MAPPING AND ANALYSIS OF THE DRUG DISCOVERY AND DEVELOPMENT PROCESS AND THE UNDERLYING UNCERTAINTIES AND THE PROBLEM OF TIME TO MARKET

by

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Abstract

The pharmaceutical industry is one of the most important and fast growing sectors in the world. By the end of year 2010, the global pharmaceutical industry is estimated to grow to $842 billion with a compounded annual growth rate of 6.9% over the period of 5 years. The industry is technologically sophisticated and characterised by highly risky and lengthy processes, intense competition and large research and development expenditures. The key process of the pharmaceutical industry constitutes of the drug discovery and development process which takes nearly 10 to 15 years for development from the earliest stage in discovery to the time it is made available for use to the patients and costs an average of $800 million.

Despite successfully translating discoveries into successful products, the process is plagued by increasing number of uncertainties which leads to an increased developmental time cycles. This delays the product's entry into the market thereby causing heavy losses to the pharmaceutical industry. This research presents techniques that enable pharmaceutical firms to reduce uncertainties as well as tackle the problem of time to market with a view to improving the product quality thereby increasing their profits significantly.

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Chapter 1

Introduction

The pharmaceutical industry is one of the most important and fast growing sectors in the world. The industry is technologically sophisticated and characterised by highly risky and lengthy processes, intense competition and large research and development expenditures. It is a capital intensive industry that is regulated by stringent regulatory regulations. By the end of year 2010, the global pharmaceutical industry is estimated to grow to $842 billion with a compounded annual growth rate of 6.9% over the next 5 years (Flatworld Solutions, 2010). The pharmaceutical industry draws such a large amount of growth rate owing to the blockbuster drugs that the pharmaceutical drug development companies produce. Pharmaceutical new product development takes place in order to meet the unmet medical needs that prevail in many disease areas.

The key process of the pharmaceutical industry constitutes of the drug discovery and development process. This process takes an average of 10 to 15 years from the earliest stage of discovery to the time it is made available for use to the patients. Besides being a time consuming process, the drug development process is also very costly. It takes an average of $800 million for a pharmaceutical company to develop a drug. The drug development process includes the identification, synthesis and screening of the compound for therapeutic efficacy. Once a positive result for the same has been established the compound moves into the preclinical stage. The compound is tested *in vivo* (in living organisms) and *in vitro* (in cells in the test tube). The primary goal of this stage is to test the efficacy and safety of the drug before it can further move onto the clinical trial stage. The clinical trial stage of the drug development process is divided into 3 phases where the drug is tested on human subjects to determine its safety and efficacy. The toxicity of the drug is reviewed and if desired effects in terms of safety and efficacy are established the new drug application is submitted to the Food and Drug Association for approval.

Despite successfully translating discoveries into successful products, the drug development process is plagued by increasing number of uncertainties which increases the development time of products thus delaying the product's entry into the market causing heavy losses to the pharmaceutical industry. There are numerous uncertainties in terms of cost, duration, resource requirements, technical uncertainty (outcome of clinical trials) and market uncertainty (revenue from sales) that the pharmaceutical drug development process faces. Supply chain congestion due to these uncertainties also leads to delays in production and new product introduction thereby affecting the market share of the products. The combination of the above mentioned factors hinders the growth of the pharmaceutical drug development industry.

1.1 Research Objectives

The pharmaceutical drug development is an intricate process involving various phases that need to be understood. Those phases also house various uncertainties that result in delays in launching the product effectively thereby leading to losses. For the purpose of this study, the researcher would be focussing on the following:

1) To understand and map the Drug Discovery and Development Process – Understand how a pharmaceutical product is produced; identify all the stages; from the Pre discovery phase involving target identification, target validation, lead identification and lead optimisation to the Development phase involving the Pre clinical phase and Clinical Phase. This would also include the New Drug Application and the Regulatory approval stage.

2) Identify the sources for reducing Uncertainty in the Drug Discovery and Development Process – One of the features that restrict the smooth functioning of the Drug Discovery process is 'uncertainty' about the drug in trail. If the drug that is being tested fails the clinical trials phase, all the investment and effort towards drug development is lost, but if it passes all the trials, it enters the marketplace and benefits the company by providing profits that are significantly larger than the development costs.

3) Identify the sources for reducing Lead Time in the Drug Discovery and Development Process – Drug development is a lengthy process ranging from 10 to 15 years costing the companies millions of dollars. Thus identification of sources for reduction in lead time and appropriate application of those steps would effectively help in launching the product quicker than usual into the market.

1.2 Structure of the Report

This dissertation has five main chapters that provide extensive information around the subject.

Chapter 2 is the Literature Review, which discusses in detail the pharmaceutical drug discovery and development process by highlighting the main findings of various authors around the subject. Besides providing detailed description of the drug discovery and development process, this chapter provides a comprehensive review on the types of inherent risks and uncertainties along with the time delays that prevent the drugs from reaching the market on time.

Chapter 3 is Research Methodology. This chapter provides details on the two different types of research methods – quantitative and qualitative methods and also presents the rationale for choosing the qualitative method. In addition to furnishing details on the research design and sources from which the data was collected and analysed, the chapter also describes the limitations to research faced by the researcher.

Chapter 4, Research and Analysis, identifies the various sources for reducing both uncertainties and time to market. For effectively reducing uncertainties, it provides a detailed analysis on the global pharmaceutical scenario leading up to the reasons for outsourcing. In addition, it also explains the factors for outsourcing research and development and manufacturing activities along with the advantages and disadvantages for the same. For reducing time to market for the product, the chapter discusses mechanisms like outsourcing, effective documentation, knowledge integration and concurrent engineering processes.

Chapter 5 is Finding and Discussions, where the present findings in research regarding the sources for reducing uncertainties and time to market will be analysed and discussed. This chapter also throws light on how the various uncertainties and the time to market problem can be tackled with the help of outsourcing and time to market mechanisms.

Chapter 6 concludes the research by providing a summary of the sources for reducing the various uncertainties and time to market in the drug discovery and development process. It also highlights areas for future research in the respective area.

Chapter 2

Literature Review

"The pharmaceutical industry can be defined as a complex of processes, operations and organisations involved in the discovery, development and manufacture of drugs and medications" (Shah, 2004, p. 929).

The industry faces unprecedented challenges and opportunities in terms of research and development. Today the pharmaceutical firms are acutely aware that in many disease areas there is immense unmet medical need (Törnell & Snaith, 2002) and while working towards filling the void, they must not only demonstrate the safety and effectiveness of their drugs but also prove that their drugs provide therapeutic or cost advantages as well (Kaitin & Dimasi, 2000).

The pharmaceutical value chain constitutes of

- The Drug Discovery and Drug Development Activity: to identify promising pharmacological candidates
- Clinical Trials : to demonstrate the safety and effectiveness of those particular drugs in human subjects
- Manufacturing : to mass produce the approved drugs (Wadhwa et al, 2008)

The sequence of such an activity is provided in Figure. 1

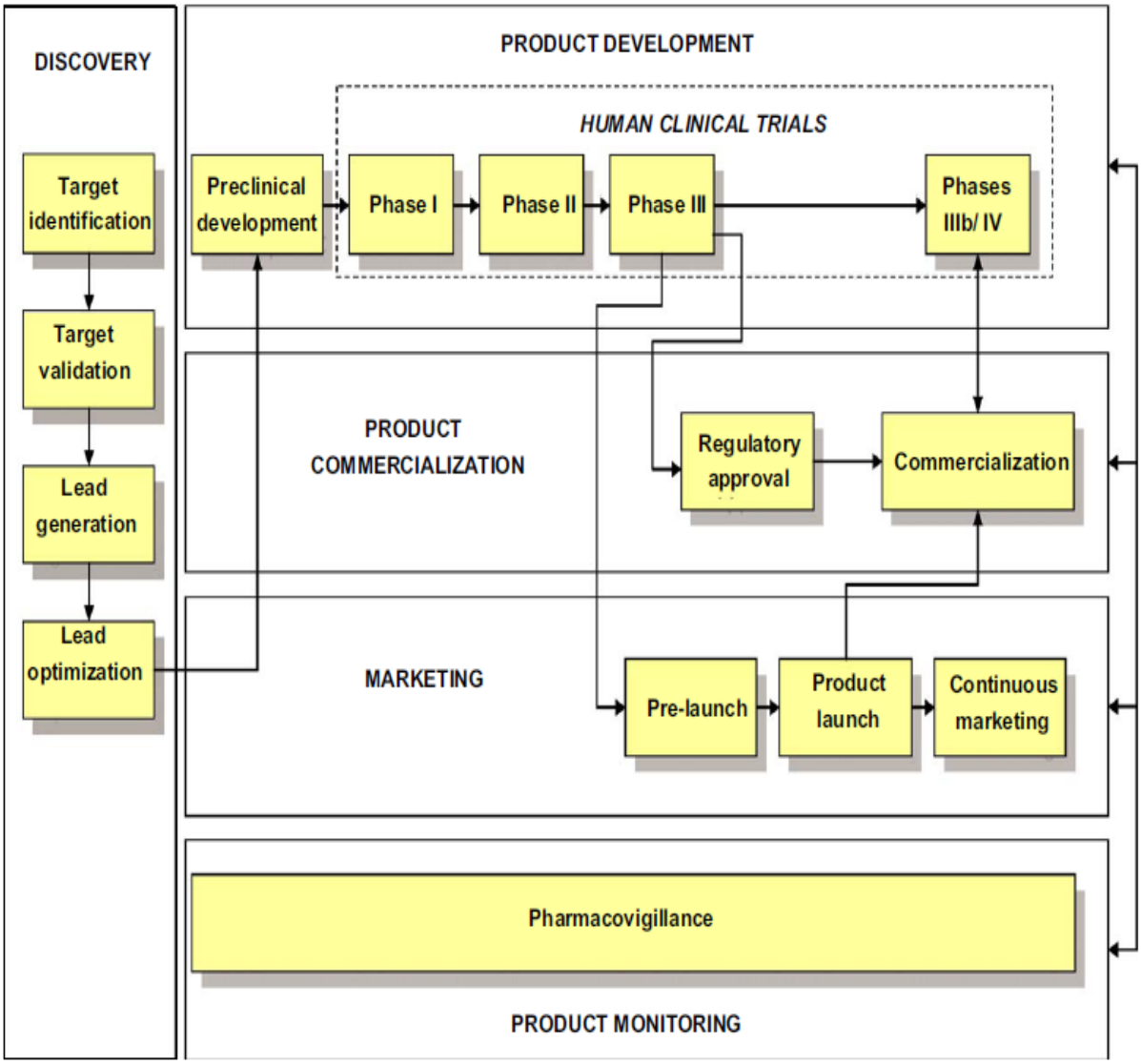

Figure 1. Pharmaceutical Value Chain

Source: (Pedroso & Nakano, 2009)

With more than 9200 new drugs in the pharmaceutical pipeline, an outdated and inefficient development process not only threatens timely delivery of the medicines to consumers, but also leads to humungous losses to pharmaceutical companies that invest in the expensive Research and Development (R&D) processes (Quintiles, 2010a).

2.1 The Drug Discovery and Development Process

"Drug discovery and development is the process employed to identify new biological compounds and then refine and develop them into a drug candidate." (Wadhwa et al., 2008, p. 58). The development of new pharmaceuticals is a long, expensive and a risky process (Colvin & Maravelias, 2010). A successful drug development process takes an average of 10 to 15 years from the earliest stages of discovery to the time it is made available for use to patients, and the average cost of developing a new drug for the pharmaceutical companies can range from $800 million to more than $1 billion (Shah, 2004; Girotra, Terwiesch, & Ulrich, 2004; Colvin & Maravelias, 2008; Colvin & Maravelias, 2010; Pharmaceutical Product Development, 2010; Tauzin, 2010). The cost of new drug development is also critically dependent on the proportion of drugs that are unsuccessful in clinical testing (DiMasi et al., 1995; DiMasi et al., 1991). Development cost of a new drug is high because the cost of failed drugs is added to the cost of successful drugs (DiMasi et al, 2003). Out of 5000 compounds (PhRMA, 2010a) that emerge from the discovery phase, only 5 compounds move into clinical testing, and only 1 out of those 5 compounds, receives the necessary regulatory approval by the Food and Drug Administration (FDA) and is introduced into the market (Girotra et al., 2004; Törnell & Snaith, 2002; Boulnois, 2000).

The drug development process is very risky as most of the compounds that undergo clinical testing are abandoned without acquiring the regulatory approval (DiMasi, 2001). Even when a drug enters the market, success is not guaranteed as toxic side effects may show up when the drug is put to use amongst a diverse population. Due to the highly stochastic nature of the pharmaceutical R&D process, if a drug fails clinical trial, its development stops and all the prior investment into the compound is lost; but if it passes all the clinical trials, it enters into the market and provides profits that are notably larger than its development costs (Colvin & Maravelias, 2008). Pharmaceutical firms embark upon this risky process because of the opportunity that it presents. It presents the pharmaceutical company with the opportunity to develop a "blockbuster" drug; a drug that generates more than $1 billion in sales revenue and has a chance to meet unmet medical needs making a significant difference to the users

of the drug (Robbins-Roth, 2001; Adams & Brantner, 2003; Colvin & Maravelias, 2008).

The drug development process is designed to ensure that both safe and effective drugs are introduced into the market (Pharmaceutical Product Development, 2010). Drug discovery and development is an iterative (Wadhwa et al, 2008) and a highly regulated process which follows a series of steps (Girotra et al., 2004) (Figure 2).

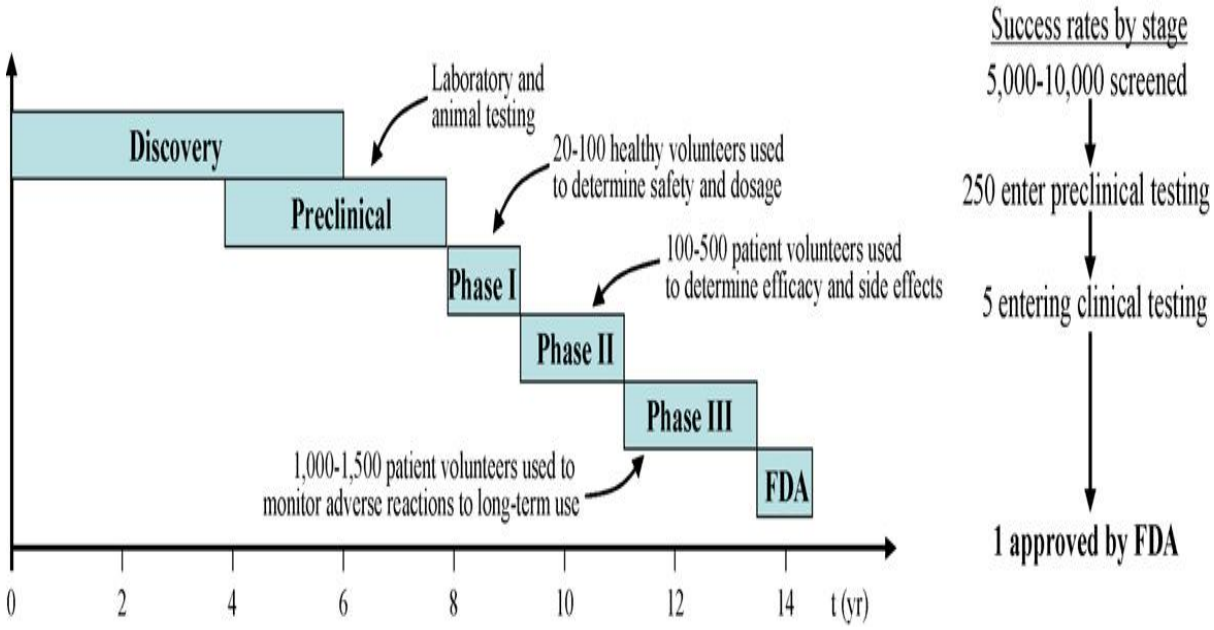

Figure 2. Drug Discovery and Development Stages
Source: (Colvin & Maravelias, 2008)

2.1.1 The Discovery and Screening Process

The Discovery Process constitutes of all the early research that scientists indulge in to identify a new drug candidate. The process which easily takes 3-6 years stimulates the scientists to identify a promising new drug candidate to test on human subjects. Clinical Trials for the compounds take 6-7 years and FDA approval takes another 2 years (PhRMA, 2010a) (Figure 3).

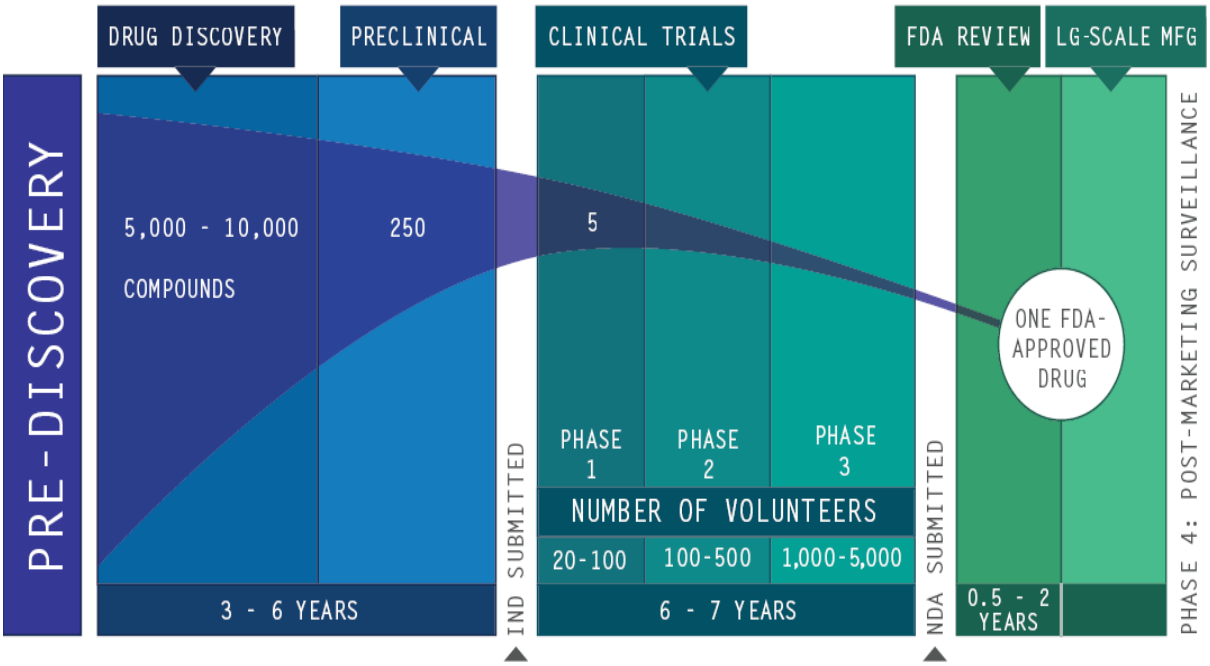

Figure 3. Discovery and Screening Process

Source: (PhRMA, 2010a)

2.1.1.1 Pre-Discovery Phase

- ***To Understand the Disease***

Before any potential new medicine can be developed, it is important to understand the underlying causes for the particular disease. Scientist's knowledge of various diseases is growing day by day (PhRMA, 2010b). They work hard to understand the disease in question by identifying the cellular and genetic factors associated with it (Pharmaceutical Product Development, 2010; PhRMA, 2010a).

"The drug discovery process can be described as the identification and validation of a disease target and the discovery and development of a chemical compound to interact with that target" (Sweeny, 2002, p. 9).

- ***Target Identification***

The objective of this step is to discover a molecular target that might be suitable to prevent, stabilize or reverse a disease (Törnell & Snaith, 2002). After carefully examining and understanding the underlying causes of the disease, researchers locate a specific biological process related to the disease. They select a 'target' for a potential new medicine (PhRMA, 2010a). A target is a specific molecule such as an enzyme or a protein that plays a crucial role in disease progression (Wadhwa et al, 2008). Even at such an early stage of drug discovery, it is essential for researchers to pick a 'drugable' target; one that can interact with, and, be affected by a drug molecule (PhRMA, 2010a).

- ***Target Validation***

The main objective of this step is to discover whether or not the target identified in the previous stage is relevant to the disease being studied. Through a series of complex experiments and based on the ability of the target to regulate biological and chemical compounds, scientists must identify the correct compounds that have an effect on the selected target (Törnell & Snaith, 2002; PhRMA, 2010a; Pharmaceutical Product Development, 2010).

- ***Lead Identification***

According to Kenny et al., (1998) a pivotal step in drug discovery process is the ability to discover new lead compounds. A lead compound is one that carries the potential to treat the disease. Scientists compare known substances with new compounds to determine the probability of success (Girotra et al., 2004). Tests are conducted on each molecule to validate its effect on the target (Pharmaceutical Product Development, 2010). They identify molecular compounds that interact with their target in a desired way; altering the course of the disease (Törnell & Snaith, 2002; PhRMA, 2010a).

- ***Lead Optimization***

This stage is considered as the most challenging phase in the development process (Wadhwa et al, 2008). It is undoubtedly the longest and the most resource intensive phase where lead compounds that were identified through screening are optimized through successive rounds of chemical synthesis of analogous and biological testing (Boulnois, January, 2000; Wadhwa et al, 2008; PhRMA, 2010a). This is done to "maximise the lead molecule in terms of its potency, selectivity, bioavailability, metabolic and pharmacokinetic profile*, and activity in suitable animal models of disease" (Boulnois, 2000, p. 32). Lead prioritization studies are conducted *in vivo* (in living organisms) and *in vitro* (in cells in the test tube) to compare different lead compounds; especially their metabolism and effect on the body (Pharmaceutical Product Development, 2010). All anticipated toxicological effects are minimized during this phase, and the molecule becomes ready for preclinical and clinical testing (Boulnois, 2000).

* Pharmacokinetic Profile – **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion and **Tox**icological (**ADME/Tox**) properties

2.1.2 The Development Process

The clinical phase in the Drug Discovery and Drug Development Process is defined as the time from the date of IND application filings to the date of New Drug Application submission (Kaitin & Cairns, 2003).

2.1.2.1 Pre-Clinical Testing

Before the clinical trial phase begins, the FDA requires verification that the drug meets the basic safety standards (Wadhwa et al, 2008). The primary goal of pre-clinical research is to assess the safety of the drug before human tests begin (PhRMA, 2010b). This is done in support of filing IND (Investigational New Drug) Application (Girotra et al., 2004).

In this process, scientists establish the cause of a specific disease. Upon successful accomplishment of this step, they work to breakdown the different

components that make a disease. This helps them to understand the abnormalities that the body undergoes when it comes in contact with the particular disease. Armed with this knowledge, they develop drugs that would treat the abnormalities by performing various tests. The goal of this process is to determine the compounds that have a chemical effect on the disease (California Biomedical Research Association, n.d).

An investigational new drug must be tested extensively to ensure its safety in humans. This process is lengthy and can take anywhere between 3 – 6 years. It must provide information about the drug's safety, pharmaceutical composition, formulation, manufacturing process and how it will be administered to human subjects (PhRMA, 2010b).

Throughout the preclinical development of a drug, laboratory tests are conducted to monitor the effect of the investigational drug *in vitro* (in cells in the test tube). After a successful "Benchtop" process (laboratory tests *in vitro*), scientists then conduct research *in vivo* (in living organisms) (California Biomedical Research Association, n.d; DiMasi et al, 1991; Törnell & Snaith, 2002; Pharmaceutical Product Development, 2010).

Key preclinical tests include Pharmacokinetic profiling; the study of the drug candidate's effects on living organisms. Scientists examine processes like **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion and **Tox**icity to ensure that the medicine effectively reaches the intended target and passes through the body properly. (Wadhwa et al, 2008; PhRMA, 2010b).

Pharmacological and toxicology testing is conducted to determine the candidate drug's effects and potential risks to human subjects respectively (Pharmaceutical Product Development, 2010). "Successful drugs must be: **A**bsorbed into the bloodstream, **D**istributed to the proper site of action in the body, **M**etabolized efficiently and effectively, successfully **E**xcreted from the body and not be **Tox**ic" PhRMA, 2010a, p. 6).

After all the tests, if the drug is considered to be a promising candidate for further development, then prior to any human testing, the company must file an Investigational New Drug Application with the FDA in United States (California Biomedical Research Association, n.d; DiMasi et al, 1991; Pharmaceutical Product Development, 2010). The results from preclinical testing are utilized by scientists to determine the best method of drug formulation for intended clinical use (Pharmaceutical Product Development, 2010). The IND application notifies the FDA of the drug sponsor's intention to perform clinical trials (Girotra et al., 2004).

Investigational New Drug (IND) Application

This application contains results of all the preclinical testing experiments:
the pharmacokinetic profile of the drug containing its functioning in the body, side effects found in living as well as cell tissues, the chemical composition of the compound with information on its purity, potency, quality and shelf life, the manufacturing plans of the compound, the amount of dosage to be given, etc. (Wadhwa et al, 2008; PhRMA, 2010b).

The IND application must also include a detailed clinical trial plan that outlines as to where, how, and by whom the studies will be conducted. The FDA carefully reviews the application to ensure that people participating in the clinical trials are not be exposed to unreasonable risks (PhRMA, 2010b; PhRMA, 2010a).

In addition to the IND application, all the clinical trials must be reviewed and approved by the Institutional Review Board (IRB) (PhRMA, 2010b). This is done to ensure that the development is taking place with informed consent of all clinical trial participants (PhRMA, 2010a; Pharmaceutical Product Development, 2010). Progress reports on the clinical trials must be submitted annually to the FDA and IRB for review (PhRMA, 2010b).

The IND Application that is submitted to the FDA is approved by default within 30 days of filing unless the FDA finds faults with the documentation. Following the IND approval, the firm may begin to test the potential new drug in human subjects through clinical testing (California Biomedical Research Association, n.d;

DiMasi et al, 1991; Wadhwa et al, 2008; PhRMA, 2010b; Pharmaceutical Product Development, 2010).

After starting the discovery process with a range of more than 5,000 to 10,000 compounds, scientists narrow down the range to just 5 compounds. These candidate drugs will now be experimented upon in detail in the clinical trial phase (PhRMA, 2010a).

2.1.2.2 Clinical Testing

The ultimate goal of clinical trial is to test the efficacy of the new drug; whether or not the new drug is effective and safe for the human body (Sweeny, 2002). These tests are conducted to understand if the drug being developed is better than the existing drugs and also to understand the appropriate dosage which provides the best response with the least number of side effects (Robbins-Roth, 2001; FDA, 2006). Of the hundreds of compounds that make it to preclinical testing, only 5 enter the clinical testing phase (PhRMA, 2010b).

There are three phases in clinical testing but before the initiation of Phase I, small doses of the candidate drug are delivered to human subjects and the pharmacokinetic profile is monitored. The aim of such a step is to single out and exclude the poorly performing drugs from the expensive clinical trial process (Wadhwa et al, 2008).

Phase I

This phase involves testing the drug to verify its safety and tolerability in humans (Pharmaceutical Product Development, 2010; PhRMA, 2005). These are the first set of studies conducted in human subjects. These studies are often conducted in a hospital setting on a limited number of 20- 100 healthy volunteers (Quintiles, 2010b ; PhRMA, 2010b ; Adams & Brantner, 2003); PhRMA, 2010a); California Biomedical Research Association, n.d; DiMasi et al, 1991; DiMasi et al, 2003; Wadhwa et al 2008).

In this phase researchers observe the *Pharmacokinetic* (Absorption, Distribution, Metabolism and Excretion) as well as the *Pharmacologic* (effect of the drug on the functioning of the human body) actions of the drug in the human body. (PhRMA, 2010a; Girotra et al., 2004; O'Donnell, 2005; University of Virginia, 2008). In addition to this, they also study the Pharmacodynamic (Is the drug producing the necessary effects or unwanted adverse-effects?) actions of the drug (PhRMA, 2010a). This process takes from 6 months to 1 year and if the drug passes in the first phase of clinical trials, it moves onto the second phase (California Biomedical Research Association, n.d; PhRMA, 2010b).

Phase II

The studies in this phase are conducted to obtain data on the effectiveness of the candidate drug for a particular indication in patients with the target disease (O'Donnell, 2005; PhRMA, 2010a). These closely monitored placebo controlled trials are conducted on a fairly larger number of human subjects as compared to Phase I (PhRMA, 2005; University of Virginia, 2008; PhRMA, 2010b); Pharmaceutical Product Development, 2010). Around 100 – 500 patients who are suffering from the disease are chosen as human subjects and examined for adverse effects and other risks associated with the disease (Adams & Brantner, 2003; Girotra et al, 2004; O'Donnell, 2005; Colvin & Maravelias, 2008; PhRMA, 2010a).

Most of the Phase II trials are conducted in random groups of test subjects. One group receives the investigational drug, the other receives a placebo containing no medication and the third group receives the equivalent existing treatment to the investigational drug. These tests are conducted in a manner where the neither the patients nor the researchers are aware of who is receiving the investigational drug and who is receiving the placebo (Pharmaceutical Product Development, 2010). The goal of this phase is to test the efficacy of the drug and also to determine the proper dose strength and schedule (Once daily or twice daily) (Wadhwa et al, 2008; PhRMA, 2010b; California Biomedical Research Association, n.d).

Significant evidence of the drug's efficacy is provided when the drug successfully passes Phase II of the clinical trials (DiMasi et al, 1991). Depending upon the type of investigational drug and the disease in question, the second phase of development can usually take from up to 6 months to 3 years (PhRMA, 2010b; California Biomedical Research Association, n.d; Pharmaceutical Product Development, 2010).

Phase III

This phase of the clinical trials is conducted after a preliminary evidence of the drug's efficacy has been obtained in Phase II. The main objective of this phase is to gain additional information about the efficacy and safety of the drug in order to assess the overall benefit-risk relationship (University of Virginia, 2008; O'Donnell, 2005). Researchers conduct randomized, placebo controlled trials of the investigational drug in a large number of patient volunteers in clinics and hospitals. These volunteers can range from 1000 – 5000 human test subjects who are closely monitored by researchers at regular intervals to determine the efficacy and safety of the drug (Adams & Brantner, 2003; DiMasi et al, 2003; Colvin & Maravelias, 2008; PhRMA, 2010b; PhRMA, 2010a ; Pharmaceutical Product Development, 2010). Due to the large sample size, this phase of the clinical trials is very useful in detecting adverse reactions (side effects) of the drug in patient population (DiMasi et al, 1991).

This phase of the clinical trials often represents a bottleneck in the development process as it is the costliest and longest phase. As this phase involves a large number of patient population for the purpose of the study, accumulation of such a diverse group of patients becomes a colossal task. A lot of effort is spent on coordination of the patient sites and data exchange. During this phase, researchers are also perform various other tasks like research on the manufacturing process, additional dosage information and preparation of the complex application required for approval by the FDA (PhRMA, 2010a; Wadhwa et al, 2008; DiMasi et al, 1991).

Results from these studies are also used to develop the *Drug Label*. These refer to the claims the manufacturer makes to the physician; during the course of study, the drug was administered the same way as it is being used for marketing (Girotra et al, 2004; Drug Development Process, 2010). Depending upon the type of drug candidate, disease, length of testing and number of volunteers, this stage of the clinical trials can take anywhere from 1 year to 4 years to complete (PhRMA, 2010b; Quintiles, 2010b; Drug Development Process, 2010; Pharmaceutical Product Development, 2010; University of Virginia, 2008; California Biomedical Research Association, n.d).

When these studies are completed and the desired effects in terms of efficacy and safety of the drug in question are established, the sponsor may submit the New Drug Application (NDA) to the FDA for approval (DiMasi et al, 1991; University of Virginia, 2008).

2.1.2.3 New Drug Application (NDA) and Regulatory Approval

2.1.2.3.1 New Drug Application

Once all the three phases in the clinical trials are completed, the company analyses all the data it has collected regarding the drug during its development process (Pharmaceutical Product Development, 2010; PhRMA, 2010b; PhRMA, 2010a). If the findings demonstrate that the investigational drug is both effective and safe, the company files a New Drug Application (NDA) with the FDA PhRMA, 2010b). NDAs are applications that document the safety and efficacy of the investigational drug and contain all the information including preclinical trials, clinical trials, dosage information, manufacturing details and labelling of the medicine (O'Donnell, 2005; PhRMA, 2010b; Pharmaceutical Product Development, 2010). This application must present significant evidence that the drug will have the desired effect that it has been produced to have upon consumption by patients or under conditions for which it has been prescribed or recommended in the drug label (Pharmaceutical Product Development, 2010).

2.1.2.3.2 Food and Drug Administration Approval

In this final stage, FDA scientists re-evaluate the results from all the tests conducted, that have been provided to them in the NDA to verify if the drug is safe and effective and whether or not it should be approved. The FDA conducts a careful examination and decides to award any one of the three. It can either

1) Approve the medicine, or
2) Send the company an 'Approvable' letter requesting them to submit more information before the formal approval can be awarded, or
3) Deny the approval.

Depending on the medicine or disease being considered, this review may include an Advisory Committee; an independent panel of FDA appointed experts, who review the data provided by company representatives. These committees vote and decide whether or not the FDA should approve the NDA. The FDA may or may not accept the recommendations provided by the advisory committee when awarding approvals (PhRMA, 2005; PhRMA, 2010b; PhRMA, 2010a).

Procurement of approval to market the new drug can take anywhere between 6 months to 2 years. If the drug exhibits the possibility to address an unmet medical need (treatment of serious or life threatening disease), it obtains fast track review and the FDA then takes 6 to 12 months to review the application. If the drug does not obtain a fast track approval then the FDA can take up to 24 months to review the application (Stonebraker, 2002; Adams & Brantner, 2003; Colvin & Maravelias, 2008; Pharmaceutical Product Development, 2010; California Biomedical Research Association, n.d). When the medicine is approved by the FDA, it becomes available for use to patients and physicians (PhRMA, 2010b; California Biomedical Research Association, n.d).

Periodic reports regarding the drug's safety and occurrence of unknown side effects after the approval process need to be submitted by the company to the FDA. For drugs where the FDA awards the 'Approvable' status but requires additional studies or testing, Clinical Trial Phase IV can be initiated (California Biomedical Research Association, n.d).

2.1.2.4 Post-Marketing Studies

Phase IV

Phase IV trials or 'Post-Marketing' studies begin after the drug receives regulatory approval. This phase involves additional testing of the drug and is employed to prove the efficacy and safety of the drug in newer indications (PhRMA, 2010b; Quintiles, 2010b; Pharmaceutical Product Development, 2010). This phase involves testing of the approved drug on a much specific subject population (children or elderly people) and comparing the efficacy with other drugs treating the same disease (PhRMA, 2005;University of Virginia, 2008; PhRMA, 2010a; Pharmaceutical Product Development, 2010). Phase IV studies can continue for years and can cost a company $20-30 million. These studies can be conducted to provide supplementary data for the NDA or for additional indications for the drug (PhRMA, 2010b).

2.1.2.5 Process Development and Capacity Management

The development process of drugs is highly connected with new product development. It is imperative for the production process to gain FDA approval, thus the production process needs to be developed way before the drug passes phase III of the clinical trials. Thus it is evident that most of the decisions regarding the production capacity are made under uncertainty of the drug even passing Phase III (Colvin & Maravelias, 2008).

2.1.2.6 Ongoing Studies

Even after a drug receives an approval, studies and other tests continue (PhRMA, 2010a). These studies focus on unknown side effects and other such risks that were non-existent during the development stage (Wadhwa et al, 2008; Pharmaceutical Product Development, 2010). As the drug enter the market, a much wider sample of population uses the drug as compared to thousands of patients in a controlled clinical trial environment (PhRMA, 2010a). At such a large scale rare side effects may occur, thus it becomes imperative for companies to monitor the drug and prepare reports regarding the safety of the

drug over the long term (PhRMA, 2005; Wadhwa et al, 2008). The FDA requires the companies to submit the reports periodically, including cases of adverse effects (side effects or other risks associated with the drug) (PhRMA, 2010b; PhRMA, 2010a).

It is necessary to take into account the length and the costs associated with the drug development processes as they have a significant impact on the allocation of R&D resources (DiMasi, 2001). Thus, it is vital for pharmaceutical companies to effectively manage their R&D pipeline, thereby reducing the development time and cost of new drugs (Grossmann & Westerberg, 2000; Shah, 2004).

2.2 Problems in the Drug Discovery and Development Process

"Today's marketplace is characterised by turbulence and uncertainty" (Christopher & Lee, 2004, p. 388). As compared to the past, this market turbulence has increased due to various reasons. Management of supply chain has also become a daunting and challenging task. With increasing number of uncertainties and risks in demand and supply prevalent in various industrial sectors, the globalisation of such marketplaces has been highly affected. With the introduction of newer and technologically advanced products, the technological lifecycle of existing products is decreasing and becoming difficult to predict. The risk portfolio of companies gets affected due to external as well as internal environments. Uncertainties in a business are not only the results of external events like wars, floods, strikes, terrorist activities etc. but also the result of internal events like changes in business rules or strategies. In case of external events like strikes, the risk is enhanced and in case of internal events like adoption of lean practices or outsourcing, the risk is reduced (Christopher & Lee, 2004).

2.2.1 Supply Chain

With a continuous increase in the usage of manufacturing and supply chain partners, a complex chain of international supply chain networks is emerging (Christopher & Lee, 2004). The definition of 'Supply chain' has always been debated by researchers and scholars. Due to the inclusion of the word 'chain', it

may seem like a linear setup of processes but it actually stands out to be a set of complex networks or processes (Peck, 2006). Amongst the numerous definitions of 'Supply chain' to be documented, Mentzer, et al. (2001, p. 4) described supply chain as "a set of three or more entities (organisations or individuals) directly involved in the upstream and downstream flows of products, services, finances, and/or information from a source to a customer." Thus, Supply chain basically refers to flow of goods and information between organisations or individuals linked by processes, activities and distribution networks (Peck, 2006).

According to Pedroso & Nakano, (2009, p. 378) "The pharmaceutical supply chain is a rich example of information flows to many stakeholders. It presents structured and unstructured, controlled and uncontrolled knowledge dissemination, so it could be important for some companies to map those knowledge flows."

2.2.2 Supply Chain Management

With a description of supply chain in the above mentioned statements, Supply Chain Management can also be described as the steps taken in order to influence the activities of supply chain to achieve the desired results. Christopher (2005, p. 5) defined Supply Chain Management as "The management of upstream and downstream relationships with suppliers and customers to deliver superior customer value at less cost to the supply chain as a whole" Simchi-Levi et al., (2004, p. 2) have stated that "Supply Chain Management is a set of approaches used to efficiently integrate suppliers, manufacturers, warehouses, and stores so that merchandise is produced and distributed at the right quantities, to the right locations, and at the right time in order to minimize system wide costs while satisfying service level requirements."

"The goal of supply chain management is the smooth, seamless flow of goods, services and information across the constituent organizations" (Pedroso & Nakano, 2009, p. 376). The authors state that demand information and material flows are essential components of an ideal supply chain wherein demand

information travels upstream to create material flows. Thus accurate information is a vital component.

Pharmaceutical companies are placed at the upstream part of the healthcare value chain and must manage upstream information flow which carries demand data from the market as well as downstream technical information flow which helps in creating demand (Pedroso & Nakano, 2009). (Figure 4)

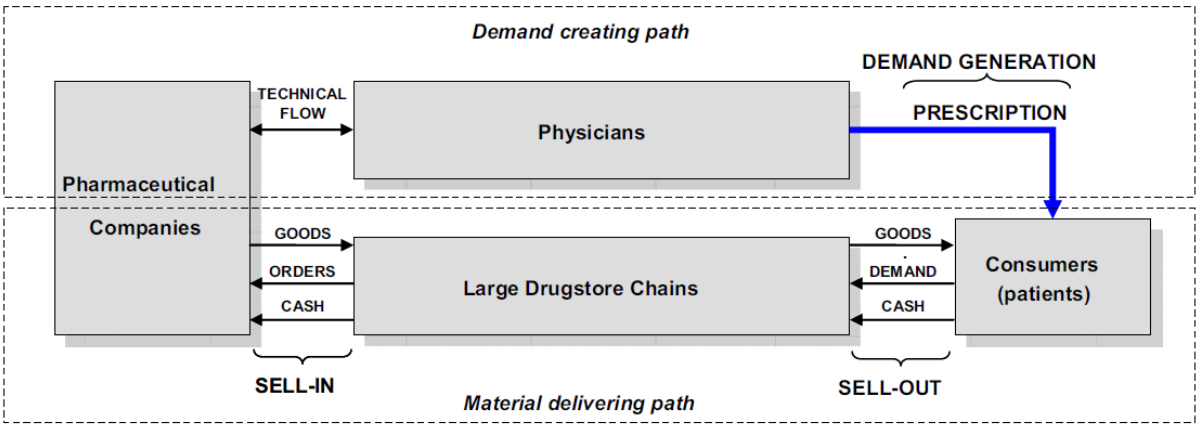

Figure 4. Demand generation in the pharmaceutical industry

Source: (Pedroso & Nakano, 2009)

Given the multi-tiered supply chain networks and the inherent complexity of various process (Peck, 2006) the chances of supply chain congestion are not only visible but also increasing at an alarming rate. Supply chain congestion not only imposes a tax on inventories but also result in risks, uncertainties and delays in production and distribution thereby increasing the lead time which invariably adds to the cost of the products (Lee & Whang, 2005).

2.2.3 Risk and Uncertainty

According to Zsidisin (2003), risk and uncertainty have been studied in various contexts in a business setting. Even though risk and uncertainty are two different concepts, in practice, they are quite often used interchangeably. Knight (1921) drew a distinction between risk and uncertainty. He stated that if one is unsure of what might happen but is aware of the odds then it may be termed as risk but when one is not even sure of the odds then it is termed as uncertainty.

Riabacke (2006, p. 1) has also distinctively defined risk as "where each action leads to one of a set of possible specific outcomes, each outcome occurring with a known probability." He also explained Uncertainty as "where actions may lead to a set of consequences, but where the probabilities of these outcomes are completely unknown."

According to Vorst & Beulens (2002, p. 413) "supply chain uncertainty refers to decision making situations in the supply chain in which the decision maker does not know definitely what to decide as he is indistinct about the objectives; lacks information about (or understanding of) the supply chain or its environment; lacks information processing capabilities; is unable to accurately predict the impact of possible control actions on supply chain behaviour; or, lacks effective control actions (non-controllability)"

According to March & Shapira (1987, p. 1404), from the supply chain perspective, 'risk' refers to "the variation in the distribution of possible supply chain outcomes, their likelihood, and their subjective values." These variations in the supply chain tend to affect the flow of information, material and products (LaLonde, 1997). Juttner et al., (2003, p. 200) have defined supply chain risks as "any risks for the information, material and product flows from original supplier to the delivery of the final product for the end user". Such complexity and uncertainty in the supply chain networks can increase the risks within the supply chain (Christopher & Lee, 2004).

2.2.3.1 Risk and Uncertainty in Drug Discovery Process of the Pharmaceutical Sector

Meyer et al., (2002) termed uncertainty as an inevitable part of most projects. They stressed on the existence of several types of uncertainties in various projects. According to Persson (1995) the level of wastage is directly proportional to the level of uncertainty in a project. He stated that if a project has high amount of uncertainty then the chances of resources wastage in that particular project are also high.

Pharmaceutical R&D is inherently risky and an uncertain process (The House of Commons: Health Committee, 2005). Development time and costs of a new drug is relatively high. Due to the highly stochastic nature of the R&D process, various sources of uncertainty emerge. These "sources of uncertainty include the cost, duration, resource requirements and outcome of clinical trials (technical uncertainty) as well as the revenues from sales (market uncertainty)" (Colvin & Maravelias, 2008, p. 2628; Colvin & Maravelias, 2010).

Cost

"Product innovation in the pharmaceutical industry is risky and time consuming, with research and development (R&D) costs representing a high proportion of sales revenues" DiMasi et al., (1991, p. 107).

It costs approximately more than $900 million to develop a new product (Colvin & Maravelias, 2010) and of that amount, 75% represents risks in the form of failed products. According to Bains (2004), costs associated with the various phases in the drug development process are shared fairly evenly; the discovery and preclinical phases (39.7%) and clinical testing phase (43.9%) and the residual (16.4%) is committed to the regulatory approval stage. The clinical testing phase is the most costly phase of the development process as most of the drugs fail during this process and the costs of failed projects are added to the cost of successful projects (DiMasi et al., 1991; DiMasi et al, 2003). Complexity of the research project and adoption of expensive new technology are also reasons for high costs in the drug development process of the pharmaceutical sector (DiMasi et al., 1991; Mohan et al., 2007).

If higher costs ensure higher probability of success then pharmaceutical R&D can be conducted even in the face of rising R&D costs, but this is not the case owing to the high uncertainty in the drug development process (DiMasi et al., 1991). The uncertainties in the R&D process result in unwarranted expenditures as the drug is unable to reach the market (DiMasi et al., 2003). The pharmaceutical R&D process is treated more as an investment with expenditures until the product either fails or receives marketing approval (DiMasi et al., 1991).

Duration

Other than the cost of the drug development process, the duration or length of time, the candidate drug takes to develop into a medicine and reach the market is also a major cause of concern for the Pharmaceutical industry (Aslani, 2008). It takes an average of 10 to 15 years for a candidate drug to move from the discovery phase and transform into a new drug to enter the marketplace. (Colvin & Maravelias, 2008; Aslani, 2008; Pharmaceutical Product Development, 2010; Colvin & Maravelias, 2010).

The total number of years is spread across various processes in the drug discovery and development process. The drug discovery process as well as the preclinical trial phase which includes all the early research conducted in order to identify a new drug candidate and lab testing accounts for approximately 3 to 6 years. The clinical trial phase, one of the most time consuming phases includes tests on patients in hospitals or in other such controlled environments. This phase takes an average of 6 to 7 years as more than often these tests result in failures. The last process of the drug discovery and development process; the NDA and Regulatory approval stage takes approximately 0.5 to 2 years. This process is time consuming owing to rigorous review that the drug undergoes to ascertain whether or not it will produce the desired effect upon consumption by patients. (PhRMA, 2010a).

Resource Requirements

According to Barney (1991) a firm's resources are all assets, capabilities, competencies, organizational processes, knowledge and information that the firm controls and executes in order to improve its efficiency and effectiveness. For the pharmaceutical sector, the drug discovery and development industry is loaded with resources that are used for the various processes from the target validation to regulatory approval stage. However, the complex trade-offs in the R&D pipeline causes various uncertainties that the industry invariably has to face.

The load on the R&D pipeline directly affects the commercialization process of the new drug. If many successful products are competing for resources then the commercialization of the new drug is delayed and if the promising products fail then the new drug may not be launched as expected. In order to maintain the regular flow of new drugs, a company must have multiple candidate drugs in the development pipeline. However, the number of drugs that can be developed is constrained by the availability of resources. Keeping in mind the vast portfolio of candidate drugs and limited resources, it becomes vital for companies to prioritize and allocate resources amongst the competing candidate drugs and choose the compounds for further development (Colvin & Maravelias, 2008).

The capacity management (manufacturing/production process) of new drugs is a decision that has to be made under uncertainty (Shah, 2004; Colvin & Maravelias, 2008). As the production process for a new drug is subject to FDA approval, thus, the investment decision for the production facility occurs approximately 5 years before the anticipated launch of the new drug. This means that the drug has not even passed Phase III of the clinical trial phase and the decision to manufacture it has to be taken (Stonebraker, 2002). The manufacturing process of drugs can take place in either one or many other geographically distributed production sites. These diverse production sites usually have varied operating costs and resource requirements. Capacity management gives way to the problem of resource allocation. There is uncertainty in the decision making process; how the limited manufacturing resources should be allocated to the selected product portfolio and also whether or not investment into additional manufacturing capacity should be made to satisfy customer demand (Levis & Papageorgiou, 2004).

The regulatory load faced by pharmaceutical companies is increasing to the point of overload. Regulatory authorities like the FDA have ever changing stringent regulatory requirements (Gupta & Maranas, 2004) like the maintenance of design history of every medical product to ensure that the product development is taking place as per the approved plan. Such a process can be time consuming and can lead to delays in the drug development process (Mohan et al., 2007). The FDA rigorously scrutinises the NDA which contains data collected from all

the tests conducted to prove the safety and efficacy of the potential new drug (PhRMA, 2010a).

Technical Uncertainty

Technical Uncertainty refers to the uncertainty in the outcome of clinical trials (Colvin & Maravelias, 2008; Colvin & Maravelias, 2010). A pharmaceutical product is given regulatory approval from regulatory authorities like the FDA upon the lengthy evaluation of the safety and efficacy of the product. New products are legally required to undergo strict and extensive testing before they are approved and allowed to enter the market. Once a new compound has been identified, laboratory tests and animal studies are conducted to develop the drug (Levis & Papageorgiou, 2004). The clinical testing stage includes three phases and tests are conducted on human subjects to test the Pharmacokinetic profile, the Pharmacologic actions as well as the Pharmacodynamic actions of the drug on the human body (University of Virginia, 2008; PhRMA, 2010a). Upon successful completion of the three phases, the regulatory authorities review the application submitted and grant the necessary approval to market the drug (Levis & Papageorgiou, 2004).

The technical uncertainties in the drug development process are manifold. A lot of time (approx. 6 to 7 years) is utilised in the lengthy clinical trials. Most of the compounds that undergo clinical testing are abandoned even without obtaining the required approval (DiMasi, 2001). Out of the 5 compounds that are passed onto the clinical trial phase only 1 makes it to the market. Here also success is not guaranteed as the threat of toxic side effects occurring amongst the vast population emerges (Rogers et al., 2002; Colvin & Maravelias, 2008).

The outcome of the drugs being tested in clinical trial phase is uncertain. If the drug successfully passes all the pre-requisites of the drug approval process then it can lead to large profits for the firm but if it fails, all the prior investment is wasted and new drugs would have to again enter the R&D pipeline. Pharmaceutical firms, nevertheless, decide to undertake the risky development process with the hope of producing a "blockbuster" drug (Robbins-Roth, 2001;

Colvin & Maravelias, 2008). Thus the outcome of the whole clinical trial testing stage is under the shadow of uncertainty and hope.

Market Uncertainty

Market Uncertainty refers to uncertainty of the revenue from sales of the product (Colvin & Maravelias, 2008; Colvin & Maravelias, 2010). According to Rogers et al., (2002, p. 6608) market uncertainties is concerned with "the volatility of the future value of a product as forecasted during R&D, which may involve market reduction, entrance of branded competitor drugs, or an economic downturn."

It is absolutely crucial for pharmaceutical firms to gain sustainable competitive advantage. In order to do so, the firms should be able to recover the investment made for development of new products (Levis & Papageorgiou, 2004). The pharmaceutical firms operate under uncertainty with regards to the market value that the drug will be able to generate. Market uncertainty linked with the drug discovery process is varied in terms of incomplete information regarding the cost structure for production of the drug, the pricing structure, etc. It is linked with the market share that the drug is capable of capturing and increasing the drug's market value (Gupta & Maranas, 2004). Thus, market uncertainties imply that the drug's technical success is not a guarantee that the drug will generate commercial revenues (Rogers et al., (2002).

2.2.4 Time to Market

According to Lee and Whang (2005), supply chain congestion not only results in risks and uncertainties but also delays in production and distribution thereby increasing the lead time which invariably adds to the cost of the products.

It is important for firms to understand that in today's market scenario, time is the most important source of competitive advantage. The way in which companies manage their time – in production, new product development, new product introduction, sales and distribution can affect the market share of their products (Stalk Jr, 1998). Thus, it is imperative for firms to reduce the time to market to gain sustainable competitive advantage (Datar et al., (1997).

As today's marketplace is characterised by shortening of product lifecycles, (Calantone & Benedetto, 2000; Christopher & Lee, 2004) there is pressure on firms to develop products quickly and bring them to the market (Calantone & Benedetto, 2000). In today's highly competitive global markets, time-to-market has become a crucial factor in determining success (Datar et al., 1997).

According to Pawar et al., (1994, p. 14) "time to market is the strategy of focusing on reducing the time to introduce new products to market." If a firm is able to gain lead time advantage (reduce the time to introduce new products), it will be able to gain a larger market share for its products. If the firm fails to gain the lead time advantage, competitor products can easily hamper the market positioning and market share of that product. The late entrant firms can easily catch up to the market leader (Calantone & Benedetto, 2000).

One of the compelling drivers in the pharmaceutical industry is reducing the time between the discovery of the drug and its delivery to the marketplace Zhao et al., (2005). Pharmaceutical firms are constantly faced with the problem of long development cycles which hinders the process of bringing the products to the market on time Boggs et al., (1999). According to Colvin & Maravelias (2008), the expected net present value of the product can be maximised if the expected time to market the drug can be reduced. Time to market directly affects the revenue from sales of the drug (Gear, 1999) in two ways. One, patent life of the drug diminishes as the time taken to develop the drug increases, and two, as time to market increases, the market share of the drug decreases (Colvin & Maravelias, 2008). Delay of the new drug's entry into the market by even a few months can lead to losses of millions of dollars in sales revenue for the company (Gear, 1999).

In order for pharmaceutical firms to gain competitive advantage, it is essential to develop the products and bring them to the market. Owing to the long R&D stages of the drug discovery and development process, the effective patent life of drugs is diminishing and the threat of generic drugs entering the market is increasing (Levis & Papageorgiou, 2004). These long development cycles are a result of various inefficiencies in the process which results in time delays and consequently reduces the profitability Boggs et al., (1999).

One of the key causes of time delays or longer lead times is the capacity management decision. The decision to set up a manufacturing process for the production of the new drug can affect the time of entry of the drug in the market (Shah, 2004). This decision of capacity investment for new drugs is made under clinical trial uncertainty (Shah, 2004; Colvin & Maravelias, 2008). Pharmaceutical companies have to make early decisions of capacity investment so as to guarantee the availability of the manufacturing resources to produce the product and bring it to the market on time (Levis & Papageorgiou, 2004).

Profitability would be greatly affected if the capacity management decision is deferred in anticipation of a positive result ensuring the success of the drug from the clinical trials (Shah, 2004). There is also a constant fear of the FDA requesting extremely detailed safety data from the companies conducting research; drugs would consequently spend longer time in the clinical trials and take even longer to reach the market (Malik, 2008).

Chapter 3

Research Methodology

Fundamentally, research implies inquiry or investigation of a particular phenomenon or process in a systematic manner and can categorically be divided into basic or applied research. Although the goal of any research is to aid practice, basic research is undertaken for the exploration of a particular phenomenon by gaining in depth knowledge about it. Applied research aims at "improving the quality of practice of a particular discipline" (Merriam, 2009, p. 3).

The research topic and the nature of research that was to be undertaken generated a keen interest for the researcher. The researcher has business interest in the pharmaceutical industry with more than 4 years of experience in the sales and distribution of pharmaceutical products. Also the research was a collaborated initiative between the Nottingham University Business School and one of the most reputed institutes in India, the Indian Institute of Technology, Kanpur. The above mentioned factors were enough to motivate the researcher to accept the internship offer extended by the Nottingham University Business School.

3.1. Quantitative and Qualitative Methods

There are two main types of research methodologies - Quantitative and Qualitative.

Quantitative research aims at testing existing theories (Creswell, 2009), using the method of deductive reasoning (Clover and Balsley, 1984). It analyses numerical data using statistical procedures in order to measure variables and generalise findings.

On the contrary, Van Maanen (1979, in Merriam 2009, p. 13) defines qualitative research as 'an umbrella term covering an array of interpretative techniques

which seek to describe, decode, translate, and otherwise come to terms with the meaning, not the frequency, of certain more or less naturally occurring phenomena in the social world'. Therefore, in essence, it attempts to understand how people interpret and understand social phenomena without quantifying it.

Qualitative research allows the researcher to view phenomena holistically, thus allowing the researcher to reflect on her/his inquiry in a highly systematic and multifaceted manner. It allows the researcher to delve into complex processes and innovative systems (Marshall and Rossman, c2011). Therefore, as an approach, it facilitates in-depth inquiry about various social, cultural or economical procedures and their manifestations. This consequent knowledge enables the researcher to identify relevant variables and the relationships between them, and link the same through a method of inductive reasoning (Hyde, 2000) for increasing output or improving current systems.

3.2. Rationale for choosing the Qualitative Method

The type of research is inextricably linked to the research question. Therefore, qualitative research is most appropriate when the question deals with the 'how' of phenomena rather than the 'how many' (Silverman, 2010, p. 118). The drug discovery and development process is characterised by long developmental cycles and faces intense pressure to develop the product and launch it in the market on time. It is also a risky and an uncertain process where success is not guaranteed even when the product is launched into the market.

The aim of this research is to examine and understand the drug discovery and development process and analyse ways to reduce the inherent risks and uncertainties therein. This phenomenon cannot be analysed quantitatively. In addition to an in-depth analysis of the types of risks and uncertainties and the reasons for a delayed entry of the product into the market, this method also enables the researcher to gain a comprehensive understanding of the various sources for reducing the uncertainties and time to market. Thus qualitative research is best suited for this study.

3.3. Research Design

3.3.1. Interview method

This study has used unstructured interviews with individuals who are well informed and have tremendous amount of expertise in the area. They are purposefully selected for their perspectives on and knowledge in this particular area. This method of interviewing is called 'interviewing elites' (Marshall and Rossman, c2011).

This approach has many advantages. Interviewing experts allows the researcher to gain relevant and valuable information owing to the positions they hold in organisations. Their experience facilitates in-depth discussion about the subject and the industry in question.

The researcher discussed the topic with his project manager Dr. Peeyush Mehta from IIT, Kanpur and his supervisor, Professor Kulwant Pawar in the UK and tried to gather information on the same. Qualitative literature surrounding the topic was collected and analysed with the central focus towards the core objectives of the research; reduction of uncertainty and time to market in the drug discovery and development process.

3.3.2. Sources of Secondary Data

For the purpose of this study, data has been collected from numerous sources. The researcher chose to use a wide variety of documents, journal articles and official information from industry websites, thus assigning reliability to data (Huettman, 1993). The sources of data directly influence the type of information gathered. This research study mainly relies on secondary sources due to limitations in gaining access to organisational information, major alterations in the planned course of the study and time constraints. However, McDaniel and Gates (1999) argue that secondary data is sometimes more useful than primary data as it helps to answer research questions more economically.

For the purpose of this study data for has been collected via many sources. Intricate use of scientific journals, business press, books and websites has been made. Data has been collected around the drug discovery process, the underlying uncertainties, problems with time to market and the various sources to reduce the uncertainties and time to market. Data has been carefully examined and only theoretically relevant information has been used in this study. In order to maintain consistency and avoid ambiguity, collected data has been thoroughly reviewed.

3.4. Limitations

The research for the study was to be conducted in Indian Institute of Technology (IIT), Kanpur, India. Before travelling to IIT and in order to gain an insight into the subject, the researcher conducted prior study on the drug development process as well as the new product development process. This study was in the form of secondary data like scientific journals and business press. The central focus of the research was aimed at the workshops that were to be conducted by the biopharmaceutical teams working on the drug discovery process at the Biological Sciences and Biological Engineers (B.S.B.E) department at IIT, Kanpur. The researcher was also provided secondary data in the form of scientific, academic as well as electronic journals to further develop an understanding of the afore mentioned subject. However, due to unavailability of key personnel, the scheduled workshops did not take place and the researcher had to return to Nottingham, UK prematurely. Therefore, secondary data was used extensively for the purpose of the study.

Chapter 4

Research & Analysis

The new drug discovery and development process is a long and expensive process (Colvin & Maravelias, 2010) coupled with various uncertainties and risks that prevent the medicine from being marketed on time (The House of Commons: Health Committee, 2005). It takes an average of 10 to 15 years from the first testing to the final FDA approval and the average cost of developing a drug can range from $800 million to more than $1 billion (Shah, 2004; Pharmaceutical Product Development, 2010; Tauzin, 2010). According to Eichle et al., (2010) drug research and time to market are two separate tasks that require different set of skills. Excellence in research does not necessarily mean success in effectively launching the drug in the market. Separate skill sets are required in order to effectively manage both.

4.1 Global Scenario

Today's pharmaceutical industry is rapidly evolving. In the past, pharmaceutical companies followed a very different strategy where the company's products were produced internally while sharing very limited information with third parties (Chaturvedi, 2010). With an increasing pressure on the pharmaceutical companies to develop new drugs, the traditional approaches to drug development process are slowly evolving (Piachaud, 2002).

Due to the pumping of continued investment into the R&D activities of the new drug development process in the pharmaceutical industry, the industry has developed the capability of carrying out full scale R&D functions including drug discovery, pre clinical testing, clinical testing, new drug applications and marketing activities (Lee, 1998). However, the pharmaceutical R&D industry presents various ambitious projects but with limited available resources to achieve them (Piachaud, 2002).

With escalating pressures across the pharmaceutical industry for R&D cost containment (Maiti & Raghavendra, 2007) as well as reduction of the time it takes for a new product to reach the market, it is important to accelerate the drug development process (Tranter & Smith, 1999). Delayed drug development process greatly affects the new drug introductions consequently affecting the potential revenue of the product. For a drug to receive marketing approval from the FDA, more than 4000 patients are required to test the drugs. Pharmaceutical firms find it difficult to recruit such patients for testing (Maiti & Raghavendra, 2007). Since patient recruitment accounts for approximately 70% of the clinical costs, it directly puts a pressure on the R&D expenditure thereby causing depletion of resources (Chaturvedi, 2010). This clearly implies that the number of drugs that are in production to the number of drugs in approval is extremely low (Piachaud, 2002).

As pharmaceutical companies struggle to fill their product pipeline, Crama et al., (2007) and in view of the constant depletion of in-house resources (Chaturvedi, 2010), firms have recognized the need to leverage resources and rely on external sources for various stages of the drug development process (Piachaud, 2002; Girotra et al., (2004).

4.2 Outsourcing

According to Getz (1997), pharmaceutical firms try to consolidate their operations while constantly trying to produce more and more compounds out of the R&D pipeline. They have recognized a successful method for effective utilisation of the firm's capital and resources. This method entails strategic outsourcing. Strategic outsourcing involves outsourcing the firm's operations through various strategies of choices like contracting, partnering and joint ventures (Piachaud, 2002). Outsourcing has been perceived as the current trend for the pharmaceutical industry wherein the outsourcing strategies are being used as the part of the company's overall business strategy (Chaturvedi, 2010).

4.2.1 Why Outsource?

Outsourcing can help pharmaceutical companies in creating efficiency and effectiveness along with consistency across the extensive manufacturing and supply chain networks. Outsourcing in the pharmaceutical industry in the form of contracting, partnering and joint ventures can help create alliances which carry with itself the 'cost-benefit advantage' (Chaturvedi, 2010). This helps pharmaceutical companies in reducing costs by transferring its non-core activities to external parties while strengthening the operations by effectively focussing on the company's core activities. Even though at one point, outsourcing in the pharmaceutical industry was limited to non-core activities of the company; there has been a shift in trend towards outsourcing the core activities of the company as well (Enyinda et al., 2009).

Lack of in-house R&D and technical expertise, high operational costs, declining blockbuster pipeline, patent expiry of drugs as well as stringent regulatory requirements are some of the reasons that pharmaceutical companies outsource their activities to Contract Research and Manufacturing Service (CRAMS) organisations. CRAMS includes Contract Research Organisations (CROs) and Contract Manufacturing Organisations (CMOs) (Enyinda et al., 2009)

According to Chaturvedi (2010), outsourcing has various benefits like:

- Reduction of 30% to 35% in the total cost
- Speedy and faster functioning of processes
- Improved manufacturing operations
- Reduction of excess production capacity
- Increase in the net revenue of the firm
- Increased focus on the firm's other competencies

If outsourcing is managed strategically it can provide the company with increased benefits that the company otherwise would not have gained.

4.3 Outsourcing in Pharmaceutical Industry

Outsourcing strategy can be used in numerous stages of the drug discovery and development process; from the drug discovery phase to the manufacturing stage.

4.3.1 Outsourcing R&D

The concept of strategic outsourcing has facilitated pharmaceutical firms to break away from the existing market setup and develop a new supply chain paradigm. With a steep rise in the global demand for superlative clinical trials, pharmaceutical firms have realised that the time consuming and costly process of new drug development can be easily dealt with by outsourcing them to CROs (Piachaud, 2002).

According to Crouch (1997), one-third of the extensive drug development process is carried out through the CROs while two-thirds of the process is conducted in-house. Such extensive outsourcing would lead to the development of 'virtual R&D' (Piachaud, 2002). CROs provide complete end to end solutions for the management of the complex drug trial process. Their services also include scientific and technical advice to the client. CROs have strategically located facilities around the world that provide them access to large pools of genetically diverse population to conduct clinical trials (Piachaud, 2002; Girotra et al., 2004).

The rationale behind outsourcing the research and technical activities to external sources such as CROs are numerous. The various factors for the same are as follows:

Factors for Outsourcing of R&D and Technical activities
Cost Savings
The speed to market
Ease of management
Access to knowledge and skills
Access to technology
Lack of capacity
Reduces risk and uncertainty

Source: adapted from (Piachaud, 2002; Howells et al., 2008).

With respect to outsourcing of research and technical activities, cost and time benefits have always been considered as the most important factors. However, according to (Piachaud, 2002; Howells et al., 2008) there are other factors that hold equal importance in the outsourcing decision making process. Ease of managing the projects, lack of in-house R&D and knowledge and ability to reduce risk and uncertainty were some of the initiating factors that influenced the decision to outsource.

Detailed descriptions of the factors are as follows:

1) **Costs Savings:** outsourcing of research and technical activities leads to conversion of fixed costs into variable costs for the pharmaceutical companies. As the service agreements with CROs do not truss the sponsor to the numerous long term obligations like hiring, training and maintenance of developmental staff, it leads to a reduced amount of downtime for the departmental activities thereby aiding the pharmaceutical companies in converting the fixed cost of department maintenance to variable cost of skill or service requirement (Piachaud, 2002).

2) **Speed to market:** there is immense pressure on pharmaceutical companies to reduce pharmaceutical pricing owing to the long development cycles Boggs et al., (1999), short patent life of products and availability of generic substitutes. Thus, in order to gain a competitive edge over the competitors, speed to market the product has become a critical factor. Outsourcing the research to an experienced CRO with specialised therapeutic expertise can help expedite the development process (Piachaud, 2002).

3) **Ease of management:** management of outsourced operations is much easier as compared to management of in-house operations. Pharmaceutical firms operate on a contractual basis with the outsourced company wherein they do not have to worry about the detailed departmental work that is being undertaken. This helps firms during the termination of weaker projects. The pharmaceutical firms can easily terminate the outsourced project and avoid the sunk costs that would have otherwise been unavoidable (Piachaud, 2002).

4) **Access to knowledge and skills:** outsourcing R&D and technical activities to CROs helps pharmaceutical firms in filling the 'gap'. In most cases, the gap is associated with lack of competency or in-house R&D and technical expertise of the pharmaceutical company. It is the specialist expertise that the company lacks in order to successfully complete the R&D and other technical activities required in the drug development process (Piachaud, 2002).

5) **Access to technology:** the R&D and technical activities of the drug development process require extensive use of technology and equipment. The decision to outsource is subject to certain variables like the cost of technology, availability of facility for installation, the lead time for acquiring and commissioning the equipment and availability of qualified personnel in-house to function the equipment. By outsourcing the R&D and technical activities to CROs the pharmaceutical firms gain access to technology that they otherwise would have to install (Piachaud, 2002).

6) **Lack of Capacity:** outsourcing in the pharmaceutical industry is also a result of lack of capacity within the pharmaceutical company. During peak periods, when firms are unable to cope with excess work load, they outsource the work to external contractors. Also, during the phase III of the clinical trials, tests are conducted on more than 10,000 patients and as these trials often exceed the in-house capacity, they are outsourced to CROs (Piachaud, 2002).

7) **Share risk and uncertainty:** risk and uncertainty vary according to the type of R&D activity being undertaken. Some parts of the R&D process, such as, compound research, have high levels of risk and uncertainty associated with them while other parts of the R&D process, such as, process or product modification, have low levels of risk and uncertainty associated with them. Outsourcing R&D and technical activities leads to the reduction of the inherent risk and uncertainty as the risk is shared with the external partner or a set of partners Howells et al., (2008).

4.3.2 Outsourcing Manufacturing

According to Plambeck & Taylor (2005), in the past, pharmaceutical firms have conducted all its activities like R&D, product design, marketing and production in-house. However, such a vertical supply chain system caused various problems for the pharmaceutical companies. As the firms used its production capacity to fulfil its demand, it resulted in inefficient use of capacity. The pharmaceutical industry is characterised by long development cycles of 10 to 15 years and undergoes intense pressure to develop the product and place it in the market on time. As a result, in order to manufacture its products in-house, pharmaceutical companies have to invest large amounts of capital investment into the production capacity even before the drug has been granted regulatory approval. With the prevalent risk of drug failure, such a risky move can result in heavy losses for the pharmaceutical company (Tully, 1994).

Faced with the problem of declining blockbuster pipeline, decreasing patent life of drugs as well as high operational costs, pharmaceutical companies are under constant pressure to streamline their operations. In order to effectively deal with these problems, pharmaceutical companies outsource their manufacturing activities to contract manufacturing services (CMO) (Greene, 2007). CMOs not only provide services for early product development stage but also for product manufacturing and testing in the later stage. (Strauss & Novak, 2009).

The use of CMOs is an important strategic step taken by pharmaceutical companies. According to Strauss & Novak (2009), there has been a steep rise in the strategic move of outsourcing manufacturing services to CMOs since 1990s. In 1998, outsourcing to CMOs accounted for only 20% of the company's operations whereas this figure rose steeply to 50% to 60% in the year 2005 (Plambeck & Taylor, 2005). Such a strong elevation clearly suggests the growing importance of outsourcing manufacturing to CMOs in the pharmaceutical industry.

There are various reasons behind outsourcing the manufacturing activities to external sources such as CMOs. The various factors for the same are as follows:

Factors for Outsourcing of Manufacturing activities
Cost Savings
The speed to market
Expand Resources
Expand Capabilities

Source: adapted from (Snee, 2006)

Similar to outsourcing research and technical activities, cost and time benefits have been considered as the most important factors for outsourcing

manufacturing activities to CMOs, but there are other important factors that also play a major role in the outsourcing decision making process.
Detailed descriptions of the factors are as follows:

1) **Costs Savings:** the outsourcing of manufacturing activities to external suppliers like CMOs enables pharmaceutical firms to cut costs and reap the benefits of production cost savings. (Snee, 2006) As opposed to the large capital investments required for the in-house manufacturing facility, pharmaceutical firms outsource their manufacturing operations to external suppliers without committing resources for the capacity investment. They tend to take advantage of the supplier's technological advancement, smooth flow of operations and centralisation of expertise. (Heshmati, 2003; Ransohoff, 2004). The pharmaceutical companies not only save the large amount of investment on plant and machinery but also the potential labour costs consequently lowering the fixed cost that the firm would otherwise incur (Gilley & Rasheed, 2000).

2) **Speed to market:** outsourcing the manufacturing activity is faster than setting up the same in-house (Snee, 2006). When a pharmaceutical company outsources, the time consuming setup of the manufacturing capacity along with the hiring, training and managing of manufacturing staff can be avoided (Piachaud, 2002). This enables ease of functioning and also reduces the time to market of the drug allowing companies to reach the market quickly and be more responsive to its customer's demands (Snee, 2006; Nannei & Rumiano, 2007).

3) **Expand Resources:** outsourcing of manufacturing activities enables pharmaceutical companies to concentrate on their core competencies while making use of the CMOs capabilities to complete the manufacturing tasks effectively Enyinda et al. (2009). Pharmaceutical companies make use of the manufacturer's pool of resources while evading the setting up of the manufacturing process in-house (Gilley & Rasheed, 2000). In short, firms expand their resources or facilities without having to make long term capital investments (Snee, 2006).

4) **Expand Capabilities:** outsourcing enables pharmaceutical companies to enhance their core competencies and develop new capabilities Enyinda et al. (2009). As the pharmaceutical company works very closely with the CMOs, they can regularly obtain the CMOs perspective on multifarious issues concerning the product. The pharmaceutical company can also seek the CMO's help in completing specialised tasks that the pharmaceutical company would otherwise be incapable of performing (Snee, 2006).

Like any other processes, outsourcing of R&D, technical and manufacturing activities too have many advantages as well as disadvantages.

Pharmaceutical firms find it beneficial to outsource R&D, technical and manufacturing activities as opposed to managing them in-house. Considering this trend, the **Advantages** of Outsourcing are as follows:

1) **Greater flexibility:** like any other company in the industry, the pharmaceutical companies in the pharmaceutical industry are also allocated resources and based on the availability of those resources, budgets are allocated. According to Cavalla (1997), for the pharmaceutical company, a major share of the budget is defined by fixed costs while the smaller portion of the budget is used for clearing bottlenecks in the R&D projects. It is the smaller portion of the budget that provides the company with the ability of re-allocating resources to more important projects. Outsourcing to CROs and CMOs enables firms to deal with the problem of insufficient capacity. During peak periods, pharmaceutical firms can cope with excess work load by outsourcing R&D and manufacturing projects to CROs and CMOs respectively without the need to invest for capacity internally. Additionally, outsourcing provides the pharmaceutical company with greater flexibility to invest in a number of small R&D projects with different CROs rather than invest in one single project with one CRO (Piachaud, 2002).

2) **Acquire Specialised Knowledge and Skills:** According to Piachaud (2002), traditionally, much of the R&D and manufacturing processes in pharmaceutical companies were conducted in-house. However, with the advancement in technology and augmentation of knowledge base, pharmaceutical firms find it difficult to hold specialised knowledge in all therapeutic areas. In-house production also restricts the pharmaceutical companies to experiment with new technology thereby confining them to use a specific type of technology (Harrigan, 1984).

   Outsourcing enables pharmaceutical firms to develop new capabilities by increasing their knowledge base or acquiring new skills (Gilley & Rasheed, 2000). With the introduction of these specialised skills, pharmaceutical firms can reorganise their R&D and manufacturing processes more effectively in a way that may provide them competitive advantage. By establishing the CROs and CMOs as a part of the firm's supply chain, the pharmaceutical firms can focus on the most relevant capabilities while learning the specialised knowledge from the collaborative partners with a view of introducing them in-house without having to commit resources (Gilley & Rasheed, 2000; Piachaud, 2002).

3) **Assist in the rapid exploitation of technology:** pharmaceutical firms find it difficult and costly to keep abreast with the rapid technological advances in the field of science and technology. Thus outsourcing to CROs and CMOs provides them with an opportunity of not only exploring new technology but also using it at lower costs. Outsourcing enables the pharmaceutical firms to use the technology without having to commit valuable resources for the use of the technology (Piachaud, 2002). These firms can easily switch suppliers and gain benefit of the new cost effective technology (Gilley & Rasheed, 2000). According to Henderson & Cockburn (1996), with respect to the R&D and manufacturing activities, pharmaceutical firms are able to experiment with the expensive technology before deciding to implement it in-house (Piachaud, 2002).

4) Freedom to concentrate on core functions: according to Enyinda et al., (2009), outsourcing of non-core activities to external contractors with specialised knowledge enables the pharmaceutical companies to effectively concentrate on its core capabilities. Kotabe & Murray (1990) and Venkatraman (1997) further state that outsourcing of the firm's operations allows pharmaceutical firms to further develop their core competencies by increasing managerial attention and resource allocation to those tasks, consequently strengthening their operations and relying on specialised external contractors to complete the tasks that the pharmaceutical firm is at a relative disadvantage (Gilley & Rasheed, 2000). This enables them to gain sustainable competitive advantage over its competitors.

5) Spread out the risk and uncertainty: risk and uncertainty are inherent features of the drug development process of the pharmaceutical industry. According to Cavalla (1997), with respect to R&D in the drug development process, risk and uncertainty can be classified into two broad elements. One, probability of the success of the clinical trials, and, two, the commercialisation potential of the new drug. With respect to the first risk, outsourcing enables pharmaceutical firms to widen their research by exploring new technology on a contractual basis rather than establishing the technology in-house. It also enables the firms to discontinue the weaker project without bearing the consequences that it would have to bear if the project were in-house. As for the second risk, outsourcing provides the pharmaceutical company with greater flexibility towards selection of the commercially viable project. The pharmaceutical company can select the project that provides the best potential; a step which the pharmaceutical company would not be able to take if the project was in-house (Piachaud, 2002).

Outsourcing the manufacturing processes also helps the pharmaceutical companies in spreading the risks that it faces (Quinn, 1992). By outsourcing the manufacturing processes to external suppliers, the pharmaceutical firms can use the latest technology without having to invest large amount of resources for the use of the technology (Piachaud, 2002). The firms can also easily switch suppliers when market conditions demand (Gilley &

Rasheed, 2000). This also tends to encourage competition amongst suppliers to provide the best quality services to the outsourcer as the suppliers stand a chance of being replaced (Kotabe & Murray, 1990).

6) **Reduce costs:** as the R&D and technical activities of the drug development process in the pharmaceutical industry require expensive technology and equipment, they are deemed costly. Outsourcing leads to attainment of the technology and equipment through service contracts rather than resource commitment. This means that the pharmaceutical company can utilise the technology and equipment without having to commit its limited resources and gain benefit from it. Due to the efficient utilisation of resources and efficiency gains, costs are lowered thereby allowing the company to gain competitive advantage (Piachaud, 2002).

   In terms of outsourcing manufacturing services, outsourcing can provide major cost advantages to the pharmaceutical company Bettis et al., (1992). Manufacturing costs for the pharmaceutical firm declines with the introduction of outsourcing and the investment in the manufacturing capacity (plant and machinery) is highly reduced. This reduced investment in the manufacturing capacity of pharmaceutical firm lowers the fixed costs that the firm would otherwise have to incur. It also enables a pharmaceutical firm to lower the break-even point thereby improving the firm's financial performance (Gilley & Rasheed, 2000).

7) **Time to market:** time is an important factor in the drug development process. In order to gain competitive advantage, it is important for pharmaceutical firms to develop and launch their products as soon as possible, and, in order to develop products quickly, pharmaceutical firms need to 'speed-up' the drug development process. Thus speed is a crucial element that affects the timely entry of a drug into the market. Outsourcing the research to efficient CROs; external contractors that possesses the appropriate resources (infrastructure coupled with trained staff), is a beneficial alternative for pharmaceutical companies as the need for hiring, training and managing the teams in-house can be avoided. Outsourcing the

research can help expedite the development process as resources are readily available, even on short notice. (Piachaud, 2002).

In terms of outsourcing manufacturing to CMOs, the timing of entry of the product is greatly affected. Collaborative manufacturing of the drugs leads to early introduction of the products into the market (Ghausi, 2002). CMOs are well equipped with the latest technology and resources are readily available, thus they can respond to the changes in demand quicker than in-house production (Plambeck & Taylor, 2005). Outsourcing of non-core manufacturing activity enables the pharmaceutical companies to concentrate on their core activities while extracting beneficial services from CMOs. This ensures optimisation of the supply chain and quick entry of the product into the market (Howard, 2003).

Working on collaborative projects with external partners can be a challenging and risky task. To highlight those factors, some of the **Disadvantages** of Outsourcing R&D, Technical and Manufacturing activities are as follows:

1) **Dependence on the supplier:** According to Piachaud (2002), pharmaceutical firms that outsource their R&D and manufacturing activities to CROs and CMOs are often at a risk of becoming increasingly dependent on the supplier. As pharmaceutical companies constantly outsource important pieces of research and manufacturing activities to the supplier, they may find themselves in a susceptible situation where the pharmaceutical company even stands a chance of losing control of its research activities (Gilley & Rasheed, 2000). As stated by Tapon & Thong (1999), owing to the capabilities that the suppliers possess (the capabilities that are of importance to the purchasers of the services, but which the purchasers lack in), the purchasers are at a risk of becoming captives to the suppliers.

2) **Lack of shared vision and objectives:** CROs and CMOs are contract organisations that provide their services to different and often competing pharmaceutical companies. The external partner must not only be committed towards the success of the project but also provide the means of

achieving the success. Since they provide their services to numerous pharmaceutical companies, often, there can be a conflict of interest. Due to this conflict, the service provider is often reluctant to take the necessary steps that guarantee a successful outcome Piachaud (2002).

3) **Loss of control over the supplier:** all outsourced projects experience loss of control to a greater or lesser extent. As a project is outsourced to an external partner, partial control of the project inexorably passes from the sponsor to the external partner. In the pharmaceutical industry, the extent to which firms can control the project depends largely upon the quality and quantity of information exchanged. Due to lack of effective communication, there could be misunderstandings or mistrust between the service provider and the company consequently delaying the project (Piachaud, 2002).

4) **Loss of Critical Skills:** one of the biggest disadvantages of outsourcing operations to external partners is the loss of critical skills. Pharmaceutical companies sacrifice their long term gains for short term benefits when they outsource R&D and manufacturing activities to CROs and CMOs respectively (Piachaud, 2002). This leads to a loss of overall market performance due to a decline in innovation. Outsourcing has often been used by pharmaceutical companies as a substitute for long term R&D. Thus the firms tend to lose touch with technological advancements. (Bettis et al., 1992; Kotabe & Murray, 1990). By outsourcing services to suppliers, the pharmaceutical companies also miss out on the opportunity to develop their own contacts, learn new manufacturing skills or explore new R&D opportunities that would otherwise prove beneficial for in-house operations (Piachaud, 2002).

5) **Problems of monitoring supplier performance:** even though a pharmaceutical company may assign the responsibility to manage a particular project to a service provider, it is still accountable for management of various other important aspects that affect the success of the partnership Gantz (1990). Monitoring and managing of multiple research collaborations with different CROs and CMOs is a challenging task. To develop an effective monitoring system, pharmaceutical companies have to invest resources like time, money and expertise (Piachaud, 2002). In addition, suppliers gain

significant knowledge about the research and manufacturing process of the product and may use that information and knowledge to start research and manufacturing on their own (Gilley & Rasheed, 2000). Effective supervision is also needed to ensure that the work is carried out as per requirements (Piachaud, 2002).

6) **Clash of Culture:** the goals and ambitions of collaborative partners working on a same project can vary. Even the work culture and management styles in these partner firms are different. Such varying degree of working styles and patterns can lead to a clash of opinions and conflict in ideas thereby disrupting the flow of the project (Piachaud, 2002).

4.4 Time to market

The drug development process is a lengthy and costly process including years of research and lengthy clinical trial processes. It takes an average of 10 to 15 years with an expenditure of more than $800 million to develop a new drug (Watkins, 2002; Colvin & Maravelias, 2008). With newer products being added onto the drug development pipeline, the development time and cost for new drugs has drastically increased creating a challenge for pharmaceutical companies to successfully launch their product into the market (Walker, 2004).

With respect to new product development, time to market has the following benefits: First, it leads to less money being spent on the development process. If the process has a shorter lead time, it means that less number of procedures need to be carried out thereby reducing the amount of money being spent. Second, lower number of procedures means concentrated efforts can be made during the development process thus resulting in occurrence of fewer problems during the later stages of the development process. Thus, for the problems that occur, inexpensive rework or corrective action needs to be taken. Third, with the integration of the effective time to market techniques in the manufacturing process, a firm can reap the benefits of an efficient manufacturing system thus producing low cost products. Experienced and competent users of the time to market techniques are not only able to minimise costs but also speed up the

manufacturing process thereby enjoying the benefits of larger market share (Pawar et al., 1994).

There are various benefits of bringing the products to the market quicker than the competitors. The first mover advantage can benefit the product by helping it achieve extra sales revenue and an early opportunity for achieving breakeven. Early entry to the market would provide the product with an extended sales life and an opportunity for premium pricing. It may also lead to development of loyalty amongst the customers invariably leading to an increased market share. Early introduction would help the company to introduce technological leadership and sustain it to maintain the lead in the market (Pawar et al., 1994).

Due to short product lifecycles and rapidly changing technology, pharmaceutical companies are under immense pressure to quickly develop and launch their products into the market (Calantone & Benedetto, 2000). In today's fast moving world, competitive advantage for companies is constantly evolving. It is important for companies not to get stuck with the perception of it source of advantage but to keep moving and create a competitive edge (Stalk Jr, 1998). One of the crucial factors for success in the pharmaceutical industry is the time it takes for a product to reach the market (Datar et al., 1997).

Pharmaceutical firms can increase their profits and improve the product quality immensely by speeding the development cycle. Even though the common perception is that cycle time can only be reduced for the non R&D parts of the development process, experts from the industry argue that if a pharmaceutical company is able to reduce its clinical cycle time, it would not only increase its profits but also improve its product quality (Boggs et al., 1999). During the development period of a drug, there are significant amount of inefficiencies and time delays that lead to lower overall profitability for a pharmaceutical company. If the average profit from a drug is estimated at $17000 per day, then delay due to extended development cycles can cause significant amount of losses for the pharmaceutical company (DiMasi et al., 1995).

Like any process, accelerating the development cycle too has effects and side effects. Cycle time improvement leading to shorter development cycles encourages pharmaceutical companies to undertake future innovation at a lower cost along with lower manufacturing concerns and develop a well equipped and integrated knowledge base. However, under the pressure of accelerating the products into the market, pharmaceutical firms tend to overlook some key issues like safety and efficacy of the drug in question, which inevitably leads to rejections of the drug by the FDA and thus delays the drug's entry into the market (Gupta & Souder, 1998; Boggs et al., 1999).

Reducing the time to market is an important element of any business strategy. Cycle time improvements in the drug development process can be achieved through various conceptual solutions. These solutions are *Outsourcing* services to CROs and CMOs, *Effective Documentation, Knowledge Integration and Concurrent Engineering Processes.*

4.4.1 Outsourcing

Outsourcing includes partnering with an efficient CRO or a CMO which provides end-to-end solutions in accordance with the regulatory requirements with respect to R&D and production activities respectively. The sponsor company should carefully select the most suitable contractor.

Outsourcing to CROs

A key criterion that pharmaceutical companies consider while selecting a CRO is whether or not the CRO has the technological infrastructure and modern instruments to manage the highly regulated clinical trial process thereby speeding up the drug development process (McNally, 2009).

Technologically advanced instruments can play a crucial role in reducing the time and costs associated with the development process. CROs are equipped with technologically advanced instruments like LC-UV (liquid chromatographic ultraviolet), LC-MS/MS (liquid chromatography-tandem mass spectrometry) and TSQ (Triple-stage-quadrupole) mass spectrometer, all of which are operated by

highly trained and skilled staff (Piachaud, 2002; McNally, 2009). These instruments can be customized to meet the sponsor' needs and provide fast and accurate pharmacokinetic analysis in the drug development process. For example, in a single run, the TSQ mass spectrometer can effectively screen up to 3000 compounds and detect the compounds with the highest probable success levels (McNally, 2009).

Another important and significant factor that can speed up the development process is the data handling infrastructure of the CRO. The sponsor company makes use of data reports prepared by the CRO for filing a new drug application for approval to the FDA. If the CRO and the sponsor company both use the same software, it can facilitate a smooth flow of information between the two organisations and expedite the time to market for a drug (McNally, 2009).

Outsourcing to CMOs

Similar to outsourcing R&D to CROs, outsourcing production or manufacturing to CMOs too can significantly reduce the time it takes to bring a product to the market (Vetter Pharma International GmbH, 2009). The sponsor company carefully selects an efficient external manufacturer; one that not only provides services in the early product development stage like pre-project consultation, but also in product manufacturing and testing stages like packaging and labelling services (Plambeck & Taylor, 2005; Strauss & Novak, 2009; Vetter Pharma International GmbH, 2009).

An experienced collaborative manufacturer has the methodological and technical expertise required to successfully implement a project thereby reducing the learning curve and consequently reducing the time to market for the drug (Vetter Pharma International GmbH, 2009). Just like CROs, the CMOs are also well equipped with the infrastructure and capacity in terms of the latest technology and well trained staff to manage the manufacturing operations. This technology can be customised according to the manufacturing needs of the project thus reducing the validation time of the drug considerably and consequently reducing the time to market (Vetter Pharma International GmbH, 2009).

Equipped with complete backup systems and readily available resources, CMOs can respond to the changes in demand quickly and help in avoiding all potential losses (Plambeck & Taylor, 2005; Vetter Pharma International GmbH, 2009). A CMO's positive track record with the regulators can also expedite the approval process thereby reducing the time to market (Vetter Pharma International GmbH, 2009). The above factors would enable a pharmaceutical company to streamline the manufacturing processes and significantly reduce the time to market for the new drug (Howard, 2003).

4.4.2 Effective Document Management

The pharmaceutical drug development process takes an average of 10 to 15 years from the earliest stages in discovery to the time it is made available for use to patients (Colvin & Maravelias, 2008; Colvin & Maravelias, 2010; Pharmaceutical Product Development, 2010; Tauzin, 2010). With the threat of declining patent life of drugs and availability of generic substitutes, pharmaceutical companies are under constant pressure to reduce the time it takes to develop the drug (Levis & Papageorgiou, 2004). In order to successfully reduce time to market of a drug, pharmaceutical firms will have to try and reduce time delays in every phase of the drug discovery process by means of effective document management (Master Control International, 2010).

The pharmaceutical drug development process is a document intensive process. Due to regulatory requirements, pharmaceutical firms need to document their activities from the early research years to the last marketing years of the drug development process. While doing so, they must manage their documentation effectively in order to avoid time delays. The preclinical stage of the drug development process ranges from discovering the drug to filing IND applications. In this phase thousands of documents are generated. The IND application alone requires accumulation of every possible detail about the safety and efficacy of the researched compound. The application must also

provide details about how the company plans on testing the drug in the clinical trial phase (Master Control International, 2010).

While the preclinical trials focus towards the IND application submission, the clinical trial phase focuses towards the submission of the new drug application. Clinical trials take up to 7 years and studies are conducted on thousands of healthy volunteers to check the toxicity of the drug in human beings. During the clinical trials numerous documents are prepared to record the toxic effects of the drug and provide information on the methods of manufacturing and packaging the drug. Like the IND application, the new drug application is intricate and voluminous containing around 100,000 to 600,000 pages of documented text to be submitted to the FDA for approval (Master Control International, 2010).

The documentation still continues while the drug awaits FDA approval. The pharmaceutical company starts gearing up for manufacturing the drug while simultaneously preparing adverse effects reports and quality control reports that need to be submitted to the FDA. With so many regulatory documents to be submitted and time in terms of market exclusivity running out, the company should follow an effective document management system. This system can lead to increased efficiency and eliminate time wastage. Under this system all the documents would be stored in a web based central repository where they can be easily updated, searched and retrieved. The virtual workspace would make document collaboration easier and eliminate redundant data. Such a flexible system would not only streamline the documentation process but also eliminate time wastage. Thus with the help of effective document management a pharmaceutical company can reduce the time to market of the drug (Master Control International, 2010).

4.4.3 Knowledge Integration

As the drug development process is plagued by increasing number of complexities and uncertainties it leads to long developmental cycles thereby increasing the time to market of a new drug. To successfully launch a new product into the market, pharmaceutical companies not only have to satisfy various regulatory requirements but also maintain an effective flow of data throughout the pharmaceutical supply chain. In a knowledge intensive industry like the pharmaceutical industry, it is important for the knowledge to be effectively managed Mohan et al., (2007). As the knowledge obtained by the pharmaceutical company during the course of development is its primary source of competitiveness, it is essential to effectively capture, communicate and re-use the knowledge (Sapienza & Lombardino, 2002).

During the drug development process, extensive knowledge is generated and consumed. Following the functional involvement of the experts from various areas like clinical trials, manufacturing, regulatory control etc. there is creation of fragmented knowledge at numerous phases of the drug development process. In order to reduce time delays it is important to share the knowledge among the stakeholders who play a significant role in the drug development process. This can be achieved by integerating the fragmented knowledge Mohan et al., (2007).

A critical component of knowledge integration is the pooling of individual knowledge to create group level knowledge (Boer, Bosch, & Volberda, 1999). This knowledge can be gathered across various stages of the drug development process and integrated into one single organisation level knowledge base. Such an integrated knowledge base can be achieved by establishing knowledge networks. "A knowledge network can be defined as a network in which nodes represent different fragmented and distributed knowledge components that are critical for medical product development and are integrated through links of different types" (Mohan et al., 2007, p. 1259).

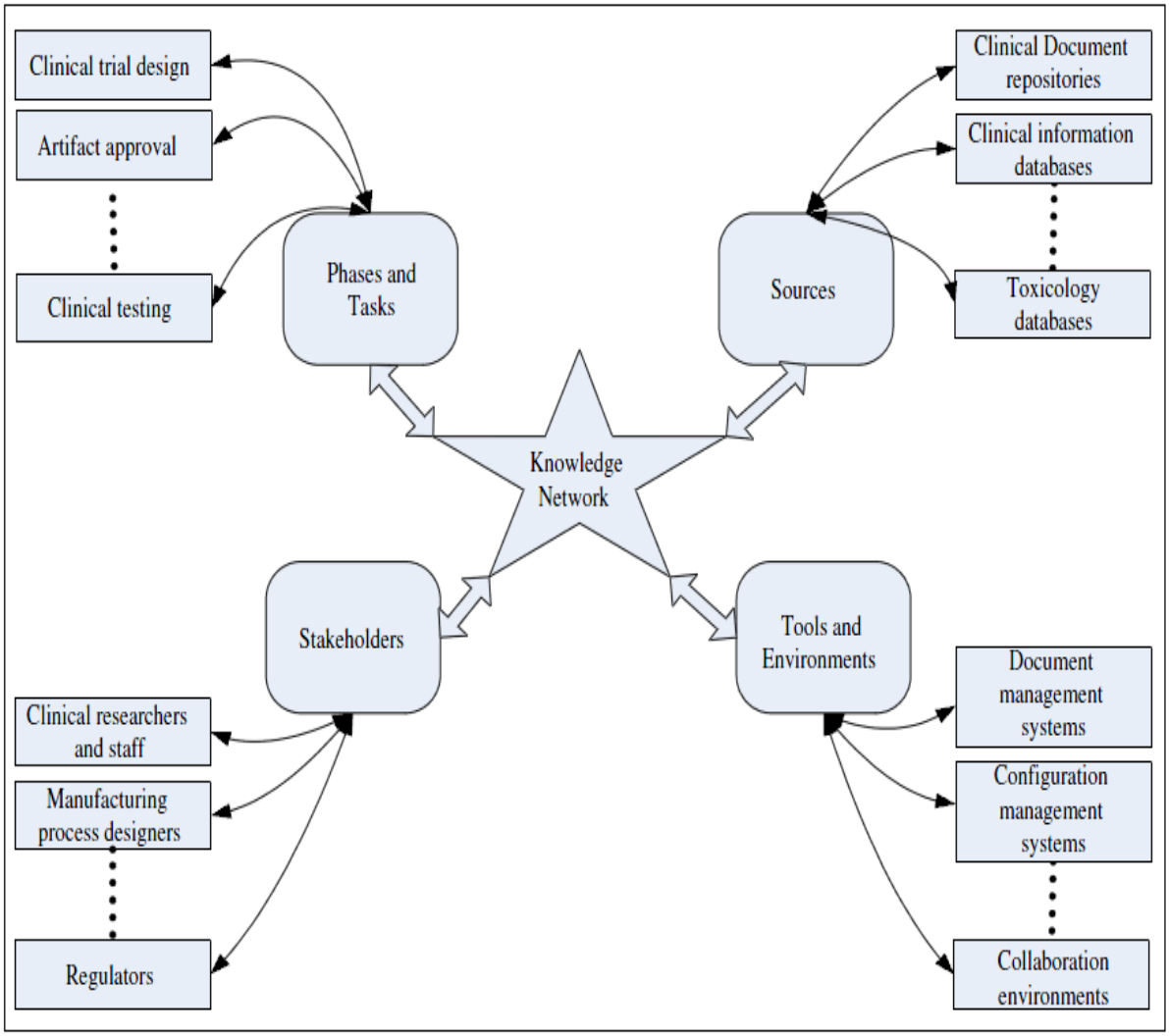

Figure 5. Knowledge Networks

Source: (Mohan et al., 2007)

This knowledge network includes stakeholders who are involved in the creation and use of the knowledge fragments. Such a network links the fragmented knowledge that is generated and used during the various stages of the drug development process. If the knowledge generated from the early phases is shared through the knowledge network, other functional teams can also participate in the later stages of the new product development process thereby accelerating the development time and consequently reducing the time to market (Mohan et al., 2007).

4.4.4 Concurrent Engineering Processes

In order to reduce the development time of drugs and bring them to the market quickly, it is important for pharmaceutical companies to adopt the concurrent engineering processes (Barius, 1994). Concurrent engineering is the technique by which numerous teams within an organization work simultaneously in order to develop a new product. (Debackere, 2010). Instead of the sequential way, concurrent engineering focuses towards performing the activities simultaneously (Barius, 1994). It is based on the premise that by performing activities in parallel organisations are effectively able to reduce the development time of the new products (Parsaei & Sullivan, 1993; Barius, 1994; Debackere, 2010).

In a concurrent engineering environment of the drug development process, experts from various areas like R&D, manufacturing, regulatory control etc. are encouraged to come together as a team and work on a single project. The main aim of the team is to work full-time on the same project from its start to its finish. This method leads to active involvement of the team members in every activity of the drug development process (Barius, 1994). With effective communication regarding the various stages of the drug development process and easy access among the core team members, pharmaceutical firms can achieve the reduction in delays thus consequently leading to reduction in time to market of the drug (Barius, 1994; Willaerta, Rob, & Minderhoudc, 1998).

Chapter 5

Findings and Discussion

The drug discovery and development process in the pharmaceutical industry is a risky and lengthy process. Besides taking 10 – 15 years for development, this process also cost more than an average of $800 million. With so many unsuccessful drugs in the R&D pipeline, pharmaceutical drug development cost increases as the cost of unsuccessful drugs is also added to the cost of successful drugs. Pharmaceutical companies develop and launch drugs into the market with the hope of creating a blockbuster drug. However, the varied uncertainties and the lengthy time to market for a new drug prevent the drugs from being launched into the market on time thereby causing heavy losses to the pharmaceutical drug development company.

The uncertainties that the drug discovery and development process endures in terms of cost, duration, resource requirements, technical and market uncertainty as well as the problem of delayed entry of the product into the market as mentioned in chapter 2 can be dealt with outsourcing and various other techniques of reducing time to market of a drug. (as mentioned in chapter 4)

It is important for the pharmaceutical industry to gain knowledge of processes and techniques employed by other industries and incorporate them within the industry to gain benefit from it. For instance, by outsourcing R&D and other technical activities to vendors, Apple was able to successfully focus on, and develop its internal resources whilst simultaneously benefitting from the vendor's R&D and technical expertise. Without making any long term investments for research and development, Apple was able to develop the Apple Disk Operating System internally while allowing vendors to provide the software for the same (Quinn & Hilmer, 1994).

In the case of outsourcing manufacturing, Nike shoes has also benefitted tremendously. The company benefits from the vendor's technical expertise and knowledge by outsourcing 100 percent of its shoe production. This provides the company with the opportunity to concentrate on its core activities of pre-

production (R&D) and post-production (marketing, distribution, and sales). Outsourcing R&D and manufacturing activities to vendors has allowed both Apple and Nike, to not only maintain flexibility to adopt new technologies but also access specialised knowledge and skills consequently reducing cost, uncertainty and time to market for their respective products (Quinn & Hilmer, 1994).

The pharmaceutical companies have the capability and capacity of conducting a full scale drug development process in-house. However, with the availability of numerous ambitious projects, pharmaceutical companies should effectively manage their R&D pipeline in order to reduce uncertainties and developmental time of new drugs thereby accelerating the product's entry into the market. Outsourcing activities to CROs and CMOs provides pharmaceutical companies with the opportunity of further developing their competencies. These external contractors are equipped with the latest technology and also employ skilled and competent staff. Companies can outsource the extensive research activities to CROs and manufacturing activities to CMOs without making long term investments in terms of technology and equipment. This allows the pharmaceutical company to take advantage of the technological advancements while simultaneously expanding their resources and capabilities.

Outsourcing not only reduces cost and time to market for a drug but also helps in effective allocation of resources. Once the R&D activities are outsourced to CROs, it is their duty to perform effective clinical trials while the firm can concentrate on its core activities. This leads to successful completion of the three clinical trial phases thereby reducing technical uncertainty and consequently reducing the time to market for a drug.

In today's fast moving world of rapidly changing technology and short product lifecycles, many companies are under immense pressure to reduce the time it takes to launch their product into the market. Like any other industry, reducing time to market has become one of the most crucial factors for success in the pharmaceutical industry as well. Along with Outsourcing, there are other techniques like Effective Documentation, Knowledge Integration and Concurrent Engineering Processes that can effectively be employed to reduce the time to market for a product.

The above mentioned techniques form a part of the long term model which pharmaceutical firms did not incorporate earlier but the integration of which has become an essential component for reducing time to market of the pharmaceutical products. As mentioned in chapter 4, Effective Documentation is an important tool that focuses towards reducing time to market in the pharmaceutical industry.

The pharmaceutical industry is a document intensive industry where as per FDA regulations; documents are prepared recording every activity of the extensive drug development process. With the involvement of varied stakeholders in the drug development process, extensive documents, from the early research stage to the very last marketing stage are prepared. Due to the creation of numerous documents, it often becomes necessary for pharmaceutical companies to manage their documents effectively. This allows documents to be stored in a central repository where stakeholders can easily search and retrieve information regarding the drug thereby reducing redundancy of data and tests. This not only increases efficiency but also eliminates wastage of time.

Another successful tool that aids in reducing time to market is Knowledge Integration. The pharmaceutical industry could learn a lot from the software industry where companies are following the sun and sharing their knowledge across a knowledge network. Research is being conducted in different parts of the world and shared on a common platform with the various stakeholders of the project. This allows the stakeholders to participate and provide their inputs. Developmental teams can come together and participate in the later stages thereby significantly reducing the time to market for their product.

Similarly in the pharmaceutical industry, extensive knowledge is generated and consumed during the drug development process. Since this knowledge is created throughout the different stages of the drug development process, it is essential to share this knowledge amongst the various stakeholders through a common networking platform. Thus the knowledge networks not only link the stakeholders with updated information on the drug but also invite them to

participate towards successful completion of the drug development process thereby reducing the time to market for the drug.

Concurrent engineering processes can be applied to any industry. This phenomenon allows companies to perform various activities simultaneously and reduce time to market significantly. Concurrent engineering processes have been successfully implemented by Polaroid, Boeing, NASA and European Space Agency. With the use of concurrent engineering processes, General Electric was successfully able to reduce the design time for aircraft engine components by roughly 19 weeks. This helped the company in establishing and maintaining flexibility for changing customer demand (Dias, 2010).

Pharmaceutical companies should also adopt concurrent engineering processes in order to effectively reduce the lengthy development time and consequently reduce the time to market. Drug discovery is a complex process involving numerous stakeholders at various stages. These stakeholders perform their respective tasks as the drug passes through to them during the various stages. By adopting concurrent engineering processes, the stakeholders would perform their tasks in parallel with other stakeholders thereby effectively reducing the development time. By effective communication through-out the drug development process and performing the tasks in parallel, pharmaceutical firms can reduce the time delays and consequently reduce the time to market of the new drug.

Thus by integrating Outsourcing, Effective Documentation, Knowledge Integration and Concurrent Engineering Processes in a seamless way, pharmaceutical firms can effectively reduce uncertainties and significantly reduce the time to market for a product. This would allow them to become more responsive to changing market conditions and gain sustainable competitive advantage over its competitors.

Chapter 6

Conclusion and Future Recommendations

6.1 Conclusion

The drug discovery process is an important aspect of the pharmaceutical industry. It is a lengthy and costly process which entails all the stages from the pre discovery stage to the regulatory approval stage for a drug. As drugs are produced to meet the unmet medical needs of the population, thus, it is very important to identify factors through which the drug can reach the market quickly. While doing so, it is important to identify the various underlying uncertainties and problems that delay the drug's entry into the market.

The pharmaceutical drug discovery and development process has uncertainties that hinder the drug's entry into the market. By outsourcing activities like R&D and manufacturing to CROs and CMOs respectively, the pharmaceutical companies gain the benefits in terms of technical expertise and smooth flow of operations. This provides the pharmaceutical companies with the opportunity to focus on and develop other competencies. By using outsourced expertise and in-house knowledge of processes, pharmaceutical firms would effectively be able to reduce uncertainties like cost, duration, resources requirements, technical and market uncertainty and consequently reduce time to market for a drug.

Other than managing uncertainties, it is equally important for the pharmaceutical companies to understand the underlying causes for time wastage during the drug discovery and development process. Besides outsourcing, pharmaceutical companies can make use of various other techniques like effective documentation, knowledge integration and concurrent engineering processes. Integration of these techniques in the drug discovery and development process would enable the pharmaceutical firms to store the multiple documents containing the drug's information in one single repository where it would easily be accessible to various stakeholders. This would reduce redundancy of data and help in avoiding repetition of tests.

Stakeholders of the drug discovery and development process would be able to share the knowledge that is created along the numerous stages with one another through a knowledge network. This would facilitate their participation in the later stages of the drug discovery and development process. Pharmaceutical firms should adopt concurrent engineering processes where instead of waiting for one activity to get completed, activities are performed simultaneously. Adoption of the above mentioned techniques can significantly reduce the time to market for a drug.

Thus, by reducing uncertainties and time to market for a drug, pharmaceutical companies can effectively launch the product quickly into the market and gain sustainable competitive advantage.

6.2 Future Recommendations

For any project in any industry research is never enough. Although a lot has been written with reference to the drug discovery and development process, there is still scope to understand and learn more about the same. There is need to learn in detail about the arguments presented by the researcher.

It is necessary to explore practical examples of the arguments stated by the researcher. A study of how these examples work and what their potential benefits and limitations are can provide future researchers with an opportunity to understand the drug discovery and development process further.

The argument that outsourcing can reduce uncertainties and consequently lead to a reduction in time to market for a drug can be studied further in detail. Detailed study of the argument, that time to market techniques like effective documentation, knowledge integration and concurrent engineering processes can accelerate the drug discovery process and lead to a quick launch of the product into the market is also required to allow future researchers to understand the drug discovery and development process better.

Another focus of study would be to explore the underlying uncertainties of the drug discovery and development process in different cultural contexts. A study on how to reduce those uncertainties in the extensive drug discovery and development process also hold character for future research. A comparative analysis of the two most probable destinations for outsourcing; India and China is also an important factor for future research.

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