Recommended Disease Indication – Diabetic Neuropathy

Diabetic neuropathy is the second most attractive disease indication to pursue. The attractiveness of the indication is attributable to a good rNPV, a large market, and a lower risk in drug development, which is very important to small biotech companies such as Company X. However, there are several disadvantages to pursuing this indication such as the dependence on diabetes treatments and variable endpoint testing.

6.2.1 Advantages to Pursuing the Diabetic Neuropathy Indication

6.2.1.1 Good Economic Value

Although not nearly as valuable as schizophrenia, diabetic neuropathy has an attractive economic value. The total net risk adjusted revenue ranks third among the four indications at $4,135,310,000, as does its peak rNPV at $2,282,959,000. However, one of the most important economic factors is the value of the drug after phase II clinical trials. According to Company X’s business model, they are most likely to out-license the drug candidate to a larger pharmaceutical company after successful phase II clinical trials. The rNPV of diabetic neuropathy after passing phase II clinical trials is $398,085,000, which is second only to schizophrenia. By out-licensing the drug after phase II, Company X is likely to receive a large up front payment and percentage of the sales of the drug. In addition, the company negates the risk of costly phase III clinical trials, which the pharmaceutical company will assume. Selling or out-licensing a successful drug candidate in the late stages of clinical development ensures that Company
X receives a guaranteed return on their investment where as if they were to continue with the drug development process and fail, the would need to endure substantial financial losses that are potentially crippling. The value of a drug candidate after successful phase II trials is a very important factor in choosing an indication for company X.

6.2.1.2 Large Market

The market size for diabetic neuropathy is large and growing at a substantial rate. Currently, over 800,000 patients receive treatment for the disease and the number is growing at a pace of 7.2% per year, second only to schizophrenia. Neuropathy is most prominent in diabetes patients over the age of 60. This factor is driving the growth of the market because the age of the overall population is increasing. Estimates indicate that over 3.5 million Americans experience pain caused by diabetic neuropathy, however the majority of patients are unaware of the disease and remain untreated. Increased patient education on the disease coupled with better diagnosis techniques in the future could further spur an increase in market growth thus offering excellent market potential.

6.2.1.3 Lower Drug Development Risks

The development of drugs used to treat pain is often less risky than the development of drugs in other therapeutic classes. The clinical success rates of pain therapies receiving approval is 25%, 38%, and 78% after successful phase I, II, and III clinical trials respectively compared to 20%, 30%, and 67% for all other therapeutic areas combined. In addition, the cost and duration of pain trials is substantially less than drugs developed for schizophrenia and Parkinson’s disease. This is a very important factor for small biotechnology companies with limited financial resources such as Company X. In
addition, shorter clinical development times allows for the drug to be on the market longer before it comes off patent protection thus generating peak revenues for a longer period.

6.2.2 Disadvantages of Pursuing the Diabetic Neuropathy Indication

6.2.2.1 Dependant on Diabetes Treatments

Diabetic neuropathy is directly caused by diabetes; therefore the prevalence of the disease is dependant on the number of diabetes sufferers. Drug companies and research institutions are sinking substantial resources into developing new treatments for diabetes. As diabetes treatments improve, the prevalence of neuropathy in patients may decline thus shrinking the market for diabetic neuropathy treatments. However, in order for this to occur, advances must be made to treat the underlying causes of diabetes, which researchers have yet to accomplish.

6.2.2.2 Subjective Endpoint Tests

The current tests used to evaluate the efficacy of pain therapies are simple and subjective. For example, the “faces” scale requires the patient to select the face that most accurately applies to the face that they make when they are in pain. The cartoon faces on the scale range from a smiling face to a face with a substantial frown, squinted eyes, and tears rolling down. Compared to the standard tests used in schizophrenia and Parkinson’s, pain assessment scales are rudimentary. In addition, the measurement of pain is subjective and depends on the pain threshold of each individual. This does not allow for an accurate assessment on the efficacy of variable doses of the drug. Variable endpoint data could result in inaccurate data and clinical phase failures.
6.3 The Third Recommended Disease Indication – Chemotherapy-Induced Neuropathy

The basis for ranking chemotherapy-induced neuropathy as the third most attractive indication to pursue is due to the low risk clinical trials and the potential for off label prescribing. However, the disease indication has several key unattractive factors such as a low rNPV, a flat growth rate, and a high dropout rate in clinical trials.

6.3.1 Advantages to Pursuing the Chemotherapy-Induced Neuropathy Indication

6.3.1.1 Low Risk Clinical Trials

Similar to diabetic neuropathy, chemotherapy-induced neuropathy has lower clinical trial risks than schizophrenia and Parkinson’s disease. In fact, it may have the lowest risk of all the indications, which makes the indication an attractive option for Company X to pursue. Clinical trial costs are low due to the small patient population of the studies coupled with the short treatment duration of the clinical phases. The efficacy of the drug can potentially be determined in less than four weeks, which is the average duration of one cycle of chemotherapy. Unlike diabetic neuropathy, the onset and progression of pain symptoms is rapid thus providing a more homogenous patient population for clinical trials, which can improve the accuracy of the results.

6.3.1.2 Off Label Prescribing

“Off label” prescribing is the prescription of drugs for indications that it did not initially receive approval for. Company X will focus the clinical trial on breast cancer patients receiving treatment with the taxane group of chemotherapeutic agents. If the drug candidate proves to be effective and receives approval for treating breast cancer
patients undergoing chemotherapy, it is likely that physicians will prescribe the drug for other forms of cancer. This could increase the size of the market substantially. Other chemotherapeutic agents used to treat cancer also have neurotoxic affects therefore; Company X's drug could potentially be effective in treating a wide population of chemotherapy patients.

6.3.2 Disadvantages of Pursuing the Chemotherapy-Induced Neuropathy Indication

6.3.2.1 Low rNPV

The risk adjusted net present value of the chemotherapy-induced neuropathy indication is substantially lower than any indication analyzed in this study. The peak rNPV is only $75,454,000 and the total net cash flow over the 16-year patent protection period is $123,087,000, which is over $4 billion less than diabetic neuropathy. This is attributable to the annual expected revenue per patient and the small market. Unlike diabetic neuropathy, schizophrenia, and Parkinson's disease, chemotherapy-induced neuropathy is not a chronic disorder. Patients experience pain during their chemotherapy treatments with the pain generally subsiding after several months. The average patient receives chemotherapy over a six-month period therefore prescription of Company X's drug may be limited to half a year per patient thus accounting for low revenues. In addition, the approved market is limited to breast cancer patients which is only 108,306 individuals in the U.S. compared to 1.5 million, 960,000, and 800,000 for Parkinson's, schizophrenia and Parkinson's respectively.
6.3.2.2 High Clinical Dropout Rate

Although overall drug development risk is low for chemotherapy-induced neuropathy, high clinical dropout rates could affect the duration of trials. The average dropout rate was 22.7%. The most common reason for dropout was adverse effects, followed by insufficient pain relief and deterioration due to disease progression. (Bell et al., 2006) Dropout rates are generally higher in clinical trials focusing on antipsychotic therapies, however a 22.7% dropout rate for breast cancer patients is substantial because the potential patient population is much smaller therefore finding new individuals for clinical studies may be difficult.

6.3.2.3 Flat Market Growth

There is no annual growth in the market size for chemotherapy-induced neuropathy in breast cancer patients. The incidence rate remains at a constant level due to an increase in the overall health of the population. Individuals are becoming more conscious of cancer causing agents thus are reducing exposure to such agents.

6.4 The Fourth Recommended Disease Indication – Parkinson’s disease

The Parkinson’s disease indication is the lowest rated choice for Company X to pursue. Although the indication has a high rNPV and a large market, it is unattractive for a small biotechnology company in Company X’s position to pursue. The main reasons for not developing a drug for this indication are the high risk of clinical trials, limited number of years of revenue, and a slow market growth.
6.4.1 Advantages to Pursuing the Parkinson's disease Indication

6.4.1.1 Good rNPV

The peak risk adjusted net present value and total net cash flow of Parkinson’s disease is second only to schizophrenia at $4,082,287,000 and $5,509,419,000 respectively. The large market is the primary driver of the value of this disease indication. Annually, 1,500,000 individuals receive treatment for Parkinson’s disease in the United States. This is by far the largest market of the four indications.

6.4.2 Disadvantages to Pursuing the Parkinson's disease Indication

6.4.2.1 High Risk Drug Development Process

The primary reason for selecting Parkinson’s disease as the least favourable disease indication for Company X to pursue is the high risk of drug development. Like schizophrenia and other CNS disorders, the clinical success rate is lower than the average therapeutic class. However, the economic risk is higher for pursuing drug development in the Parkinson’s indication. This is due to longer clinical trial durations and higher patient populations, which combine to increase costs substantially. The average clinical period from the start of phase I to the end of phase III is 8.8 years in comparison to 6.3 for schizophrenia and 3.8 for both diabetic neuropathy and chemotherapy-induced neuropathy.

A closer examination of the rNPV analysis exemplifies the high clinical development risk. The market size for Parkinson’s is almost twice that of diabetic neuropathy. This factor should provide a higher valuation for Parkinson’s disease over diabetic neuropathy. However, it is only after the drug successfully completes phase III trials that it has a higher valuation over diabetic neuropathy. The rNPV for diabetic
neuropathy is greater during the entire clinical process due to far lower clinical development risks. The rNPV for Parkinson’s jumps 502% once the drug completes phase III trials in comparison to 435% for schizophrenia, 248% for diabetic neuropathy and 240% for chemotherapy-induced neuropathy.

Company X is currently conducting two-phase II clinical trials and early stage clinical evaluation on several other disease indications. The company has not received approval for any drug therapies and thus does generate any substantial revenue. The high cost of developing a drug to treat Parkinson’s disease would impose a huge financial risk to a company with limited cash flow and is not recommended at this time. The Parkinson’s disease indication may be more feasible to pursue when the company generates revenue from the approval of a drug currently in development. Pursuing a disease indication with a comparable economic value and far less development risk such as diabetic neuropathy is much more suitable for the company at this stage.

6.4.2.2 Limited Revenue Period

Due to the lengthy clinical development period, there are only five years of peak revenue generation before the patent protection ends on the drug compared to 10 years for diabetic and chemotherapy-induced neuropathy and 7 years for schizophrenia. The introduction of cheaper generic drugs can drastically decrease the sales of the name brand drug.

6.4.2.3 Low Growth Rate

Although the market size is largest of all indications examined in this study, the growth rate is the second lowest at 4% annually compared to the strong growth rates of
schizophrenia at over 10% and diabetic neuropathy at over 7%. Estimates indicate that
60,000 individuals will receive proper diagnosis for Parkinson’s disease each year.

6.5 Summary of Recommendations

The best disease indication for Company X to pursue at this time is schizophrenia.
The basis for choosing this indication is its high risk adjusted net present value, which is
greater than the three other indications combined. The high potential value of this
disease indication outweighs the clinical development risks associated with CNS
diseases. In addition, schizophrenia is the fastest growing market and can generate a
great deal of name recognition for the company.

Diabetic neuropathy is second most attractive indication for Company X at this
time followed by chemotherapy-induced neuropathy. Parkinson’s disease is the least
recommended disease indication due to its high risk clinical development process
attributable to high clinical trial costs.
### APPENDICES

#### Appendix 1 Diabetic Neuropathy rNPV

**CASH FLOW (NPV and rNPV) - Diabetic Neuropathy**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Development Stage</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 3 Approval</th>
<th>Approval</th>
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<th>Ramp</th>
<th>Revenue</th>
<th>Revenue</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Likelihood of Reaching Revenue</td>
<td>25%</td>
<td>38%</td>
<td>78%</td>
<td>78%</td>
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## Appendix 2 Chemotherapy-Induced Neuropathy rNPV

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## Appendix 3 Schizophrenia rNPV

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### Appendix 4 Parkinson’s disease rNPV

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<tr>
<td>NPV</td>
<td>873,447</td>
<td>1,004,640</td>
<td>1,155,513</td>
<td>1,329,260</td>
<td>1,529,068</td>
<td>1,758,648</td>
<td>2,024,503</td>
<td>2,330,005</td>
<td>2,681,333</td>
<td>3,085,361</td>
</tr>
<tr>
<td>Risk-added Cash Flow</td>
<td>(853)</td>
<td>(853)</td>
<td>(1,484)</td>
<td>(1,484)</td>
<td>(1,484)</td>
<td>(2,605)</td>
<td>(2,605)</td>
<td>(2,605)</td>
<td>(2,605)</td>
<td>(1,235)</td>
</tr>
<tr>
<td>rNPV</td>
<td>156,270</td>
<td>179,887</td>
<td>282,963</td>
<td>325,827</td>
<td>375,121</td>
<td>1,070,746</td>
<td>1,233,185</td>
<td>1,419,990</td>
<td>1,634,815</td>
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<tr>
<td></td>
<td>Likelihood of Reaching Revenue</td>
<td>81%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>REVENUE</td>
<td>Product Revenue</td>
<td>-</td>
<td>1,405,483</td>
<td>2,923,405</td>
<td>3,040,341</td>
<td>3,161,955</td>
<td>3,268,433</td>
<td>-</td>
<td>-</td>
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<tr>
<td>($1,000s)</td>
<td>Manufacturing &amp; Marketing (60%)</td>
<td>-</td>
<td>843,290</td>
<td>1,754,043</td>
<td>1,824,205</td>
<td>1,897,173</td>
<td>1,973,060</td>
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<tr>
<td>COSTS ($1,000s)</td>
<td>NDA/BLA Preparation Fees</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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</tr>
<tr>
<td>Net Cash Flow</td>
<td>(500)</td>
<td>562,193</td>
<td>1,169,362</td>
<td>1,216,136</td>
<td>1,264,782</td>
<td>1,315,373</td>
<td>-</td>
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<tr>
<td>NPV</td>
<td>3,549,315</td>
<td>4,082,287</td>
<td>4,048,108</td>
<td>3,310,558</td>
<td>2,408,585</td>
<td>1,315,373</td>
<td>-</td>
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</tr>
<tr>
<td>Risk-added Cash Flow</td>
<td>(617)</td>
<td>562,193</td>
<td>1,169,362</td>
<td>1,216,136</td>
<td>1,264,782</td>
<td>1,315,373</td>
<td>-</td>
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</tr>
<tr>
<td>rNPV</td>
<td>2,874,850</td>
<td>4,082,287</td>
<td>4,048,108</td>
<td>3,310,558</td>
<td>2,408,585</td>
<td>1,315,373</td>
<td>-</td>
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