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Risk Management in the Development of New Products in the Pharmaceutical Industry

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1. Introduction

1.1 Trends in R&D spending and production of new drugs

Due to the excessive new product research opportunities and limited financial resources, deciding which new pharmaceutical products to develop can be a challenging and lengthy process for many pharmaceutical companies. The returns on investment are attractive, but they vary considerably between drugs. New pharmaceutical products usually undergo costly and time-consuming testing before receiving government approvals for distribution to patients (Congressional Budget Office, 2006).

Only about one percent of researched chemical molecules withstands the three phases of clinical trials, the scrutiny of the Food and Drug Agency (FDA), and becomes available for patient use. In addition, research and development (R&D) costs can reach more then $800 million to develop and test a potential drug, so the selected product must return at least the accrued financial expenditures over its lifecycle (Nelson, 2009). With such high development costs and low probability of product success, project-prioritization and new product-portfolio selection are of high importance to pharmaceutical managers. Trading off available resources and investment opportunities helps identify drugs worthwhile to bring to market (Ogawa & Piller, 2006).

In the pharmaceutical industry, the risk management problem includes deciding which new products to develop, continue to research, terminate, and invest in. These decisions include trading off risks, returns, and time horizons for future payoffs. In theory, such tradeoffs are easily undertaken by optimization problems; however, the complexity and uncertainty of the new drug development process can make the optimal solution hard to obtain, and may result in employing less complicated, and therefore, less precise methods of new product identification (Gino & Pisano, 2006).

This chapter will focus on assessing the different risk management methods employed by pharmaceutical executives in the new product portfolio evaluation and consequently, which pharmaceutical products to bring to market. First, however, a review of the product development process, as well as the costs associated with research and development of new drugs in the U.S. will be presented. The process of product development will be described as it happens in the United States, although the R&D approach is not that different between the U.S. and the European countries. After the short R&D process summary, a description of the

risk assessment methods will follow. Pharmaceutical executives will find this chapter useful in making their product portfolio investment decision, as it will list several well known and widely used techniques of risk evaluation, as well as provide guidance on how they compare to each other, how they differ, and when should they be used.

2.The cost of developing a new drug

Over the past 20 years, the total costs associated with research and development (R&D) of new drugs has tripled. In 1980, U.S. pharmaceutical companies spent a total of $5.5 billion on research and development of pharmaceutical products, while in 2003, these costs increased to more than 17 billion (NSF, 2005). Continued growth in the R&D spending, however, has just a small effect on the pace at which new drugs have been developed in the past 20 years, as the number of innovative molecules in research has steadily increased (Congressional Budget Office, 2006).

On average, it is estimated that R&D of new innovative pharmaceutical products costs nearly $802 million, and takes about 12 years for a pharmaceutical company to bring a drug to market (DiMasi et al., 2003). The R&D cost estimates include the actual accrued R&D expenditures that are estimated at $403 million, as well as expenditures of failed projects and the value of foregone alternative investments, which in total amount to $399 million (DiMasi et al., 2003; Rawlins, 2004).

R&D costs for new drugs are highly variable, and depend on several factors that include the type of drug being developed, whether the drug is based on either a new molecular entity (NME) or it is an incremental modification of an existing product, the likelihood of product failures and government agency (i.e. Food and Drug Agency) approvals, and finally the expected revenues associated with product sales (Congressional Budget Office, 2006). In the next few sections, these topics will be described, as well as their impact on driving the R&D costs and development decisions of new and innovative pharmaceutical products.

2.1 Types of pharmaceutical products in development
2.1.1 Acute illness vs. Chronic disease product research

Until the late 1980s, pharmaceutical companies invested mostly in treating acute illnesses[1], such as common colds, flu, and headaches, as these products are usually cheaper to develop, and can provide a quick return on investment (Congressional Budget Office, 2006). In the past 30 years, the industry's developmental efforts have grown to include therapeutic classes, such as diabetes, cancer, and cardiovascular diseases. These diseases are referred to as chronic illness[2], and tend to develop slowly over time. They can never be cured, and require advanced treatment (Congressional Budget Office, 2006).

The shift in the product development type is associated with the changing population demographics. For example, today in the U.S., there are almost 100 million adults that are 50

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[1] An Acute Illness typically starts suddenly and is short lived. Two common examples are colds and the flu. Acute illnesses, caused by viruses, may go away by themselves, while others can be cured either with antibiotics or other medical treatment (Carlson, 2008).

[2] A Chronic Illness develops slowly over time and lasts a long time. Examples of common chronic illnesses include diabetes, arthritis, congestive heart failure, and Alzheimer's disease. Chronic conditions are typically caused by multiple factors including family history, diet, stress levels, and surrounding environment. Some chronic diseases will never be cured, and require advanced treatment (Carlson, 2008).

years old or older, and every year more than 3.5 million of Americans join this age group (Pirkl, 2009). As a result of the changing demographics, the need for treating chronic conditions has been also increasing. It is estimated that a 1% growth, in the potential market for a category of drugs treating chronic disease, leads to an increase of roughly 4% in the entry of new drugs in that category (Lanjouw & Cockburn, 2001). In addition, growth in sales revenue for these types of drugs has provided the financial opportunities for additional research and development in this area, resulting in an increase in the number of targets in development from 500 to more than 3,000 in recent years (Congressional Budget Office, 2006).

As the pharmaceutical products treating elderly population grows over time, the number of new drugs in therapeutic areas associated with treatment of young people, such as attention deficit hyperactivity disorder (ADHD), juvenile diabetes, pediatric vaccines, has declined in the recent years. The decrease is associated with the continuously declining number of births (in 2009, the U.S. birth rate was 14%), and consequently, lower expected returns on R&D investment related to products for treatment of children and teenagers (Center for Disease Control, 2010).

2.1.2 New molecular entity vs. Incremental modification of an existing product

The cost of R&D typically depends on the type of developmental drugs being pursued by pharmaceutical companies. There are two types of products developed in the pharmaceutical industry: new molecular entity and an incremental modification of an existing product. New molecular entity (NME) is defined as a drug that contains no active molecule previously approved by the FDA. In addition, an NME can also represent a 'me-to-drug', which is still an innovative entity, but works in a similar way to an NME already available for patient use (Congressional Budget Office, 2006).

The other drug category is an incremental modification of an existing product. The product modifications can include changes in drug delivery system, dosing scheme, as well as obtaining additional treatment and indication approvals ('new label'). Most pharmaceutical companies pursue testing of current products to identify opportunities for patent extension for other product uses (Congressional Budget Office, 2006).

On average, it is more costly to develop an NME compared to the incremental modification product, due to a longer time frame for development and testing, a higher probability for a clinical trial failure, and a more restrictive FDA approval system. On average, R&D costs of an NME are between $300 and $500 million higher compared to the product extension research costs (Piturro, 2006; Rawlins, 2004).

2.2 The likelihood of product failures in clinical trials

Research and development of a new pharmaceutical product relies heavily on clinical research and product testing. Product clinical trials are conducted to collect safety and efficacy data on the researched molecule. On average, only 1% of tested products successfully completes the three phases of testing, and can accrue more then $450 millions in R&D expenses (Rawlins, 2004). If a drug successfully passes through clinical trials, it usually is approved by the Food and Drug Agency (FDA) (or a European equivalent) for use in the general population (Pocock, 2004).

Phase I clinical trials are the first stage of molecule testing in patients, and require from 20 to 100 healthy volunteers. The test phase takes about 1 year to 2 years, and includes trials designed to assess safety and tolerability of a potential drug (Pocock, 2004). Once the initial

safety level of the studied drug has been confirmed in Phase I trials, Phase II clinical trials are performed on a larger group of about 20-300 patients to assess how well the drug works. They usually take anywhere from 2 to 4 years. Phase III clinical trials are performed on large patient groups, usually of 300–3,000 patients, depending upon the disease and medical condition studied. These experiments examine how effective the drug is in comparison with current treatments. Due to the size and comparatively long duration, even up to 6 years for chronic illness trials, Phase III trials are the most expensive, time-consuming, and difficult tests to design and successfully run (Pocock, 2004).

2.3 Food and drug agency new drug approvals

Once the new pharmaceutical product positively tests in clinical trials, the next step is to obtain an approval from a federal agency responsible for regulating pharmaceutical products available for patient use. In the U.S., this agency is called the Food and Drug Administration (FDA), while in the European Union it is called the European Medicines Agency (EMEA).

In the U.S., the Food and Drug Administration (FDA) is the federal agency responsible for protecting and promoting public health through the regulation and supervision of food, pharmaceutical, and healthcare products. The group responsible for the pharmaceutical product evaluation is the Center for Drug Evaluation and Research (CDER). The center evaluates new drugs before their availability for patient use, while ensuring that potential drug candidates work correctly, and their health benefits to patients outweigh their known risks. The review process can take up to two and a half years, and the obtained approvals allow the approved product to be sold only with a prescription (FDA, 2010).

On average, one-third of new drugs applications submitted to the FDA are for new molecular entities (NMEs). Most of the rest are for incremental modification of existing drugs, which include the additional health conditions, for which an existing drug can be prescribed. In the past 15 years, the FDA approval rate declined, and the total number of NMEs approved each year fell from 53 in 1996 to 20 in 2005. The drop in approvals might be a result of longer research and development (R&D) cycles, and increased scrutiny of new pharmaceutical products by federal agencies (Congressional Budget Office, 2006).

2.4 Sales, revenue, advertisement, and patent impact on development of new drugs

The current and future R&D expenditures are also associated with the expected sales and revenue trends from launching new drugs to market. Usually, the potential product will not be investigated if it is expected not to recover accrued R&D costs.

2.4.1 Sales and revenues of new drugs

In the past 20 years, the U.S. profit growth has been about the same every year during that time period. The average yearly return on revenue is about 17%. The high and consistent growth places the pharmaceutical industry as the third most profitable of all industries in the U.S., and second best industry to invest in (Fortune 500, 2009). In the past decade, retail sales of prescription drugs has increased by 250% from $72 billion to $250 billion, while the average price of prescriptions has more than doubled from $30 to $68 (Census Bureau, 2008).

The continued profit growth is partially related to the drug exclusivity rights, ranging from 3 years to 20 years after product approval for patient use. Patent protection enables the pharmaceutical companies to recover the costs of research and development through high profit margins for their drugs. When the patent protection for the pharmaceutical product

expires, a generic drug is usually developed and sold by a competing company (Kaufman, 2005).

2.4.2 Managed care and formulary status impact on new drug success

Besides product's exclusivity rights, managed care system and formulary status of the pharmaceutical drugs also impact the future profitability levels of the pharmaceutical industry. Private insurance (i.e. Keystone and Aetna) or public health bodies (i.e. Medicare and Medicaid) can restrict the drug access to patients through the use of formularies and required out-of-pocket expenses (Shih & Sleath, 2004).

Government agencies also impact the prices and availability of pharmaceutical products by passing laws and bills enabling a greater access to healthcare services and drugs. For example, in 2010, the U.S. Congress passed a Health Care Bill, mandating all American citizens to purchase either a privately owned or government provided insurance plan to improve a public access to healthcare services and providers, as well as pharmaceutical products (Tumulty, 2010).

2.4.3 Pharmaceutical brand advertising impact on new drug success

The last factor, impacting sales, revenue, and profitability of pharmaceutical companies, is advertising of pharmaceutical products already available for patient use. In the U.S., pharmaceutical companies spend nearly $19 billion a year on pharmaceutical product promotion to impact sales numbers and profitability margins of their products (Moynihan, 2003).

Product advertising is common in healthcare journals, as well as through more mainstream media routes, such as radio and TV (Moynihan, 2003). Pharmaceutical companies also promote directly to healthcare providers via employing sales representatives. Every year more then $5 billion is spent to support this type of promotion (Robinson, 2003). Finally, with the technological development of computers and handheld devises, such as Smart Phones and iPads, pharmaceutical brand advertising has also moved into the digital arena. Brand specific websites, as well as electronic detailing to physicians have become a popular venue of pharmaceutical promoting in the last 5 years (Howie & Kleczyk, 2011b).

2.5 Summary of the new pharmaceutical product R&D process and associated costs

New pharmaceutical products usually undergo costly and time-consuming testing before receiving government approvals for distribution to patients (Congressional Budget Office, 2006). Only about one percent of researched chemical molecules can withstand the three phases of clinical tests, the scrutiny of the Food and Drug Agency (FDA), and becomes available for patient use. Research and development (R&D) costs have reached more then $800 million, and the product development process takes 12 years to complete. As a result, the selected pharmaceutical molecule must return at least the accrued financial expenditures over its lifecycle (Nelson, 2009).

With the changes in demographic population, as well as enhancements in technology, more emphasis is placed on chronic illness product development, instead of acute illness product development. Although these drugs are more expensive and require more time to develop, they have the opportunity to return not only the invested financial capital, but also increase significantly net profits of the pharmaceutical companies, due to the changing population demographics towards a higher proportion of elderly citizens. With the continued high

spending allocated to advertising of pharmaceutical products, as well as increased use of internet and digital media to inform healthcare providers and patient population of their treatment options, expected sales and revenues can be increased even more. The only barrier in the entire process is the rate of FDA approvals and the formulary status of the new products, which tend to slow down the speed at which products are brought to market, as well as their affordability and access to the patient population.

3. Risk management evaluation methods

Deciding which new products to develop is a major challenge for many pharmaceutical companies with an excess of opportunities, but limited resources. Project prioritization and new product-portfolio selection has long been the domain of the new product arm of the corporation (Blau et al., 2000). Pharmaceutical product development, as any other management task, requires important decisions about the tradeoffs between the available resources, as managers decide which drugs to bring to market (Ogawa & Piller, 2006).

Assuming a fixed research and development budget, the management problem includes deciding which new products to develop, continue to research, terminate, and invest in. In making these decisions, managers face tradeoffs between risks, returns, and time horizons for future payoffs. In theory, such tradeoffs are easily tackled by optimization problems; however, the complexity and uncertainty of the new drug development process can make the solution hard to obtain, and result in employment of less complicated, and therefore, less precise methods of new product identification (Gino & Pisano, 2006).

Currently in the pharmaceutical industry, there is no one recommended method of risk assessment for evaluation of investment opportunities. There are, however, a variety of methods cited that can help mangers in making these decisions. Depending on the needed precision, complexity, and objectives of the analysis, the pharmaceutical managers can choose between different risk management methods to meet their study goals. Due to the importance of selecting the right approach of risk evaluation, and making the right decisions in selecting products for investment, several of the currently utilized methods will be reviewed and evaluated in this part of the chapter (Howie & Kleczyk, 2011a).

There are two types of risk management methods: Net Present Value (NPV) methods and Consumer Theory based approaches. These NPV based methods include Net Present Value of Income analysis, Capacity Constrained NPV approach, and Stochastic Dominance. All of the above methods account for the financial impact of the chosen alternatives (Grabowski & Vernon, 1998; Blau et al., 2000; Smit & Trigeorgis, 2006). The Consumer Theory based approaches do not take into account the financial aspects of the new product development and analyze consumers' preferences for different product alternatives instead. These models usually involve Conjoint Analysis / Discrete Choice models, determining the most preferred product attribute mix (Dakin et al., 2006).

The above methods will be compared to each other on the basis of the inputted information (i.e. R&D expenditures, future drug prices, and probability of FDA approvals, etc.), complexity of the theoretical model (i.e. mathematical simulations, econometric and statistical analyses), as well as the precision and reliability of the theoretical frameworks, in selecting product portfolios with the highest return on investment.

3.1 Net present value (NPV) based risk assessment methods

There are several NPV (otherwise known as a payoff) based methods of the new product development identification process. These approaches include Net Present Value of Income

(NPV) analysis, Capacity Constrained NPV approach, and Stochastic Dominance analysis. All of these methods account for the financial impact of chosen alternatives, but differ by their complexity level, precision, and reliability of product selection (Grabowski & Vernon, 2000; Blau et al., 2000; Smit & Trigeorgis, 2006).

3.1.1 Net present value of income analysis

Until the late 1980s, cash flows, expected returns, and net present value of income were the key variables in the decision-making process of the new drug development and investment. The relationship between investment and cash-flow statements provided pharmaceutical managers with a working framework for resource-allocation decisions (Grabowski & Vernon, 1998). This most widely used framework, called the Net Present Value (NPV) of Income, is described by cash inflows and outflows being discounted back to their present value (PV), and then being summed together. As a result, NPV of Income is the sum of all of following terms:

$$NPV = \sum R_t/(1+i)^t, \tag{1}$$

where t is the time of the cash flow, i is the discount rate defined as the rate of return that could be earned on an investment in the financial markets with similar risk, and R_t is the net cash flow (the amount of cash inflow minus cash outflow) at time t (Khan, 1993). This analysis is performed for every potential product, and the drug with highest NPV of income is usually selected for pharmaceutical investment, and future market availability and sales.

Although the NPV of Income framework provides a very simple and clean approach of investment profitability, as potential product investments can be ranked by their NPV amount, it is still the subject to change, and depends on a range of prices and operating costs associated with the investment and development of new pharmaceutical products. Demand, drug prices, as well as development and operating costs are the source of uncertainty within the framework. Modeling this uncertainty is the primary struggle observed within this approach (Grabowski & Vernon, 1998).

3.1.2 Capacity constrained NPV approach

In the early 1990s, pharmaceutical managers started leveraging a Capacity Constrained NPV approach to evaluate new potential pharmaceutical products. This method includes analysis of capacity planning and development management. This approach not only focuses on the cash flows and NPV framework, but also on the rate of FDA approvals and success rate of clinical trials. As a result, the new additions to the model account for the uncertainty associated with the dynamics of the pharmaceutical market (Rogers et al., 2004).

In 2000, Blau et al. introduced a probabilistic simulation model of a pharmaceutical product development into this framework to prioritize candidate drugs, based on their risk-reward ratios. Their approach captures the complexity of the new pharmaceutical product research and development process, by incorporating probability of clinical trial success into the NPV concept (Blau et al., 2000; Lave et al., 2007). As a result, this model helps select innovative product candidates that provide an acceptable exposure level to risk, while also providing adequate financial returns.

The chosen risk level depends on the risk attitude of the management and stakeholders, as well as the status of the current commercial products and the characteristics of new drug candidates already in the development pipeline. A risk-averse management might prefer

molecules with high technical success ratio and low resource requirement, while a risk-taking management might be willing to push molecules with greater returns at a greater risk (Blau et al., 2000). Most of the R&D drug information is generally available from researchers and engineers developing these products, while sales and marketing executives can provide estimates for expected sales upon marketplace launch (Blau et al., 2000).

A simulation model, using data representing R&D related variables, as well as expected sales and revenues, is usually used to analyze the different investment options, while incorporating the risk-reward analysis and the probability distribution of production success. Once a portfolio of molecules is selected, the next issue is the speed at which these molecules can be pushed through the developmental and production pipeline, without violating the resource constraints, and therefore maximizing the net present value (NPV) of the selected portfolio. This is a 'resource constrained scheduling problem under uncertainty' and involves use of linear mathematical programming for the analysis (Blau et al., 2000). The problem is usually described as maximizing a NPV function subject to multiple constraints (financial and human capital resources):

$$\text{Maximize a NPV function: } F(x_1; x_2; \dots ; x_n) \tag{2}$$

Subject to the following constraints:

$$a_{1,1}x_1 + a_{1,2}x_2 + \dots + a_{1,n}x_n \leq b_1$$

$$a_{2,1}x_1 + a_{2,2}x_2 + \dots + a_{2,n}x_n \leq b_2$$

$$a_{3,1}x_1 + a_{3,2}x_3 + \dots + a_{3,n}x_n \leq b_3$$

$$\dots$$

$$a_{n,1}x_1 + a_{n,2}x_2 + \dots + a_{n,n}x_n \leq b_n, \tag{3}$$

where $(x_1 \dots x_n)$ define the inputs for the NPV optimization, and b_n represents the constraint values. Constraints are usually defined as human and financial capital, time frame of product development, expected sales and revenues, and any other important to the management variables that should be controlled for when deciding, which potential molecules to invest in and bring to market (Champ et al., 2003).

The constrained problems can range from a single project optimization with no resource constraints (Schmidt & Grossmann, 1996) to a more complicated problems defined by sequencing and scheduling of multiple testing tasks under resource constraints for a fixed set of products (Jain & Grossmann, 1999). To estimate the latter approach, a mixed-integer linear programming (MILP) model is usually utilized, and maximum resource availability is employed to enforce resource constraints (Honkomp, 1998). In 2003, Submarinian et al. even further extended the framework by formulating a simulation-optimization problem that combines mathematical programming with discrete choice simulation to also account for planning and scheduling uncertainty.

Although these models account for the high level of complexity regarding new product development, they tend to be time-consuming, and are not easily executable by pharmaceutical managers. Consequently, not many pharmaceutical executives actively use this type of product portfolio optimization methodology, and tend to turn to easier and more practical ways of deciding, which products to develop and bring to market (Baker, 2002).

3.1.3 Stochastic dominance method

As the Capacity Constrained NPV approach tends to be time-consuming, and rather difficult to implement by pharmaceutical management, Kleczyk (2008) applied a Stochastic Dominance methodology to eliminate the complexity in the decision of new chemical molecule investment. Stochastic Dominance evaluates the pharmaceutical product development process and chemical molecule prioritization via accounting for not only the uncertainty in drug prices, but also for development and operating costs related to product research and development (R&D). In addition, it is an intuitive and easily implemented tool that is uniquely suited to the objectives of new product development selection process (Kleczyk, 2008).

Stochastic Dominance is usually employed in the analysis of financial portfolio optimization, which attempts to maximize financial portfolio's expected return for a given amount of risk, or equivalently to minimize risk for a given level of expected return, by carefully choosing the appropriate investment choices (Edwin et. al, 1997). The basis for this method is not only how each potential product performs on their own (i.e. NPV), but also how each potential product changes its expected revenues relative to other products' changes in their expected revenues too (Edwin et al, 1997). The analysis includes trading off risk and expected returns. For example, for a given amount of risk, the method describes how to select a potential product with the highest possible expected return; and for a given expected return, how to select a drug with the lowest possible risk (Markowitz, 1952).

The framework makes many assumptions about pharmaceutical managers and drug companies, including the use of Normal Distribution function[3] to model expected returns, the utility maximization framework[4], unlimited credit availability to the pharmaceutical companies, and no transaction costs or federal and state taxes. Unfortunately, in reality, some of these assumptions, such as no transaction fees and unlimited credit amount available for lending, are relaxed to better represent the current environment, and provide realistic estimates of potential chemical molecules' payoffs. As a result, more complex versions of the financial portfolio model can take into account a more sophisticated view of the world, such as one with non-normal distributions and taxes (Markowitz, 1959; Shleifer, 2000).

There are two types of Stochastic Dominance methods that can be employed in the analysis of potential pharmaceutical products for market use: First and Second Degree Stochastic Dominance. The First Degree Stochastic Dominance (FSD) informs which potential product's NPV distribution dominates all other choices. For example, if a decision maker prefers NPV distribution for molecule 1, which is mathematically presented as [$f(x_i)$], to NPV distribution for molecule 2, which is mathematically presented as [$g(x_j)$], then $f(x_i)$ dominates $g(x_j)$ by FSD:

$$f(x_i) \geq g(x_j) \text{ by FSD.} \tag{4}$$

As a result, the cumulative probability distribution function[5] of NPV for molecule 1, [$F(x_i)$], is less or equal to cumulative probability distribution function of NPV for molecule 2, [$G(x_j)$], (Kleczyk, 2008):

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[3] Normal Distribution Function describes real-valued random variables that tend to cluster around a single mean value (Varian, 1992).
[4] The Utility Maximization Framework represents maximization of a utility function based on a specified pharmaceutical company's financial resource constraint requirement (Varian, 1992).
[5] Cumulative Probability Distribution Function represents the probability that a real-valued random variable X with a given probability distribution will be found at a value less than or equal to x (Varian, 1992).

$$F(x_i) \leq G(x_j). \tag{5}$$

Furthermore, when molecule 1 dominates molecule 2, the expected value of the payoff for molecule 1, [NPVf(x_i)], will be greater than the expected value of the payoff for molecule 2, [NPV(g(x_j))] (Kleczyk, 2008):

$$NPV(f(x_i)) \geq NPV(g(x_j)). \tag{6}$$

The other commonly used type of Stochastic Dominance is the Second Degree Stochastic Dominance (SSD). For two chemical molecules 1 and 2, molecule 1 has second-order stochastic dominance over product 2, if the former is more predictable, involves less risk, and has at least as high of a mean. All risk-averse expected-utility maximizers prefer a second-order stochastically dominant potential product to a dominated product (Kleczyk, 2008). In terms of cumulative probability distribution functions: [F(x_i)] of NPV and [G(x_j)] of NPV, chemical molecule 1 is second-order stochastically dominant over molecule 2, if and only if, the area under [F(x_i)] of NPV is less than or equal to that under [G(x_j)] for all real numbers [R] x, with strict inequality at some x:

$$\int_{-\infty}^{x} F(x_i) \leq \int_{-\infty}^{x} G(x_j), \text{ for } x \in R. \tag{7}$$

The analysis typically assumes that all managers are risk-averse, and therefore, no investor would choose a potential molecule that is second-order stochastically dominated by some other molecule (Kleczyk, 2008).

The inputs needed to perform this type of analysis are similar to those used in the NPV of Income and Capacity Constrained approaches, and include the excepted sales, revenues, potential product sales price point, operating costs, taxes, as well as the probability of passing the clinical trial and being approved by the FDA. The risk level can be adjusted depending on the management risk aversion level and product portfolio in the company's pipeline. The above analyses are usually conducted using Monte Carlo simulation and sensitivity analysis to indentify, which potential products are worth of pharmaceutical companies to invest in. The final stage of the analysis involves comparing between NPV values for each molecule, and choosing a molecule with the highest NPV, as a recommendation for pharmaceutical company's investment. The model can be extended to incorporate a linear programming approach, in order to add workforce and planning constraints into the model. The extension, however, implies that the analysis may again morph into a complex and time-consuming framework that might be difficult for pharmaceutical executives to execute on (Kleczyk, 2008).

3.1.4 Summary of the NPV based risk assessment methods

In summary, the basic NPV of Income analysis and Stochastic Dominance are simple methods to implement by pharmaceutical management, when prioritizing portfolio of chemical molecules. The NPV framework has been used for more than 80 years in the decision of resource allocation by estimating the net present value of the expected future revenues and expenses. Stochastic Dominance allows for executing against the financial and strategic company goals, while controlling for the important factors of the FDA approvals rate, the clinical trial success rate, expected sales and revenues, operating costs, and the tax base. Both of the above approaches allow for comparing NPVs of all potential products, and choosing the molecule with the highest expected NPV.

The items not accounted for in these two approaches are the production capacity constraints that include production scheduling, human capital availability, and currently produced and available for patient use drugs. The Capacity Constrained NPV approach accounts for these constraints by including them in the maximization of the NPV function. Both of the Stochastic Dominance and NPV methods can be extended to include the additional assumptions; however, the optimization process may become more complicated, time-consuming, and therefore might be not easily understood by pharmaceutical executives.

3.2 Consumer theory based risk assessment methods

There are also other risk management methods that help in deciding, which new chemical molecules to invest in and bring to market. They do not necessarily take into account the financial aspects of new product development, but rather analyze healthcare providers' preferences for different potential product alternatives. These models are usually based on the Consumer Theory, and involve employment of Conjoint Analysis (CA) (otherwise known as Discrete Choice Analysis) models, determining the most preferred new product attribute mix (Dakin et al., 2006).

The Conjoint Analysis (CA) framework has been applied successfully to several marketing decisions, including designing of new products, targeting market selections, pricing of new products, and studying competitive reactions. One of the advantages of CA is its ability to answer various 'what if' questions when employed for analysis of hypothetical and /or real choice alternatives (Rao et al., 2008). This approach, however, can be very lengthy and complicated, due to the multiple steps required to design and complete the research. The required steps include, but are not limited to: a development of survey instruments, development of product stimuli based on a number of potential pharmaceutical product attributes in consideration, interviews of healthcare professionals and patients, an econometric and statistical analysis, mathematical simulations, and employment of the estimates in tackling any managerial problems, such as new product forecasting.

The Conjoint Analysis (CA) is a stated-preference study that uses a survey instrument, as well as an experimental design to elicit pharmaceutical costumers' preferences for pharmaceutical goods. Pharmaceutical customers are usually represented by healthcare providers and patients. They participate in market research studies to provide their responses to survey questions, regarding alternatives of pharmaceutical products, varying in attribute levels to inform their preferences for multiple states of a potential drug. The introduction of the expected drug price and / or formulary status of the potential product, as an attribute, extends the application of the method into welfare analysis. Based on the preference function knowledge, simulation and optimization algorithms aid the process of determining the preference level for each product-attribute combination (Champ et al., 2003; Rao, 2007).

3.2.1 Theoretical framework: random utility maximization theory

The theoretical model, guiding the CA preference elicitation methodology, is the Random Utility Maximization (RUM). RUM is based on consumers' (i.e. healthcare providers and patients) choices from a set of competing alternatives of potential pharmaceutical products. Each survey respondent chooses the most preferred alternative from a set of drug alternatives, while at the same time making tradeoffs between attributes of each alternative. Each respondent is trying to select an alternative that would provide them with the highest satisfaction, otherwise known as utility (Champ et al., 2003).

The basic problem of utility or preference maximization represents the set of all pharmaceutical chemicals (alternatives) satisfying financial resource constraints. The financial constraint can include the financial restrictions of pharmaceutical companies, healthcare providers, and patients. The company's primary end-users' (i.e. physicians, nurses, patients, etc.) are assumed to have preferences for each potential new product within a developmental product set X. As a result, the preference maximization problem is defined as maximization of a utility function based on a specified financial resource constraint requirement (Varian, 1992):

$$\text{Maximize utility function: } u(x) \tag{8}$$

$$\text{Subject to: } px \leq m, \text{ where } x \text{ is in } X, \tag{9}$$

where u(x) represents the utility function, and px ≤ m represents the financial resource constraint, with m being the fixed amount of money available to a company for product R&D, as well as healthcare providers' and patients' available funds for medical and healthcare needs (Champ et al., 2003).

3.2.2 Survey development process

In order to forecast a product potential, a survey instrument has to be developed first. Healthcare providers are usually invited to participate in questionnaires created to elicit their preferences and attitudes regarding a set of potential products. The survey format varies from a paper version to an internet based exposure. The collected data is then analyzed via employing econometric and statistical tools. A Conjoint Analysis depends on the design of stimuli, which describes potential pharmaceutical product profiles. Employment of experimental design allows generating a set of potential drug profiles for review when surveying respondents (Champ et al., 2003; Rao, 2007).

The survey information collected from healthcare providers include preference rating data of selected product alternatives, ranking of product profiles, and choosing the preferred product over another option. In case of preference rating surveys, ratings are collected from respondents using attribute based pharmaceutical product profiles. The rating scale questions appeal to many researchers, due to the simplicity of the econometric analysis, and the ease with which respondents answer rating questions. The rating scales values can rage from 1 thru 5 values, where 1 is the least preferred, and 5 is the most preferred, to 1 thru 9 values, implying the same preference scheme, but a larger response variability (Champ et al., 2003).

In the choice-based surveys, respondents rank a set of product profiles from most to least preferred. For example, a preferred hypertension product is selected from among multiple alternatives, described by set of product attributes, such as product efficacy and safety (Champ et al., 2003). The framework assumes the most preferred profile to be chosen first from the choice set, followed by the second ranked alternative chosen from the remaining choice set, and so forth. The participants might get fatigued, while proceeding through the sequence of choices, which in turn might result in unreliable analysis, and imprecise potential product forecast (Champ et al., 2003).

In addition to selecting their preferred pharmaceutical product, healthcare providers are asked to present their anticipated use of the chosen alternatives when it becomes available on the market, as well as indentify the change in the use of the current treatment options, as

a result of the new entrant. Based on their responses, market share forecast for new products are developed to help in the decision-making process. The forecasts might vary from one single data point to monthly 1 to 5 year forecasts, depending on the need and confidence in the product potential predication (Howie & Kleczyk, 2011a).

3.2.3 Econometric and statistical analysis

The most commonly used econometric and statistical models, employed in estimation of healthcare providers' preferences and attitudes for new products, include logit and probit models. Depending on the type of data collected, either binary or multinomial logit and probit models are employed. Binary choice models relate to either selecting or not selecting a presented product alternative; while multinomial models relate to choosing a product alternative from a provided set (ranking or rating exercise). Multinomial probit and logit models are more often selected for the analysis of choosing the right product attribute combination, as pharmaceutical managers are mostly faced with evaluation of multiple chemical molecule alternatives at one time.

Both probit and logit models are based on the utility maximization framework of a healthcare provider choosing a particular pharmaceutical alternative over another. As a result, the respondent also maximizes the probability of a potential product being chosen from a presented set of alternatives. The probability specification is expressed as a function of observed variables, relating to the pharmaceutical product alternatives and the respondent. In its general form, the probability [P_{ni}] that a person n chooses a molecule alternative i is expressed as follows:

$$P_{ni} = P(x_{ni}, x_{nj}; s_n, \beta) \text{ for } j \neq i, \tag{10}$$

where x_{ni} is a vector of attributes of molecule i faced by a healthcare provider n, x_{nj} is a vector of attributes of the other alternatives (other than i) faced by person n, s_n is a vector of characteristics of person n, and β is a set of parameters that relate variables to probabilities, which are estimated statistically. A vector of respondent characteristics includes the type of treatment expertise, age, gender, geographic area of practice, and healthcare provider's function at the medical office (i.e. nurse, physician, etc).

Today's econometric and statistical software include both of the above models in their analysis menu, so the preferred pharmaceutical molecule evaluation is easily executable. The econometric model estimates the coefficients for each product attributes [β], which then allow identifying the preferred product alternative with the greatest market potential. Mathematical optimizations and simulations are usually employed to compute forecasts for the different product alternatives and attribute combinations (Champ et al., 2003).

3.2.4 Product potential analysis and forecasting

The described econometric and statistical models allow indentifying the preferred chemical molecule for research and development. In addition, the results are used to simulate and compute market potential of each alternative, in terms of product market share, as well as expected sales and revenues. The market potential forecast can span from just one data point at the end of a defined time period to monthly predictions, spanning from 1 year to even to up to 5 years after product availability for patient use. These data points are analyzed by pharmaceutical mangers to inform their investment decisions into new chemical molecules. Alternatives with the greatest market potential are usually considered for the R&D investment (Champ et al., 2003; Howie & Kleczyk, 2011a).

While surveying healthcare providers, to learn their preferred treatment options, is the appropriate approach to learning the new product potential, the problem with this approach is respondents' ability to correctly identify the 'future drug use,' once approved for patient use. These product 'future use' estimates can be unreliable and overstate the future prescribing behavior of the pharmaceutical drugs. As a result, the overstatement leads to an unreliable forecast for the product potential (Howie & Kleczyk, 2011a).

While experience may provide some guidance, as to how to correct for this overstatement, every product is unique, and the appropriate 'correction factor' is itself highly unreliable. Depending on the brand and treatment categories, the estimated product market shares are adjusted without employing a methodologically sound approach. For example, some pharmaceutical managers employ a rule of lowering these estimates by half and then by third to adjust for physician drug future prescribing overestimation (Howie & Kleczyk, 2011a).

In 2011, Howie and Kleczyk analyzed healthcare provider level data for 75 product uptakes after their market availability combined with respondents' pre-launch stated product uptake series. Based on their analysis, they developed a unique 'correction factor' for each service provider and each drug profile. Consequently, they determined the various levels of each drug's expected performance. The 'correction factor' is derived based on individual respondents' answers to questions of product use and thoughts about the product profile. In addition, questions regarding the speed of new product adoption, perceptions of the product over the current product treatments, level of knowledge about the new product, and intended use (in either first or second line of therapy) are also employed to adjust each provider's estimates. Their new approach of product potential estimation has been shown to be highly predictive of the actual future prescribing behavior of each healthcare provider. Their unique approach increases the forecast accuracy from R-square[6] of 0.233 to 0.796 (Howie & Kleczyk, 2011a), which can further help inform decision-making process when evaluating several chemical molecules for investment.

3.2.5 Summary of the consumer theory based risk assessment methods

As presented above, the Consumer Theory based framework is yet another way of managing risk when deciding which new product to develop. This approach can be based on healthcare providers' preferences (as well as patients, pharmacists, and other healthcare decision makers, depending on the study objective) and their perceived needs for new patient treatment options. Based on their potential product preferences and predicted 'future use' upon product availability, pharmaceutical managers are able to make informed investment choices of new chemical molecules. The output allows for analysis of future sales and revenues, and also for analyzing whether the proposed product meets the current market needs (product attribute evaluation). In addition, the improvements to the product market potential forecast, introduced by Howie and Kleczyk (2011a), allow pharmaceutical mangers to make even more informed decisions, regarding future product investment, due to increased reliability and precision of the data analysis.

The above approach can also be inputted, as expected product sales / revenues, into the NPV based approaches. The combined analysis effort increases managements' confidence in the potential product forecast results, as well as ensures that all aspects, related to product development, such as R&D costs, as well as clinical trials success and FDA approvals rates,

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[6] R-square refers to the fraction of variance explained by a model (Champ et al., 2003).

are accounted for in the process of choosing the new chemical molecule. Consequently, the management ensures that investment in the selected product profile will return pharmaceutical company the financial capital expenses accrued during the drug research and development process.

3.3 Comparison of risk management methods

As discussed in the above sections, there are several risk management methods that differ from each other with regards to inputs, complexity, and the precision of product potential evaluation. As there is no one recommended approach for risk assessment in the pharmaceutical industry, it is important to understand how these methods differ and which situations should be used in. This section compares the NPV and Consumer Theory approaches based on the following criteria: 1) theoretical model; 2) inputs (i.e. R&D expenditures, future drug prices, and probability of FDA approvals, etc.); 3) analysis (i.e. mathematical simulations, econometric and statistical analyses); 4) complexity of the framework; 5) the recommended use in the product selection process. The presented analysis can assist pharmaceutical managers in deciding on the appropriate risk management method for their product assessment process.

As shown in Table 1 below, the Net Present Value of Income analysis is the simplest method of risk assessment in the pharmaceutical industry. It is based on the investigation of cash flows, requires fewest inputs, and is simple to compute, as well as to employ into the decision-making process. For example, this approach can be used for preliminary evaluation of the pharmaceutical products in development to indentify the potential candidates for investment, while requiring only limited information on future costs and revenues. In comparison to other methods, however, the NPV of Income analysis is the least reliable and precise in predicting the market potential of an evaluated product, and therefore recommending products for R&D (Grabowski & Vernon, 1998).

When more precise forecast is required, but a moderately complicated approach is preferred, Stochastic Dominance is usually employed. As shown in Table 1, this framework is still somewhat simple, but provides more reliable investment recommendations. The required inputs include cash flows and rate of return, as well as the FDA approvals rate, clinical trial success rate, and financial resource information (i.e. tax rate, operating costs, etc). These additional variables improve the precision of the analysis, and help better guide the decision-making process (Kleczyk, 2008).

When precision and reliability of the forecast are an issue, as well as capacity constraints (i.e. financial, workload, resource planning) are an important input into the analysis, the Capacity Constrained NPV approach is recommended. This method provides highly reliable and precise product return on investment prediction, due to accounting for the many variables important in the development, production, and sales of pharmaceutical products. As mentioned previously, however, the main problem, with the Capacity Constrained NPV, is the complexity level of the analysis, as it requires a high level of linear mathematical programming knowledge, as well as utilization of mathematical optimization and simulation. The method is recommended for use after the initial assessment of the potential products for investment is completed, in order to aid resource allocation and management during the product research and development process (Blau et al., 2000).

The last approach described in Table 1, the Conjoint Analysis method, can be also somewhat complex and time-consuming to employ, due to the multiple steps required to execute this

framework successfully (i.e. survey development, healthcare providers study recruitment, analysis, etc). Differently from the former methods, the Conjoint Analysis (CA) is based on the Consumer Theory instead of NPV, and analyzes end-users preferences for potential products. It is usually utilized by marketing mangers to help in forecasting product market potential (i.e. market share, revenue, sales), deciding order of product release to the market, as well as in the development of marketing strategies (i.e. market positioning, defining / confirming clinical end-point, etc). As it can be a reliable and precise forecasting tool, it is also employed as an input into the NPV based approaches to even further improve these methods' precision and reliability. Differently from the NPV based methods, the required inputs include product profile information and development of a survey instrument. To account for the financial aspect of the analysis, the expected drug prices and the formulary status of the product might be included. The mathematical analysis can become somewhat complex, and usually involves use of econometric and statistical tools, such as regression analysis, as well as mathematical optimization and simulation, to help identify the best product / product profile / attribute mix that will also result in the highest expected return on investment (Champ et al., 2003).

As the different methods of risk management vary with regards to the inputs, analysis, complexity of the framework, and the recommended use in the product selection process, pharmaceutical managers should consider the following criteria, when choosing the right approach for evaluation of potential pharmaceutical products: 1) the stage of the product development; 2) the preferred precision of the output; 3) the complicity of the model; and finally 4) the objective of the study. If quick and simple study of product assessment is needed, either the NPV of Income or Stochastic Dominance analysis should be an adequate tool to complete the task. If human and financial capital constraints are considered in the investment evaluation, then the Capacity Constrained NPV would be the preferred model. Finally, when product market share forecast still needs to be defined and / or preferred product attributes of a potential investment confirmed, the Consumer Theory based approach might be the best choice to pursue.

4. Concluding remarks

In this chapter, the research and development (R&D) process of new drugs, as well as methods of evaluating potential risks related to this procedure were discussed. As presented, new pharmaceutical products usually undergo costly and time-consuming testing, before receiving government approvals for distribution to patients. At the end, only about one percent of researched chemical molecules withstands the clinical trials, the scrutiny of the Food and Drug Agency (FDA), and becomes available for patient use. The costs associated with the R&D process has reached more then $800 million in recent years, and they are continually increasing. The average time length of product development is now 12 years, and will increase to even a longer time frame, due to the shift from the acute illness product development to chronic illness product development (Nelson, 2009). The shift is associated with a greater percent of elderly population, which is more prone to develop chronic diseases. Development of drugs that help either slow down or cure these types of diseases requires a longer time frame of clinical trials, as well as greater amounts of financial investments. Although these pharmaceutical products are more expensive and require more time to research and develop, they may return not only the invested financial capital, but also increase significantly net profits of pharmaceutical companies.

	Net Present Value of Income	Capacity Constrained NPV	Stochastic Dominance	Conjoint Analysis
Theoretical Framework	Net Present Value	Net Present Value	Net Present Value	Consumer Theory
Inputs	Expected R&D expenses; expected revenues; rate of return	Expected R&D expenses; expected revenues; rate of return; company financial information (i.e. taxes base; operating costs; financial resource constraints); FDA approval rate; clinical trial success rate; workload & planning constraints; currently manufactured product portfolio	Expected R&D expenses; expected revenues; rate of return; company financial information (i.e. taxes base; operating costs; financial resource constraints); FDA approval rate; clinical trial success rate;	Product attributes & clinical end-points; expected price point & expected formulary status *Survey instrument development
Analysis	Simple mathematical computation	Linear mathematical programming; mathematical optimization & simulation	Mathematical optimization & simulation; sensitivity analysis	Regression analysis (probit / logit); mathematical simulation & optimization
Complexity	Low	High	Moderate	Moderately High
Precision / Reliability	Low level of precision & reliability	High level of precision & reliability	Moderate level of precision & reliability	High level of precision & reliability
Recommended Use	Quick / preliminary product investment selection	Selection of highest potential product that meets all pre-specified criteria and constraints	Selection of highest potential product with financial, clinical trials, and FDA approvals constraints	Forecast of product sales / market potential; development of marketing / product positioning strategies; an input into the NPV based approaches (expected sales)

Table 1. Comparison of Risk Management Methods

The promotional efforts of pharmaceutical products also impact the risk management and future investment returns of the new drugs. With the continued high spending allocated to the advertising of these products (Direct-to-Consumer advertising and personal promotion to healthcare providers), as well as increased use of internet and digital media to inform healthcare providers and patient population of their treatment options, the expected sales and revenues can be increased even more in the near future. The increased financial revenues provide return on the past R&D investments, but also develop a stream of financial capital for future developmental projects.

The only, but quite a large, barrier in the entire product research and development process is the rate of FDA approvals and the managed care and / or formulary status of the new products. These agencies tend to slow down the speed at which products are brought to the market, as well as impact their affordability and access to the patient population. The FDA standards for product approvals are increasingly more stringent, while new drugs receive the lowest formulary status (a highest copay amount to be paid by patients) when launched to market for patient use, in comparison to more mature brands and generic competitors. To overcome the access and affordability issues, many pharmaceutical companies are assisting patients with their out-of-pocket costs to lower the financial burden, and to increase their product use. However, with an expected increase in the number of generic products on the market, even if this strategy might not benefit pharmaceutical companies in the long run (Alazraki, 2011).

In order to ensure recovering the high R&D costs invested by pharmaceutical companies, choosing the appropriate products for research and development requires important decisions about the tradeoffs between the available resources, as well as risk levels, returns, and time horizons for future payoffs. In theory, such tradeoffs are easily tackled by optimization problems; however, as discussed in this chapter, the complexity and uncertainty of the new drug development processes can make the solution hard to obtain, and might require employment of less complicated, and therefore, less precise methods of new product identification (Gino & Pisano, 2006).

Most risk management methods employed in the pharmaceutical industry include two types of methods: NPV and Consumer Theory based, to solve the new product research and development problem. As these method types differ on the basis of the analysis, inputs, precision and reliability of the approaches, as well as recommendations, knowing and understanding the differences between the various theoretical frameworks can help in selecting the right evaluation process of product selection and investment.

However, it is also important to know that each approach investigates a different angle of the risk management problem, and multiple analyses are usually recommended to ensure making informed investment decisions. Starting with a quick and simple NPV of Income analysis of potential product, and extending it to Stochastic Dominance, followed by the Capacity Constrained NPV approach for increased forecast precision, should help in predicting the success probability of brining the product to market, and the required resources for development and production. The Consumer Theory based methods can help further define the best product attributes, product positioning, and estimate the true product uptake when available for patient use. Knowing possible challenges, as well as benefits of the product of choice can help managers to avoid potential product failures, and recommend a product or set of products that will maximize investment returns for the pharmaceutical company in the future. In addition, it is recommended not to limit the risk

management analysis only to performing the computation internally, but rather to inquire for a third party / expert opinion. Having an outside expert, provide an unbiased opinion on the product investment options, can only strengthen the decision-making process, and help guide successful investment choice for the company.

In conclusion, the process of new pharmaceutical product research and development is complicated and requires a large financial and time investment. Since the financial and time costs are extensive, having the right tools in making investment decisions is vital in ensuring successful product selection. Currently available methods of risk management can help define the potential investment opportunities, and guide the selection process. These methods will grow to be even more important, as the R&D resources become in even more scares, and the product development costs increase.

5. Acknowledgment

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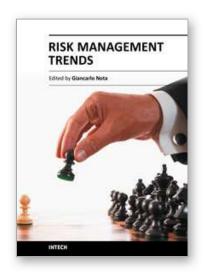Fortune 500. 2009. Fortune 500 Annual Ranking of America's Best Corporations. Accessed: January 2011, Available Online from: http://money.cnn.com/magazines/fortune/fortune500/2009/performers/industries/profits/ .

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Risk Management Trends

Edited by Prof. Giancarlo Nota

In many human activities risk is unavoidable. It pervades our life and can have a negative impact on individual, business and social levels. Luckily, risk can be assessed and we can cope with it through appropriate management methodologies. The book Risk Management Trends offers to both, researchers and practitioners, new ideas, experiences and research that can be used either to better understand risks in a rapidly changing world or to implement a risk management program in many fields. With contributions from researchers and practitioners, Risk Management Trends will empower the reader with the state of the art knowledge necessary to understand and manage risks in the fields of enterprise management, medicine, insurance and safety.

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