CHAPTER

1

The Pharmaceutical Market

World Pharmaceutical Market

The pharmaceutical industry across the world continues to reel under pressure from all sides. Patents of one blockbuster drug after another are expiring. The innovator-drug industry is caught up in a gap of revenues that is widening continuously between an old way of developing drugs that is increasingly tapped out with each blockbuster patent expiry. What is more, it is becoming increasingly difficult to replenish the drying pipelines with blockbusters-to-be drugs.

Managed-care companies in the US, the world's largest generics market are successfully pushing patients away from high-priced new drugs and toward low-priced generics to reduce their already-overstretched drug outlays. Governments even in other developed countries in the European Union and Japan are also driving aggressively cost-containment to check the increasing healthcare expenditures.

All these pressures that the industry has been facing slowed down the rate of growth for prescription drug sales to a snail's pace of 1.8 percent between 2011 and 2017. However, the growth rate is likely to improve to a healthy CAGR of 6.4 percent for 2018 through 2024 according to the forecast of Evaluate Pharma, a leading consultancy firm.

Evaluate Pharma, in their World Preview 2018 Outlook to 2024 for Pharmaceutical Industry present a snapshot of key drivers and brakes.

Key Drivers

1. Increase in the number of new drug approvals doubled from 27 in 2016 to 55 in 2017.
2. Increased focus on orphan drugs. Orphan drugs to generate an additional $124 billion between 2018 and 2024.
3. Oncology drugs to grow almost twice as rapidly as the market at 12 percent during the next six years.

4. Advanced therapies to the fore. Advanced therapies to generate an additional $5billion in the next six years.

Brakes

Factors hindering performance or putting the brakes on the growth are:

1. Continued payer-pressure on budget-growth.
2. Patent cliff. The impending patent expiries during the next six-year period affect a total sales volume of $251billion.
3. Increase in R&D costs. Increase in average spend per new molecular entity (NME) since 2007 to $3.97 billion suggesting that a significant improvement in R&D efficiencies is needed.
4. Reducing R&D spend by industry at the same time from 20.9 percent of drug sales in 2017 to 16.9 by 2024 suggests a reduction in innovation.

The Turf

Turf implies ownership, possessiveness, and protectionism in that order. The point of conflict in the globalization process lies in the ambivalent attitude of gaining market access and denying market access to one's products. Understanding the sensitivities involved in gaining market access assumes paramount importance. The shades and hues of social, political, cultural and technological colors make the management of diversity a challenging task.

The world pharmaceutical industry can broadly be divided into two categories — single-source and multi-source products. Single-source products industry is the research-based pharmaceutical industry popularly known as the Big Pharma. Since its products have patent protection, they enjoy market exclusivity as long as the patent lasts and therefore available only from one source and hence called single-source, which is the innovator or discoverer of the drug. Although the life of a pharmaceutical patent is 20 years from the date of filing, its effective patent life is ten to twelve years on average as the gestation period of a pharmaceutical product — from concept

to commercialization is quite long and takes an average of eight to ten years for a drug to reach the market from the lab.

The Federal Drug Administration (FDA) approves marketing of generic versions or copies of the original drug subject to their matching the bio-equivalence with the original drug after the drug's patents expire. After patent expiry, there can be any number of generic versions available in the market. As these are available from multiple companies (sources), these products are also known as multi-source products. When a drug's patent expires and generics enter the prices fall drastically — sometimes by 80 to 90 percent of the original drug's price before patent expiry.

Research-Based Pharma Industry

For many years, it was fairly simple and straightforward to outline the structure of the research-based pharmaceutical industry. One could classify the companies into three easily identifiable and separate segments in the industry such as:

A. Big Pharma comprising large prescription-drug companies, which discover, develop, manufacture and market New Chemical Entities (NCEs).
B. Biotechnology companies such as Amgen, Biogen, and Genzyme, which focus on discovering, manufacturing and marketing biological products.
C. Generic drug firms, which produce the bio-equivalent products of the research-based pharmaceutical companies when their patents expire. Notable examples of generic drug firms are Teva, Mylan, and Sun Pharma.

The following table illustrates the blurring lines between Big Pharma and Biotechnology segments of the pharmaceutical industry. Only one company - Amgen out of the ten companies in the following table has started as a biotechnology company. The rest of the nine pharmaceutical companies, who have been a part of the Big Pharma for a long time, boarded the biotechnology bandwagon in time and had become active participants garnering a sizable share of the rapidly growing biotechnology pie.

Table 1.1 Big Pharma Companies and their Biotechnology Share in 2017

Company	Total Sales (US $ Billion)	Contribution of Biotechnology Products to Total Sales (%)
1. Merck & Co	35.4	31
2. AbbVie	27.7	70
3. Bristol-Myers Squibb	19.3	47
4. Amgen	21.8	88
5. Novo Nordisk	17.0	74
6. Eli Lilly	18.5	49
7. Pfizer	45.4	24
8. Roche	41.7	82
9. Johnson & Johnson	34.4	41
10. Sanofi	34.1	40

(Source: Evaluate Pharma)

Today, it is not quite as simple to divide the industry in this way. The merger and acquisition (M&A) activities and licensing arrangements have blurred the traditional lines dividing these segments. Patricia Danzon, the Celia Moh Professor of Healthcare Management at Wharton School, University of Pennsylvania clearly explained this phenomenon:

> The biotechnology revolution has transformed the nature of drug discovery and the structure of the industry. Increasingly, new drugs originate in small firms, which often out-license their products to more experienced firms for late-stage development, regulatory review, and commercialization.

It is not that only the dividing lines between the Big Pharma and biotechnology are blurred. That is happening between the brand-name drug companies and generic drug companies too. Consider the following facts for example:

- Pfizer, which has the world's largest generic platform termed Pfizer Established Products alongside its substantial Greenstone (subsidiary generic company) business took a significant step to reinforce the generics business with the $16 billion acquisition of Hospira.
- Endo Pharmaceuticals acquired PAR pharmaceuticals, a generic drug company for $8 billion.

The Generic Drug Industry

The US generic drug industry, which has the largest share of the world generic drug market in terms of value is experiencing dramatic growth with generic prescriptions approaching almost the 90 percent level and it is poised for even rapid growth with impending patent expiries worth a whopping $251 billion in sales value. The generic drug industry is in for a dramatic change with a consolidation spree sweeping it.

The aggregate value of the generic drug industry on a global basis exceeded $900 billion for the first time in 2016 according to the estimate of Torreya Partners, the leading consultants to the generic drug industry. It was only $150 billion a decade ago. Furthermore, the global generic industry accounted for about $200 billion in total sales in 2015 is expected to reach $380 billion by 2021, growing at a CAGR of around 10.8 percent between 2016 and 2021.

Evolution of a Research-Based Drug Company

What is the ultimate goal of a generic manufacturer, be it in the developed world or developing world? When you ask this question, you are likely to get three types of responses.

A. Some of the leading generic drug companies in the specialty space would like to be research-based pharmaceutical companies.

B. A few others would like to compete in the generic space that is rapidly growing and become international generic drug companies.

C. And then, there are others would like to position themselves as 'partners-of-choice' or preferred partners in the CRAMS (Contract Research and Manufacturing Services) space that is expanding fast.

Whatever be the space in which a company chooses to compete, every company wants to become an integrated company competing across the pharmaceutical value chain. The journey or transition or perhaps the metamorphosis from a generic drug industry to a research-based pharmaceutical company is tough and arduous to say the least. The evolutionary process (Figure 1) would take anywhere between 20 to 25 years provided one works towards this goal with unflinching determination. It can take a minimum period of ten years for a generic drug manufacturer to graduate into a branded generic drug company and to an international generic company with the right investment and the relevant capabilities. From an

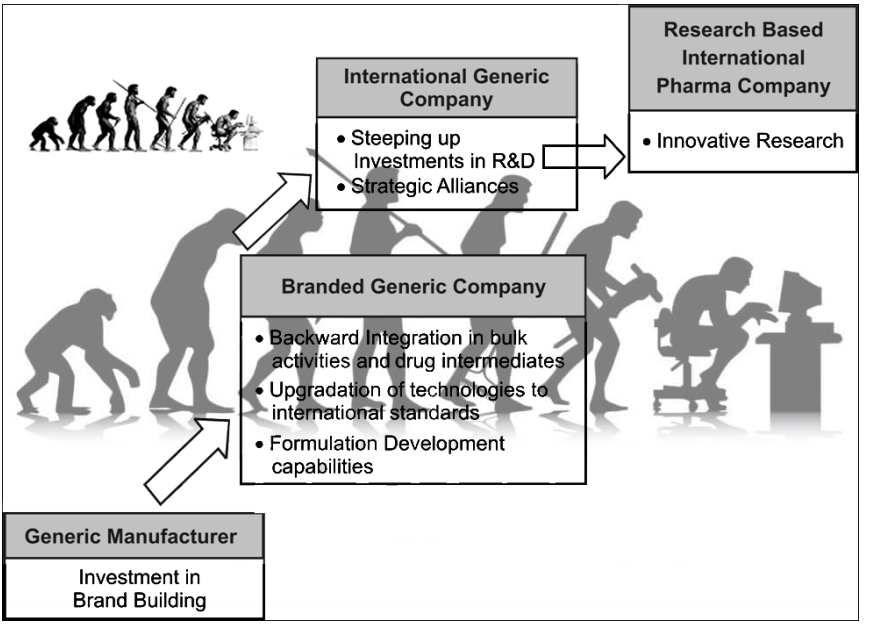

Figure 1. 1 Evolution of A Research-Based Pharma Company

international generic company to a research-based pharmaceutical company it could take ten to fifteen years with the right combination of competencies, capabilities, strategies, and investments.

There seems to be a well-defined hierarchy of goals in the pharmaceutical industries in the pharmaceutical world. All firms virtually start off with as manufacturers and marketers of finished-dosage forms (FDFs) which are generally known as formulations or Active Pharmaceutical Ingredients (APIs) and drug intermediates. Then they integrate backward or forward depending upon the point from where they started, to become fully or vertically integrated pharmaceutical companies.

Vertical integration gives a significant and sustainable advantage to a pharmaceutical firm. It gives the firm the much-needed control on costs, timely availability, and quality of inputs. The underlying assumption here is that the integrated firm has cost-effective processes, superior technology, and therefore holds the key to successful integration.

Fifteen to twenty years ago, Teva, the Israeli drug major was perhaps the only fully integrated international generic drug company in the world. Teva, today, is among the top twenty of the Big Pharma with its own New Chemical Entity (NCE) that had become a billion-dollar molecule. Taking a cue from Teva's journey to become a research-based pharmaceutical company, a few other international generic companies are on their way to compete with the Big Pharma on their turf — with their drug discovery programs.

The Turf Wars

The battle lines are clearly drawn between the Big Pharma and the generic drug firms. The Big Pharma wants to protect their patents and exclusivity as long as it can whereas the generic drug firm wishes to enter the market as soon as a drug's patent expires. Till the mid-1980s, the brand-name drug firms dominated the industry. In fact, when generic drugs first emerged in the 1980s as a potentially formidable source of profits, the major pharmaceutical companies controlled much of the segment through ownership of generic firms.

From the late 1980s, brand-name drug companies have come under increasing pressure from generics since the passage of the Hatch-Waxman Act, which is instrumental in creating the modern generic drug industry as we know today. Not content with their achievements, some of the leading generic drug companies are raising the bar constantly and shifting the battle lines by entering the turf of the innovator drug companies by fielding their new drug candidates and launching their New Chemical Entities (NCEs) after they reach the required critical mass to invest in the drug development process.

Innovator drug companies too are taking the battle to the generics camp with their offensive moves such as launching their own generic versions and authorized generics to hit them where it hurts most — their profits during the market exclusivity period. The battle lines are shifting and blurring. The fighting is all over the field. The world's leading generic drug company – Pfizer Established Products, for example, is the subsidiary of a Big Pharma major, Pfizer. Likewise, the world's largest generic drug company – Teva Pharmaceutical Industries is also a top-twenty company in the world pharmaceutical league table with its innovator drug that has over a billion dollars in worldwide sales.

Innovator-drug companies are launching generics, partnering with generic companies to fight generic companies. The generic drug companies are into discovery research already with a combined pipeline of over one-hundred molecules covering a wide range of therapeutic areas at various stages of development.

Truly when titans clash the turf shrinks!

Surviving Patent Expiration: Defensive Strategies by the Big Pharma

When the generic drugs first emerged in the 1980s, they were considered as a potentially formidable source of profits and growth. Some of the drug majors owned and controlled the segment to beef up their profits and growth. However, the potential did not result in a promising performance, and it did not take much longer for the

Pharma majors, who were disillusioned with their generic-arms to divest and keep a distance from them ever since.

Big Pharma companies, therefore, are continuously exploring ways and means to fix the situations that they are in. They are looking at every strategy in the book and are also evolving new strategies to defend themselves against the generics onslaught.

The 1984 Hatch-Waxman Act put the US Pharma industry on an innovation treadmill. Within a year of the bill's passage, nine of the industry's top-ten best-selling drugs had new generic rivals forcing sales precipitous declines rather than a long, slow tapering off sales as in the past. Faced with the prospect of continuing patent expirations and with not enough products to replenish the declining sales, innovator-drug companies have started applying every strategy they could think of for protecting their patent rights as long as possible (ever-greening patents) and delaying the generic entry as long as possible. Innovator-drug companies have been working more vigorously than ever before to defend their market and profit shares. Here are fifteen of the more important and commonly applied strategies by the Big Pharma to delay the generic drugs from entering on to their turf.

1. Strategic Patenting
2. Strategic Lobbying
3. Strategic Litigation
4. Metabolite Defense
5. Pediatric Exclusivity
6. Citizen Petition
7. New, Improved Successor-Drug Candidates
8. New, Improved Dosage Forms
9. New Uses (Indications)
10. Predatory Pricing
11. Aggressive Marketing
12. De-Marketing - Launching Own Generics
13. Reverse Payments

14. Prescription-to-OTC-Switches
15. Voluntary Licensing

Exploiting Patent Expiries: Generic Drug Firms' Offensive Strategies

The generics drug industry has come a long way since its humble beginnings in the 1980s. Three factors are mainly responsible for changing the complexion of the generic drug industry to the pink of health that it is in today:

1. Many generics companies have become highly competitive and built up their capabilities across the pharmaceutical value chain.
2. The rise in health care costs, while painful for the big pharmaceutical companies, has considerably benefited the generic drug firms. Substitution laws and managed healthcare system from the Health Maintenance Organizations (HMOs) to hospitals in the US and elsewhere create significant pressure on physicians to prescribe *generics first* to contain healthcare costs.
3. Generic drug companies have been setting their sights high and are aspiring to become fully integrated, research-based pharmaceutical companies. Once they reach the critical mass required, they move up from process to product development. As generics manufacturers have improved and moved rapidly upstream in the pharmaceutical business system developing R&D capabilities, they have sharply increased their technology and in-licensing skills.

Generic drug firms have not only been trying to defend their turf but also are launching their offensives and taking the battle to the Big Pharma's turf. Here are seven commonly followed offensive and defensive strategies by the generics drug industry:

1. Paragraph IV Filings
2. Strategic Litigation
3. Strategic Lobbying

4. Strategic Alliances
5. Branded Generics
6. Transformational Strategies
7. Compulsory Licensing
8. Invading the Innovators' Turf

While it is beyond the scope of this book to discuss all the strategies that the research-based and generic pharmaceutical companies apply to defend their respective turfs, three specific strategies need a special mention. They are – Voluntary licensing, which the research-based Pharma practices, and Compulsory licensing and Paragraph IV filing, which the generic drug firms try to exploit.

Voluntary Licensing (VL) - An Alternate Strategy?

Voluntary licenses, as the name indicates are licenses that patent holders give at their discretion to other parties on an exclusive or non-exclusive basis, the right to manufacture, import and distribute a pharmaceutical product.

Ever since the government of India gave its first compulsory license of Bayer's Nexavar to Natco Pharma, multinational pharmaceutical companies have been rethinking about strategy to launch their new drugs in India. The strategy? Voluntary licenses. Here are the details of some of the voluntary licenses that MNC pharmaceutical companies gave to their local partners in India.

- MSD Pharmaceuticals gave Sun Pharma an exclusive marketing license for marketing two patented diabetes drugs - Januvia and Janumet in India.
- Novartis, a top-ten Big Pharma company, entered into a marketing tie-up with Lupin, the Indian drug major for its Onbrez inhaler.
- Bayer plans to license most of its patented products for India to its local joint venture company, Cadila Healthcare - Bayer.
- Gilead Life Sciences gave voluntary licenses to seven Indian generic drug manufacturers – Cadila Healthcare, Cipla, Hetero

Drugs, Mylan Labs, Ranbaxy, Sequent Scientific and Strides Arcolabs for its blockbuster hepatitis-C drug Sovaldi (sofosbuvir).

Voluntary licensing to a local partner under mutually agreed terms will not only help patent holders to expand the market but also avoid compulsory licensing action. While government intervention through a compulsory licensing will lead to a drastic reduction in price as it is typically without the consent of the patent holder, voluntary licensing may get a more remunerative price albeit much lower than its original price.

Innovative drug companies with patented drugs realize that voluntary licensing is a wiser option to avoid a likely invocation of the compulsory licensing Act. Besides, a voluntary license offers two advantages:

A. A voluntary license helps minimize loss and also ensures better access of the patented drug to more domestic patients.
B. It helps counter one of the most common reasons for issuing a compulsory license — inadequate patient access.

Compulsory Licensing

A compulsory license is an authorization given to a third-party by the government to make, use or sell a particular product or a particular process, which has been patented, without the need of the permission of the patent owner. Compulsory licenses, therefore work against patent holders. However, then, they are given only in certain cases of national emergency and health crisis.

There are certain prerequisite conditions, which need to be fulfilled if the government wants to grant a compulsory license in favor of someone. At least three years should pass from the date of grant of a patent before anyone interested in making an application to the controller for grant of compulsory license on any of the following three conditions:

A. That the reasonable requirements of the public concerning the patented invention have not been satisfied or

B. That the patented invention is not available to the public at a reasonably affordable price or

C. That the patented invention is not worked in the territory of India

Thus, the use of a compulsory license effectively withdraws a patent from a drug completely if it is seemed prohibitively expensive to a domestic market and a vital public health need.

Paragraph IV Filing

Certification under the Paragraph (IV) is called Paragraph IV certification. It is the most complicated of the four certifications as the generic drug companies required to notify the innovator drug company about the NDA filing and explain the reasons it believes the generic version will not infringe the listed patent or the listed patent is invalid. Within forty-five days of receiving the notification, the innovator company has to file an infringement suit. The FDA withholds the approval of Abbreviated New Drug Application (ANDA) for 30 months or until the case is decided if the innovator files a lawsuit. The Act Permits such an action by the patentee even if no infringement is taken place in reality. FDA will approve the ANDA depending on the outcome of the case. If the generic product is found to be non-infringing, FDA approves the ANDA.

The following four cases illustrate how the innovator and generic pharmaceutical companies try to fight for their turf.