Chapter 1

PharmTech Industry...
1.1. MARKET REVIEW

1.1.1. World PharmTech Market

The world pharmaceutical market is estimated to swell to 550 billion USD by 2005\(^1\).

The year wise details of global pharma forecasts from 1996 are given in Table 1.1\(^2\).

The world pharmaceutical market grew by \(\sim0.92\%\) in 1997, with an estimated sales reaching $ 294 billion from $ 292, to $ 505.8 billion in 2004, with an average annual global sales growth of \(\sim7.16\%\)\(^3\). Looking in the market trend Dr. Joe Zammit – Lucia, president of Cambridge Pharma Consultancy comments, “The sustained growth of the world pharmaceutical market shows that consumers and health care professionals continue to appreciate the value of pharmaceuticals as a convenient, cost effective form of treatment”.

Table 1.1. World pharmaceutical market size.

<table>
<thead>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (in USD billion)</td>
<td>292.0</td>
<td>294.8</td>
<td>304.2</td>
<td>338.0</td>
<td>373.0</td>
<td>406.9</td>
<td>438.0</td>
<td>469.4</td>
<td>505.8</td>
</tr>
</tbody>
</table>

Source: Global Pharma Forecasts\(^3\).

1.1.2. Leading Countries

The top ten worldwide markets represent approximately 79% of all unaudited and audited sales\(^4\) is given in Table 1.2. The US remains the largest pharmaceutical market by far, growing 17% to $130.1 billion in sales in 1999, and representing 39% of the total worldwide market. Japan, the second largest market, recovered last year from three consecutive years of negative performance, growing 23% with sales of $53.5 billion. Within the top five European markets, Germany remains in the lead, achieving sales of $18.5 billion with 1% growth over 1998. The fastest growing Western European markets in 1999 were the UK, growing 8%, and Spain, with 6% growth over 1998. Brazil, the seventh largest audited world pharmaceutical market in
1998, dropped to eighth place last year, experiencing a 26% decline in growth due to economic conditions. China, ranked ninth for the third consecutive year, achieved $6.2 billion in 1999 sales and 12% year-over-year growth.

Table 1.2. Leading countries global pharmaceutical sales.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>1999 Sales*</th>
<th>% Global Sales</th>
<th>% Growth Year-on-Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>United States</td>
<td>130.1</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>2.</td>
<td>Japan</td>
<td>53.5</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>3.</td>
<td>Germany</td>
<td>18.5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4.</td>
<td>France</td>
<td>17.8</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>5.</td>
<td>Italy</td>
<td>11.3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6.</td>
<td>United Kingdom</td>
<td>11.0</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>7.</td>
<td>Spain</td>
<td>6.6</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>8.</td>
<td>Brazil</td>
<td>6.3</td>
<td>2</td>
<td>(-26)</td>
</tr>
<tr>
<td>9.</td>
<td>China</td>
<td>6.2</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>10.</td>
<td>Canada</td>
<td>5.5</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

Source: IMS HEALTH\(^4\), (*Growth measured in USD Billion).

1.1.3. Domestic Market

The total annual domestic pharma sales is pegged at Rs. 18400 crores, according to retail audit figures for 12-month period ending June 2003\(^5\), Table 1.3. The largest therapy segment are antibiotics and antibacterial systemics with a sale of 3137 crores but is showing degrowth by 2%. The hypotensive constitutes the eight largest segments under the study with the highest growth of 20.8%, while the anti-diabetic is second with 17.6%. The study shows that hypotensives, anti-diabetics and anti-asthmatics are registering good growth while antibiotics, the largest segment is
showing degrowth by 2%. A share of 54.73% of total annual sales comes from the top 10 therapy segments.

1.1.4. World Market Favorable To Generics

According to Glossary of Terms, United States Food and Drug Administration (US FDA), a "generic" drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. Before approving a generic drug product, FDA requires many rigorous tests and procedures to assure that the generic drug can be substituted for the brand name drug. The FDA bases evaluations of substitutability, or "therapeutic equivalence" (TE) of generic drugs on scientific evaluations. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as TE can be expected to have equal effect and no difference when substituted for the brand name product.

Generic drugs have assumed a prominent role in the pharmaceutical industry. The modern generic industry only began in 1984 with the passage of the Drug Price Competition and Patent Term Restoration Act. "It is an established trend world over that the prices of generic drugs are much lower than the branded versions" says Mr. H. S. Sikka, Senior President, Corporate Affairs, Nicholas Piramal India Ltd. because they do not have to duplicate the cost of research and marketing conducted by the original manufacturer. Generic medicines are considered as cheap bio-equivalent copies of molecules for which patents have expired; typically introduced at 20 to 25% of the branded drugs price. Pankaj Patel, Managing Director, Zydus Cadila: "With rising healthcare cost, governments in the developed countries are coming out with regulations that increasingly favor generics. In France for instance, the government has started encouraging prescription of generics." It is estimated
that drugs worth US $31 is expected to face patent expiry in the years leading to 2010\textsuperscript{12}, Table 1.4.

Table 1.3.  
Domestic sales and trends of top 10 therapy segments.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Segment</th>
<th>Sales (in Crores)</th>
<th>Trends (in %)</th>
<th>Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Antibiotic &amp; Anti bacterial</td>
<td>3137</td>
<td>-2</td>
<td>17.05</td>
</tr>
<tr>
<td>2.</td>
<td>Vitamins</td>
<td>1079</td>
<td>+3.5</td>
<td>5.86</td>
</tr>
<tr>
<td>3.</td>
<td>Anti-inflammatory &amp; Anti-rheumatologicals</td>
<td>1023</td>
<td>+2.6</td>
<td>5.56</td>
</tr>
<tr>
<td>4.</td>
<td>Cough &amp; Cold</td>
<td>909.5</td>
<td>+1</td>
<td>4.94</td>
</tr>
<tr>
<td>5.</td>
<td>Antacids &amp; Anti-flatulents</td>
<td>847.9</td>
<td>+5.9</td>
<td>4.61</td>
</tr>
<tr>
<td>6.</td>
<td>Antidiabetics</td>
<td>788</td>
<td>+17.6</td>
<td>4.29</td>
</tr>
<tr>
<td>7.</td>
<td>Cardiac</td>
<td>698.9</td>
<td>+7</td>
<td>3.8</td>
</tr>
<tr>
<td>8.</td>
<td>Hypotensive</td>
<td>650.16</td>
<td>+20.8</td>
<td>3.35</td>
</tr>
<tr>
<td>9.</td>
<td>Anti-anemics</td>
<td>477.98</td>
<td>-2</td>
<td>2.6</td>
</tr>
<tr>
<td>10.</td>
<td>Anti-asthmatics</td>
<td>457.99</td>
<td>+11.8</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Total 10069.43

Source: EPP New Bureau, Express Pharma Pulse, 2003\textsuperscript{6}.

Taking a cue from UK's National Health Services (NHS), the Indian Government is looking at the option of asking the medical fraternity to prescribe generic drug, in order to bring down the prices of essential drugs\textsuperscript{9}. However, generic companies allow middlemen and retailers to milk patients by quoting Maximum Retail Price (MRP) at par with branded names. A study initiated by the Chemicals and Fertilizers
Table 1.4. Values of drugs going off-patents.

<table>
<thead>
<tr>
<th>Values of drugs facing expiry till 2010</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values (in US $ billion)</td>
<td>6.6</td>
<td>3.8</td>
<td>7.0</td>
<td>2.8</td>
<td>4.0</td>
<td>2.0</td>
<td>3.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Source: lyer, Express Pharma Pulse\textsuperscript{12}.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Ministry has revealed that the difference between the cost of production of a generic drug and its MRP is very wide and the margins are either given to the chemists or doctors who prescribe them.

Office of Planning, US FDA, in November 2003\textsuperscript{13}, released **White Paper** stating that generic drug prices in the US are lower than drug prices in Canada. Canadian branded and generic prices relative to U.S. generic prices for these seven drugs appear in the Fig. 1.1. Only one (metformin) sold for less in Canada either generically or as a brand name. Furthermore, metformin did not become available generically in the US until January 2002, so US generic prices have likely not fallen to the level they will eventually reach.

1.1.5. **Reforms In Generic Marketing**

Recent reforms by the US FDA to the procedures required for entry into the generic market and to the protections provided to patents of the innovator companies were put forth to restore and enhance balance to the playing field of pharmaceutical marketplace\textsuperscript{15}. The new rules come in response to what many consider loopholes in the original 1984 **Hatch-Waxman Legislation** for abbreviated generic approval. The reforms, labeled the Final Rule by the FDA, have two central accomplishments. The first is the elimination of the possibility of obtaining multiple 30-month stays against a
single **Abbreviated New Drug Application** (ANDA). And second are more stringent requirements for patent listing in **Orange Book**. It will behoove those on both sides of the issue to pay close attention to the new regulations.

![Canadian drug prices are higher than U.S. generic prices](chart)

**Fig. 1.1.** Canadian drug prices are higher than US generic prices.¹³

### 1.1.6. **Origin of Patents and Development**¹⁶

Developed countries first linked intellectual property rights with the development of trade, investment and services during the **General Agreement on Tariffs and Trade** (GATT) negotiations, which began in Uruguay in 1896. This international regime, given a final shape in **Trade Related Intellectual Property Rights** (TRIPS) had no caveats and no member country could withdraw from it. The only concession given to developing and **Least Developed Countries** (LDCs) was an initial discretion in implementing the provision, which were to be progressively eliminated.

However, the derailment of the **World Trade Organization's** (WTO) Seattle Ministerial Conference in 1999 by anti-globalization activists forced a rethink. The Doha Ministerial Conference in 2001 adopted the Doha Declaration in which
countries agreed to implement the TRIPS agreement in a manner supportive of the WTO member’s right to take measures to protect “human, animal, plant life or health or of the environment at the levels it considers appropriate”. India, along with Brazil and South Africa, played a crucial role in bringing together developing countries on the issue.

According to TRIPS, while developing countries (which includes India) had time until January 1, 2005, to enact domestic legislation to conform with the agreement, LDCs were given time until 2016.

1.1.7. Intellectual Property Rights

Thomas Jefferson on intellectual property – “If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of everyone, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it. He, who receives an idea from me, receives instruction himself without lessening mine; as he who light his taper at mine, receives light without darkening me. That idea should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature, when she made them, life fire, expansible over all space, without lessening their density at any point, like the air in which we breath, move, and have our physical being, incapable of confinement or exclusive appropriation. Inventions then cannot, in nature, be a subject of property.” But still, we continue to have Intellectual Property Right (IPR) Law it, with unlimited justifications and reasoning in the interest of development of Science and
Technology in the service of the mankind! The steps\textsuperscript{19} involved in obtaining a patent is given in fig.1.2.

1.1.8. Indian Patent Act, Post GATT Scenario and Strategic Transnational Growth

Intellectual property has assumed a completely new dimension in India after the turmeric, neem and the basmati disputes\textsuperscript{18}. The story of patents in India dates back to the first Indian Patent law - which was enacted in 1856 and modeled on the same lines as the British Patent Act of 1852. A proper institution and authority for the administration of patents, however, was not established until the appointment of the Controller of Industrial Patents and Designs by the Indian Patents and Designs until as late as 2000, when the Indian Designs Act of 1999 was enacted.

In 1959, the Government of India appointed the Justice Rajagopala – Ayyangar Committee\textsuperscript{20} to suggest revisions to the Patent Law. In 1965, based on this report, a bill was introduced, but this bill lapsed in 1965 and again in 1966. This bill was reintroduced in 1967 and eventually passed as the Indian Patent Act (IPA) of 1970. The rules based on this act were passed in 1971 and the act along with the rules came into force in 1972. This legislation prevailed in the country undisturbed despite the passage of Super and Special 301 and threats from the US\textsuperscript{19}. The conclusion of the Uruguay Round in 1994 paved the way for the change in this area of law. More importantly, India joined the WTO\textsuperscript{21} and became obligated to comply with the TRIPS\textsuperscript{22}.

Today the market potential in India has attracted a new wave of investment by foreign multinationals and the talent generated in India is recognized across the world, making the need to merge with the rest of the world even more imminent, for which there need to develop a system were in the Indian companies and lawyers
Fig. 1.2. Key steps involved in obtaining a patent.
meet their foreign counterparts in national and international forums. With lack of professional depth and efficiency will be the causalities, which will be detrimental to India on the long run\textsuperscript{23}.

Ganeshan\textsuperscript{24} reports that around 650-patented drugs were introduced in the world market in the past 15 years (from 1983 to 1998) of which 72 were introduced into the Indian market under the existing dispensation between 1986 and 1988. In the last five years, i.e. 1994 to 1998 alone, 39 new drugs were introduced in the Indian market. There has generally been a gap of three to five years, if not more, between the introductions of a new patented drug in the world market and its subsequent introduction in the Indian market. It can therefore be surmised that the Indian market may, on an average, see 5 or 6 new patented drug introduction each year for the foreseeable future.

The Indian pharmaceutical industry has grown significantly after independence. The IPA 1970 was a landmark legislation, which in may way far exceeded the restrictions put on the patent system by other like minded counties such as Brazil, Argentina, Chile and China to enable local production and marketing of patented drugs at prices much lower than their counterparts in the patent-strong developed countries\textsuperscript{25}. With only the process patent, various drugs, intermediates and chemicals were prepared by shorter synthetic routes than originally reported by the inventor, within a few months, by highly cost effective process\textsuperscript{26}. Even though in terms of value terms, the Indian Pharma Industry has only 1% of the world market, in volume terms, Indian production of bulk drugs in 7-8% of global pharmaceutical output in view of low prices commanded by the Indian Industries\textsuperscript{25}. However, India become signatory to the GATT Patent Law effective from January 2005 which has taken Indian pharmaceutical industry at the crossroads. It is imperative that none can make drugs originally discovered and patented by others even by innovative new process without
paying royalties to the inventor. The increasing national and international competition, the collapse of geographical barriers, changing world markets, liberalization and globalization would radically influence the direction of the industry\textsuperscript{26}.

Shri. K. R. Narayanan, the 11\textsuperscript{th} President of India (then an Member of Parliament) in his speech at the 3\textsuperscript{rd} World Patent Convention\textsuperscript{27} said, “You know that the field (pharmaceutical and medicines), where the maximum pressure is being put on us. Almost all our countries are poor, our health standards are appalling and the great ideal of Health for All by 2000 A. D. – all these are before us. We will not be able to reach those targets. Not only that, we will not be able to provide even a minimum health standards for our people if markets for pharmaceuticals and medicines are cornered by the great transnational and not by our own developing, rapidly growing pharmaceutical industries. This is a human question, protecting the health of our people, and providing the human infrastructure for the development of our country…; now we cannot just afford to yield on these issues because as we know our own future, our own development, our own welfare depends on the application of this new knowledge of science and technology particularly to the economic processes. It is not only for industries but also for agriculture ...”. Addressing the Asian Symposium\textsuperscript{28} on Healthcare Industry titled “Regulatory policies and growth constraints” the OPPI President Mr. Ranjit Sahani who is also the Vice-Chairman and Managing Director of Novartis Ltd., that the country had substantial growth potential in areas of contract research, custom synthesis and generics. He also said, “the competition itself regulates the markets in terms of price stabilization as evinced by the recently introduced voluntary price cuts in insulin”.

The Indian pharmaceutical industry has stood to the times. Is known to produce cheapest quality medicines, approved by the worlds leading regulatory authorities, says Pankaj Patel, Managing Director of Zydus Cadila, India\textsuperscript{11, 16} (Table 1.5). It is the
probably the only industry of the country that has not suffered from any recession. Already, Indian Pharma Companies have rolled up their sleeves for the post GATT situation, have made massive investments and are streamlining their strategies for the transnational growth by one or more of the following approaches:

2. Be aggressive on Para IV filings – patent challenge route.
3. Launch innovative specialty products - Drug Master Files (DMFs – for bulk drugs) and Abbreviated New Drug Applications (ANDA –for formulation.

Besides, most of the India pharma companies have been investing substantial time and efforts in cutting edge Research and Development in areas of New Chemical Entities (NCE), Novel Drug Delivery Systems (NDDS), process research and collaborative research.

The Indian pharma market is currently valued at $4 billion, which is just 1% of the global pharma market of $400 billion. Of the total global pharma market, 90% of the total market is with the US, Europe and Japan. It is estimated that after 2005, large numbers of many blockbuster-patented drugs are going to be off patent, whose market size is $40 billion. After 2010, the size of the off-patent drugs market is estimated around $80 billion. This will provide attractive opportunities to Indian companies to tap the international market for these products. Key players of the Indian pharma industry who are making substantial investments are Dr Reddy's, Ranbaxy, Wockhardt, Sun Pharma, Cipla, Zydus Cadila Pharmaceuticals, Torrent Pharmaceuticals, Lupin's, Aurobindo Pharma, Alembic Ltd., JB Chemicals & Pharmaceuticals Shasun Drugs and Chemicals, Ind Swift Laboratories.
1.1.9. **Headlines, Comments and Quotes**

Matters concerning to Patents, its impact on industry and people has created lot of news. The opinion and views, developments and moves at international and national level by people, pharma-industry and government is cited below as perceived by the researcher crucial that would govern the future course of action, in this area affecting every citizen in health care policy matters.

Table 1.5. **Comparison of drug prices, Indian and International (in Indian rupees)**

<table>
<thead>
<tr>
<th>Drugs, dosage &amp; packaging details</th>
<th>India</th>
<th>Pakistan</th>
<th>Indonesia</th>
<th>United Kingdom</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-infective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin, 500 mg, 10 Tabs.</td>
<td>29.00</td>
<td>423.86</td>
<td>393.00</td>
<td>1.185.70</td>
<td>2,352.35</td>
</tr>
<tr>
<td>Norfloxacin, 400 mg, 10 Tabs.</td>
<td>20.70</td>
<td>168.71</td>
<td>130.63</td>
<td>304.78</td>
<td>1,843.66</td>
</tr>
<tr>
<td>Ofloxacin, 200 mg, 10 Tabs.</td>
<td>40.00</td>
<td>249.30</td>
<td>204.34</td>
<td>818.30</td>
<td>1,973.79</td>
</tr>
<tr>
<td>Cefpodoxime rosin, 200 mg, 6 Tabs.</td>
<td>114.00</td>
<td>357.32</td>
<td>264.00</td>
<td>773.21</td>
<td>1,576.58</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-ulcerants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac Sodium, 50 mg, 10 Tabs.</td>
<td>3.50</td>
<td>84.71</td>
<td>59.75</td>
<td>60.96</td>
<td>674.77</td>
</tr>
<tr>
<td>Ranitidine, 150 mg, 10 Tabs.</td>
<td>6.02</td>
<td>74.09</td>
<td>178.35</td>
<td>247.16</td>
<td>863.59</td>
</tr>
<tr>
<td>Omeprazole, 30 mg, 10 caps.</td>
<td>22.50</td>
<td>578.00</td>
<td>290.75</td>
<td>870.91</td>
<td>2,047.50</td>
</tr>
<tr>
<td>Lansoprazole, 30 mg, 10 Caps.</td>
<td>39.00</td>
<td>684.90</td>
<td>226.15</td>
<td>708.08</td>
<td>1,909.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovasculars</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol,</td>
<td>7.50</td>
<td>71.82</td>
<td>119.70</td>
<td>N.A.</td>
<td>753.94</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
<td>10 tabs</td>
<td>Anti-viral/fungal</td>
<td>7.80</td>
<td>200.34</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------</td>
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<td>-------------------</td>
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</tr>
<tr>
<td>Amlodipine Besylate, 5 mg, 10 Tabs.</td>
<td></td>
<td></td>
<td></td>
<td>77.00</td>
<td>313.47</td>
</tr>
<tr>
<td>Zidovudine, 100 mg, 10 caps.</td>
<td></td>
<td></td>
<td></td>
<td>274.00</td>
<td>N. A.</td>
</tr>
<tr>
<td>Zidovudine, 300 mg, 10 Caps.</td>
<td></td>
<td></td>
<td>Anti-histamine</td>
<td>6.00</td>
<td>35.71</td>
</tr>
<tr>
<td>Caterizine, 10 mg, 10 Caps.</td>
<td></td>
<td></td>
<td>Anti-anxioltics/psychotics</td>
<td>7.00</td>
<td>160.57</td>
</tr>
<tr>
<td>Alpramazoo, 0.5 mg, 10 Tabs.</td>
<td></td>
<td></td>
<td></td>
<td>25.80</td>
<td>444.53</td>
</tr>
<tr>
<td>Fluxetine, 20 mg, 10 Caps.</td>
<td></td>
<td></td>
<td></td>
<td>190.00</td>
<td>554.69</td>
</tr>
<tr>
<td>Boposide, 100 mg, 10 Tabs.</td>
<td></td>
<td></td>
<td>Cholesterol reducer</td>
<td>39.00</td>
<td>N. A.</td>
</tr>
<tr>
<td>Atorvastatin 10 mg, 10 T-abs.</td>
<td></td>
<td></td>
<td></td>
<td>210.00</td>
<td>N. A.</td>
</tr>
<tr>
<td>Salmeterol, 25 mcg</td>
<td></td>
<td></td>
<td>Anti-asthamatic</td>
<td>48.00</td>
<td>N. A.</td>
</tr>
</tbody>
</table>
1.1.9.a. International

- **Global Impact of Indian Patent Act**\(^{30}\)

  "Seldom has India’s Parliament considered anything of such global import. If Parliament can preserve India’s ability to provide generic(s) … it will make the difference between life and death for millions of people at home and abroad".

- **India failing to take full advantage of WTO regime**\(^{16}\)

  "A double hit that will cut off the supply of affordable medicines and remove generic competition that drives down the cost of brand-names", *Editorial*, The New York Times, Jan 18, 2005. It further the ordinance was (i) heavily influenced by multinational and Indian drug-makers eager to sell patented medicines to India’s huge middle class; and (ii) so tilted towards the pharmaceutical industry that it did not even take advantage of the rights countries enjoyed under WTO regime to protect public health.

- **Indian contribution in cutting HIV/AIDS therapy cost**\(^{16}\)

  "Two thirds of the world’s population will be systematically deprived of life-saving drugs as of January 1, 2005. Countries in Africa dependent on Indian generic products, the WHO and AIDS organizations worldwide have written to Indian Prime Minister asking him to reconsider ordinance". Indian generic companies brought down the prices of antiretroviral therapy for HIV/AIDS from $12,000 to $140 a year.

- **Gaps in Patent Protection**\(^{31}\)

  "At present, there are certain structural weaknesses in the Indian regulatory framework with regard to the drug approval process. The country also suffers from inadequate supporting infrastructure in patents protections…..; if you want to
compete with China, you need to significantly improve your long-terms investments in infrastructure and never compromise on global quality standards”, Dr. W. A. Saseltime, Chairman, Scientific Advisory Board, Matrix Labs at BioAsia 2005.

- **Cautious Compliance**

“The fact that an Ordinance has been passed by the UPS Government amending the Patents Bill to comply with the TRIPS mandate does not necessarily mean that it has to become law”, K. P. P. Nair, Former Science Foundation Professor, Royal Society of Belgium.

- **America’s Patent System**

“America’s patent system has become sand rather than lubricant in the wheels of American progress”, Adam Jafee & Josh Lerner.

- **Indian Pharma-Company Globally Competent**

“India’s pharma companies have achieved worldwide acceptance for their competency…..; Indian pharma companies offer above-average management, achieving superior revenue growth while maintaining good margins in a high competitive segment”, excerpts from the report prepared by Mehta Partners, a New York-based global healthcare investments firm.

1.1.9.b. **Experts**

- **The People Commission Report on America’s Stand**

“Whatever be the international commitments or agreements signed by it, if any agreement conflicts with the interests of the American people, the American law will prevail; the American law will subdue that commitment” - excerpts from The
People Commission Report (PCR) that refers to US making clear that its own interests will prevail when there is clash of other interests, as cited.

- Patent – a techno-legal document

"Patent is a techno-legal document. It is an important piece of legislation and should be considered by either a joint committee or a standing committee of Parliament", A. D. Damodaran, Former Director, CSIR, Regional Research Laboratory, Thiruvanthapurum.

- Who Rules The Rooster

"It is important to remember that industry-advanced countries such as the U.S. and the European Union together hold 97% of all patents world-wide and multinational corporations account for 90% of all product and technology patents, and if they choose to hold the rest of the world to economic ransom and we unwittingly succumb the perils of this game by thoughtless haste, posterity will blame us for out foolhardiness" K. P. P. Nair puts a word of caution.

- Sustaining Post-Doha Obligations

"By rushing through the Third Patents Amendment without proper parliamentary scrutiny, India is short changing its post-Doha obligations to both its own and the world's poor.....; patents are not a gift for drug companies to exercise power without responsibility", R. Dhavan.

- Crux of WTO

"WTO helps developed countries by design and developing countries by default", Mr. Rahul Bajaj, as cited.
1.1.9.c. National

1.1.9.c.i. Pharma-industry

- **Product Patent Regime***

  "India embarks a new regime of product patent after a gap of 35 years. The infrastructure need for a new regime is created, but not yet tested. The Patent Office has yet to demonstrate its maturity and skill sets for dealing with the new regime. Its track record so far has been dismal. It’s tow of the four decision on EMS for pharmaceutical products (Glivec, an anticancer drug and Cialis, an impotency drug) are embroiled in the High Courts of Delhi, Chennai and Mumbai" – Representative, Indian Pharmaceutical Alliance (IPA) Representative cautioned the Government on the need to “clearly define” terms such as patentability.

- **Mailbox***

  "One doesn't know what will happen when the mail-box is opened", Mr. Malvinder Mohan Singh, Ranbaxy President – Pharmaceuticals and Executive Director, expressing concern over 'Mail-box Provision'.

- **Patent Bill In Present Avatar – Chaotic***

  "This could lead to chaotic situation as several companies would be forced to withdraw their bands from the market and the innovator entity will be able to jack up prices, hurting patients", Mr. Habil Khorakiwala, sounding a note of caution on Patents Bill in present avatar before the parliament;
• Drug Price Control
  
  o "We are against price control for these drugs as these are high-tech drugs and low volumes. Any type of control will hit availability as companies could stop manufacturing", Mr. S. Reddy, MD, Dr. Reddy’s Lab. Ltd.
  
  o "It has been amply proved that competition is the best controller of prices", cited from a recent study commissioned by IDMA.

• Patenting and affordability
  
  "If medicines have to remain affordable, countries will have to watch out that minor/trivial developments in a drug molecule do not get patented", Mr. D. G. Shah, Secretary General, Indian Pharmaceutical Association.

1.1.9.c.ii. Government

• Drug Price Control
  
  o The new Patent Ordinance would not affect drug prices because the process of granting patent would take around two to four years and 3 per cent of the drugs would be patented and 97 per cent would remain outside its purview", Mr. Ashok Jha, Secretary, Dept. of Industrial Policy and Promotions (DIPP), reacted over new patent norms and its impact on drug prices.
  
  o "We will allow low margins up to a limit. The Government will take action if margins are very high", Mr. Ram Vilas Paswan, Minister, Chemicals and Fertilizers in a meeting with representatives of the pharmaceutical industry.
• **Compulsory Licensing**

"Certain drugs, which are protected by patent, must be made available through the compulsory licence route", Mr. Ram Vials Paswan, Minister of Chemical and Fertilizer, addressing the Group of Ministers (GoM) set up to look into the amendments to the Patent (Amendment) Bill 2004.

• **Pre-Grant Objections**

"We did not want a situation where pre-grant cases can be dragged. The Law will take care of genuine concerns. Specific timelines have been put in place for grant patents has been reduced from a maximum period of 104 months to 52 months and the minimum period from 27 months to 5 months" Mr. Ashok Jha, Secretary, Dept. of Industrial Policy and Promotions (DIPP), reiterating Government keeping in mind the interest of the consume and the domestic industry.

• **Opposition for the Patent Amendment Bill**

"We hav told the government that we will oppose the ordinance as tis is not in the national interest. It will have serious implications for the pharmaceutical industry, agriculture and biodiversity. The government have to amend it drastically keeping in mind the national interest. This is bound to come up in the coming Budget session and Left parties will take up the issue clause by clause", D. Raja, Secretary, National Communist Party, India.

• **Profiting from life and death**

"My idea of a better ordered world is one which medical discoveries would be free of patents and there would be no profiteering from life and death", Ms. Indira Gandhi in World Health Assembly, 1981 Geneva, as cited.
1.1.9.c.iii. People

- Democratising Drug Availability To Save Life

'The Ranitidine preparation costs Rs. 740 (in rupee value) in the U.S. and Rs. 196 in Pakistan and this may well happen here. The process of patent system has been replaced by the product patent system because the Government in Delhi has placed its international obligations under GATT above national considerations....; considering that we have 18 lakh children dying each year because of lack of medical treatment and 1.3 lakh pregnant women dying during delivery, we cannot make medicine beyond the reach of those who badly need them'. Mr. Kumaraswamy, Convenor, Swadesh Jagrana Manch, Karnataka, expressing implications of the Ordinance amending the Indian Patents Act issued on December 26 by the Union Government.

1.1.10. Patent Issues

Experts of international repute in the field of Law, Economics, and Social Sciences etc. have expressing their opinion, cautioned over the consequences and suggested tactful ways of pursuing the issue in the interest of people at large. The article by Abbot et al suggests how the four vital issues need to be dealt at the concerned level.

I. To prevent "evergreening of Patents", patents only for modifications to New Chemical Entity (NCE) and for modifications to these entities that are clinically demonstrated to be significant therapeutic improvement over any previously patented form of the medicine should be granted. Such demonstrations, though not required under US or European Patent Law, is permitted by TRIPS.
II. Indian Law should retain maximum flexibilities available in TRIPS Articles 30, and particularly Article 31 relating to compulsory licensing. India currently allows the grant of compulsory licenses, but the procedure is cumbersome and offers many opportunities for patent holders to delay or prevent the grant of such licences. This process must be streamlined. In addition, the Ordinance imposes unnecessary hurdle on many developing countries without their own manufacturing capacity who might want to buy low-cost drugs from India as permitted under the Waiver to Article 31(f) and (h) of TRIPS adopted on August 30, 2003 by the WTO General Council. The Ordinance requires them to grant a compulsory patent licence even if the drug is not patented there. This hurdle is unnecessary, benefits no one, and is not required by the Waiver, of which India was, in fact, a champion! India’s generic producers, who could produce for export, need as much breathing space as can legally provided without violating TRIPS so that they continue their successful supply of low-cost products to Indian and World markets.

III. IPA of 1970 included a so-called “pre-grant opposition” right to third parties seeking to challenge a patent application before the patent was granted. The Ordinance apparently changes this from a right to a discretionary act by the Controller General of Patents who decides whether a challenge should be allowed. Since, the TRIPS Agreement as well as patent laws in a number of developed countries permit the use of pre-grant opposition, it is important for India to allow them. This is particularly important with respect to the Mailbox application because, without effective pre-grant opposition, generic producers may need to challenge thousands of improvidently granted patents in the courts, placing them at a significant disadvantage compared to the better financed foreign multinationals.
IV. Indian government should consider whether India would benefit from a global
exhaustion regime – i.e., from allowing medicines that have been lawfully placed
on the market with the consent of patent holder in another country to be imported
into India. The US Congress is considering this as a strategy to lower the price of
medicines. Finally, India should join with other like-minded developing countries
in the ongoing Doha Round of multilateral trade negotiations in pressing for
further liberalisation of Article 30 and 31 of TRIPS to enable developing countries
to meet public health concerns in the manner they deem best. Countries should
have the freedom to apply social cost-benefit calculus relevant to their
circumstances in a transparent and predictable manner in determining whether to
grant a patent and, if so, on what terms.

1.1.11. Survival Strategies of Indian Pharmaceutical Companies\(^{25}\)
Post 2005, survival will largely be governed by fundamental strengths in developing
NCEs. The average cost of developing an NCE is 350 million USD with a time span
of 10-12 years and a success rate of 1 in 10,000. Considering the cost and the
uncertainty of new drug discovery, an alternative strategy would possibly be to
produce and competitively exploit technologically advanced products in new areas
with demonstrable benefits, preferred by clinicians and patients over the less
expensive generic version of original branded products\(^{8}\). This strategy would include
the development of NDDS, an area hitherto neglected by the industry due to lack of
product patents.

1.1.12. Indian Market of Cardiovascular Drugs
From the study\(^{51}\) over a period of two years from April 2000 to April 2002 it is
concluded that the drugs for cardiovascular diseases account for Rs. 591.87 crore, or
\(\sim 3.81\%\) of the total pharma sale of Rs. 15,533.84 crore per year in 2001. The top
sellers considered in this category amount to a total to Rs. 417.17 crore, i.e., ~70% of the total sales of all cardiovascular products. The prices of cardiovascular drugs show an overall rise of nearly 5% over April 2000.

1.2. CONTROLLED DRUG DELIVERY SYSTEM

A separate industry has arisen that focuses on the improvement of drug delivery systems. Since R. P. Scherer & K. V. Pharmaceuticals were founded in the pre-World War II era, more than 100 companies have become actively involved in developing drug delivery systems\(^8\), and the industry is growing at a considerable pace. In 2002, revenues of pharma products, which utilized advanced drug delivery technology reached US $38 billion growth and will continue to steady average growth rate of 28% over next 5 years, reports Mindbranch, a market research group\(^6\). It is expected that by 2007, drug delivery will account for 39% of all pharmaceutical sales. The fast growth of this industry sector can be attributed to the following major developments:

1. The need for effective delivery of new, revolutionary biopharmaceuticals.
2. Upcoming patent expirations driving pharma companies to reformulate their products.
3. New technologies can minimize side effects and lead to better compliance.

The worldwide market growth of controlled drug delivery systems\(^2\) is shown in Table 1.6.

**Table 1.6.** Worldwide market growth in novel drug delivery segments (in US $ billions).

<table>
<thead>
<tr>
<th>Technology</th>
<th>2000</th>
<th>2005</th>
<th>Growth (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled release</td>
<td>14.2</td>
<td>26.3</td>
<td>85</td>
</tr>
<tr>
<td>Pulmonary, inhalation</td>
<td>11.7</td>
<td>22.6</td>
<td>93</td>
</tr>
<tr>
<td>Delivery Method</td>
<td>Market Share 1</td>
<td>Market Share 2</td>
<td>Total</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------</td>
</tr>
<tr>
<td>Transnasal delivery</td>
<td>8.2</td>
<td>16.0</td>
<td>95</td>
</tr>
<tr>
<td>Transmucosal</td>
<td>2.4</td>
<td>6.5</td>
<td>171</td>
</tr>
<tr>
<td>Transdermal delivery</td>
<td>6.7</td>
<td>12.7</td>
<td>90</td>
</tr>
<tr>
<td>Injectable/implantable</td>
<td>3.8</td>
<td>7.2</td>
<td>89</td>
</tr>
<tr>
<td>Needle-less injection</td>
<td>0.4</td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>Rectal</td>
<td>0.5</td>
<td>1.2</td>
<td>140</td>
</tr>
<tr>
<td>Liposomal</td>
<td>1.2</td>
<td>3.3</td>
<td>175</td>
</tr>
<tr>
<td>Cell/gene therapy</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.5</td>
<td>2.5</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>50.6</td>
<td>104.3</td>
<td>106</td>
</tr>
</tbody>
</table>


The growing global market in new technologies\textsuperscript{52} could be of the following types of drug delivery:

1. Polymers
2. Monoclonal Antibodies
3. Liposomes
4. Oral (controlled release) Delivery
5. Pulmonary Delivery
6. Injectable Delivery
7. Transdermal Delivery
8. Transmucosal Delivery
9. Implant Technology

The US demand for the oral drug delivery systems will expand 7.8% per year to $36.5 billion in 2007, according to a press release by the Cleveland-based industrial
market research firm, reports Mumbai's EPP News Bureau. Details are given in Table 1.7.

Table 1.7. Drug delivery systems demand (US $ bn).

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>1997</th>
<th>2002</th>
<th>2007</th>
<th>02/97*</th>
<th>07/02*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>12.1</td>
<td>25.1</td>
<td>36.5</td>
<td>15.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Parenteral</td>
<td>110.2</td>
<td>18.6</td>
<td>30.7</td>
<td>12.8</td>
<td>10.6</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5.4</td>
<td>8.6</td>
<td>12.1</td>
<td>9.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Transdermal &amp; implantable</td>
<td>0.9</td>
<td>1.5</td>
<td>3.0</td>
<td>10.4</td>
<td>14.2</td>
</tr>
</tbody>
</table>

% Annual Growth.
Ref.: EPP News Bureau, Mumbai.

With the availability of new polymers and better understanding of how to circumvent first pass metabolism, drug delivery companies in developed countries, apply their technologies across a range of clinical segments. The challenges in drug delivery will be multiplied for delivering biotechnology based products, which due to their poor solubility, bioavailability, stability and extensive first pass have conventionally been delivered by the invasive injectable route, by non-invasive routes.

1.2.1. Advantages of Controlled Drug Delivery Systems

The sources of value in reformulation include extending patent life, patient convenience/ compliance improvement, improved therapeutic efficacy, reduced manufacturing costs, and market share expansion.

1.2.1.a. Value Of Patent Extension

Because patents guarantee market exclusivity and artificially high premiums, patent expiration translates into rapidly declining sales for brand-name pharmaceuticals. In
US, generic versions of drugs are typically introduced at 20-25% of the branded drugs' prices. The branded drug's market erodes rapidly and loses 60-80% of the total days of therapy within 6 months⁸ - the influence of managed care and mandatory substitution laws²⁶. A typical example is that for Diltiazem⁸,²⁶. This drug was discovered by Hoechst Marion Roussel and patent on its product, Cardizem, expired in 1988. A drug delivery company, Mylan, reformulated it as Cardizem CD - a once-daily version of the drug, in 1992. In spite of the launch of a generic version of the conventional drug in 1993, the company retained 86% of sale of diltiazem after patent expiration only due to the CD version, details are shown in Fig.1.3.

![Graph showing sales over years](image)

Fig. 1.3. Life cycle extension of Diltiazem, by developing a controlled delivery system thereof⁸,²⁶.

1.2.1.b. Value Of Compliance Improvement

One of the most significant impediments to keeping patients healthy and curing disease is noncompliance with prescribed medication regimens. Regardless of any therapy's potential benefits, adherence to the prescribed regimen – the correct timings, dosage, method of delivery, physical status - determines the drug's ultimate success. Many factors influence patient compliance, including the nature of the
disease and disease symptoms, cognitive or functional ability, and financial resources. Some important factors influencing compliance, the frequency and mode of administration and the extent of drug-related side effects, can be modified through drug reformulation. A survey study on relating to this aspect is shown in the later chapter.

1.2.1.c. Frequency and Mode of Administration

Clinicians have learned that to achieve high patient compliance, in the absence of serious noncompliance penalties, drug regimens must be convenient and uncomplicated. Inconvenient (injectables) or complex (many dosage per day) regimens lead to poor compliance. The oral formulation is the most preferred mode of administration as it is the easiest form for patients to tolerate. Fig. 1.4 shows that 76% of the market value for top selling 100 conventional drug products in US comes from the oral systems; similarly, as shown in Fig. 1.5. among the drug delivery systems, oral drug delivery systems contribute a major portion of the pie.

![Pie Chart](chart.png)

Fig. 1.4. Top 100 Drugs - U.S. Market Value.

In terms of the frequency of administration, less is more. Drugs that must be taken only once per day are ideal, because they gain the highest compliance. Compliance has been shown to drop off sharply for drugs that have to be taken more than three
times per day, thus drugs with more frequent dosing schedules are generally considered unacceptable for therapies that must be taken chronically\textsuperscript{26}.

Fig. 1.5. Types of Drug Delivery Systems

A sustained release oral reformulation that allows for once per day dosing is the preferred form of drug delivery. Aerosol formulations have not been as convenient as oral because they have often required frequent (three or more times per day) dosing. In addition, the effectiveness of aerosol formulations has been hampered by the inconsistency of inhalers, which results in inadequate or varying levels of drug absorption. Nasal delivery has also lacked consistency in dosage absorbed due to backflow of drug after administration and variations in nasal architecture and volume of mucus between patients. Transdermal systems although usually providing dosing from 3-7 days, are perceived by patients as less attractive because patches can result in skin irritation and may not adhere to the skin efficiently. Depot injections offer significant improvement over frequent injections or intravenous infusions\textsuperscript{6}.

The most successful drug delivery formulations have been, as would be expected, oral sustained release formulations. Currently, Bayer AG's Adalat CC product for
hypertension leads the oral sustained release market. Reformulated in 1993 from a 3-4/day to 1/day, Adalat CC has climbed the sales of $1.1 billion worldwide in 1997. Another highly successful reformulation has been TAP Pharmaceuticals’ Lupron Depot for prostate cancer and endometriosis. Reformulated from a daily injection in 1989 to a once per month injection, Lupron Depot has climbed to worldwide sales of $990 million in 1997.\textsuperscript{8,26}

1.2.1.d. Therapeutic efficacy\textsuperscript{8}

Drug delivery technologies can improve medical outcomes not only by affecting compliance but also by improving therapeutic efficacy. Improvement in bioavailability may help drugs work more effectively, as can technologies that allow the release of the drug at specific times. For example, Covera HS, an Alza reformulation of hypertensive drug initially launched by Searle in 1996, is designed to deliver peak concentrations when blood pressure and heart rate are at their highest.

1.2.1.e. Extent and nature of side effects\textsuperscript{8}

Side effects are common with many drugs and eliminating them can significantly increase the value of therapy. Side effects may be caused by the action of the drugs’ active ingredient and therefore are unavoidable. However, drug delivery technologies can reduce or eliminate side effects.

1.2.1.f. Value of Reduced Manufacturing Costs\textsuperscript{8}

One method of increasing profitability on a drug is decreasing manufacturing costs. Often orally formulated drugs with poor bioavailability must be administered in high doses, because only a small percentage of the active ingredients is absorbed by the body. Drug reformulations that improve the bioavailability of the drug require less active ingredient to produce an equivalent therapeutic effect, thereby reducing
manufacturing costs. Maximizing the bioavailability of these types of agents will be rewarded in the market.

1.2.1.g. **Selection of drug candidates**\(^8,26\)

One of the most critical components of a drug or drug delivery company's strategy is the choice of which compounds to reformulate. This process should include the following explicit steps: developing a starting list of drug candidates, examining the delivery technology, assessing the therapeutic or administrative unmet needs, performing a competitive screen, and sizing the market.

Because there is considerable value in extending the patent life of a compound, drug companies often focus on their blockbuster drugs that are coming off patent for developing novel drug delivery systems. The pharmaceutical industry's "graveyard" is another source of drug candidates that have clinical potential but have failed in clinical trials due to side effects or administrative problems. There may be even more value in resurrecting these drugs that have consumed costly drug approval and / or market acceptance without reformulation.

The sophistication of controlled drug delivery technologies is advancing rapidly and companies' success rates are growing. As a result, in the longer term, pharmaceutical companies will proactively elect to reformulate drugs well before they reach their patent maturities. As a recent example, Pfizer announced that is was teaming with R. P. Scherer to reformulate a faster-acting form of its blockbuster Viagra less than 4 weeks after it launched the drug. In fact, as drug delivery matures as a science, pharmaceutical companies will involve the technologies in their initial formulations.
References


