ALPHA INVESCO RESEARCH SERVICES LTD.

INDIAN PHARMACEUTICAL INDUSTRY

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INDEX

Understanding How The Indian Pharmaceutical Industry Works – Part 1

Following article is first in the series of articles on the Indian Pharmaceutical Industry, the first article is written to familiarize ourselves with the terminology or the jargons of the pharmaceutical industry. We will briefly touch upon terms like API, Intermediates, Formulations, Innovator drug, Generic drugs, life cycle development etc.

The Indian Pharmaceutical industry is about $ 17 bn industry (2016) with as many as 20,000 registered companies (includes MNC's and small scale units) directly or indirectly involved in the business of selling medicines. India has the distinction of being the lowest cost producer of medicine in the world. India also has the feather of being the largest exporter of generic drugs in the world, we have some great franchises like Lupin, Sun Pharma etc.

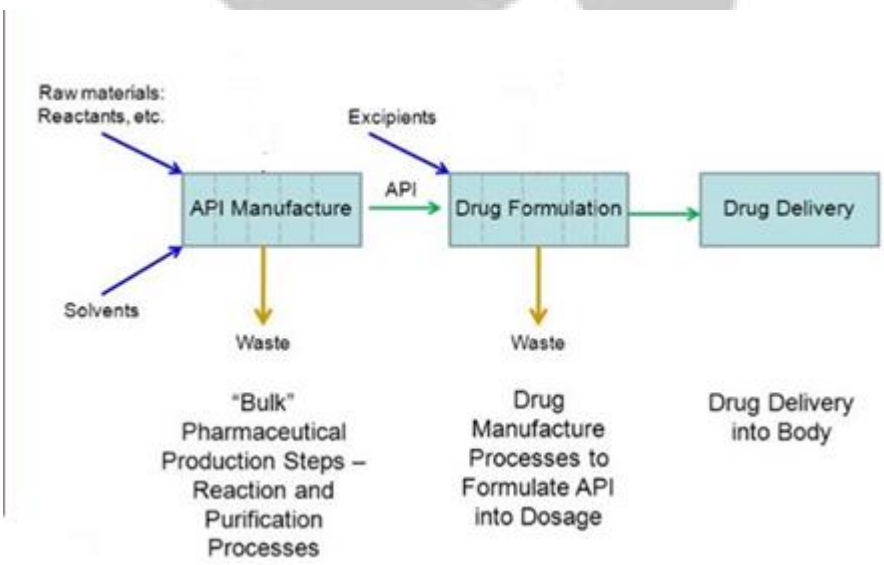
Terminologies

API-Active Pharmaceutical Ingredient – It is the basic drug itself with the desired medicinal pharmaceutical properties, also known as bulk drug.

Intermediates – Most chemical reaction are step wise, that is they take more than one elementary step to complete and the intermediary formed in the process of making an API is called an intermediate.

Finished Dosage or Formulation – It is the form in which the drug is consumed by us. A dosage form of a drug is usually composed of two things: The API, which is the drug itself; and an excipient, which is the substance of the tablet, or the liquid the API is suspended in.

Pharma Supply Chain from Intermediates to API maker to Formulations maker.



Oncology – Oncology deals with the prevention, diagnosis, and treatment of cancer.

Tentative Approval – Tentative Approval is granted prior to patent exclusivity expiry for a blockbuster drug, however companies getting tentative approval cannot market the drugs in USA until they receive final approval.

Blockbuster Drug – A blockbuster drug is an extremely popular drug that generates annual sales of at least $1 billion for the company that sells it. Blockbuster drugs are commonly used to treat common medical problems like high cholesterol, diabetes, high blood pressure, asthma and cancer.

DMF- Drug Master File – API manufacturers need to file a document known as Drug master File (DMF) with regulatory bodies. A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

New Drug Application – The final step formally taken by a drug sponsor, wherein it applies to the Food and Drug Administration (FDA) for the approval required to market a new drug in theU.S. An NDA is a comprehensive document with 15 sections that includes data and analyses on animal and human studies, the drug's pharmacology, toxicology and dosage, and the process to manufacture it. When an NDA is submitted, the FDA has 60 days to decide whether to file it for review, or reject it because some required information is missing. The goal of the FDA's Center for Drug Evaluation and Research (CDER) is to review and act on at least 90% of NDAs for standard drugs within 10 months after the applications are received, and six months for priority drugs.

ANDA (Abbreviated New Drug Application) – Abbreviated New Drug Applications are "abbreviated" since they do not require the applicant to conduct clinical trials and require less information than a New Drug Application. If an ANDA is approved, the generic drug will be listed in the Orange Book, which lists all medicines the FDA has found to be safe and effective. An ANDA contains all the information the it needs to evaluate on how safe and effective a proposed generic drug is compared with its brand-name equivalent. The FDA will not approve the generic unless it is equally safe and effective.

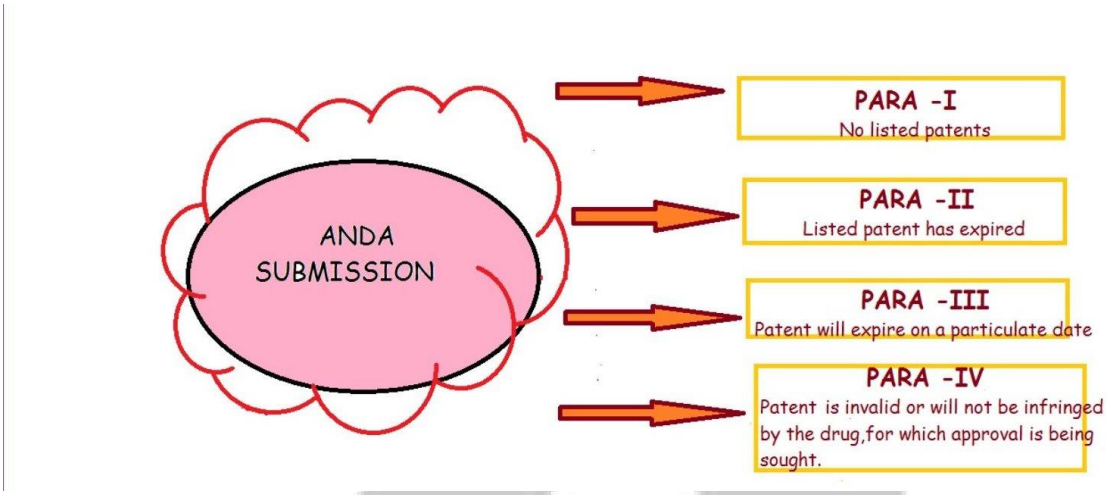
Bio Similars – Bio similar is an approved drug that it is highly similar to an FDA-approved biologic product, and has no clinically meaningful difference in safety or effectiveness from the originally approved product. However, bio similar is not chemically identical to the drug they refer, and may include slight differences. Medical practitioners or pharmacists don't have the liberty to give a bio similar drug in place of the biologic.

PARA 1 – A Para 1 filing is made during the launch of a generic drug when the innovator has not provided the required information in the orange book.

PARA 2 – Para 2 filing is made when the drug is already off patent.

PARA 3 – Para 3 filing is made when the applicant does not have any plans to sell the generic drug until the original drug is off patent.

PARA 4 – A Para IV filing for the launch of generic drug is made when the applicant believes its product or the use of its product does not infringe on the innovator patents or where the applicant believes such patents are not valid or enforceable.



Acute Disease – An acute disease is a disease with a rapid onset and/or a short course.

Chronic Disease – A chronic condition is a human health condition or disease that is persistent or otherwise long-lasting in its effects.The term chronic is usually applied when the course of the disease lasts for more than three months.

CRAMS – Contract Research and Manufacturing – One of the fastest growing segments in the pharmaceutical and biotechnology industry. It pertains to outsourcing research services/ manufacturing products to low-cost providers with world class standards.

Generic Drug – A generic drug is a drug that is not branded but is similar to a branded or reference listed drug in terms of dosage, administration and performance.

505 (b)(2) – The 505(b)(2) new drug application (NDA) is one of three U.S. Food and Drug Administration (FDA) drug approval pathways and represents an appealing regulatory strategy for many clients.A 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant.

Biologics – A biologic is manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are very large, complex molecules or mixtures of molecules. Many biologics are produced using recombinant DNA technology.

Exclusivity Period – Exclusivity period refers to certain delays and prohibitions on approval of competitor drugs available under the statute that attach upon approval of a drug or of certain supplements. Exclusivity period was designed to promote a balance between new drug innovation and greater public access to drugs that result from generic drug competition.

Orange Book – The publication Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act) and related patent and exclusivity information.

Purple Book – The "Purple Book" lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA under the Public Health Service Act (the PHS Act). The Purple Book includes the date a biological product was licensed under 351(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) of the PHS Act.

CCS (Custom Chemical Synthesis) – Custom Chemical synthesis is a purposeful execution of chemical reactions to obtain a product, or several products. This happens by physical and chemical manipulations usually involving one or more reactions. In modern laboratory usage, this tends to imply that the process is reproducible, reliable, and established to work in multiple laboratories.

FTF (First to File) – First to file is another category where even before the first five years are over a company can challenge the drug if approved that company gets an 180 days exclusive approval to market its generic version of the Innovator drug. This can prove very lucrative for the challenger if granted. On the other hand there are Litigation Risks where the Innovator tries to prove that the challenger has infringed on its patent/process while developing the generic version.

Innovator Drugs – A generic drug is bioequivalent to a drug that has a brand name, also called an innovator drug. It will have a different name and will look different from its innovator counterpart, but the active ingredients will be the same.

Dispensing – Selling out properly on a lawful prescription. A prescription can only be filled by a registered pharmacist, veterinarian, dentist or member of the medical profession. The law requires that a prescription be written only for patients that are under doctor's care.

CFA (Clearing and forwarding agents) – These organizations are primarily responsible for maintaining storage (stock) of the company's products and forwarding SKUs to the stockist on request. Most

companies keep 1–3 CFAs in each Indian state. On an average, a company may work with a total of 25–35 CFAs. The CFAs are paid by the company yearly, once or twice, on a basis of the percentage of total turnover of products.

Stockist – He is the distributor, who can simultaneously handle more than one company (usually, 5–15 depending on the city area), and may go up to even 30–50 different. They pay for the products directly in the name of the pharmaceutical company after 30 to 45 days.

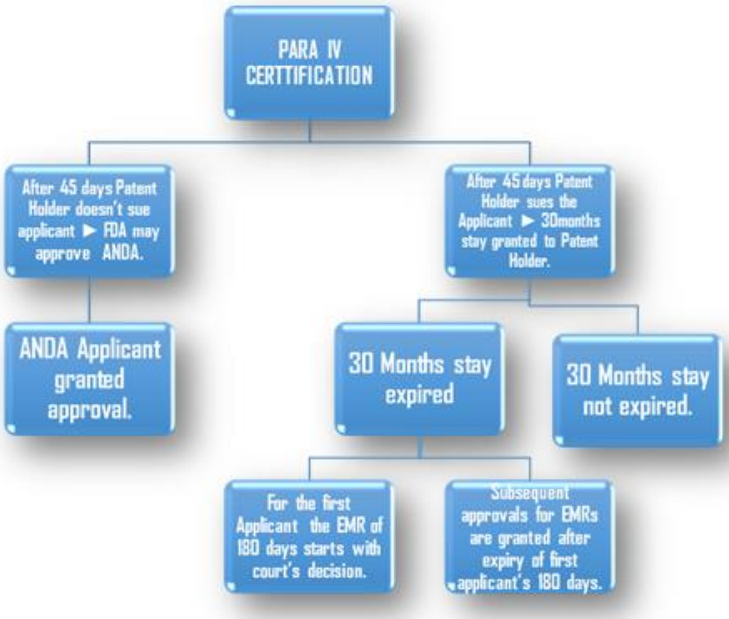
Bio-equivalence – Bio-equivalence is the similarity between two drugs which essentially means that they both have the same effect on the patient. Bio equivalence means that two drugs release their active ingredient into the bloodstream in the same amounts and at the same rate. When assessing how well a generic drug works, scientists evaluate its bio equivalence to the name-brand version.

CGMP – Current Good Manufacturing Practice, CGMP is to follow the current guidelines to produce the best quality pharmaceutical products.

Pediatric Exclusivity – 6 more months added to existing patent exclusivity.

Orphan Drug Exclusivity – To treat a disease that affects fewer than 200,000 people in the United States.The orphan drug law offers tax breaks and a seven-year monopoly on drug sales to induce companies to undertake the development and manufacturing of such drugs, which otherwise might not be profitable because of the small potential market.

Para-Filings

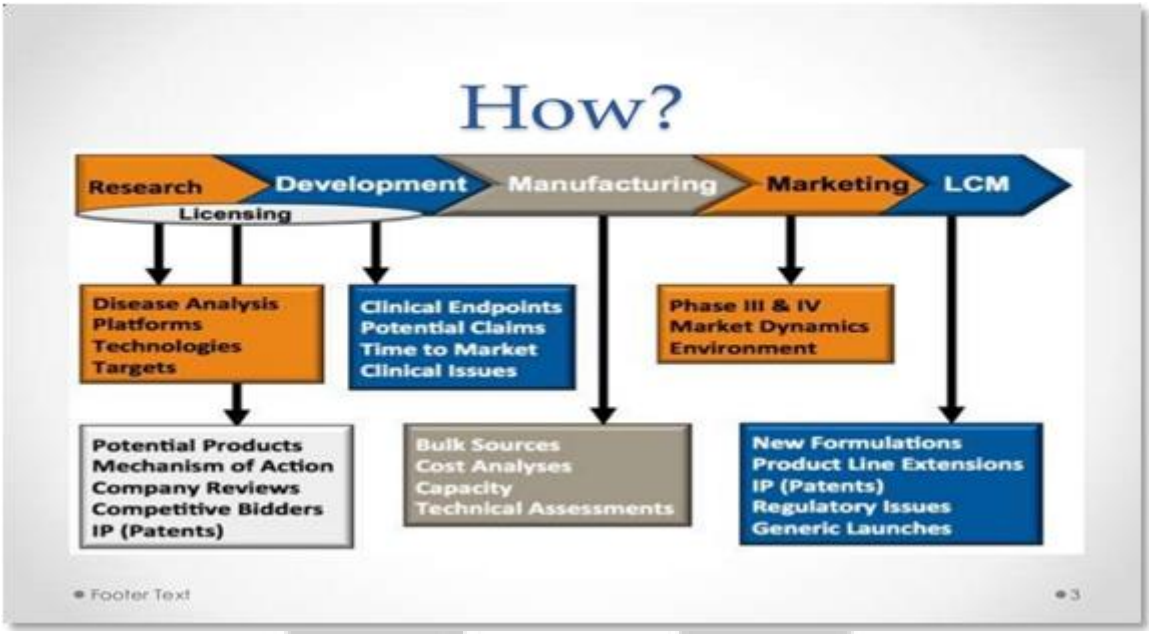


Drug Types

There are two types of drug:

1. Innovator drug
2. Generic drug

Manufacturing stages of a medicine.



1. Innovator drug

Drug is build up from the scratch, thus a much rigorous process and even the patent is filled which leads into huge prices of drug in its patent life as there is no competitor. And when a drug goes off patent at that time price crashes roughly 70%. Usually the player who gets the 180 days exclusivity corners 60% of this market as his brand gets established.

Drug Development Life Cycle

Drug Development Life Cycle is a complex and a very long process which lasts 10-15 years. 1000 of tests are conducted on the drug across the country. Research teams from various labs work hard day and night to analyze the disease. When any new drug is launched there are clinical trials done with first to file. We have drug development phases which are regulated by the authority like FDA, these phases are phase 1, phase 2, phase 3 etc.

The video embedded will explain the whole process of Drug Discover.

https://youtu.be/DhxD6sVQEYc

Discovery

- Represents first stage. It is the process by which drugs are discovered and/or designed. We identify cellular and genetic factors that play a role in specific diseases and it can take 10-15 years for drug approval.

Development

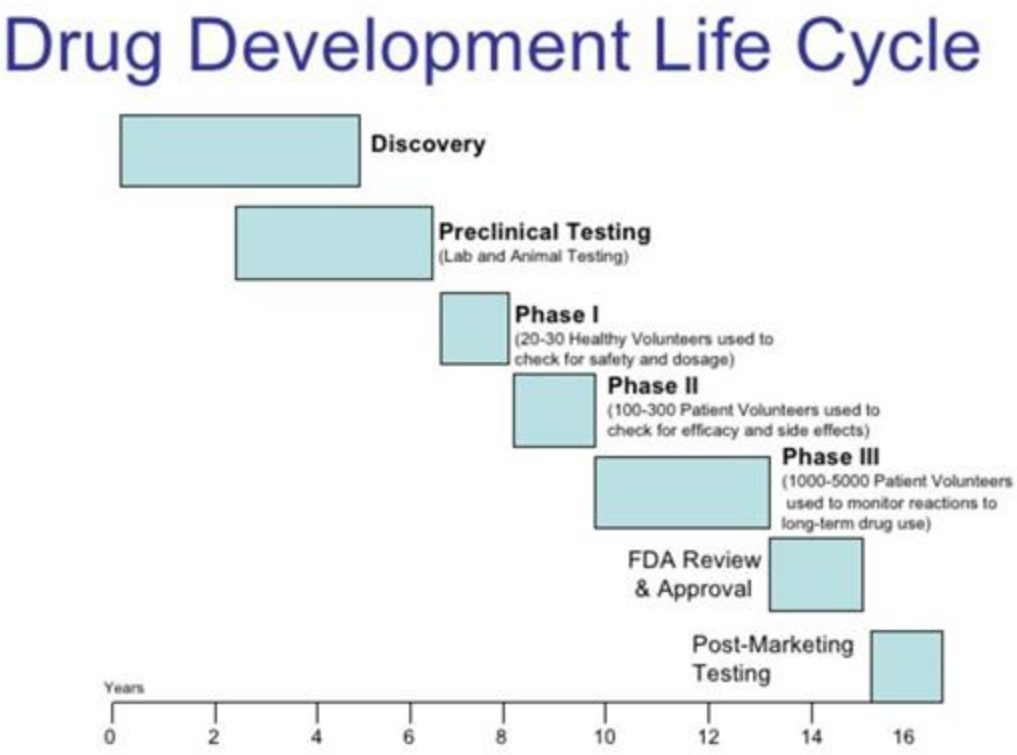
- It is a phase where promising compound is transformed into a marketable product. It is a process of taking a new chemical through various stages necessary to allow it to be tested in human clinical trials.

Pre-Clinical Tests

- The beginning of the drug approval process. To see the potential effects on humans, tests are performed on: Isolated tissues, Cell Cultures and Animals. Company decides whether to put the drug into the human testing process, based on the marketability of the product and their financial situation. On average, only one compound in a thousand will actually make it to human testing

IND Filings

- The goal is to provide pre-clinical data of high quality to justify the testing of the drug on humans. FDA has 30 days to review the Investigational New Drug (IND) application. It must be filed annually until the completion of clinical testing. During this time patents are applied; patents last generally for 20 years. About 85% of all IND applications move on to begin clinical trials. If they succeed, there is a 20% chance of the product making it to the market.



NDA Filing

Upon desirable results from Phase III, New Drug Application (NDA) will be submitted. NDA contains data supporting the efficacy and safety of the drug. Approval can take 2 month to several years, but on average, it takes around 18 to 24 months. Drugs are subject to ongoing review, making sure no adverse side effects appear. After FDA's approval, the drug can be marketed and distributed.

Patent

Generally lasts for 20 years. Since most companies file for patent during pre-clinical trials, usually the patent is only good for another 10 years or so after it gains FDA approval. What can be patented – product, method and use.

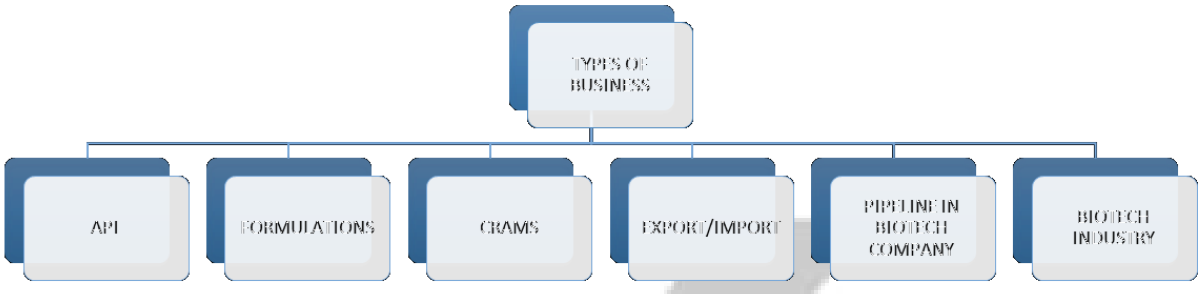
2. Generic Drug

A generic drug is a medication created to be the same as an already marketed brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. These similarities help to demonstrate bio equivalence which means that a generic medicine works in the same way and provides the same clinical benefits as its brand name version. In other words, it can be treated as an equal substitute for its brand name counterpart.

In the next article i.e. part 2 of the series, we will take a look at other aspects of the Indian pharma industry.

Understanding How The Indian Pharmaceutical Industry Works – Part 2

Different Business Segments Of Pharma Company



1) API- Active Pharmaceutical Ingredient

To understand the pharmaceutical business model, it is worth understanding the price relationship between the API, the tablet, and the drug market price. The *main ingredient in Pharmaceutical is API [Active Pharmaceutical Ingredient]*. It is the main drug which cures the disease. There are many companies which produce and are specialist in only producing APIs. In producing APIs the companies either purchase intermediates from different players and mix them to produce a final API or they themselves produce all the intermediates and mix at their own place. These are the companies which deal only in API. They sell their produced APIs to different formulation players who then further process it to make it a consumable drug. The companies who produce and sell APIs need their product to get registered with US FDA by filling a Drug Master File [DMF] which makes sure that the facilities of the API manufacturing company are in proper shape and are safe. The companies in this business do not attract high profit margins because there are many players who produce a single chemical and even if they try to charge high price from their customers then they can lose their revenue because of high competition in the market. However, such business work in bulk deals as the formulation players purchase finished API from them in bulk due to which even if they lose a single customer a good amount of revenue is lost. Generally, the size of the market of the API used in a formulation is 10% of the total formulation market. The great expense that goes into a patent challenge means that API suppliers working in support of such challenges must be extremely reliable, sophisticated and capable of working on a highly confidential and exclusive basis. DMFs are filed with USFDA, MHRA UK, Japan and other country specific bodies for receiving a marketing authorization grant. A DMF provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more drugs. There are basically three streams of API's sold by the companies : Oncology, Hormones & Steroids. Major revenue is earned from oncology segment. This is basically because it costs a lot to put up manufacturing facilities for these streams, usually 5-6x than normal, as these drugs require specialized handling. These facilities require stringent entry procedures and isolation

chambers/procedures to reduce risks of product contamination, cross-contamination and also protecting people from hazards and toxicity. These are as mandated by the regulatory Authorities. Scaling up proves very costly and barriers to entry are strong.

2) Formulations

Pharmaceutical formulation, in pharmaceutics, is the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product. The word formulation is often used in a way that includes dosage form. There are two types or classifications for Pharmaceutical Formulation, these types are the following:

Oral formulation – The most important characteristic for oral formulation it must be overcome the problems which associated with oral administration. The most critical problem is rate of drug solubility i.e., the active ingredient of the drug must be soluble in aqueous solution in a constant rate. This point can be controlled through some factors like particle size and crystal form. The oral formulation divided in two parts which are: A- Tablet form & B- Capsule form.

Topical medication forms – This type include several parts as the following: **A-Cream, B-Ointment, C- Gel, D- Paste,** and **E- Powder**.

Within the Domestic formulations market the major therapeutic categories are - Antinfective, gastrointestinal, cardiac, gynecology and dermatology.The leading drug classes were Cephalosporin, Antipepticulcerants, oral antidiabetic and Ampicillin / Amoxycillin, etc. The top ten drug classes contributed 35% of total domestic market. Formulations are the end-products of the medicine manufacturing process, and can take the form of tablets, capsules, injectables or syrups, and can be administered directly to patients. The production of formulations in India increased at a CAGR of 17% during the period FY1991-2001. The exports of formulations from India increased at a CAGR of 29% during FY1991-2000. The strong growth in formulation exports during the 1990s can be attributed to exports made to the developing markets and the access gained by Indian players to the generics markets of developed countries. Formulations account for over 50% of the total pharmaceutical exports from India. A series of mergers and acquisitions in the pharmaceutical industry has resulted in the concentration of market share among the leading players in the formulations segment. Also, over a period of time, the incumbent players in the formulations market have been able to set up extensive distribution networks, thus driving sales of their brands and increasing market share.

3) CRAMS-Contract Research and Manufacturing

Pharmaceutical companies are increasingly outsourcing research activities to academic and private contract research organizations (CROs) as a strategy to stay competitive and flexible in a world of exponentially growing knowledge, increasingly sophisticated technologies and an unstable economic

environment. It has been widely recognized that the global pharmaceutical industry is currently experiencing dynamic change. Under high pressure to contain fixed costs, all drug companies are currently reducing their internal capacities in R&D, manufacturing, and even marketing and, instead, increasing their outsourcing. To a significant extent, the drug companies, large or small, now rely on outsourcing service providers more than ever to fulfil their tasks, solve their problems, and improve their efficiency and productivity. The worldwide outsourcing demand for preclinical research and development is, however, still soft at present. Almost all major pharma companies have publicly announced that their current and near future R&D focus will be on the late-stage drug candidates. Meanwhile, many drug companies also are shifting their research methodologies for toxicology (tox) studies to include molecular biomarkers, imaging, and companion diagnostics, as these innovative technologies are able to provide better safety profiles of trial compounds. There are three broad outsourcing opportunities available to India – Custom Chemical Synthesis or CCS, clinical trials and contract manufacturing or CRAMS. The most scalable business opportunity for Indian players would be contract manufacturing or CRAMS. This is because: CCS would typically involve supply of material at gram or kilogram level, while CRAMS involves supplies in tons. CCS supplies are linked to the success of the partner's R&D pipeline and are, hence, volatile. CRAMS supplies, on the other hand, are linked to the success of a product post commercialization and can provide relatively stable revenues (since probability of success post commercialization is higher than that at the R&D level). However, custom synthesis or CCS skills are important from the following perspective: CCS assignments give Indian players an opportunity to lock-in into MNC relationships very early in the product lifecycle. This augurs well for the partnership approach that lays the foundation of the outsourcing business. CCS projects demonstrate a company's ability in process innovation. CCS skills can help a company to graduate from only a 'supplier' to a 'preferred strategic partner'. CCS projects are characterized by high margins but low scale, but CRAMS projects offer scale plus reasonable margins. Hence, a proper mix of CCS and CRAMS projects is a prerequisite for success in the outsourcing space. It can be observed that CRAMS player who is also a substantial API player can enjoy very good profitability.

The *key factors* that help win outsourcing (CRAMS) contracts:

- *Time and quality*: Time and quality are of extreme importance to the innovator companies. In R&D, time is very important to save on the limited patent life, and in manufacturing, it is a matter of reputation for innovator companies to market the drugs during the entire patented period. Also, high quality products are essential to win contracts. Due to the nature of pharmaceuticals, threat of product contamination or excess impurities is enough to scare the potential customer. Also, the drug quality has significant implication on the reputation of the innovator and financial liabilities of the company.
- *Availability of manufacturing capacity*: Just as timeliness of supply is critical, sufficient capacity is key to the new business especially for contract manufacturing. Innovative

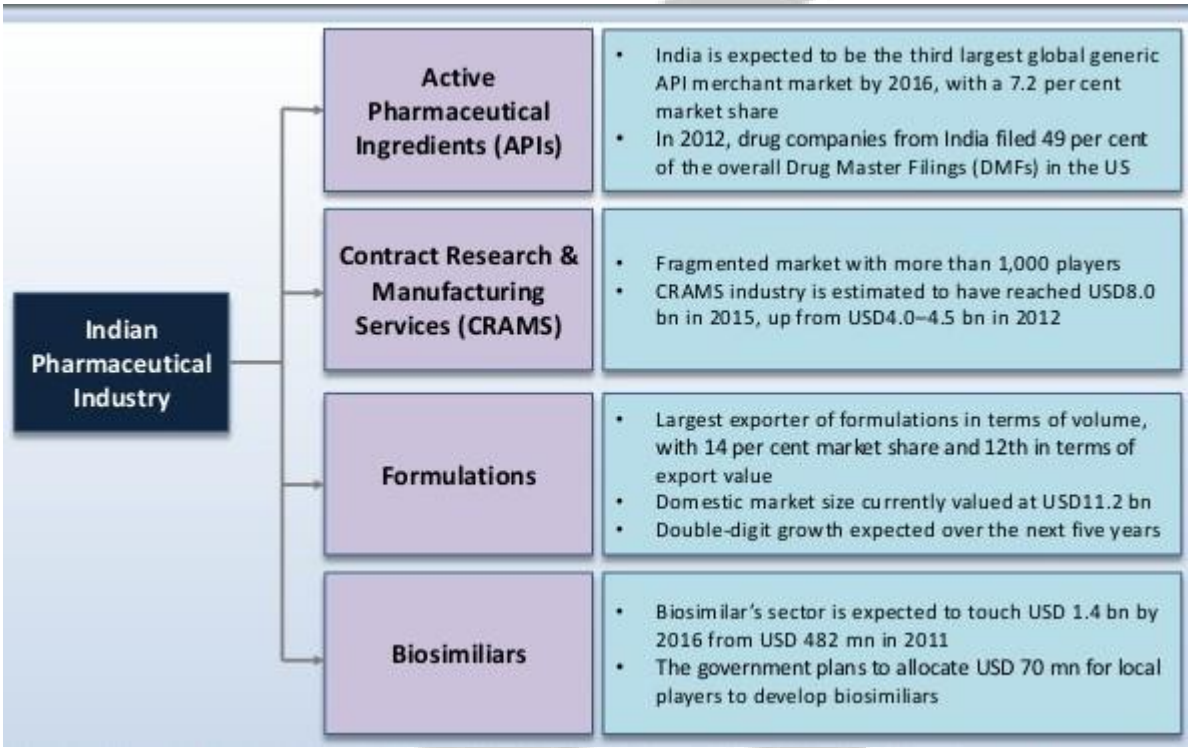
companies generally request rapid turnaround time. Existing manufacturing capacity is critical for time-sensitive projects. However, where supply relationships already exist, the ability to plan for projected new capital needs can be jointly accomplished.

- *Reputation and track record*: If the CRAMS player was the service provider for the innovator company in the past, and had delivered satisfactory services, the customer will most likely opt for the same CRAMS player for similar or new projects on the basis of the trust that has been built. Also, innovator companies will generally prefer big CROs and CMOs due to available infrastructure and service quality.
- *Array of services offered* : Generally, innovators like to get maximum possible services from same contract research company due to ease in administration and effective communication regarding requirements. For example, if a company has synthesized a chemical, it might be a good choice for other services such as process chemistry too.
- *Reliability and flexibility* : Suppliers should be reliable in terms of dedicated management team, financial stability, strong track record of supply, manufacturing, logistics, etc. Flexibility is also extremely important to innovators, as CMOs often collaborate with them to develop a new drug. In particular, the ability to adjust manufacturing schedules to meet deadlines, adjust manufacturing processes, and meet critical timelines is very important.
- *Scalability*: Pharmaceutical customers prefer suppliers who have the ability to increase their scale of production, as products move from early stages to later stages of drug development. In general, this means suppliers should have ready availability of CGMP capacity as products pass through FDA hurdles, or the means to rapidly build additional capacity in conjunction with the anticipated product launch. In addition, it requires a scalable process used to manufacture the molecule. In other words, the contract manufacturer must develop a process that can effectively and affordably manufacture commercial quantities of the molecule. This ties closely to contract-manufacturing process chemistry skills. We believe that these skills are critical, yet very difficult to assess (other than increased contract wins).

4) Biosimilars

Biosimilar are medicines made from living cells through highly complex manufacturing processes and must be handled and administered under carefully monitored conditions. Biosimilar are used to prevent, treat, diagnose, or cure a variety of diseases including cancer, chronic kidney disease, autoimmune disorders, and infectious diseases. A biosimilar is exactly what its name implies — it is a biologic that is "similar" to another biologic drug already approved by the FDA. The clinical trials carried out on a potential biosimilar are designed differently to those for approval of a novel biologic. When assessing a potential biosimilar, the aim is to confirm that there are no clinically meaningful differences in its efficacy and safety compared to the reference product. Biosimilar approval is based on the totality of data demonstrating similarity between the biosimilar and the reference product, including quality characteristics, biological activity, safety, and efficacy. Because of this complexity,

there is a significant difference between the development of a generic drug and a biosimilar: on average, a generic drug takes 3-5 years to develop at a cost of USD $1-5 million; a biosimilar, on the other hand, takes on average 7-8 years to develop at a cost of USD $100-250 million. It's worth highlighting that the technology involved in manufacturing and characterisation of biologics has advanced significantly. Manufacturers are now able to develop highly detailed characterisations of the molecular and functional attributes of products, including tracing potential product impurities, uniformity, and concentration. This allows for a multi-level assessment of the purity, safety, and potency of biological products. The biologics market is predicted to continue to grow faster than the total pharma market and is expected to account for almost 30% of global prescription sales by 2020. Interestingly, according to some analysts, by 2020 biosimilars will comprise between 4% and 10% of the total biologics market, with their market value expected to exceed $25 billion.



5) Export/Import Business:

The Indian pharmaceutical industry is the largest supplier of cost effective generic medicines to the developed world. With the widest range of medicines available for exports and with the availability of the largest number of approved pharmaceutical manufacturing facilities, India is all set to become the leader of pharmaceutical exports to the world. The domestic Indian pharmaceutical industry is estimated to be $ 26 billion in 2014 growing at nearly 20 percent and is expected to reach nearly $ 50 billion in 2020. It is evident that a lot of internal factors are responsible for the growing Indian pharmaceutical industry. The year on year growth has taken a promising growth since 2008 with an incremental increase in the range of $ 1-1.5 billion each year. The US is the largest consumer of Indian pharmaceutical exported medicines followed by the UK. Many of the top 50 domestic Indian

pharmaceutical companies contribute to this growth both in value and volume. The size of Pharma industry in India is expected to increase to USD 48 billion by 2017-18, growing at a CAGR of 14%. The industry has a large part of its revenues coming from exports. India exports pharmaceutical products to more than 200 countries. The Government of India has come out with its policy document – 'Pharma Vision 2020', which aims to make India a global leader in end-to-end drug manufacture. Both the domestic and export market are set to witness high growth.

Export Through API (Bulk Drugs)

API's exports are likely to grow at a CAGR of 12-14 % over 2013-14 to 2018-19, driven largely by exports to regulated markets as well as continued growth in the semi-regulated markets. Exports to the regulated markets would be driven primarily by three factors:

- A large value of drugs going off-patent in the next 5 years
- The expected rise in penetration of Indian API players in regulated markets
- The need of global pharmaceutical players to outsource API manufacturing to cut costs.

We expect that major global innovators will not only extend existing deals with Indian players but will also look to increase sourcing of bulk drugs from Indian companies. The exports in the year 2008-09 was 43% which increased to 49% in the year 2013-14 and is expected to rise by 51% in the forthcoming years 2018-19.

Export Through Formulations (Domestic)

The growth story of the domestic formulations market is expected to remain strong, led by a rise in life-related diseases, better healthcare diagnostic infrastructure adding to increasing disease detection rate, new product introductions, volume growth driven by increasing penetration, and better access to healthcare. Domestic formulation sales are set to grow at a CAGR of 12-14% between 2013-14 and 2018-19, with the market size crossing USD 20 billion.

Export Through Formulations (International)

India's formulation exports are expected to grow at a CAGR of 14-16% between 2013-14 and 2018-19. Steady growth is expected in exports to both regulated and semi-regulated markets over the next 5 years. During the period between 2012 and 2018, drugs generating annual sales of about USD 130 billion are likely to lose patent protection and will be exposed to generic competition. We therefore expect sales of generics to grow at a CAGR of 7-9% over the next 5 years, outperforming the overall global pharmaceutical market, whose growth is expected to be limited to 3-5%.

6) Pipelines In Biotech Companies:

The word pipelines in biotech companies generally refers to the stages of clinical trials. In the pharmaceutical industry, pipelines are frequently used when describing and evaluating a

biotechnology company's activities, research and development progress and overall potential for success and growth. The status of a drug in the pipeline refers to the stages of clinical trials that it is at (or must pass through) before being approved for sale and/or public use. The pipeline overall is the group of unique products or processes reported or in development by a company. Drugs that have entered into clinical trials and are pending approval by the U.S. Food and Drug Administration (FDA) are said to be "in the pipeline". A company that has several drugs in various stages of development has multiple products in the pipeline. Likewise, a product in the pipeline is one that we can anticipate hearing more about and, possibly using, in the future. However, the value of each individual pipeline drug depends upon its progress through clinical trials and, ultimately, approval. When evaluating a company pipeline, each drug is assigned a weighted value which increases as it progresses through these trials.

7) Biotech Industry:

The Indian Biotechnology sector is presently divided into five segments based on the products and services offered. These segments are Bio-Pharmaceuticals, Bio-Services, Bio- Agriculture, Bio-Industrial and Bio-Informatics. Bio-Pharma is the largest sector contributing to 62% of the total revenue followed by Bio-Services (18%)Bio-Agri(15%) and Bio-Industrial(4%). Bio-Informatics is still at a nascent stage contributing to only 1% of the total revenue.

Growth Drivers Of Biotech Industry: *Increasing cost of bringing a new drug to the market*: India can play a key role in reducing cost and time to market for new drug development through outsourcing of various components of the drug development process. Top pharma companies spend a large part of their research for in licensing new modules: There is an opportunity for R&D focused Indian biotech companies to enter into such alliances through collaborative development projects. Inflammatory & Infectious disease segment high on agenda: In the Indian context these are the two of the strongest disease segments with a huge domestic market. Early stage deals are more common compared to the middle and late stage deals: Indian companies with limited financial resources can optimize business models by partnering with larger companies for product development and licensing at an early stage.

How pharmaceutical companies make money

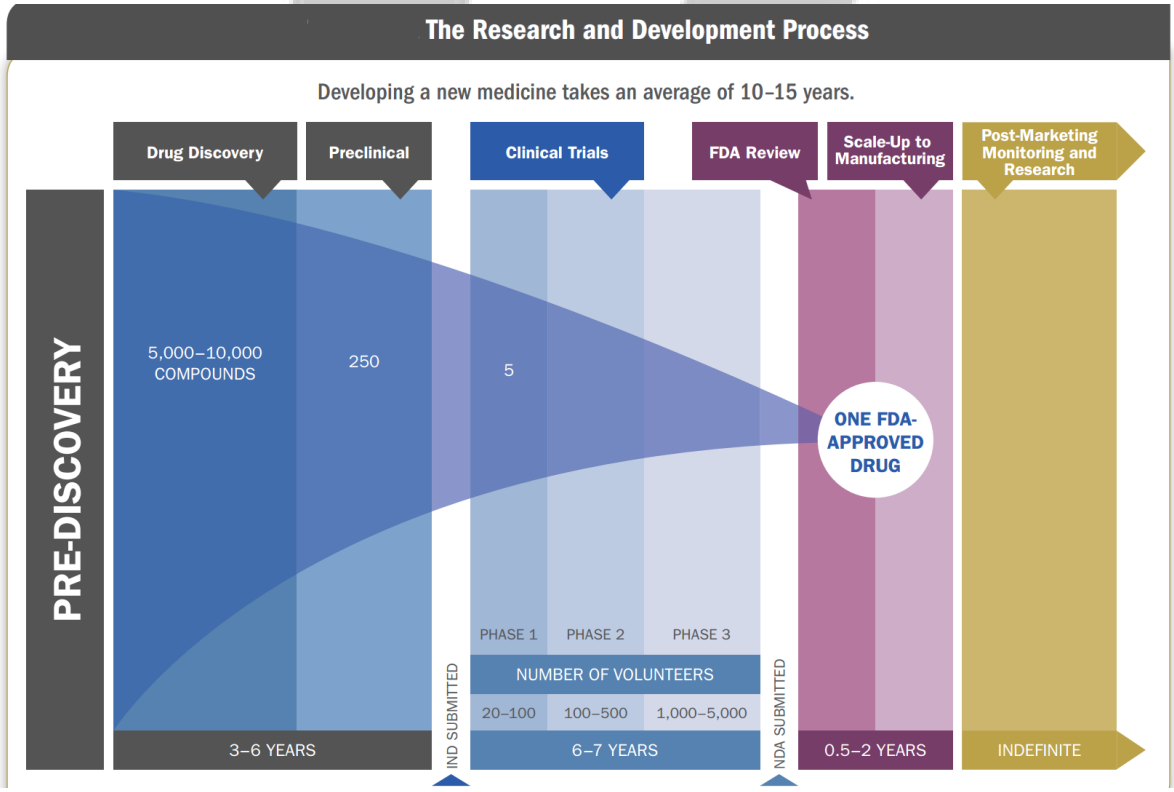
1) Research And Development

Research and development factors plays a vital role in pharmaceutical industry, as major part of revenue is dependent on research and development. Company spends its major revenue in R&D spending as once research of a new formulation is done profit can be booked for future. Pharmaceutical markets, however, are extremely complex in many respects. Large public-sector investments in basic biomedical R&D influence private companies' choices about what to work on and how intensively to invest in research and development. The returns on private-sector R&D are attractive, on average, but they vary considerably from one drug to the next. Consumer demand for

prescription drugs is often indirect, mediated by doctors and health insurers. New drugs must undergo costly and time-consuming testing before they can be sold. Moreover, it may cost hundreds of millions of dollars to develop an innovative new drug that then will cost only a few cents per dose to manufacture—and the price of the drug will have no obvious connection to either cost. Research and development costs vary widely from one new drug to the next. Those costs depend on the type of drug being developed, the likelihood 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. Research and development spending per NME has grown significantly in recent years, for various reasons.

- **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 acute illnesses and toward drugs for chronic illnesses. Drugs that treat chronic 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.

The research and development process of a drug is as follows:



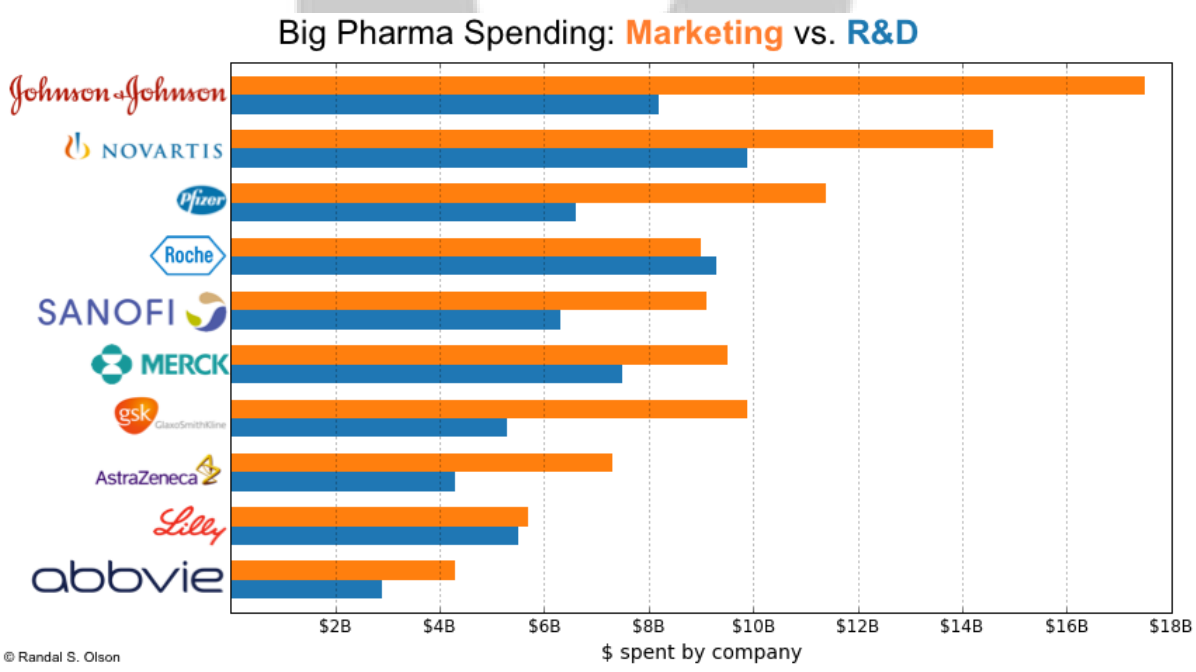
2) Marketing

Marketing always starts with the customer and ends with the customer as they are the valuable assets for the country. Marketing is a business activity by which it means the flow of goods and products from the manufacturer to the customer (End user). Pharmaceutical marketing is a well organized information system. It helps the physicians to update about accessibility safety, effectiveness and techniques of consuming the medicine. The Indian pharmaceutical industry has been gaining momentum in the recent years and is expected to move towards an upward trend. Pharmaceutical marketing costs are phenomenal. The end users must have awareness about these high technology industries. Complex information must be communicated to customers properly.

What are the needs for Pharmaceutical Marketing?

India is emerging as the global hub for contract research and manufacturing services due to its low cost advantage and world class quality standards. The introduction of product patent in India has brought some fundamental changes in strategies of Indian pharmaceutical companies, with focus shifting more towards Research and Development. The major revenue to the Indian pharmaceutical industry has been gained through exports. India pharmaceutical products are exporting to more than 200 countries around the world. Therefore Pharmaceutical marketing helps:

- To have a healthy competition
- To increase the customer knowledge
- To have a better customer relationship
- To reduce the initial development costs.



3) Distribution

Drug distribution in India has witnessed a paradigm shift. Before 1990, pharmaceutical companies established their own depots and warehouses. Now they have been replaced by clearing and forwarding agents (CFAs). Recording of what has been consumed at various supply chain nodes and replenishing it at the front end by the previous supply chain node. It is an end-to-end solution involving the front end distribution system, operations and procurement as well. It enables the company to be more agile in meeting market demands and helps to meet the two major challenges: *Excess Inventory & Shortages in system*. In pharmaceutical industry *selling and distribution* plays key role. If the product manufactured in the unit doesn't reaches to its end customer on time it becomes use less and companies start losing their brand name.

In pharma industry *selling and distribution channels flow in the below manner*.

The distribution of medicines in most markets is carried out by importers and wholesalers, which act as a link between manufacturers and retailers to ensure the continuous supply of medicine, regardless of the geographical location and portfolio of medicine required. For those medicines which are imported, there is often an additional step from the importer who organises the logistics of bringing the medicine into the country which are then transferred to the wholesaler for domestic distribution. In some cases the two entities are vertically integrated, decreasing the number of steps in the distribution stage of the value chain. Pharmaceutical distribution needs to meet the logistical challenge of serving a large number of pharmacies with products sourced from many manufacturers and often in a short period of time.

4) Dispensing

This step includes the transportation and handling of the medicine from the manufacturer to the end user, whether this is a retail pharmacy (retailer), hospital or dispensing doctor. The complexity of this journey will differ depending on manufacturer location, the need for importation of the medicine, the nature of special handling requirements, and the geographic location of the end user which will vary between large urban centres and remote rural villages. Providing the correct medicine dosage and form, to the right patient, in a convenient and timely manner is the final step in the value chain. This step can also involve a number of additional activities, including checking for potential interactions, providing advice, and processing reimbursement claims, each of which is intended to ensure the patient receives the full benefit and value from the medicines they receive. In some markets, retailers make a loss from selling prescription medicine, profit is instead generated from additional over-the-counter and health and beauty sales. An alternative business model finds other retailers which are very much focused on prescription drug dispensing to drive their business profitability.

At the time of dispensing There are *various types of products produced in pharmaceutical industry, such as*:

a. Prescription drugs are the main pharmaceutical industry products. These products are generating high revenue amounts but there are also other types of products that make up the whole pharmaceutical industry.
b. Biologics are composed of a variety of products that include vaccines, antibodies, blood, blood components, therapeutic proteins, tissues, allergenics and somatic cells. They are used for variety of medicinal, pharmaceutical and other important purposes.
c. Generic drugs are used interchangeably with branded drugs in the market. Basically, a generic drug is quickly approved in the market. Regulators of drugs would not necessarily require detailed testing and clinical trials for generic drugs. What the manufacturer of generic drugs needs to do is show evidence of the generic drugs' equivalence to the original and branded version.
d. OTC or Over-the-counter drugs are those medicines that one can buy from pharmacies and drug stores even without prescriptions from physicians or doctors. There are many types of over the counter drugs in the market. There are those which relieve pains, itches and aches. Others may also be used in curing ailments and diseases like athlete's foot and tooth decay. Migraines and other recurring problems may also be treated using OTC drugs.

After various types of products that are dispensed in the market there company start building its brand and after company becomes the famous brand in all the markets globally that's the time when revenue flow becomes easy.

5) Making A Brand

Pharma Companies define a Mega Brand as a drug with the annual sale of more than $ 1billion. Many a times to make a brand pharma companies indulge themselves to partnership with foreign players. When any company wants to make itself a global brand at that time company goes for Merger & Acquisitions(M&A) with foreign reputed player which gives them a good edge in market and helps them to become a big brand. Pharma companies have mastered various product launch strategies to build the next billion dollar brand.

Some of these strategies include:

a. Involving key opinion leaders in the clinical trials.
b. Designing the trials based on payers needs.
c. Educating providers on new disease and usage under the garb of continuing medical education.
d. Working with the healthcare organisations to create disease protocols.
e. Providing grants to healthcare advocacy groups.

f. Educating the general population on why they should get themselves treated for the advertised disease.

6) Government Tarrifs, Taxes And Charges

Taxes have been shown to be one of the larger components contributing to the price build-up of medicines. To take careful steps which are in favour of customers as well as the manufacturer , Government is of the opinion that to streamline and simplify the procedure and to bring about a greater degree of transparency as well as objectivity, *an expert body should be constituted with the powers, interalia, to fix prices and notify the changes therein, if any, of bulk drugs and formulations, from time to time, under the Drugs (Prices Control) Order*. Government have now decided to establish an independent body of experts to be called as the **National Pharmaceutical Pricing Authority**. The National Pharmaceutical Pricing Authority shall be empowered to take final decisions, which shall be subject to review by the Central Government as and when considered necessary. The Authority shall also monitor the prices of decontrolled drugs and formulations and oversee the implementation of the provisions of the Drugs (Prices Control) Order. There are various orders that have been passed by (N.P.P.A) such orders are as follows: To implement and enforce the provisions of the Drugs (Prices Control) Order in accordance with the powers delegated to it. To deal with all legal matters arising out of the decisions of the Authority. To monitor the availability of drugs, identify shortages, if any, and to take remedial steps. To collect/maintain data on production, exports and imports, market share of individual companies, profitability of companies etc. for bulk drugs and formulations. To undertake and/or sponsor relevant studies in respect of pricing of drugs/pharmaceuticals. To recruit/appoint the officers and other staff members of the Authority, as per rules and procedures laid down by the Government. To render advice to the Central Government on changes/revisions in the drug policy. To render assistance to the Central Government in the parliamentary matters relating to the drug pricing. (link: http://nppaindia.nic.in/index1.html) The most prominent of these in certain markets is the import tariff, which is a customs duty imposed by importing countries on the value of goods brought in from other countries. Import duties are used to raise government revenues and help domestic producers by providing a price advantage versus international competitors. It is expected that GST would have a constructive effect on the Healthcare Industry particularly the Pharma sector. It would help the industries by streamlining the taxation structure since 8 different types of taxes are imposed on the Pharmaceutical Industry today. An amalgamation of all the taxes into one uniform tax will ease the way of doing business in the country, as well as minimizing the cascading effects of manifold taxes that is applied to one product. Moreover, GST would also improve the operational efficiency by rationalizing the supply chain that could alone add 2 percent to the country's Pharmaceutical industry. GST would help the Pharmaceutical companies in rationalizing their supply chain the companies would need to review their strategy and distribution networks. Furthermore, GST implementation would also enable a flow of seamless tax credit, improvement the overall compliance create an equal level playing field for the Pharmaceutical companies in the country. The biggest advantage for the companies would be the reduction in the overall transaction

costs with the withdrawal of CST (Central Sales Tax). GST is also expected to lower the manufacturing cost.

7) Margins

- In India, under the Drugs Price Control Order 2013, both the wholesaler and retailer margins are differentially regulated based on essential drug classification, with maximum margin for distributors at 8% for scheduled drugs and 10% for non-scheduled drugs. Retailer remuneration is determined by two key factors.
- Firstly the level of discounts negotiated from the wholesaler, which determines the acquisition cost of the medicine. Secondly, the margin made on the acquisition cost of the medicine paid by the end user.
- *Importer margin* : applied by the importer who is tasked with procuring and receiving delivery of imported goods.
- *Distributor margin* : applied by wholesalers and sub-wholesalers to perform the logistical role of storing and subsequently transporting medicine to point of sale.
- *Retailer margin* : applied by retailers in the final step of the distribution chain, the point at which medicines are dispensed to patients.

Understanding How The Indian Pharmaceutical Industry Works – Part 3

Key Performance Indicators Pharmaceutical Sector

Sales & Marketing

Marketing always starts with the customer and ends with the customer as they are the valuable assets for the country. Marketing is a business activity by which it means that the flow of goods and products will flow from the manufacturer to the customer (End user). Pharmaceutical marketing is a well organized information system. It helps the physicians to update about accessibility safety, effectiveness and techniques of consuming the medicine. The Indian pharmaceutical industry has been gaining momentum in the recent years and is expected to move towards an upward trend. The end users must have awareness about these high technology industries. Complex information must be communicated properly. Proper use of medicines will enable the companies to cut down their costs which in turn help to increase their profits. This post gives an insight about the evolution of Indian pharmaceutical markets, its need and characteristics. It also highlights the present scenario, future prospects, challenges and the strategies to be adopted by the Indian pharmaceutical companies.

Current Scenario Of Indian Pharmaceutical Market

The Indian Pharmaceutical industry has been witnessing phenomenal growth in recent years, driven by rising consumption levels in the country and strong demand from export markets. The Indian pharmaceutical industry is the most progressive and advanced among all the developed and developing countries. Today, India is among the top five pharmaceutical emerging markets in the world. Demand from the exports market has been growing rapidly due to the capability of Indian players to produce cost-effective drugs with world class manufacturing facilities. Pharmaceutical Marketing helps to raise awareness about treatments for Chronic Diseases, the leading driver of health care spending. India is also expected to become a pharmaceutical research and development (R&D) hub in the next decade with the Department of Pharmaceuticals planning a road map for India to be a global player in the industry by 2020. A recent survey indicates that the Indian Pharmaceutical sector has given employment to approximately 2.86 million people, through 20, 053 units. It is estimated that by the year 2020, India's potential in Research & Development will reach between US$ 8 billion to US$ 10 billion. In order to combat the growth slowdown, Pharmaceutical companies need to join hands with Governmental agencies and other stakeholders to redness the challenges and grievances.

Research & Development

The pharmaceutical industry is characterized by heavy R&D expenditure. It is only the large pharmaceutical companies who can allocate significant resources for R&D to introduce new products.

As the products are an outcome of significant R&D expenditures incurred by these companies, they have their products patented. The patent allows the companies concerned to wield immense pricing power for their new products. The pharmaceutical industry is one of the most research intensive industries. Pharmaceutical firms invest as much as five times more in research and development, relative to their sales, than the average manufacturing firm. Because increases in spending on drug R&D have been nearly matched by increases in revenue from drug sales, the industry's R&D intensity, the ratio of research and development spending to total sales revenue, has not risen to the extent that R&D expenditures have. Over the past 25 years, R&D intensity has grown by about 50 percent. Most of that growth occurred in the 1980s; since then, the industry's R&D intensity has hovered around 19 percent. A relatively close relationship exists between drug firms' current R&D spending and current sales revenue for two reasons. First, successful new drugs generate large cash flows that can be invested in R&D (their manufacturing costs are usually very low relative to their price). Second, alternative sources of investment capital from the bond and stock markets are not perfect substitutes for cash flow financing. Those alternative sources of capital are more expensive because lenders and prospective new shareholders require compensation (in the form of higher returns) for the additional risk they bear compared with the firm, which has more information about the drug under development, its current status, and its ultimate chance of success. The relative stability of the relationship between pharmaceutical R&D and sales revenue suggests that firms find it most profitable to invest any additional dollar of sales revenue in their own drug research. However, changes in real drug prices can affect companies' R&D intensity or their propensity to invest in R&D from their revenue.

ANDA Filings

A generic company is rewarded for a Para IV filing. The first applicant to submit a substantially completed ANDA (Abbreviated New Drug Application) is given marketing exclusivity for 180 days. Exclusivity means that no company is allowed to launch its product during this period. As a result, there isn't any competition. As the first mover, this helps the manufacturer have an advantage. It can give a boost to market share. This is a valuable opportunity to maximize profit margins without any competition. A branded company can file a case of violation against a generic manufacturer within 45 days of receiving notification from the generic manufacturer. If a case is filed on time, then the stay order for 30 months is given to a brand company. Also, the FDA suspends the approval of the ANDA for the next 30 months. If the court finds that the patent isn't valid or wouldn't be trespassed, then the FDA can approve the ANDA. Otherwise, it won't be approved.

Operating Segment

It is to be seen that the company basically operates in which segment for e.g : acute or chronic. Reason behind this is that due to present conditions it is observed that people are more reliable on medications. Changes in lifestyle and food habits, aided by higher disposable income, have caused an

unprecedented rise in chronic diseases such as cardiovascular (CVS), diabetes, oncology and central nervous system (CNS), according to experts. The middle class has been growing in both the emerging and developed markets. People in these markets have more disposable income and expect better healthcare solutions. Chronic disease cases have risen in number. This has made people become more dependent on medications and health supplements. chronic segments, are increasing rapidly due to the many changes that the country has witnessed over the past few years. These changes could be classified as lifestyle changes, driven by rapid urbanisation, rising incomes of households, westernisation of dietary habits, lack of physical efforts due to improved transportation facilities.

Product Pipeline

A drug pipeline is the set of drug candidates that a pharmaceutical company has under discovery or development at any given point in time. This involves various phases that can broadly be grouped in 4 stages: discovery, pre-clinical, clinical trials and marketing. A Pipeline product is a series of products, either in a state of development, preparation, or production, developed and sold by a company, and ideally in different stages of their life cycle. A product pipeline is an assortment of products and services at various stages of development. At any given time, a company typically has many items in the pipeline. Some of them will make it all the way to production and begin to generate income for the company. One end of the product pipeline is the finished result. At the other end is the brainstorming that leads to a new product. Sometimes company personnel may meet to discuss a new invention, while in other cases, they may engage in discovery activity with the goal of finding potentially new compounds, as seen in the chemical and pharmaceutical industries.

Patent Filing

Patents are a vital aspect of the global pharma industry. Patent protection is essential to spur basic R&D and make it commercially viable. Patents protect drugs from copycat versions for 20 years after the drug is invented. This is a bitter pill for pharmaceutical companies because it can take eight years or more after invention to accumulate enough data to get a drug pass the U.S. Food and Drug Administration. Since initial investment in pharmaceutical R&D is costly, strong patent protection is an important step to provide the opportunity to recoup investments in new products. Patents are the legal protection for inventions, including new medicines discovered by research-based pharmaceutical companies. This protection allows a company time to recoup their significant investment in research and development. For a patent to have any commercial value there must be a market for the invention embodied in the patent, which will support the cost of development of the invention and return a profit. In return for such protection, a patent-holder discloses to the world patented research and science underlying the invention. Thus, important scientific information behind a new cancer drug becomes available immediately to researchers worldwide. The market exclusivity and higher prices are made possible by the patent rights function as a reward for the risk undertaken by those who financed the research and development leading to the new technologies.

Prescription Market

The prescription drug market is divided into two categories:

1. Branded, or patented
2. Generics, or off-patented

- Branded drugs are patented drugs. When a pharmaceutical company discovers a new drug, it files for a patent. Then, the company is awarded a license for 20 years to exclusively sell the drug. Exclusivity is provided to recoup research and development expenses incurred during the development of a drug.
- Generics are off-patented drugs. They're bioequivalent—in terms of dosage, form, strength, quality, effect, intended use, side effects, and route of administration—to the branded drugs. A route of administration is a way the medication is introduced to a site in a patient. This could be oral, intravenous, intramuscular, nebulizer, and topical. A few of the leading generic drugs are: Acetaminophen, or Paracetamol, Alprazolam, Amoxicillin, Asprin, or Acetylsalicylic Acid, Azithromycin, Diclofenac
- A Drug Generally Has Two Names
- Generic name – a molecular formula
- Brand name – the company's proprietary trademark used for marketing
- Patented drugs are patented by an innovator company.
- Generics are off-patented drugs with a generic name.
- Branded drugs are either patented or generics marketed under a company's specific name. Patented and branded drugs are used interchangeably across the industry.

Key Financial Metrics Used In Pharmaceutical Industry

To understand the pharma business the most important trackable financial metrics are as follow:

Research And Development Expense As A Percent Of Revenue

Analysing expenses as a percent of revenue is also useful when evaluating pharma companies. Most pharma companies have very high research and development (R&D) budgets because they can only survive and grow by discovering and developing new drugs. Knowing the R&D budget as a percent of revenue helps understand if the company is creating a strong pipeline of future drugs to come on the market. Compare the percent of R&D to revenues to industry standards and also to the company's own spending in past years. Declining R&D ratios can be an indication of a declining pipeline for a company which is a negative signal. R&D as a of revenue in an increasing trend portrays that company has a strong pipeline of drugs which is going to be launched in future and will lead to increase in revenue.

Profit Margin

Profit margin is another vital metric. Operating profit margin lets the investor understand the impact from R&D to see if the program is bringing successful candidates to the market, whether the marketing and selling costs are having a positive impact on revenues (market share gains), and whether external factors are negatively impacting the company. It is not uncommon for new, novel drugs to have high profit margins, while the overall company margins are much lower.

Selling Cost As A Percentage Of Revenue

Selling cost as a percentage of revenue in an decreasing trend portrays that company is able to sell its product in the market without expensing much on advertisement as well as on selling and distribution cost and that clearly states that demand for that product is prevailing in the market.

Employee cost as percentage of revenue

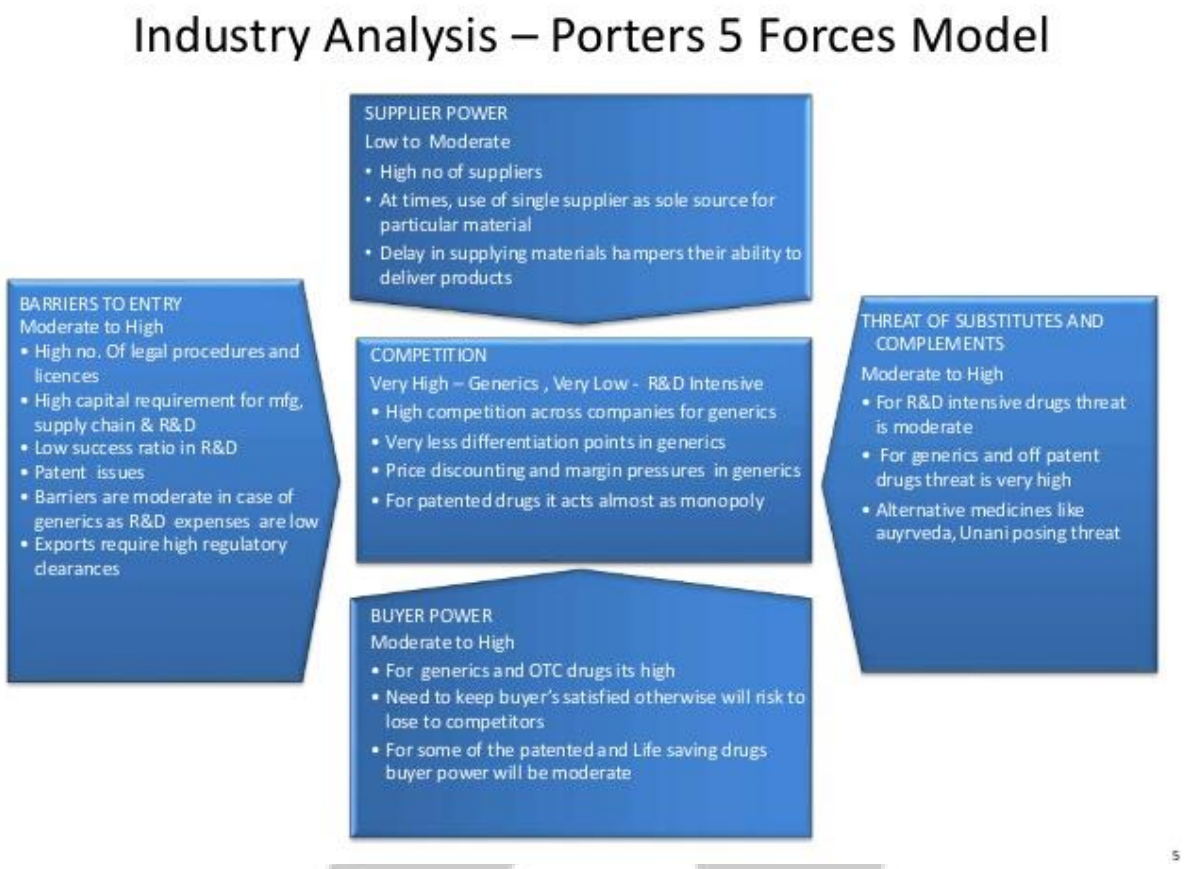
Employee cost as percentage of revenue says that company is spending more and more revenue on employee expenditure which can be concluded as company is employing more no. of people to meet the future demand and there fore it can be said that company is able to see a good future for the company in coming few years.

Dividend to earnings

Dividend to earnings in a pharma company is an important ratio because as major pharma companies are cash rich companies , investors expects these company to redeploy capital back to shareholders in form of dividends or any other capital structure programme.

Porter's Five Force Analysis

One model for examining an industry and a company's strategic position within its industry is Porter's Five Forces analysis.



1) Barriers To Entry

The big payoffs available in the pharmaceutical industry lead to a steady flow of new companies being created. A team of researchers with an innovative idea or newly granted patents can find venture capital funds eager to provide millions of dollars in startup funding. These smaller companies pose no serious threat to big pharma. In fact, one of a startup investor's main exit strategies is to sell out to a big pharma firm when new products are through the initial development phase.

2) Supplier Power

Suppliers have very little power in the pharmaceutical industry. The raw materials for manufacturing drugs are commodity products in the chemical industry, which are available from numerous sources. Most of the equipment used in manufacturing and research is available from multiple manufacturers. Suppliers usually offer multiple products to the manufacturer, which moderates pricing on rarer materials and unique equipment.

3) Buyer Power

Pharma is unique among industries because the medical patient has an absolute lack of power regarding pricing. The prescriber of the drugs, the physician, ethically is not allowed to profit from the sale of drugs. The entity that pays for the drugs, the insurance company, only has a say in how much

it will pay to the distributor of the drugs, meaning it has little power with the drug manufacturers. The insurer can refuse to pay for treatments it believes are overpriced. The only entities with any negotiating power are the pharmacies and medical institutions that fulfill the medical patients' prescriptions. Even these entities have little power over newer drugs under patent or drugs with only one manufacturer. Pharmacies focus on their profit margins and have little incentive to provide patients with the lowest possible pricing.

4) Threat Of Substitute And Compliments

The effect of substitutes is dependent on the individual drug. A new FDA-approved blockbuster drug that has patent protection, treats a major health condition and is first to market in its category has a license to print billions of dollars. The development of a new drug that cures a major disease could be worth tens of billions of dollars per year. Once a drug loses its patents, generic drug manufacturers start selling copycat versions at substantially lower prices. A drug that netted $100 million a year in profit could become one that earns only $1 million a year in profit overnight. Additionally, there is a major international problem with counterfeit drugs. The best of these counterfeits duplicates a real drug's formula and sells it at a lower price, which hurts corporate profits. The worst counterfeits are made with low-grade materials and can destroy the reputations of the legitimate products.

5) Competition

With more than $1 trillion in global sales, pharmaceutical business can be cutthroat. The huge importance of intellectual property results in strong competition for high-level workers and leading researchers. Even strong non-disclosure and non-compete clauses cannot prevent the leaking of competitive information. Any potential new drug has its public information analysed for the possibility of creating a similar drug to market as a substitute. The industry exhibits a pattern of firms merging and larger firms buying smaller firms that have promising research or new drugs.