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1. INTRODUCTION

Pharmacology is the study of drugs. Pharmacy, although often confused with pharmacology, is an independent discipline concerned with the science of the preparation, compounding, and dispensing of drugs.

There are several terms related with pharmacology, as given below:

- ✓ Pharmacodynamics- it is the study of mode of action of drugs or biochemical and physiological effects of drugs.
- ✓ Pharmacokinetics- it deals with what body does with the drug.
- ✓ Pharmacogenetics- it is the science and study of the inheritance of characteristic patterns of interaction between drugs and organisms.
- ✓ Pharmacotherapeutics-it is the study of the use of drugs in the diagnosis, prevention, and treatment of disease states.
- ✓ Pharmacognosy- it is the study of medicines derived from natural sources.
- ✓ Ethanopharmacology-it is study of pharmacological qualities of traditional medicinal substances.
- ✓ Bioprospecting-it is the search for high value natural products, derived from biological sources (including genes) with diverse applications in medicine.
- ✓ Bioactive compounds- these are derived from one organism to inhibit other organism. e.g. - antibiotics.
- ✓ Routes of administration-these are the pathways through which drugs are administered, like oral(via mouth),sublingual(placed under tongue), rectal(via rectum),parenteral(using syringe) such as intracavity(in body cavity), intravenous(in veins), intradermal(in dermis), subcutenous(in subcutenous layer), intramuscular(in muscles), intrarterial(in arteries), topical(applied on skin) etc.

1.1. History of Pharmaceutical industry

The earliest drugstores date to the Middle Ages. The first known drugstore was opened by Arabian pharmacists in Baghdad in 754, and many more soon began operating throughout the medieval Islamic world and eventually medieval Europe. By the 19th century, many of the drugstores in Europe and North America had eventually developed into larger pharmaceutical companies.

Most of today's major pharmaceutical companies were founded in the late 19th and early 20th centuries. Key discoveries of the 1920s and 1930s, such as insulin and penicillin, became mass-manufactured and distributed. Switzerland, Germany and Italy had particularly strong industries, with the United Kingdom, the United States, Belgium and the Netherlands following suit.

Legislation was enacted to test and approve drugs and to require appropriate labeling. Prescription and non-prescription drugs became legally distinguished from one another as the pharmaceutical industry matured. The industry got underway in earnest from the 1950s, due to the development of systematic scientific approaches, understanding of human biology (including DNA) and sophisticated manufacturing techniques.

Numerous new drugs were developed during the 1950s and mass-produced and marketed through the 1960s. These included the first oral contraceptive, "The Pill", Cortisone, blood-pressure drugs

and other heart medications. MAO inhibitors, chlorpromazine (Thorazine), haloperidol (Haldol) and the tranquilizers ushered in the age of psychiatric medication. Diazepam (Valium), discovered in 1960, was marketed from 1963 and rapidly became the most prescribed drug in history, prior to controversy over dependency and habituation.

Attempts were made to increase regulation and to limit financial links between companies and prescribing physicians, including by the relatively new U.S. Food and Drug Administration (FDA). Such calls increased in the 1960s after the thalidomide tragedy came to light, in which the use of a new anti-emetic in pregnant women caused severe birth defects. In 1964, the World Medical Association issued its Declaration of Helsinki, which set standards for clinical research and demanded that subjects give their informed consent before enrolling in an experiment. Pharmaceutical companies became required to prove efficacy in clinical trials before marketing drugs.

Cancer drugs were a feature of the 1970s. From 1978, India took over as the primary center of pharmaceutical production without patent protection.

The industry remained relatively small scale until the 1970s when it began to expand at a greater rate. Legislation allowing for strong patents, to cover both the process of manufacture and the specific products, came into force in most countries. By the mid-1980s, small biotechnology firms were struggling for survival, which led to the formation of mutually beneficial partnerships with large pharmaceutical companies and a host of corporate buyouts of the smaller firms. Pharmaceutical manufacturing became concentrated, with a few large companies holding a dominant position throughout the world and with a few companies producing medicines within each country.

The pharmaceutical industry entered the 1980s pressured by economics and a host of new regulations, both safety and environmental, but also transformed by new DNA chemistries and new technologies for analysis and computation. Drugs for heart disease and for AIDS were a feature of the 1980s, involving challenges to regulatory bodies and a faster approval process.

Managed care and Health maintenance organizations (HMOs) spread during the 1980s as part of an effort to contain rising medical costs, and the development of preventative and maintenance medications became more important. A new business atmosphere became institutionalized in the 1990s, characterized by mergers and takeovers, and by a dramatic increase in the use of contract research organizations for clinical development and even for basic R&D. The pharmaceutical industry confronted a new business climate and new regulations, born in part from dealing with world market forces and protests by activists in developing countries. Animal Rights activism was also a challenge.

Marketing changed dramatically in the 1990s. The Internet made possible the direct purchase of medicines by drug consumers and of raw materials by drug producers, transforming the nature of business. In the US, Direct-to-consumer advertising proliferated on radio and TV because of new FDA regulations in 1997 that liberalized requirements for the presentation of risks. The new antidepressants, the SSRIs, notably Fluoxetine (Prozac), rapidly became bestsellers and marketed for additional disorders.

Drug development progressed from a hit-and-miss approach to rational drug discovery in both laboratory design and natural-product surveys. Demand for nutritional supplements and so-called alternative medicines created new opportunities and increased competition in the industry. Controversies emerged around adverse effects, notably regarding Vioxx in the US, and marketing tactics. Pharmaceutical companies became increasingly accused of disease mongering or over-medicalizing personal or social problems.

1.2. Biopharmaceutical Evolution

From the beginning of time, products derived from living beings had played a role in human health, influencing the evolution of civilizations and cultures, human migrations, wars, art, mythology, religion and so on. Examples include the plants like tulsi, which is known for its medicinal importance. The use of biopharmaceuticals is as old as mankind itself. Ayurveda, unani, kampo etc. contribute to today's biopharmaceuticals. Nearly 25% of modern medicines were first used traditionally.

A biopharmaceutical is a medical product that is produced from biological sources, like plants, animals and micro-organisms. The term bio comes from the Greek word bios meaning life and pharmaceutical comes from Greek word pharmakon which means drug. So, they are basically drugs produced with the help of biotechnology from life forms. They make up about one-third of the drugs being produced today. More than 150 biotech drugs, including hormones, antibiotics, insulin, interferons and thirteen blockbuster drugs are currently marketed around the world today. In other words, biopharmaceuticals have truly revolutionized the treatment of many grave diseases like diabetes.

Biopharmaceutical drugs structurally mimic compounds found in the body. They have the potential to cure diseases, rather than just treat them. They are proteins (including antibodies), nucleic acids used for in vivo diagnostic or therapeutic purposes.

Biopharmacology is the study of manufacture, use and effects of biotechnologically produced medicinal drugs. The key areas of investigation include drug production as well as elucidation of biochemical and molecular mechanisms of action. It is a relatively new area in the field of pharmacology.

Biopharmaceuticals can be developed from a number of different sources like microbial, plant and animal sources and can be extracted directly from living sources, via tissue culture, via recombinant DNA technology and via gene therapy.

The developments in biopharmaceuticals began with the development of biotechnology, and the major breakthrough in this field was the production of artificial insulin, which was the first biological drug. Before this development, insulin production was a relatively costly affair. It was derived from ox and dogs. Production of human insulin via biotechnological methods made insulin available in large quantities. This left a huge impact on the minds of consumers as well as manufacturers, leading to extra emphasis on biological drugs.

As compared to chemical drugs, biological drugs are considered to be relatively safer, as due to their specificity, they have fewer side effects. But there are several constraints that are being faced by manufacturers in the production of biologics, like financial, regulatory and technical barriers. Absence of sufficient funds, unavailability of required techniques, absence of proper regulatory

measures and experienced personnels to implement these measures are some of the limitations faced by the industry. Other than these, the problems faced during biopharmaceutical development are legal issues, like patent rights, ethical issues etc.

According to Paul Snelgrove, "we know more about the surface of moon and mars than we know about our oceans." That is why an important part of biopharmacology is marine pharmacology. It deals with discovery of biopharmaceuticals from marine source. Oceans cover three-fourth of Earth's surface, and only 1% of it is known. There are thousands of unknown organisms of all kingdoms in the ocean, making it a source of attraction for pharmacologists and making oceans a strong contender for the discovery and development new biopharmaceuticals.

1.3. Indian Pharmaceutical Industry

The number of purely Indian pharma companies is fairly less. Indian pharma industry is mainly operated as well as controlled by dominant foreign companies having subsidiaries in India due to availability of cheap labor in India at lowest cost. In 2002, over 20,000 registered drug manufacturers in India sold $9 billion worth of formulations and bulk drugs. 85% of these formulations were sold in India while over 60% of the bulk drugs were exported, mostly to the United States and Russia. Most of the players in the market are small-to-medium enterprises; 250 of the largest companies control 70% of the Indian market.Thanks to the 1970 Patent Act, multinationals represent only 35% of the market, down from 70% thirty years ago.

Most pharmaceutical companies operating in India, even the multinationals, employ Indians almost exclusively from the lowest ranks to high level management. Homegrown pharmaceuticals, like many other businesses in India, are often a mix of public and private enterprise.

In terms of the global market, India currently holds a modest 1–2% share, but it has been growing at approximately 10% per year. India gained its foothold on the global scene with its innovatively engineered generic drugs and active pharmaceutical ingredients (API), and it is now seeking to become a major player in outsourced clinical research as well as contract manufacturing and research. There are 74 US FDA-approved manufacturing facilities in India, more than in any other country outside the U.S, and in 2005, almost 20% of all Abbreviated New Drug Applications (ANDA) to the FDA are expected to be filed by Indian companies. Growth in other fields notwithstanding, generics are still a large part of the picture. London research company Global Insight estimates that India's share of the global generics market will have risen from 4% to 33% by 2007. The Indian pharmaceutical industry has become the third largest producer in the world and is poised to grow into an industry of $20 billion in 2015 from the current turnover of $12 billion.

1.4. Biopharmaceutical Viability

Bio pharmaceuticals are drugs produced using biotechnology. They are proteins nucleic acids, DNA, RNA used for therapeutic or for vivo diagnostic purposes, and are produced by means other than direct extraction from a native biological source. The first such substance approved for therapeutic use was recombinant human insulin. Traditional Pharmaceutical products more commonly known as medicines or drugs, are a fundamental component of traditional medicine. It is essential that such products are safe, effective, and of good quality, and are prescribed and used rationally. Majority of the biopharmaceutical products are pharmaceuticals that are derived from life forms.

Traditional medicine is a broad term used to define any non-Western medical practice. Ethno pharmacology is a diversified approach to drug discovery involving the description, observation and experimental investigation of indigenous drugs and their biologic activities. According to the World Health Organization (WHO), almost 65% of the world's population has incorporated into their primary modality of health care. There are numerous advantages and disadvantages of traditional medicine. Most traditional medicines are well tolerated by the patient while in some cases bio-pharmaceutical products are not.

Another advantage to traditional medicine is cost. Cost is much less than biopharmaceuticals. Yet another advantage of traditional medicines is their availability. They are available without a prescription, and some can simply be grown at home. While the high cost of biopharmaceuticals and the low reimbursement levels from insurance companies present a major challenge. It is needed to explore various strategies to counter this challenge such as developing technologies that bring down the cost of drugs as well as manufacturing biopharmaceuticals with substantial market size.

For sudden, serious illnesses, mainstream medicine still reigns supreme. A traditional medicine would not be able to treat serious trauma, such as a broken leg, nor would it be able to heal appendicitis or a heart attack as effectively as a conventional doctor using modern diagnostic tests, surgery, and biopharmaceutical drugs. Biopharmaceutical medicine treats sudden illness and accidents much more effectively than traditional.

Another disadvantage of traditional medicine is the very real risks of doing oneself harm through self-dosing. That is consciously maintained by biopharmaceutical product. There's a very real risk of overdose. Traditional products are not tightly regulated; consumers also run the risk of buying inferior quality. That is why it is best to use biopharmaceutical product. As the biopharmaceutical industry enters the 21st century, the pressure on companies to maintain the level of productivity required for consistent year-on-year growth is increasing.

This is the primary means by which the developer of the drug can recover the investment cost for development of the biopharmaceutical. In 1978 the total patents granted was 30. This had climbed to 15,600 in 1995, and by 2001 there were 34,527 patent applications. Modification of products is one target of drug design for enhancement of efficacy manufacturing process and discuss.

Simultaneously, raising public and clinician awareness of the cost benefits of biopharmaceuticals and collaborating with other insurance companies and government agencies to introduce reimbursement for biopharmaceuticals can help resolve this challenge to some extent. Traditional medicine remains largely an unproven, inexact science. Despite the criticism of traditional medicine amongst mainstream medical professionals, it is wise to remember that many common drugs we use today were derived from plant-based sources. Traditional pharmaceutical products are less safe, that is assured in modern biopharmaceutical products.

1.5. Importance of Biopharmaceuticals

Biopharmaceuticals are large and complex biological molecules. Their final biological activities very much depend on the methods used for their production. Recombinant proteins such as blood coagulating factors, erythropoietins, gonadotrophins, granulocyte colony-stimulating factors (G-

CSF), human growth hormones, interferons, interleukins and monoclonal antibodies are among the most important biopharmaceuticals marketed in past decades.

Biopharmaceuticals represent a rapidly growing market. It is reported that 32% of the products in development pipelines and 7.5% of marketed medicines are biopharmaceuticals. By 2020, biopharmaceuticals are forecasted to sell for around US$23 billion in the EU and US$29 billion in the US. Although currently many original brand-name biopharmaceuticals are protected by intellectual property laws and regulations, with expiration of their patent protection in the next few years the pharmaceutical industry faces a unique business challenge from both well regulated rival biosimilars as well as less regulated copied biopharmaceutical. Despite the increasing clinical significance of biopharmaceutical medicines, economic barriers limit their use for many patients, especially in developing countries. In the World Trade Organization (WTO) member countries, failure of the pharmaceutical industry to meet the needs of national health services may result in compulsory licensing regulation changes in order to permit local industries to produce and market copies of such patented medicines to be sold at more affordable prices.

The biotechnology industry's trade group, estimates that over 400 biopharmaceuticals are currently in clinical trials for over 200 diseases, some of which currently do not have treatments. In the past five years, the FDA has approved biopharmaceuticals for an increasing range of conditions. As a result, expenditures on biopharmaceuticals have more than doubled, from $35 billion in 2004 to $73 billion 2008. Autoimmune and oncology drugs make up 46% and 17%, respectively, of the biopharmaceutical product sales today. The revenues generated from the sales of today's generation of drugs encourage biopharmaceutical companies to invest in research and development for tomorrow's generation.

'Biosimilars' are biopharmaceuticals that are manufactured and marketed, usually by non-originator pharmaceutical companies, following expiration of the originator patents. Currently, marketing authorization of such biosimilars for highly regulated markets depends on demonstration of 'similarity' between a biosimilar and its corresponding originator biopharmaceutical. In the next few years substantial numbers of biopharmaceuticals will lose their patent protection and therefore will be open to the production and competitive marketing of such medicines. However, in contrast to small molecule medicines the replication of the biopharmaceuticals is not an easy task. In many cases even small changes in the structure of the final molecule can create a different safety and efficacy profile. This is why adequate evaluation of biosimilars has become such a challenge for both the scientific community and regulatory agencies.

Generic small molecule medicines are usually approved on the basis of their established bioavailability compared to the originator brand comparator. In most cases, generic medicines are also considered as interchangeable with their corresponding original brand medicines. In contrast to small molecule medicines, biopharmaceuticals are manufactured in living systems, e.g. plant or animal cells. The methods used to produce the biopharmaceuticals; including cloning, expression system, expansion, recovery, purification and formulation of the final product, determine the ultimate biological activity of these products. Therefore, any change in any of these steps could create substantial changes in the efficacy or safety profile of the medicine, including its immunogenicity. Despite the introduction of biosimilars into world pharmaceutical markets many years ago some countries still lack regulations for registration of these medicines. The European Medicines Agency (EMA) was the first well-established regulatory authority to develop

comprehensive guidelines in 2004. WHO has also published its guidelines for the evaluation of biosimilars in 2010. These guidelines are mainly focused on a head-to-head demonstration of biosimilarity with a registered original brand biopharmaceutical through both preclinical and clinical trials. The clinical studies must be designed in a way that can demonstrate comparable safety and efficacy between biosimilar and the reference biopharmaceutical.

Biopharmaceuticals are also important due to their novelty. Only biopharma allows the study and illustration of the pathway of drug action, so as to uncover the method by which a given drug prevents a disease.

It has the importance in the field of research as well. The illustration of drug action helps in further elucidation of various research pathways that overall result in betterment of medical facilities available.

There are certain breakthroughs in the field of biopharmaceuticals like gene therapy that has created a huge hope for curing various genetic disorders like severe combined immunodeficiency diseases (SCID). Although requiring a lot more development, it is techniques like these that will become the next generation of medical care.

With the increasing importance of biopharmaceuticals in disease therapy and their high costs, the lower costs of their alternatives, biosimilars, is a driving force for their marketing. Due to very high costs both for each treatment, and over a full treatment time period, even a slight cost reduction through the marketing of biosimilars could facilitate access to biopharmaceuticals; especially in resource limited healthcare systems. As has happened with generic versions of small molecule medicines, the introduction of biosimilars is expected to create substantial reductions in national healthcare expenditures. Published data show that these medicines will result in savings of about US$9–12 billion for the US Medicare program in a decade. It is also reported that biosimilars could create savings of between Euros 11.8 and Euros 33.4 billion between 2007 and 2020 for European healthcare systems. The savings for erythropoietins alone could be between Euros 9.4 and Euros 11.2 billion. However, most of these savings will come from administration of biosimilar monoclonal antibodies.

It is estimated that developing a biosimilar for highly regulated markets such as the EU and the US will cost between US$75 and US$250 million. Since many pharmaceutical companies in developing countries cannot afford such costs, national companies try to meet local demand by manufacturing copied biopharmaceutical medicines without actual demonstration of biosimilarity. Obviously, these copied biopharmaceuticals cannot be compared to the original brand biopharmaceuticals approved in highly regulated markets. These countries instead must perform close pharmacovigilance of copied biopharmaceuticals for both patient safety and proving efficacy of these medicines.

1.6. Differences between Pharmaceuticals and Biopharmaceuticals

Pharmaceuticals and Biopharmaceuticals Differences

The following are the differences between pharmaceuticals and biopharmaceuticals

- ✓ Pharmaceuticals are the chemically produced medicinal products, formulated as single active component, or as a combination of several active components. Biopharmaceuticals are medicinal products obtained or manufactured from biological sources, used as such or modified biotechnologically.

- ✓ Pharmaceuticals usually includes low molecular weight organic molecules derived from chemical synthesis while biopharmaceuticals includes recombinant proteins, vaccines etc. as well as different therapies like gene therapy, cell therapy etc.

- ✓ Pharmaceuticals have structures composed of very few atoms, which can be portrayed by a diagram showing linkages between different atoms. Biopharmaceuticals are structurally more complex, involving many atoms and a molecular mass much higher making their structural representation more complex.

- ✓ Pharmaceuticals are more sure and simpler. They are very easily defined and reliable. Biopharmaceuticals are more random and diverse. They are not consistent and are very assorted.

- ✓ Pharmaceuticals can have a number of side effects and complications, given their external origin. As they are really not compatible with the human body, there always is a chance of complications. One out of every 100 people is susceptible to side effects caused by any particular average drug. Biopharmaceuticals usually do not have any side effects. Due to their production from biological sources, they are well matched with the human body and therefore, are safer.

- ✓ Pharmaceuticals are cheaper and easier to produce. Most of the time, they are produced in mass production which further reduces the cost. This is why; they are easily available and are preferred by common people. Biopharmaceuticals are costlier and more difficult to produce. High cost, in turn, reduces the market demand as people are not able to afford it. This, therefore, increases the cost further. Also, a lot of technique is required to produce biopharma products that add to the cost. In short, it is not easily available and cannot be reached by everyone.

- ✓ Most of the chemically synthesized drugs are easily available. This is because of its synthetic nature that makes the availability of raw materials easily available. Biologically produced drugs are relatively scarcer than chemical drugs as the raw materials are not easily obtainable.

- ✓ There is no need to describe the source of intermediates in chemical synthesis of drugs. This is because chemicals used in the pharmaceuticals are not of any biological origin. The source of biological drug is a necessity due to ethical reasons. People of different communities have different reservations regarding the use or ingestion certain animal or plant product. Therefore, it is essential to describe the source of biopharmaceutical products.

- ✓ Chemical drugs have a disadvantage of being risky if over-dosed by accident or on purpose. This again is due to the incompatibility between the synthetic drugs and the human body. Usually, no such risk prevails in biological medicines. It is because of the companionable nature of biological drug.

- ✓ Pharmaceuticals are medicines that manage diseases, and protect people from infection. If there is an inherent problem, it cannot be solved by pharmaceutical drugs. Neither can they stop the recurrence of a disease. Biopharmaceuticals seeks to duplicate or change the functions of a living cell. This stops the recurrence of the disease and also cures the inherent problem.

- ✓ Pharmaceutical function inside body is less reliable as predictability of its function is not there. While designing a drug, its path of action is not illustrated. Biopharmaceuticals works in a more predictable and controllable manner inside body. This is because the entire path of function is fully elucidated before forming the drug.

- ✓ Pharmaceuticals unpredictability makes it less likely candidate for finding the answers of incurable diseases. Since we do not know the pathway, no logical answers can be found out regarding the irrepressible diseases. Biopharmaceuticals, due to its predictability, it holds great promises for finding solutions of incurable diseases like cancer and autoimmune diseases.

- ✓ Pharmaceuticals are manufactured with high consistency and using standardized chemical processes. It is because of mass production of the drugs via industrial processes. The machines used during the production maintain a high degree of constancy. In biopharmaceuticals consistency of drug manufacture cannot be determined. It is because many of the biopharmaceuticals are not mass produced. Also, since the source is biological, it cannot be guaranteed.

- ✓ The purity of pharmaceuticals finished products can generally be readily analyzed and demonstrated. Purity of the biopharmaceuticals finished products cannot be generally analyzed. It is due to lack of uniformity and reliability of the biopharmaceutical finished products.

- ✓ Many of the pharmaceutical drugs are administered orally. Biopharmaceutical drugs usually cannot be administered orally, as oral administration may render it inactive. It is because enzymes and hormones from animal and plant sources are rendered inactive inside humans. Also it usually requires systems for stabilization, like addition of a stabilizing component.

- ✓ Pharmaceuticals are fairly similar, even from different manufacturers, therefore are easily regulated. It is because even the different manufacturers use similar ingredients and process of manufacture. Biopharmaceuticals from different manufacturers may be different, including having different efficacy and safety profiles (as safety of a biological drug depends on the method of manufacture) which complicates regulation. It is due to the use of different source and different handling of substances.
- ✓ Pharmaceuticals processes involved are not usually under any controversy, as it is clinically well approved and does not involve any ethical issues. Biopharmaceuticals includes many controversial methods like production of transgenic organisms, and therefore, elicit ethical problems.

- ✓ Pharmaceuticals are developed only in the industrial laboratories. Biopharmaceuticals are developed in both academic and industrial laboratories.

- ✓ Pharmaceutical companies are far more widespread and geographically expanded. It is due to widespread demand and availability of market. Biopharmaceutical companies are more clustered geographically, mainly to remain closer to prominent research facilities.

- ✓ Pharmaceuticals are in their prime state and not much needs to be done to promote it. Various improvements are needed to be done to make biopharmaceuticals as popular as pharmaceuticals, such as development of new techniques that will make the production easy and bring down the cost of production, expanding the industry in a more worldwide level, advertising the industry so as to make it a more household name etc.

- ✓ Patents involving pharmaceuticals protect the chemical structure and method of production. Patents involving biopharmaceuticals protect the biological information.

- ✓ Examples of the companies includes Abbott Laboratories, Eli Lilly & Co., Merck & Co., Pfizer etc. Examples includes Amgen, Genzyme, Human Genome Sciences, Incyte corp., Vertex pharmaceuticals, United therapeutics etc.

- ✓ The Pharmaceutical industry in India is the world's third-largest in terms of volume. According to Department of Pharmaceuticals of the Indian Ministry of Chemicals and Fertilizers, the total turnover of India's pharmaceuticals industry between 2008 and September 2009 was US$21.04 billion. India's biopharmaceutical industry clocked a 17 percent growth with revenues of Rs. 137 billion ($3 billion) in the 2009–10 financial year over the previous fiscal. Bio-pharma was the biggest contributor generating 60 percent of the industry's growth at Rs. 88.29 billion, followed by bio-services at Rs. 26.39 billion and bio-agri at Rs. 19.36 billion.

1.7. Present Scenario

Many people believe the bio-pharma industry is oligopolistic, similar to the car or airline industries, with only a few huge players in the game. The reality, however, is that it is extremely fragmented with many players of all shapes, sizes and styles—with the largest ones commanding no more than a 10% or so total market share (depending how you calculate it). This is at the corporate level; of course, things are different at the therapeutic-area level where few players do tend to dominate or hold a substantial share (over 30%) of some therapeutic classes, but this is more of a time-limited dominance subject to product lifecycle pressures, pricing dynamics and generic cliffs, with somewhat different strategic implications.

During the last 30 plus years we have seen a major consolidation in the industry through mergers and acquisitions. This article and, most importantly, the accompanying graphics, attempt to summarize and provide a retrospective look at how this consolidation has taken place over the years. This kind of review is not only intellectually thought provoking, and perhaps nostalgic, but also gives a sense of the range of strategies that have been employed across the board. Moreover, it highlights the types of strategic choices that seem to be preferred by certain companies or groups. Some prefer sequential acquisitions of smaller players; some turn to sequential acquisitions of similarly sized companies; and others tend to like mergers of industry behemoths. We have also seen a renewed appetite for disinvestments and break-ups.

One remarkable conclusion in the analyzed cohort is that approximately 110 companies have consolidated to about 30; in other words, the absorption along the way of some 70% of companies that have existed in a relatively short period. One casualty has been the loss of many jobs, especially in non-customer-facing roles that tend to be duplicative among companies coming together; though we have also seen major reduction in customer-facing functions as, among other dynamics, companies combine portfolios and product assignments.

1.8. Industry Future

Advances in genetics and genomics, including the sequencing of the human genome, have resulted in the development of new biologic drugs to treat cancer and other serious diseases. So-called targeted therapeutics are the first step in creating drugs that home in on disease without affecting healthy cells and tissues. Not surprisingly, the arrival of these drugs about a decade ago has raised lingering questions about their clinical and financial value, how they should be regulated, and whether changes in patent policy are necessary to promote innovation. Because the new biological agents are more difficult to manufacture than traditional chemically synthesized drugs, how "follow-on" biologics should be tested, approved, and regulated continues to be the subject of debate.

Herceptin, a genetically engineered monoclonal antibody that targets the HER2-neu receptor on breast tumors in some patients, is the ideal example of a biopharmaceutical that is truly targeted. (Unlike many of the newer drugs, it does not affect both healthy and malignant cells.) There is an immediate need for more scientific knowledge as well as the financial incentives that will drive innovation toward "personalized" medicine.

1.9. Emerging Trends for the Industry

- ✓ The re-organization and break up of companies to allow the most innovative and dynamic parts of their businesses to thrive and not get bogged down or diluted by the rest of the product line—which may have different valuation drivers.
- ✓ Along these same lines, we may see the formation of multiple small companies under an overall umbrella. Presumably this would allow for a degree of independence, speed and innovation. One can call this the J&J model.
- ✓ The arrival and expansion of relatively unrecognized players in the innovative sector such as Actavis, Israeli companies (e.g., Teva) and Canadian companies (e.g., Valeant).
- ✓ The arrival and expansion of Indian companies is still a big question beyond their established and ever-growing generic lines. Much has been said and speculated but little has transpired.
- ✓ The appetite for big players to buy other big players will continue. Often these moves are driven by a desire to combine product lines and sales revenues, while at the same time dramatically lowering the costs of the combined companies through the removal of human and capital duplication.

Most biopharmaceutical organizations today have established their India and Asia strategies or they are rapidly recognizing the importance of the historic changes occurring and the potential opportunities that are emerging there. This column is the first in a monthly series on the growth and challenges facing this market. Future columns will cover biogenerics, the regulatory situation, intellectual property (IP) protection, how clinical trials are driving this industry segment, bioinformatics, distribution hurdles, government support for the industry, contract manufacturing, and other key topics.

A few of the key findings in India's biopharma-ceuticals industry that are shaping international collaborative and investment strategy include

- ✓ Growth in India is primarily export-driven. Export sales of Indian biopharmaceutical products are currently rising at an annual rate of 47%, while domestic sales of Indian biopharmaceutical products have risen only 4–5% per annum for each of the past two years. The value of India's biopharmaceutical exports is already double the value of its domestic biopharmaceutical sales.
- ✓ Vaccines are the largest and fastest-growing sector. Indian vaccine sales currently account for about 43% of the country's total biopharmaceutical sales, compared to 16% for diagnostics and 13% for therapeutics. Most of the growth in Indian biopharmaceuticals is because of vaccines, sales of which rose by about 42% from 2005 to 2007, compared to just 23% for therapeutics, and only 5% for diagnostics. India is one of the world's leading suppliers of vaccines for measles and other childhood vaccinations.
- ✓ Industry growth is concentrated in a relatively small number of companies. About 30 Indian companies account for the great majority of the country's biopharmaceutical sales. This group is led by companies in India such as Biocon (Bangalore), Serum Institute (Pune), and Panacea Biotec (New Delhi), which are all domestic players. The list also includes Indian-based subsidiaries of Novo Nordisk (Bagsvaerd, Denmark), GlaxoSmithKline (Middlesex, UK), Eli Lilly (Indianapolis, IN), and others.
- ✓ Indian companies manufacture an increasingly wide range of biopharmaceutical products. These include recombinant insulin, erythropoietin (EPO), G-CSF, recombinant hepatitis-B vaccine, streptokinase, interferon alpha-2b, rituximab, and an anti-EGFR MAb product.
- ✓ Indian biopharmaceutical R&D is increasing rapidly. Since 2003, the R&D budgets of the top 10 Indian pharmaceutical companies have more than doubled. Much of this increase has come in biopharmaceutical R&D, and the pipelines of Indian biotech companies are filling with novel large-molecule drugs for diabetes, cardiovascular disease, oncology, and anti-inflammation applications, among others.