USING VALUE BASED ECONOMICS TO EVALUATE COMPETITIVE ADVANTAGE OF ANTIFUNGAL THERAPIES IN FEBRILE NEUTROPENIA IN BC

by

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ABSTRACT

The Canadian health care system has faced unprecedented demands for its resources. The aging population, newer technologies and refined treatment protocols are examples of causes that drive up costs. Health care administrators are looking for ways to balance effective treatment outcomes and related treatment costs. In order for companies to compete in this business environment, a meaningful strategic partnership must be established to address the needs of the buyers and administrators.

In the case of anti-fungal treatments relating to febrile neutropenia, this paper tries to demonstrate a sustainable competitive advantage of company M's product C by utilizing value based economic models. By taking the buyers' economic concerns into consideration, these models can address product C's two main business challenges: restricted product usage and competition.

Keywords: Febrile Neutropenia, Value based economics,

Subject Terms:

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

GLOSSARY

Immunocompromised   Patients with poor immunity

Empirical therapy   Interventions that do not rely on a specific diagnosis and are implemented early in the course of (in this case) infection

Afebrile/Ferile   No-fever/Fever

Candidemia   Infection of a type of fungus called Candida

Genericization   A drug loses its patent and market exclusivity to generic companies

Therapeutic line extension   A drug can extend it's patent by applying for new indications or for a new formulation

Pharmacotherapy   Therapy with drugs

Therapeutic dosage   The amount of drug needed to achieve desire clinical outcome

Nephrotoxicity   Toxicity to the kidneys

1: INTRODUCTION

Company M[1]

Company M Canada is headquartered in XXXXX. It employed over XXX people across all aspects of pharmaceutical businesses including sales and marketing, research and development, finance and HR, and manufacturing. Its annual revenue exceeds $XXX million and is the Xth largest pharmaceutical company in Canada.

Company M Canada is a subsidiary of Company M US. It is one of the largest research based pharmaceutical companies in the world. The company boasts a wide range of therapies and is a recognized leader in the treatment of asthma, osteoporosis, glaucoma, prostate disease, migraines and infectious diseases. The company prides itself on its commitment to research as it spends over $115 million annually in research and development in Canada. More than 300 of the world's leading scientific personnel with advanced degrees now work for the company in six research groups: Medicinal Chemistry, Biological Sciences, Process Chemistry, Pharmacology, Pharmaceutical Research and Development, and Clinical Research.

Company M values quality medical education. It partners with universities and hospitals regionally to develop education for physicians and other health care professionals. Nationally, accredited non-biased medical education programs and non-

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[1] The name of the company and product will be disguised to preserve anonymity.

1

restricted education grants to major research centres across Canada are also evidence of company M's commitment to the medical community.

Product C and its challenges

Product C belongs to Company M's infectious diseases franchise. The product is an antifungal treatment to prevent fungal infection for post chemotherapy patients. Product C is the first of a new class of antifungal treatment. It has enjoyed a solid growth in the antifungal market as company M invested heavily in educating the clinical advantage of the new class of treatment since the launch of Product C in xxx year.

Product C will, however, face two strong competitors in 2008. Clinical trials have demonstrated similar efficacy and adverse events among the three agents. Company M is seeking a strategy for Product C to minimize the impact of the competition and sustain growth.

The main challenge, which is discussed in detail, for Product C is the escalating patient management costs for hospitals. As the administrators focus more and more on resource containment, traditional promotion of a product's clinical advantages without cost strategy is becoming less effective. A good value based economics model that engages the buyers' input can determine the acceptable costs for them. By demonstrating overall cost savings and establishing a partnership, company M can expand the use of product C while excluding the competition.

1.1   Clinical Background

1.1.1   Cancer

Cancer, one of the most feared words in human health, can develop in any tissue or any organ at any stage in the body. Malignancy is defined as a proliferation of cells whose unique trait loss of normal controls results in unregulated growth, lack of differentiation, local tissue invasion and metastasis. Timely diagnosis and appropriate therapies are crucial to optimal clinical outcome. Physicians must discuss all therapeutic options with patients who have good chance for cure or reasonable palliation. However, patients with cancer that has a low cure rate, need to be educated frankly on realistic expectations of treatments and the side effect they may produce.

1.1.2   Principles of Cancer Therapy

Successful treatment of cancer requires elimination of all cancer cells including malignant cells in the primary site, extended to local-regional areas, or metastasis to other areas of the body. The major treatments of cancer are surgery, radiotherapy and chemotherapy.

Surgery is the oldest form of effective cancer therapy. It, however, requires the malignant cells to be localized and focused with little or no spread to other region to be effective. The advantage of surgery is a clean removal of malignant tissue with minimum impact to surrounding healthy cells.

The most common form of radiotherapy is an external beam with a linear accelerator, which largely delivers photons (γ radiation). Electron beam radiotherapy has a short tissue penetration and is best used for skin or superficial cancers. Another

common form of radiotherapy is Brachytherapy, which involves placing a powerful radioactive source into the tumour bed itself. Radiation provides important palliative control of cancer, even when a cure is not possible. However, radiation injury to cells is random and non-specific, with largely unknown effect on the DNA of surrounding healthy cells.

Chemotherapy is a drug therapy that targets the cancer cells and preserves normal cells. It is shown to be effective in treating selected cancers. However, because of the narrow therapeutic index between malignant cells and normal cells, the ideal chemotherapy of 100 percent cancer specific cells does not exist. Patients often suffer from drug related side effects and toxicity. In the case of leukaemia, a bone marrow transplant is often used if a matching donor is available to induce production of healthy blood (Beers and Berkow, 1999).

1.1.3   Febrile Neutropenia

Febrile Neutropeina is a condition common to very sick patients who have undergone chemotherapy for cancer or a bone marrow transplant. It is defined as an absolute neutrophil count (ANC) of $<1.0 \times 10^9$/L and a fever of >38.2 degree Celsius (single event) or >38 degree Celsius (multiple events). Neutropenia is often caused by myelosuppression due to an antineoplastic chemotherapy, particularly when this therapy is administered at a maximum dose. The extent and the duration of neutropenia positively correlates with the development of infection due to the patients' lack of inflammatory response (Rolsto & Bodey, 2001). Between 40% to 60% of neutropenic patients with fever have an infection (Casta et al, 2003). These infections may be bacterial, fungal protozoa or viral. The most common are bacterial; however, with better

anticancer and antibacterial treatments, immunocompromised patients are living longer and fungal infections have become a significant problem. Because of such concerns, empirical uses of anti-fungal medications are recommended for presumed fungal infections in febrile neutropenic patients (BC Cancer, 2007).

Figure 1 summarizes the recommended approach for the management of infection in febrile neutropenic patients.
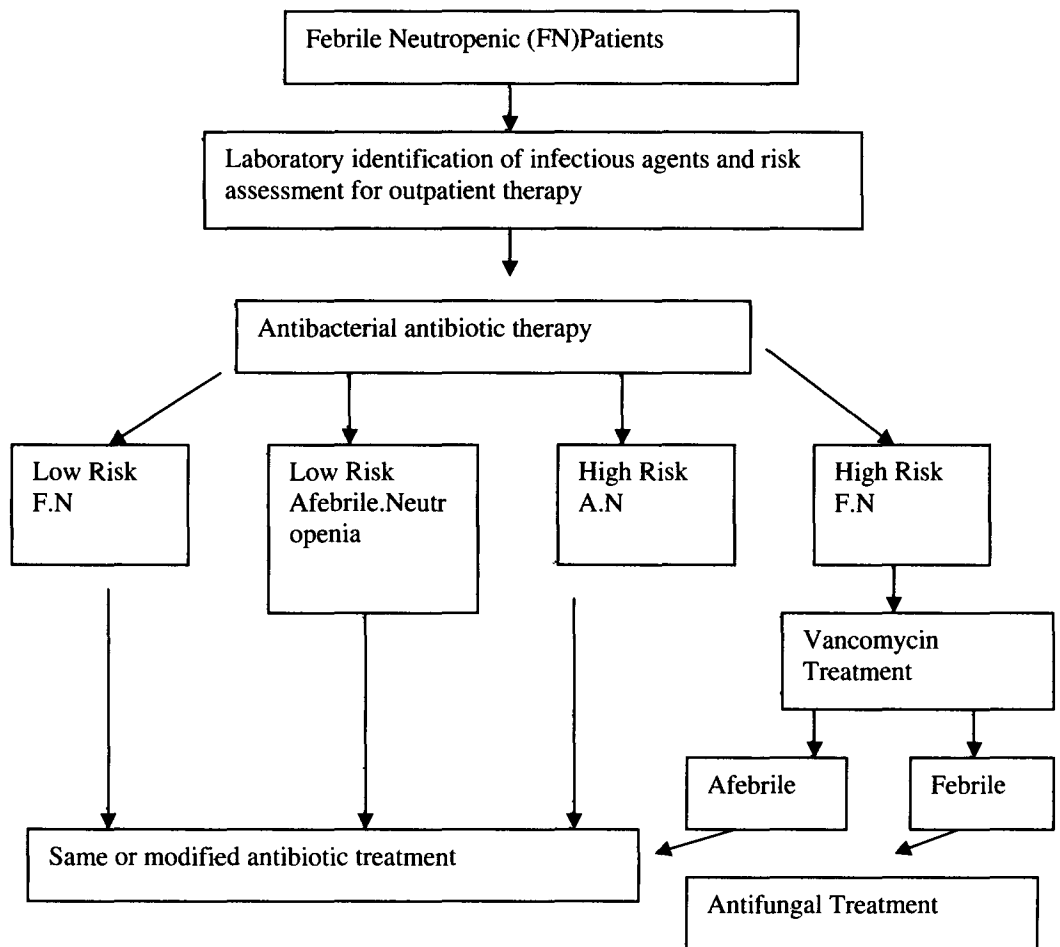
Figure 1: Treatment Protocol for Febrile Neutropenia, Source: Rotstein, 2003

1.1.4   Clinical complications for fungal infections

Several studies have found crude mortality rates for candidemia, a common type of fungal infection, between 25% and 60%, although these vary according to the study design and the population. However, many studies do not take into account other influential factors on morbidity and mortality, such as age of patients and underlying disease, which could lead to large variations in the crude mortality rate.

Wey and colleagues (Bassetti et al, 2006) investigating data from a large teaching hospital, found a mortality of 38% directly attributable to candidemia and, when only survivors were considered, the median length of hospital stay was 30 days longer for cases compared with control group. This represents a significant increase in the use of health care resources. The study also suggests the length of hospital and ICU stay can contribute to the negative outcome of the infection. (Bassetti et al, 2006)

1.2   Cost of Health Care

Between 1985 and 2006, the cost of Canadian health care system grew more than 100 billion dollars. The cost in 2006 was estimated at 148 billion dollars. The increase is largely due to inflation (41%) and population growth (13%). However, newer treatments, technologies and practice have all contributed to the increased costs. In addition, hospitals are getting a smaller percentage of health care dollars. To preserve the integrity of comprehensive health care, the hospitals and health authorities are facing immense pressure to keep costs contained (CIHI, 2007).

1.2.1 Increasing drug costs

Amongst the increased costs, pharmaceuticals remain the number one cost to the system representing 16.7% of total health care costs. Prescription medication costs were $18 billion dollars and accounted for 80% of the total $21.8 billion drug costs. According to Canadian Institute of Health Information, 56% of the total prescription drugs reimbursed were category 3, which represents drugs with little or no improvement over the existing treatment; 31% were category 1, which are line extensions (new usage or new formulation) of current therapies; only 8% were class 2, which represents breakthrough medications (CIHI, 2007). This data suggests the government is spending more on newer medication with little return-on-investment on clinical outcome. The cost containment strategy for the government is likely to minimize the approval of me-too drugs and line extension applications.

In BC specifically, the Pharmacare cost has risen 17.4% from 2003 to 2005 totaling just over $770 million dollars. According to the Canadian Institute of Health Information shown in table 1, BC's total drug expenditure represents 15.4 percent of total health expenditure. Prescription drugs represent roughly 83% of the total drug expenditure. Also shown in table 1, BC has one of the lowest total drug expenditure per capita at $690 million behind Quebec, Ontario, Saskatchewan, Alberta, and most of the Atlantic Provinces. (BC Pharmacare, 2005)

Province	Total Drug Exp. ($ in millions)	Total drug Exp. As a % of Total health Exp. (%)	Total Drug Exp. Per Capita ($)	Prescribed Drug Esp. Per Capita ($)
BC	2970.6	15.4	690.37	587.39
N.L	374.9	16.5	727.74	631.34
N.S	748.5	17.4	796.64	659.98
N.B.	572.7	17.2	760.69	639.87
Que	6170	20.3	807.43	698.96
Ont	10286.7	17	811.13	674.86
SK	719.7	15.3	725.9	607.08
Alta	2343.4	14.4	711.19	580.15
Man	816.5	14.1	690.13	578.19

Table 1: Provincial/Territory drug expenditure Source: Canadian Information Institute of Health

In addition, BC has one of the lowest percentages of public funded drug expenditures as demonstrated in figure 2. This is in part due to the Fair Pharmacare program the Liberal government introduced in May, 2003. The program incorporates level of income in the amount of drug reimbursement granted. This is an attempt to control the drug costs and to allocate financial resources to those who are less financially secure.
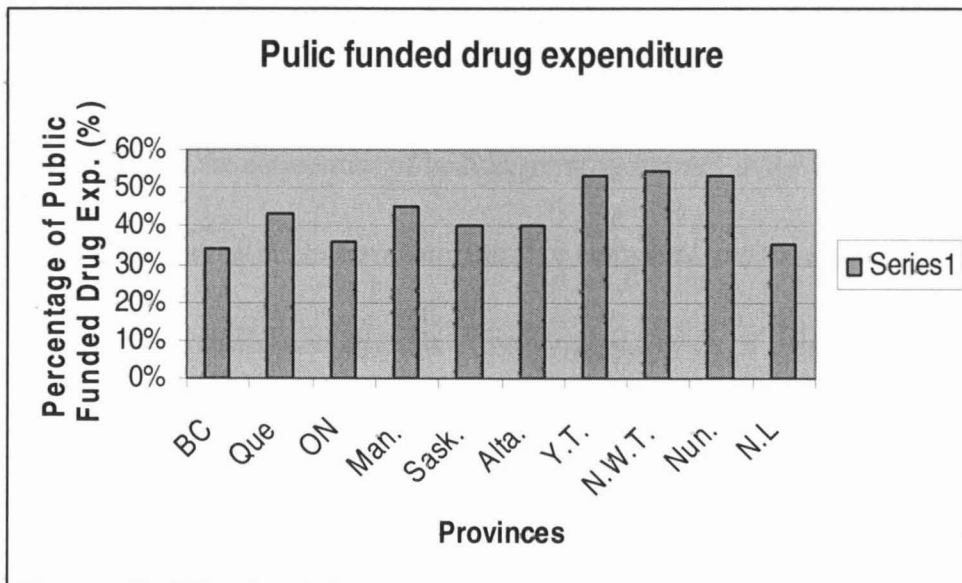
Figure 2: Provincial/Territory Drug Expenditure by Source of Finance:
Source: Canadian Institute of Health Information

BC's public strategy to combat drug prices is to (Pharmacare, 2007):

1. Accelerate access to non-patent drugs and achieve international price parity for non patent drugs, and,

2. Pursue purchasing strategies to obtain the best prices for prescription drugs and vaccines in Canada.

The strategy creates a challenging commercial environment for the research based pharmaceutical companies.

1.2.2 The role of value based economics in health care decision making

As the healthcare system continues to face rising costs, healthcare administrators will provide even greater scrutiny of spending. A greater understanding of value

associated with new pharmaceutical products should lead more effective outcome and more cost efficient decision making. Mauskopf et al, 1998, identified six different types of analysis to evaluate the economics of healthcare programmes in the literature.

1. Cost analysis considers only costs of compared programmes.

2. Cost minimisation analysis equates the outcomes of compared programmes, and finds the least costly solution.

3. Cost effective analysis, examines the value of outcomes of comparative programme in terms of natural units without assigning monetary value.

4. Cost utility analysis assigns utility scores to the natural units of the cost effective analysis. The utility score allows patient inputs in terms of outcome (such as pain management) to be captured.

5. Cost benefit analysis expresses outcome in monetary values, allowing comparisons across disease states.

6. Cost consequences analysis examines all the relevant costs associated with the healthcare intervention, and the outcome is expressed in a factored ratio, which is applied to the cost of treatment.

The challenge for the administrators is to determine the appropriate model for the program/treatment they intend to investigate. The decision should be made based on complexity of the treatment and current available resources.

1.3　The Challenges for Pharmaceutical Industry

The pharmaceutical industry is facing a number of threatening challenges. The latest IMS Health report on November 1, 2007 summed it up as follows:

1. The global pharmaceutical market will grow at 5 to 6% in 2008: the lowest growth since 1960.

2. The decline of the seven largest markets: the seven largest markets (US, 5 largest European countries and Japan) will only contribute to 50% of the growth, while the seven largest emerging markets (China, Brazil, Mexico, South Korea, India, Turkey and Russia) will contribute to almost 25% of the growth worldwide.

3. This is the first time that the size of the primary care market, which represents the drugs being prescribed by family doctors or general practitioners, will decline.

4. Genericization will continue as the pressure for cheaper drug prices continues: It represents a loss of around $20 billions in sales for the research based major pharmaceuticals in 2008. The generic companies are actively challenging existing patents to capitalize the demand for cheaper medications.

5. There continues to be an increased uncertainty over safety, pricing and market access, and intellectual property in the market.

In addition to challenges summarized by the IMS report, the industry reputation has suffered in recent years regarding its ethical practices around clinical trials and drug promotion.

1.3.1.1 Political threat

The political landscape has turned against not only the pharmaceutical industry, but also the drug reviewing authorities such as the Food and Drug Administration, in light of numerous drug recalls and litigation. The public has lost confidence in drugs approval processes, and concerns are rising over drug promotion to the public and to the health care professionals. The call for longer clinical trials to demonstrate long-term safety means significant increase in drug development costs. Non-industry sponsored education programs are demanded to provide non-biased opinions are reducing the industry's ability to influence.

The rising cost of drug therapy has made health policy makers look more favourably to generic companies, who manufacture and sell patent expired drugs at a significant discount. As indicated in the IMS report mentioned above, over 20 billion dollar worth of sales in 2008 will leave the hands of research based drug companies to the generics. The call for shorter patent length and longer clinical trials while limiting its ability to market products is posing great threats to the growth of the industry.

1.3.1.2 Lack of innovation

While the political landscape is troubling, the biggest problem that research based pharmaceutical companies face is lack of innovative production from research and development. Figure 3 tells a story of the industry's lack of return from its research and

development investments. The worldwide investment on research and development has doubled from year 1996 to year 2003 while the number of approved drugs has decline by roughly 50%. The cost of developing a drug ranges from US $500 million to $1.1 billion depending on the disease. The average cost is estimated in the excess of $800 million US.
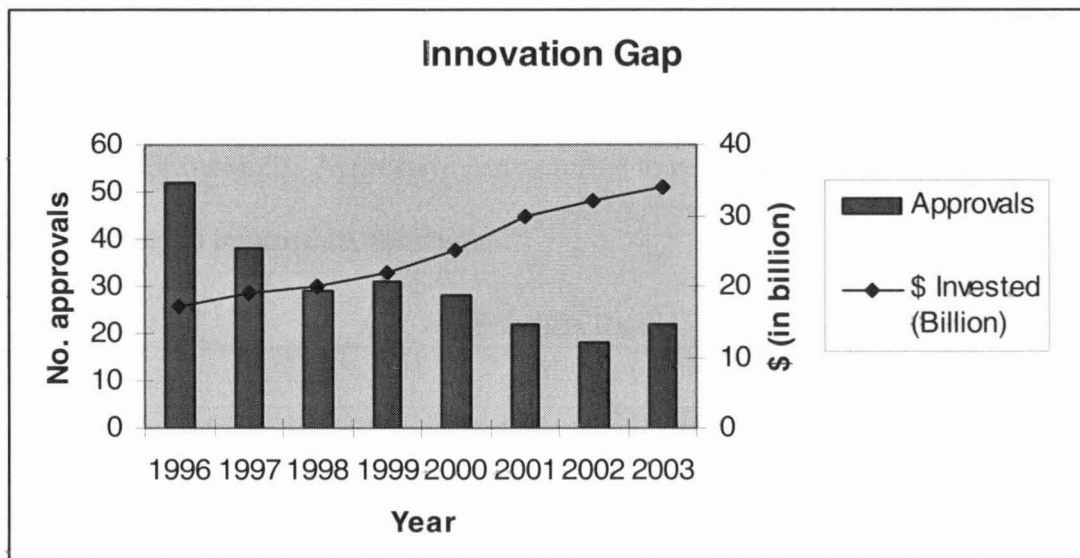
Innovation Gap

Figure 3: Drug Innovation Gap Source: Burill & Co

Furthermore, global competition for research and development has been reduced. There is a significant shift in research and development from Europe to the US. The shift to the US may be due to the free market environment, which awards scientists financially for their successes. In 1990, the US spent roughly 30% of the world's research and development costs. It has grown to nearly 55% in 2001 meaning the US is spending more research and development costs than the rest of the world combined.(United

Kingdom Parliament, 2005) The reduced diversity in the research environment may be one factor contributing to the lack of innovation.

The drug innovation gap along with generic competition is the major reason why the value of pharmaceutical companies shrunk in the eyes of investors. The index of the shares of major research based pharmaceutical firms (DRG) has underperformed the Standard and Poor, NASDAQ and Dow in the last 5 years. The industry has not kept pace with investors expectations and the poor stock performance eventually translates into fewer dollars for research. Aggressive restructuring to reduce cost is one measure the industry is taking to improve its valuation.
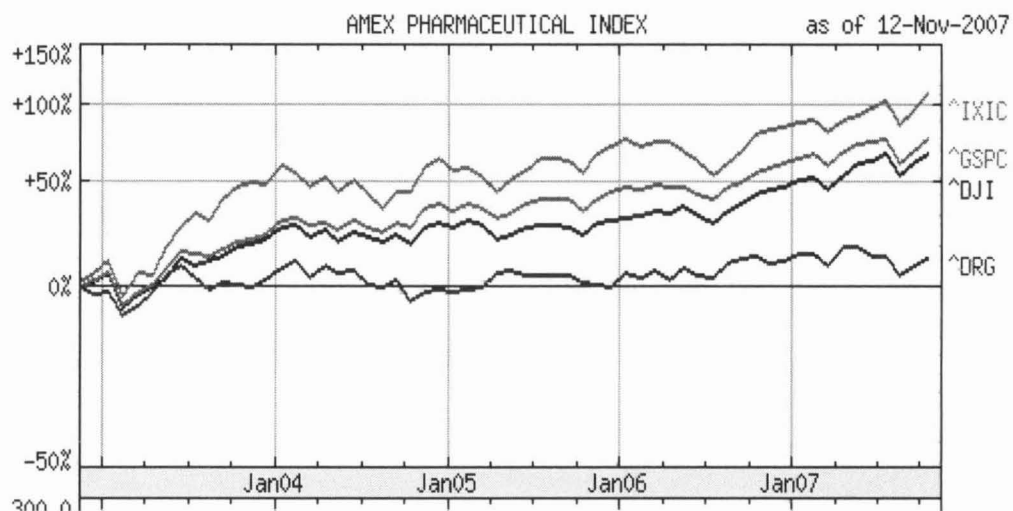
Figure 4: Financial performance comparing drug companies and major indexes

2: THE ANALYSIS OF THE ANTIFUNGAL MARKET

2.1 Market segments

2.1.1 Antifungal market potential

The anti-fungal market was estimated at $2.4 billion worldwide in 2003 with projected growth to over $3.1 billion in 2008 (Bioseeker, 2004). According to BioSeeker's research, the growth of the market is due to several factors. (Bioseeker, 2004)

1. An increase in the number of people who are living in an immunocompromised state which makes them more susceptible to fungal infections.

2. As with antibiotics, the efficacy of the standard anti-fungal therapy is reduced due to fungi resistance.

3. Many of the standard therapies have a high toxicity and/or significant adverse events which results in a need for more efficacious antifungal treatment.

4. The fungal infections resulted from fungi such as Candida, Aspergillosis have become a significant factor in the management of immunocompromised patients.

In evaluating the impact of febrile neutropenia on Canadian hospitals, using a 2001 data (CIHI, 2001), it was assessed that 0.055% of Canadians were diagnosed with

neutropenia, which pose risks of fungal infection. Amongst those who are infected, 0.018 % of whom are infected with candidiasis and 0.003% with aspergillosis. Based on the information requested from the Canadian Institute for Health Information (CIHI), estimated febrile neutropenia cases for Canada were forecasted at 7248, 7281 and 7425 patients annually from 2005 to 2007. Close to 250 cases of invasive candidiasis and invasive aspergillosis, combined, are expected to occur yearly in Canada among neutropenic patients. Numbers vary greatly among provinces. In BC, there were 1223 cases of neutropenia in 2001 and with the projected number of cases to be 1294, 1308 and 1376 in 2005 to 2007 respectively (Statistic Canada, 2006)

2.2 Treatment options

There are three major classes of antifungal therapy, Amphotericin B, Azoles, and Echinocandins.

2.2.1 Amphotericin B

Amphotericin B is the oldest and first line treatment. It is a cell membrane modifier which acts by binding to the sterol component of the fungal cell membrane leading to alteration of cell membrane and cell death. However, mammalian cell membranes also contain sterols, and it has been suggested that the damage to human cells and fungal cells may share common mechanisms. This is a potential concern for patients as this shared mechanism is believed to contribute to the drug's potential toxicity effect to the kidneys. Amphotericin B is an effective antifungal medication if its adverse events are monitored accordingly. The conventional Amphotericin B has significant price advantage to the other class of antifungals.

The Amphotericin B is the first line treatment in BC and is used on roughly 300

patients annually in managing febrile neutropenia. Examples of amphotericin B products

are

- Fungizone® Intravenous, product of Squibb Canada, Division of Bristol-
  Myers Squibb Canada

- AmBisome® for Injection (liposomal amphotericin BC), product of
  Fujisawa Canada

2.2.2 Azoles

The second type of cell membrane modifiers is Azoles. The Azoles inhibit fungal

cytochrome P450-dependent synthesis of ergosterol. This action causes depletion of

ergosterol. By inhibiting ergosterol synthesis, the azoles alter fungal cell membranes

resulting cell death. The subsequent loss of normal sterols in cell membrane correlates

with the accumulation of 14α methyl sterols in fungi and may be responsible for its

fungistatic/fungicidal activity. Examples of Azoles are

- Sporanox (itraconazole), product of Janssen Pharmaceutical, Division of
  Janssen Ortho Inc.

- Dflucan (fluconazole), product of Pfizer Canada

- Vfend (Voriconazole), Product of Pfizer Canada

2.2.3 Echinocandins

Echinocandin is a new class of antifungal drug that inhibits the synthesis of β

(1,3)-D-glucan and thereby compromises the integral component of the fungal cell wall.

The β (1,3)-D-glucan is not present in human cells. This class of medications is safer and better tolerated by patients. Echinocandins are currently second line choice for managing fungal infections in febrile neutropenia.

Examples of echinocandins are:

- Product C (xxxxxxx), Company M

- Competition A (xxxxx), Company A Inc.

- Competition B (xxxxx), Company B Inc.

3: INTERNAL ANALYSIS

3.1 Product C

Product C is a member of the echinocandin class of antifungal agents. It is a sterile, lyophilized product for IV infusion, and used mostly as an inpatient treatment. The major clinical advantage over the older polyene and azoles is the improved safety of the treatment. The product was introduced in 2001 and priced per vile at $xx dollars, which is roughly 10 times the cost of the conventional Amphotericin B, the reference product in BC hospitals.

The cost of the medication has been the main issue here in BC. While the administrators agree with the scientific evidence, the product is used as a second or third line treatment to patients who failed the cheaper reference treatments. As of 2008, product C will see two new competitors who demonstrate similar clinical evidence.

3.1.1 Scientific information and indicated use

Clinical highlights of Product C include:

- Product C's safety and tolerability: Product C's unique mechanism of action, which targets antifungal cells, better than polyenes and azoles, provides better safety and tolerability.

- Product C has significant fewer drug interactions because of its unique metabolism pathway.

- Product C has an expanded clinical profile and is indicated for:

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- Convenient once-daily dosing and administration

3.1.2 Sales channel

As with most major pharmaceuticals, the field sales team is one key asset to deliver information to health care professionals. The representatives, who are supported by a brand team based out of head office, targets Intensive Care Unit doctors and nurses, infectious diseases specialists, medical oncologists, and hospital head pharmacists. The sales representatives are responsible for clinical and scientific education for the product and the disease and for sales order of the products. In addition, a brand team provides market research, product management and promotional messages. The promotional focuses are on major teaching hospitals, which are equipped with established cancer treatment facilities.

3.1.3 Formulary listings

There are 5 major health authorities in BC, Northern Health, Interior Health, Fraser Health, Coastal Health, and Providence Health Care. Each health authority has its own formulary committee, which is typically made up of head pharmacists with PharmD designation. The committee reviews the list of medication used in its respective hospitals and decides on formulary listings and treatment protocols for hospitals to follow (British Columbia, 2007). The listing is revisited when new medicine or new pricing takes place in the market.

As an example, when a product is adopted into the formulary listing. A typical treatment protocol is shown in figure 5

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┌─────────────────────────┐
│   Diagnosis of Disease  │
└─────────────────────────┘
            │
            ▼
┌───────────────────────────────────────┐
│   1ˢᵗ Line Reference Therapy to treat  │
└───────────────────────────────────────┘
            │
            ▼
┌─────────────────────────────────┐
│  If intolerance or infusion-related │
│  reaction, may consider Product X  │
└─────────────────────────────────┘
```
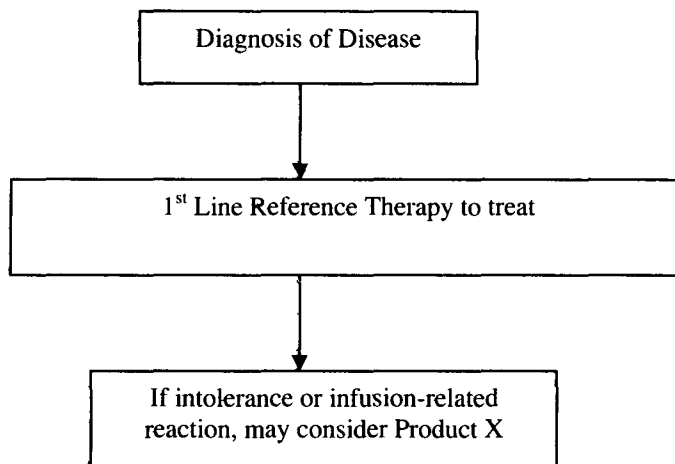
Figure 5: Example of treatment protocol Source: BC Health Guide

Product C has been adopted into formulary listings as a second line treatment in many health authorities.

The usage difference between first line and second line treatment is significant. From the sales data gathered from Company M comparing market share of 1st and 2nd line usage, product C represent about 10%[2] of the market.

3.2   Financial performance

Product C has seen strong growth in Canada since its adoption by hospital formularies beginning in 2005. The sales in Canada in 2007 are tracking to surpass $XX million with a growth rate of XX percent over last year. The sales in BC represent a modest 7 %[2] of the total national sales of Product C. However, a growth rate of 70[2] percent over last year demonstrates a belated shift in physicians' attitudes toward using product C. Company M believes this late adoption is a typical example of the pharmaceutical business climate in BC, as the decision makers have a more cautious approach to adopting newer agents compared to those of other provinces.

3.3   Business opportunity

Product C's strong 2007 sales growth in BC represents a potential tipping point in a wider use of the medication. However, the timing of this late adoption has not been ideal for company M as competition A and competition B are around the corner to capitalize on the growing use of echinocandin class.

In order to sustain growth for product C within its current treatment applications, company M has two strategies available to it:

1. Expand the existing usage of product C by improving its formulary status in all indicated therapies.

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[2] The number is for exercise purposes only and is not a true value to respect confidentiality of the sponsor.

2. Reduce competition entries by differentiating product C from competition A and competition B.

To improve product C's formulary status from second or third choice to first choice requires detailed analysis of cost of treatment. A value based economics model such as Forbis and Mehta's (Forbis and Mehta, 1981) economic value to the customer (EVC) model allows company M to demonstrate product C's cost effectiveness compared to the existing reference product. The EVC model fits well with the cost benefit model discussed in 1.2.2. as the model will demonstrate a benefit of resources savings when product C is used after considering the total treatment costs.

To limit the threat of competition, product C must differentiate itself from the competition. A value based cost consequence model is recommended because of its ability to quantify non-numerical variables. The cost consequence model discussed in 1.2.2. provides the decision makers a wider perspective on the treatment options. Qualitative measures such as product history, dosing ease, and compliance can be taken into account to differentiate product C.

These two analyses are detailed in the section below.

4: SOLUTION ANALYSIS

To address the business opportunity discussed for product C, company M needs to

demonstrate to the buyers that the buyer's own economics considerations are addressed,

and there is a commitment to find a win-win solution for both parties.

4.1   Expand Product C usage

To gain wider use over existing first line agents, product C must demonstrate an

overall cost saving in treating patients. A value based economics model can demonstrate

the dollar impact clinically in comparative treatments. The model can differentiate length

of treatment and overall maintenance costs that captures the difference in clinical

outcome for Product C and the reference product, Amphotericin B.

4.1.1   The Economic Value to the Customer Pricing Model

The value based economics model takes into account the buyer's economics

circumstances. In the case of disease management, the buyers' economics are determined

by the total cost of treatment per one patient. The model is adopted and modified from

one interpretation of the Forbis and Mehta's Economic Value to the Customer (EVC)

pricing model (Thompson & Coe, 1997). The model in figure 6 shows despite the higher

direct pharmacotherapy cost (PC) for subject product Y, the total treatment cost (TTC) is

less because of product Y's positive impact on maintenance cost (MC).   In company M's

case, the reference product X is Amphotericin B, the current preferred treatment in the

hospital. The product Y represents the subject product, which is Product C in this case.

To use the model, one must determine the total treatment costs (TTC), which

represent a combination of Initial Cost (IC), Pharmacotherapy Cost (PC), and

Maintenance Cost (MC). Initial cost such as diagnosis of treatment is considered neutral

as the same protocol applies to every patient prior to his or her pharmacotherapy.

Pharmacotherapy cost is the cost of medication during the course of therapy.

Maintenance cost is the cost of management post treatment and it varies depending on the

outcome of the pharmacotherapy.
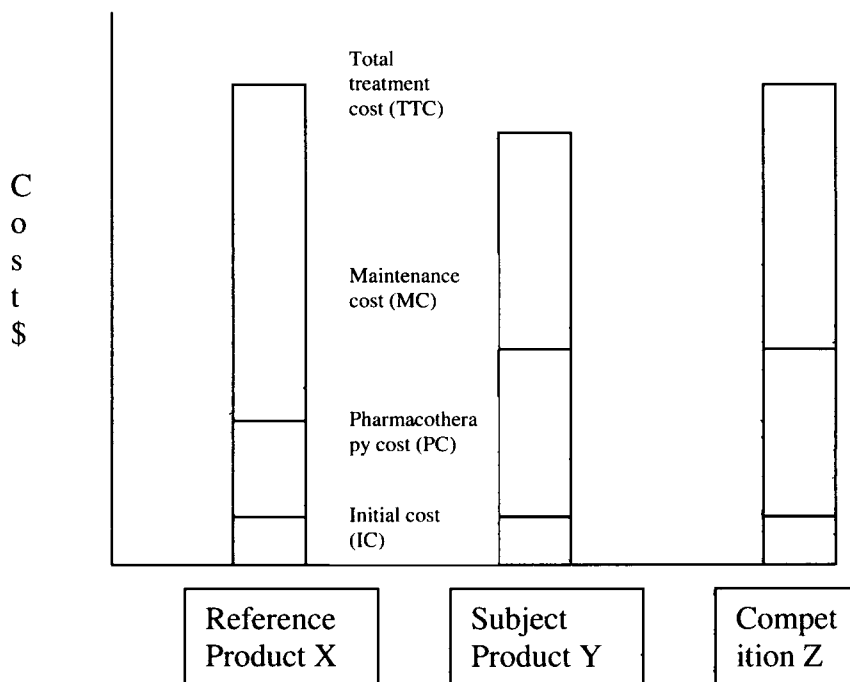
Figure 6: EVC Model

As shown in figure 7, in order to demonstrate a competitive advantage and trigger

a buying behaviour, TTC of product Y must be equal or less than TTC of product X, the

reference product despite the higher cost of product Y (PCy). In other words, the new

drug treatment must have a better clinical outcome so the cost of post therapy

management is reduced and results in overall savings in management resources.
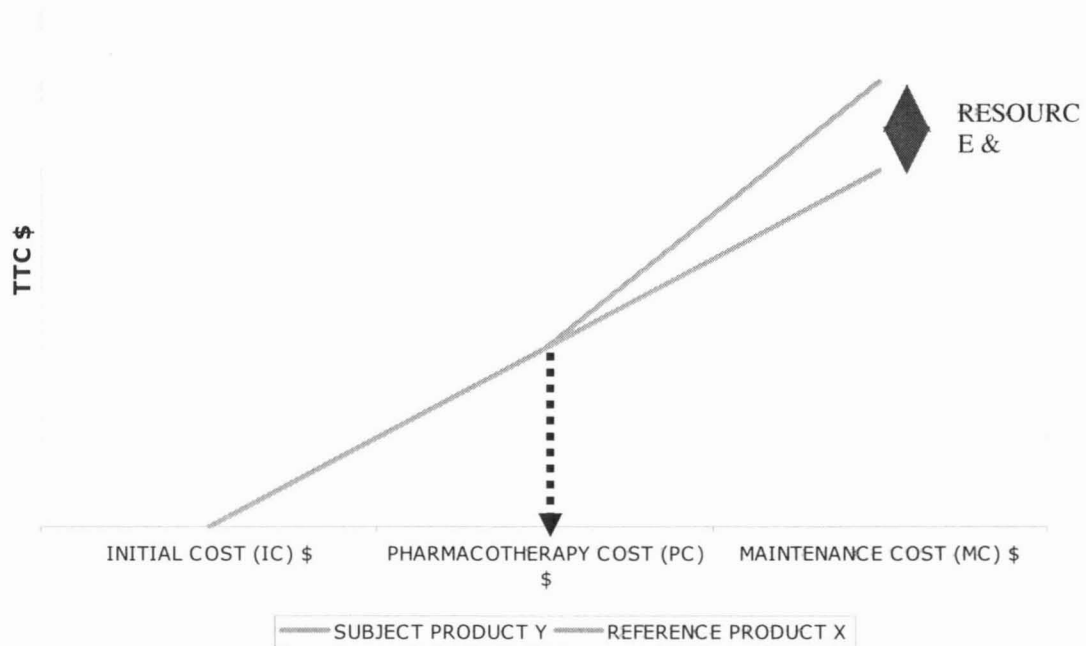
Figure 7: Resource saving

4.1.2   Total cost of treatment

The costs involved for febrile neutropenia can be categorised into the three cost

bases of the EVC. The Initial Costs are procedure and tests, which provide positive

diagnoses for fungal infections for ferile neutropenic patients after the patients' cancer

treatments. The definition of the disease was described in the disease section. The

diagnostic tests and lab tests are summarized in Table 2 and 3.   The actual Initial Costs

are irrelevant in our analysis as the procedures are applied to patients prior to medical

treatment and hence the same across the treatments.

Procedures
- Biopsy of solid organs (in the events death)   - Bronchoscopy   - Central Venous catheter insertion   - CT Scan of the brain   - CT Scan of the lung Gallium Scan   - GI endoscopy   - Lumber puncture   - Ultrasound of the abdominal   - Ultrasound of the kidneys

Table 2: Diagnostic Procedure for FN

Lab tests
• Alkaline Phospatase (IU/L)
• ALT (IU/L)
• AST (IU/L)
• Bilirubin (umol/L)
• Serum Creatinine (umol/L)

Table 3: Common lab tests for FN diagnosis

4.1.3   Pharmacotherapy cost

To evaluate the pharmacotherapy costs for the treatment, one must consider

variables such as therapeutic dosing and treatment duration. The added nursing cost for

variable dosing and added cost associated with drug compliance or switching due to lack

of efficacy are not included as part of the maintenance costs in this analysis. The

outcome differential is a conservative estimation. For Product C, the drug cost is based

on selling price; for conventional amphotericin B and liposomal amphotericin B, drug

cost is estimated from a survey of Canadian hospital acquisition costs. The daily drug

cost and the average treatment duration allow us to obtain of the average direct cost per

treatment with the different antifungal agents.

The costs quoted in table 4 represent therapeutic price per day. Unit price does

not represent the therapeutic dosing cost (Welsh, 2004; Welsh 1999; Bates, 2001). Some

medications require multiple vials to reach therapeutic dose, and some require different

volume packages.

Outcome Parameter	Product C	Conventional Ampho B	Liposomal Ampho B
Dosage	N/D*	0.6 mg/kg/d	3.0 mg/kg/d
Mean duration of therapy	12 days	10.8 days	10.3 days to 12.5 days
Daily drug cost	$700**	$46	$820
Total Direct Drug cost over treatment duration	$8400	$496	$8446 to $10250

Table 4: Direct pharmacotherapy cost *No disclose to protect sponsor identity; **Price shown is not true price of product C

4.1.4   Maintenance cost

Based on direct drug cost alone, product C bears a high cost over the conventional Amphotericin B treatment. However, when maintenance cost is taken into consideration as part of the total treatment cost, a different economic picture emerges.

One major variable based on the clinical profile of the treatments is the risk of renal toxicity. Clinical studies have suggested the observed rate of nephrotoxicity varies greatly across antifungal agents. Renal toxicity occurs in 2.6% of patients treated with product C while 33.7% of patients treated with conventional amphotericin B experience nephrotoxicity (Bates, 2001). Bates et al, 2001, estimate the additional hospital resources needed for one case of confirmed nephrotoxicity at $47879. Table 5 summarizes the maintenance costs across treatments.

Outcome Parameter	Product C	Conventional Ampho B	Liposomal Ampho B
Rate of Renal Toxicity	4.5%	33.7%	11.5% to 18.7%
Expected Maintenance Cost/Cost impact of renal Duration	$2154	$16135	$5506 to $8953

Table 5: Maintenance cost based on renal toxicity variable

(Cost impact= incremental cost at $47879 x incidence of renal toxicity)

4.1.5 Discussion

Once the cost variables are identified, the expected average total treatment cost (TTC) can be determined as the combination of pharmacotherapy cost (PC) and maintenance cost (MC). The results are shown in figure 8
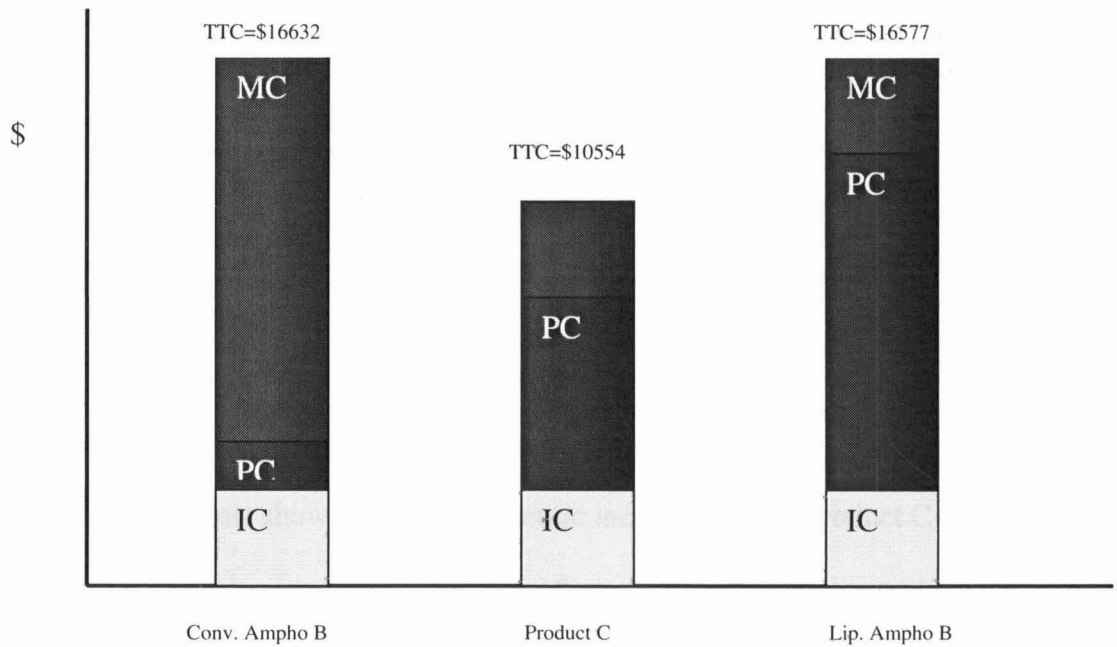
Figure 8: Total Treatment Costs among treatments

Despite the higher direct pharmacotherapy cost, product C offers the most economical treatment option for febrile neutropenic patients. Figure 9 demonstrates the resources saved by product C compared to the two reference products.
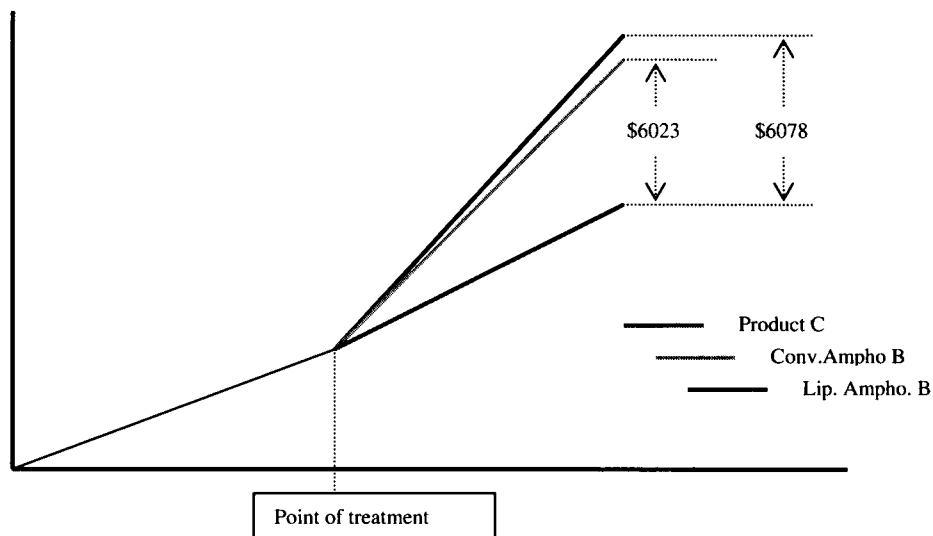
Figure 9: Resources ($) saved by product C

Although the analysis shows a strong economic incentive to use Product C as the first line treatment for febrile neutropenia, company C needs to be cautious as to how the data is presented. A clear understanding of clinical adverse events and the potential consequences must be established for the buyers, who in this case are hospital pharmacists who may not be as aware of these effects as clinical physicians. This analysis extrapolates data from studies looking at the Canadian market as a whole. BC local data (such as cost for nephrotoxicity) should be developed to enhance credibility. Understanding that the cost is a major issue, this value based approach puts the customer's economics in the forefront as company M discusses a win-win situation with the buyers.

4.2　Limit competitive entry

4.2.1　Cost consequence calculator

Product C faces another challenge, as it is no longer the only echinocandin class drug on the market. Two new competitive products from reputable companies have gained the approval for the Canadian market. Product C's market share soon will be challenged by the competition. To ensure survival in the echinocandin class, Company M must identify competitive advantages over the competition. It is common for companies to use a discounted price to penetrate the market (Prasad, 1997). To avoid a price war with the competitors, company M needs to use a tool, which can capture the advantages of qualitative variables that differentiates it. Company M again should put itself in the shoes of the customer and develop a strategy that ensures Product C remains the most attractive treatment option for patients.

A cost consequence analysis is a tool that can capture qualitative variables like product experience on the market, compliance, adverse events, etc. in addition to pricing.

4.2.2　Efficacy

Product C and the competitive products A and B are all from the echinocandin family. Comparative studies have suggested that all three agents have similar efficacy when the optimal therapeutic dosing is used. However, the three products all have unique indication profile. Table 6 summarizes the indications for the three agents.

Indication	Product C	Competition A	Competition B
Candida infections			
candidemia			
Intra-abdominal			
Peritonitis			
Pleural Space			
Esophageal			
Neutropenic fever			
Prophylaxis HSCT			
Aspergillosis			

Table 6: Indications for available echinocandins (The indications are hidden to protect the identity of the sponsor)

It is evident that the strength of being on the market longer provides product C with wider approved indicated use compared to its competition. The benefit of having widely indicated use is to provide physicians with confidence in using the treatment. An off label use of a medication can subject the physicians to medical legal liability. This is, however, a strength that will expire as competition will likely to apply for the same status as product C in the months to come.

4.2.3 Compliance

The clinical compliance of the agents is again similar. However, differentiation can be made in the agent's dosing schedule. The dosing detail is kept confidential in this paper to respect the confidentiality of the sponsor. Product C and one competitor have a straightforward dosing while one competitor requires dose titration, which requires more time and cost to determine the therapeutic dose for each patient.

4.2.4 Adverse events

The adverse events are similar among three agents.

4.2.5 Treatment Cost

The treatment costs for the three agents at therapeutic dosage is described in the following table,

	Product C	Competition A	Competition B
Therapeutic dosing	N/D (not disclosed)	N/D	N/D
Weighted average Cost/dose	$4*	$3*	$3.5*

Table 7: Price comparison between echinocandins*Prices are falsified to respect confidentiality

4.2.6 Multi-attribute utility theory and cost consequence analysis

In order to avoid a price war where companies undercut one another's price to gain market share, company M must develop a solid value based cost consequence analysis to incorporate key variables, which satisfy buyers' value while differentiating product C from competition. Multi Attribute Utility (MAU) theory is a good tool for establishing meaningful attributes.

According to Peacock et al, methodological steps in the MAU approach are as follows (Peacock, 2007):

1. *Identifying attributes in the MAU function.*

    A panel of decision makers define attributes that are relevant to the organisational context and the objective of the decision makers.

2. *Describing attributes.*

The panel determines the scales of measurements for each attribute. In order to do so, the panel provides descriptions for the best, worst and intermediate scenario for each attribute.

3. Scaling attribute levels

The attributes are then scaled from 0-100 based on their relative importance to the decision maker.

4. Quantifying trade-offs between attributes

The panel assesses the relative importance of each attribute.

5. Evaluating programmes

The panel evaluates each programme by scoring using the attribute measurement scales. Scores should be based on evidence based data.

6. Combining attribute scores

Panel combines the scores to calculate combined benefit of the programme.

An example of a cost consequence calculator is shown in table 8

Indicated use: Febrile Neutropenia

Variables/Attribute	Cost	Compliance	Indications	Adverse event	Utility Score	Cost Consequence analysis
Importance Weight						
Therapy option						Cost per utility
Treatment A						
Treatment B						
Treatment C						

Table 8: Cost consequence calculator adopted from healthstrategy.com

The MAU model allows company M to discuss openly the perceived value of each treatment from the buyer's perspective. Well-defined attributes lead to important information on how company M should structure its pricing.

4.3   Gaining commitment

Once company M has successfully demonstrated product C's economic value to its buyers regarding its expanded use, it can then move forward to gaining exclusive sales commitments to avoid constant challenges from the competition. It is important to understand that a simple price drop without the work of value based economic analysis can lead to product being treated as commodity with little or no profit margin. The buyer, without seeing the value, would simply demand the cheapest option.

Assuming the value based economics analysis convinces the buyer of the cost advantage of using product C as the first line treatment and the new competition offers no

added benefits, company M can move on to sales contract discussions. Hospital formulary listings are revisited when new prices or new agents are submitted. This means that the competition would constantly challenge product C's new status with its new pricing and if applicable, new indications. Therefore, it is in company M's best interest to discuss an exclusivity contract to guarantee revenue. In return, company M can offer additional discounts as added incentives to the buyers who might be concerned about giving Company M a monopolistic price advantage.

Two general types of exclusivity contracts are described below:

4.3.1 Exclusivity by Volume

The exclusivity by volume fixes the terms of contract on volume. The more the buyer orders, the better discount he/she gets. The advantage of exclusivity by volume is gaining revenue upfront. However, there are two major drawbacks to this contract:

1. Product C and all antifungal medication are delivered intravenously. The storage and the shelf live of the products are short. The number of patient needed therapy varies greatly from month to month. Both the buyer and Company M risk wasting.

2. Contract by volume does not guarantee exclusivity. It only excludes one transaction at a time. It is more prone to price war as competition can easily match what you offer.
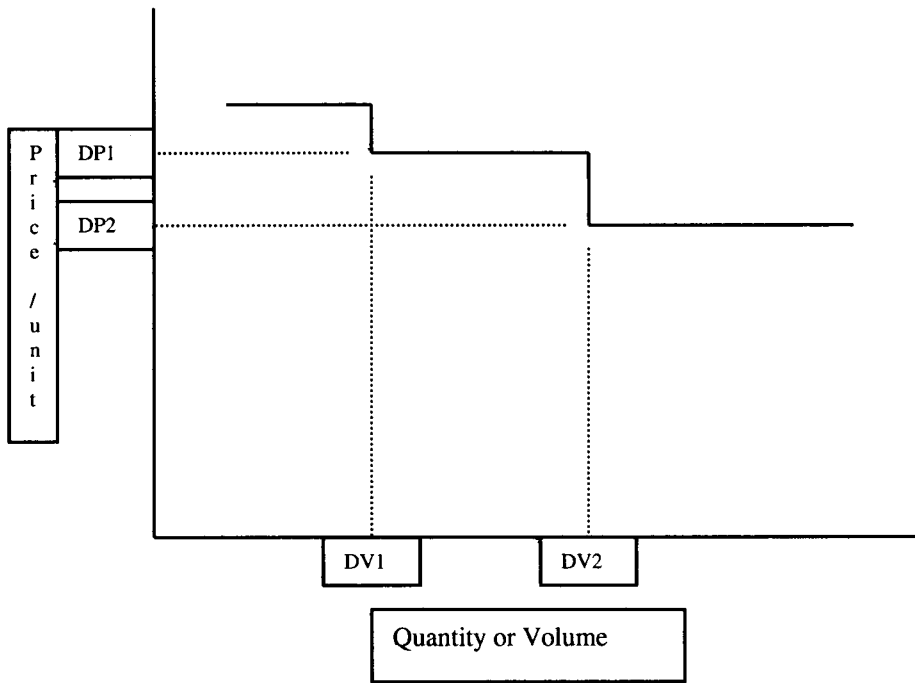
DP1= Discount Price 1 DP2= Discount Price 2
DV1= Discount Volume for DP1 DV2= Discount Volume for DP2
Seller's Revenue= Volume x Price based on the discount schedule.

Figure 10: Sales contract by quantity/volume

4.3.2   Exclusivity by Time

On the other hand, a contract fixed over time, can deter competition from entering. Company M offers discount incentives based on the length of the contract. The advantage is market exclusivity, and the drawback is that the buyer may fear monopolistic price advantage, and therefore may demand a greater discount compared to volume contracts. Company M is also committed to provide the goods in this agreed period.
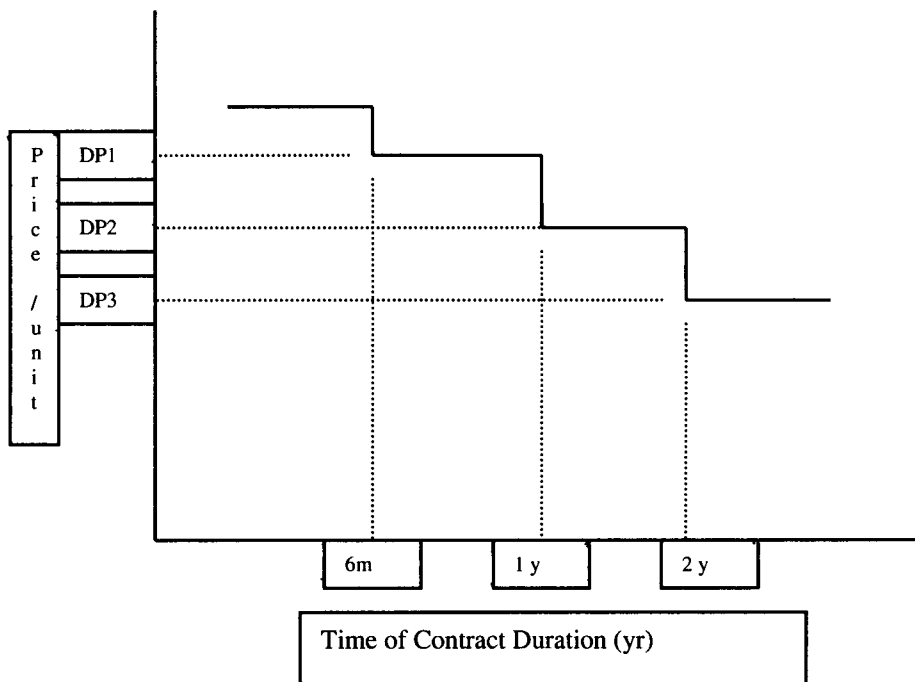
Seller's revenue= volume per year x duration of contract x Price of contract

Figure 11: Contract by length of time

In addition to single product contract, company M may assess its entire portfolio of products sold to the hospital to see if there is a bundling opportunity. Bundling gives further discount incentives, which is good for the buyers. Furthermore, it guarantees market share and gives the company strong hospital presence.

5: CONCLUSION AND RECOMMENDATION

As the pressure on Canadian health care resources continues to rise, the hospital administrators are becoming less likely to grant access to medication based on clinical and scientific data alone. Pharmaceutical companies are pushed to re-evaluate their promotional strategy to ensure they maintain a strong share in the public funded formulary market.

Product C has gained popularity over the current first line treatment of Amphotericin B. It has seen remarkable success in most Canadian markets, some better than others. However, it remains a second line treatment to the older agent as the direct cost of medication stands in the way of the best medicine being delivered first line. Product C is facing upcoming threats from competition, as it no longer enjoys monopoly in its class, echinocandins. The combined pressure from the two challenges forces company M to look for creative ways to engage customers and ensure product C's continued success.

To gain sustained competitive advantage, company M needs to communicate beyond the clinical benefit of the medication. As discussed earlier, the value based economic analyses help to address the two immediate challenges:

1. Economic value to the customer model (EVC) demonstrated the cost benefit of product C over the current first line treatment.

2. Cost consequence analysis can differentiate product C from new

    competitors as the analysis takes qualitative measures into account.

    The qualitative measures such as product's length of time on the

    market, simplicity of dosing, approved indications are some examples

    of important disease management variables.

The two analyses imply that there is opportunity for growth. A quick financial

projection based on product C becoming first line choice is summarized below:

Price/day	Estimate no. of patients	Duration of therapy	Non-compliance/failure	total
$4	BC: 1,376	14days	20%	61,645
$4	Can: 7,425	14days	20%	332,640

Table 9: Financial projection

The price/day and the failure rate are fictional. To put the information into

perspective, product C is currently used as second or third line treatment in BC

representing roughly 10%[2] of the treating population. The growth potential is significant

even if we consider an equal market share for all three echinocandin players.

To implement the analyses and to fulfil the market potential, company M needs to

rely on its strength: its professional sales representatives. These are the individuals who

are the company's contacts with the buyers, and have strong understanding of the

business challenges buyers are facing. In addition to their scientific and product training,

the representatives should have the full understanding of the value base economics

models and the ability to modify them as they see fit with their respective buyers. It is

the representatives' responsibility to build trust and credibility with the customers. It is

crucial that buyers perceive the economics models as credible to maintain the trust

between the reps and buyers.

The representatives also need support from the head office. They need

information that would help the buyers to populate the model. Furthermore, they need to

have certain flexibility on pricing so they could quickly gain commitment after presenting

the analyses successfully to stay ahead of competition.

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