CHAPTER 1

PHARMACEUTICAL INDUSTRY

1.1 INTRODUCTION

The global pharmaceutical industry, in the last few years, has been showing interest in India pharma industry because of its sustained economic growth, healthcare reforms and patent-related legislation. Indian Pharmaceutical Industry has already been placed among the top four emerging markets in pharma industry by the market research report published by IMS Health Inc. The positive approach towards product and patient has encouraged the Indian pharmaceutical companies to invest more in Research and Development. India’s traditional strength lies in small molecule APIs and generics. India ranks third in worldwide volume of production and is 14th largest by value. The main reason for this discrepancy has been determined to be the lower cost of such drugs in India, compared not only to the traditional markets but to smaller markets like Zimbabwe and Sri Lanka.

1.2 IMPORTANCE OF PHARMACEUTICALS

In the United States, emergence of health maintenance organizations (HMOs), combined with rising private medical care costs and Government management of Medicare and Medicaid health programs, has contributed to a trend toward finding the most cost-effective way of treating illnesses. As a result of these trends, consumption of both ethical and over-the-counter (OTC) pharmaceuticals increased during 1993-97. And during the
same period, Increases in Western European and Japanese consumption of pharmaceuticals also occurred. Hence Pharmaceuticals are important in all aspects of health care and have been shown to be the most cost-effective means of treating some diseases when compared with surgical procedures.

1.3 CHALLENGES AND OPPORTUNITIES FOR PHARMA INDUSTRY

Due to increased regulatory scrutiny such as - stringent safety and quality regulations, combined with the effect of innovations in medical science and healthcare, and a complex and costly design-to-market process, the pharmaceutical industry faces some unique challenges and is going through major changes in operating procedures. Regulations and regulatory compliance is a legal requirement mandated by the regulatory agencies to ensure public health and safety. With blockbuster drugs representing more than $50 billion in annual revenue coming off patent in the next few years’ pharma companies are contending with a series of challenges which will affect their revenues. It takes an average of 15 years and more than $800 million to bring new product from the research stage to market. During this process the agency’s review and approval is highly dependent on the quality of data submitted to the regulatory agencies. Faced with the continuing financial and competitive pressure, many companies are moving beyond the traditional barely focused relationships and discovering new types of strategic partnerships designed to deliver project oversight cost reductions and time savings without affecting the core business processes.

1.3.1 Pragmatic Shift in Regulatory Environment

The demand for globally acceptable products enhances the imperative for management of regulatory requirements to lend efficiency and cost effectiveness to the process of product development, manufacturing and
expediency to global access. Hence Management of regulatory requirements is also enabling the globalization of regulatory affairs activities. Many of the global pharma companies are publicly pursuing aggressive growth strategies, in this respect, a truly “global” regulatory affairs organization needs to substitute local knowledge, cultural understanding and personal contacts in these markets to support ambitious commercial strategies through achieving timely and full approvals, and ultimately market access.

1.3.2 Challenges in Pharma Industry

The regulatory agencies are working towards the management of regulations and regulatory guidelines at global level pharma industry are facing tough time. The major challenges faced by industry are:

1.3.2.1 Changing Regulations

As the developing country’s economy is growing they are emphasizing more on the public health and their well-being. The regulated countries like Europe, US is emphasizing on more stringent guidelines and regulation concerning the development and manufacturing of the drugs for human use. Earlier days when the emphasis was given only on quality, now the regulators have become more demanding and expecting the industry to match the standards which comply with the concepts such as quality by space, quality by design, quality risk management.

1.3.2.2 Strict timeline for implementing new changes

At the latest, marketing authorization holders shall electronically submit to the Agency gen on all medicinal authorized products for human use. Medicinal product gen for new or varied, suspended or revoked marketing authorizations shall be submitted by marketing authorization holders
electronically to the Agency immediately and no later than 15 calendar days from the date of authorization, variation, suspension or revocation.

1.3.2.3 Product life cycle management

Maintaining the product life cycle is another challenge, while companies are busy in keeping in maintaining their new submissions up-to-date at the same time assuring the compliance to the existing and new standards enforced by the regulatory agencies.

1.3.2.4 Barriers to implement electronic reporting

Few barriers that industry is facing to adopt or implement the electronic data interchange (EDI) are accompanying business process change. The existing process built around slow paper handling may not be suited for EDI and would require changes to accommodate the new processes. Another yet main crucial factor is cost in time and money required in the initial set up. The preliminary expenses and time that arise from the implementation, customization and training can be costly and therefore may discourage some businesses. The adoption of the new technologies threatens the records and information in older systems.

1.3.3 The Developing cost of a New Drug

Research and development costs vary widely from one new drug to the next. Those costs depend on the type of drug being developed, the probability of failure, and whether the drug is based on a molecule not used before in any pharmaceutical product (a new molecular entity, or NME) or instead is an incremental modification of an existing drug.
1.3.4 Innovation in Drugs

The cost of developing an innovative new drug can be very expensive and it reflects the research strategies and drug-development choices that companies make on the basis of their expectations about future revenue. If companies expected to earn less from future drug sales, they would alter their research strategies to lower their average R&D spending per drug. The cost estimate also calculated how long it takes to develop a new drug and the relative contribution of investment costs to a drug’s total R&D costs. On average, developing an innovative new drug takes about 12 years, the study concluded, and a firm’s actual expenditures make up only about half of the total reported cost. The rest represents the financial cost of tying up investment capital in multiyear drug development projects, earning no return until and unless a project succeeds.

First, failure rates in clinical trials have increased, possibly because of greater research challenges or a willingness to test riskier drugs in such trials. Second, larger drug firms are said to have shifted the focus of their development efforts away from drugs for severe illnesses and toward drugs furlong-lasting illnesses. Drugs for long-lasting illnesses can be more expensive to develop because they often require larger and longer clinical trials. Third, greater technological complexity in drug development and greater specificity in disease targets have helped to raise average R&D costs, as firms now identify drugs with particular molecular characteristics rather than using trial-and-error methods to find compounds that work in some desired way.
1.3.5 Incrementally Modified Drugs

Most new drug products have much lower R&D costs than NMEs because they are incremental improvements on existing drugs. Those costs can still be considerable if the new product requires clinical trials. Incrementally modified drugs sometimes provide significant benefits to consumers. For example, more convenient dosing forms (a pill that can be taken once a day rather than every four hours) can increase the probability that patients will take their medicine as directed and can result in better health.

1.4 CHALLENGES AND OPPORTUNITIES IN ORAL FORMULATION DEVELOPMENT

New chemical entities that are poorly soluble provide challenges as well as opportunities to scientists working in formulation development. The conventional solubilization approaches such as physical modifications of drug crystals usually lead to a limited dissolution and solubility enhancement, but when developing a medium or high dosed formulation, the non-conventional formulation (water-insoluble compounds) approaches are often required.

Dosage requirements in the drug development also introduce opportunities to explore the other non-conventional formulation approaches for enhanced solubilization. Liquid and solid dispersions, especially, are widely considered the alternative methods, which may require a range of factors for selecting one versus the other. These formulation approaches are excipients-driven. With limited scope in the excipients’ selection, the industry is seeking new excipients to bring the drugs to the market faster and with a better performance. Furthermore, the development of safe and efficacious formulations (solid and liquid dispersions) requires complete
evaluation of dosage stability, therapeutic efficacy and mitigation of food effect among other factors. In the past, the liquid dispersions have been preferred over the solid dispersions for new drug candidates. Since in the early formulation development, it reduces the development time and cost. However with the development of new technologies, the preparation of solid dispersions and new excipients are going to change the formulation types.

![Diagram](image)

**Figure 1.1 An outline of complexity in drug development**

Figure 1.1 illustrates the complexity of formulation development in highly regulated environments. And it requires multi-facet components to achieve a particular dosage with sound quality, safety and efficacy. It is not only the active ingredients (APIs) and excipients, but also the manufacturing and/or the delivery technologies that plays an equally important role in achieving the desired quality, safety and efficacy of a drug product.

The scope of this study is to cover the challenges and opportunities curtailing from poorly soluble molecules for oral delivery. And also it leads an industry to adjust by adopting new non-conventional formulation technologies to bring new drugs into the market. The study will cover the biopharmaceutical classification systems (BCS) of drugs, and the factors that
could lead to the increase of solubility and permeability of drugs, and an understanding of super saturation, and the excipients’ role in development of liquid and solid dispersions.

1.4.1 Biopharmaceutical Classification Systems (BCS)

The solubility and/or permeation enhancement of molecules for Class II, III and IV can be achieved to meet the so-called biopharmaceutical fitness by many approaches. Over 90% of the marketed drugs qualify under Class II and Class IV. The continued trend of increased number of poorly soluble and permeable molecules is alarming and has brought the industry nearly to a halt. The work continues to overcome these formulation challenges to find the appropriate solutions for these poorly soluble and permeable molecules.

Table 1.1 Shows the classification of drugs according to the current understanding of BCS

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<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>High</td>
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<tr>
<td>II</td>
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<td>III</td>
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<tr>
<td>IV</td>
<td>Low</td>
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This study aims at examining the challenges in developing stable formulations and the role excipients play in maintaining the super saturation of drugs in the dosages.
1.5 ROLE OF EXCIPIENTS IN THE FORMULATION DEVELOPMENT

1.5.1 Liquid Dispersions

Liquid dispersions have been the subject of continued interest in drug delivery and development. The lipid-based delivery systems (LBDS) have been identified as “true liquid dispersions for self (micro) emulsification drug delivery systems “(S(M)EDDS)” and applied successfully in development of poorly soluble lipophilic molecules with SEDDS and SMEDDS provide an easy scale up for manufacturing of these dosages in oral solutions, liquid/semi-solid for soft gel, and/or pellets for hard gel capsules or tablets, and are amenable to those requiring highest achievable doses.

![Figure 1.2](image_url) Factors lead to increased solubility and permeability of Class II and IV, and Class III drugs.

1.5.2 Solid Dispersions

Solid oral dosages formulations (SODF) have continued to be the focus in the industry. Especially, the solid dispersions are fully exploited for
highly crystalline and high melting lipophilic drugs wherein the drugs are converted to a high energy amorphous powder to increase the solubility and bioavailability. This study will focus on the amorphous solid dispersions in general and lay out the role of excipients in the formulation development.

1.6 TABLET FORMULATION IN PHARMACEUTICS

A tablet is a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. In order to ensure efficient tableting the excipients include binders, glidants (flow aids) and lubricants. Disintegrants to ensure that the tablet breaks up in the digestive tract, sweeteners or flavors to mask the taste of bad-tasting active ingredients and pigments to make uncoated tablets visually attractive. A coating may be applied to hide the taste of the tablet's components to make the tablet. A tablet can be formulated to deliver an accurate dosage to a specific site; its usually taken orally but can be administered sublingually, rectally or intravaginally. Tablet formation represents the last stage in down-stream processing within the pharmaceutical industry smoother and easier to swallow.

Tablets are often stamped with symbols, letters and numbers, which enable them to be identified. Sizes of tablets to be swallowed range from a few millimeters to about a centimeter. Some tablets are in the shape of capsules and are called caplets. Medicines to be taken orally are very often supplied in tablet form; indeed the word tablet without qualification would be taken to refer to a medicinal tablet. Medicinal tablets and capsules are often called pills. Other products are manufactured in the form of tablets which are designed to dissolve or disintegrate.

The tablet is composed of the Active Pharmaceutical Ingredient (that is the active drug) together with various excipients. These are biologically inert ingredients which either enhance the therapeutic effect or are necessary to construct the tablet. The filler or diluent is abulking agent,
providing a quantity of material which can accurately be formed into a tablet. Binders hold the ingredients together so that they can form a tablet. Lubricants are added to reduce the friction between the tablet and the punches and dies so that the tablet compression and ejection processes are smooth. Disintegrants are used to promote wetting and swelling of the tablet so that it breaks up in the gastrointestinal tract; this is necessary to ensure dissolution of the API. Super-disintegrants are sometimes used to greatly speed up the disintegration of the tablet. Additional ingredients may also be added such as coloring agent, flavoring agents, and coating agents. Formulations are designed using small quantities in a laboratory machine called a Powder Compaction Simulator. This can prove the manufacturing process and provide information for the regulatory authorities. Big Pharma’s crisis in R&D productivity is not going to be solved soon. From declining rates of innovation to increased costs of development, the industry is getting hit from every side.

However, with the industry facing its greatest challenges in history, R&D productivity is a topic that few companies can ignore. Although many of the strategic alternatives highlighted above could help improve R&D productivity. It is likely that the next decade will see hybrid model of pharmaceutical R&D that incorporates several of the strategic alternatives highlighted above. The possibility also exists for a ‘disruptive innovation’ to blindside the industry and change the way pharmaceutical companies operate. The benefit to the pharmaceutical company is that it only pays for success – not failure or effort, thereby reducing costs by orders of magnitude. It is estimated that this model could reduce the average costs of new drugs from $1.7 billion to $170 million within a fairly reasonable time frame, says Michael Raynor, author of “The Innovator’s Solution”. The consequences of that are surely world-changing. At the end of the day, no matter what strategies Big Parma adopts, the future of R&D will be unpredictable.