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# Role of India in global pharmaceutical sector with emphasis on USA

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## INTRODUCTION

Drugs are a necessity in ailments. But sometimes the drugs prescribed may be costly and may not be affordable for the patient. In such a scenario, generics companies manufacturing the same costly drugs at affordable prices are a boon for the patient.

India currently represents just U.S. $6 billion of the $550 billion global pharmaceutical industry but its share is increasing at 10 percent a year, compared to 7 percent annual growth for the world market overall.

Indian drugs are exported to around 200 countries in the world. The United States is the world's largest single market for pharmaceutical products accounting for nearly 50 percent of the value of the total world market. India's five largest export markets are the United States (28 percent), Russia (11 percent), Germany (10 percent), the United Kingdom (8 percent), and China (7 percent). Exports to these countries consist primarily of bulk drugs that account for nearly 60 percent of India's pharmaceutical exports. The remainder, mostly formulations are exported to the countries of the former Soviet Union (CIS) and developing countries (Southeast Asia, Africa, and Latin America). India continues to be a leading supplier of less expensive antibiotics, cancer therapy, and AIDs drugs to the developing world. Many of India's leading Indian pharmaceutical companies have also been certified by regulatory authorities in Australia, South Africa, and the EU.

The patents on a number of blockbuster drugs are scheduled to expire over the next few years. In addition, more and more governments worldwide are seeking to curb their soaring prescription drug costs through greater use of generics. These opportunities are presenting themselves not only in India's traditional wealthy client markets such as the U.S. and European Union nations but also in emerging economies with vast populations such as Africa, South America, Asia, and Eastern and Central Europe.

These are some points for consideration by Indian pharmaceutical companies to sustain and boost the presence in the world's drug market including generics:

### CONTRACT RESEARCH AND MANUFACTURING SERVICES (CRAMS)

CRAMS can be divided into 3 basic segments: the production of intermediates, active pharmaceutical ingredients for new chemical entities, and the manufacture of generic drugs. India has emerged as one of the world's leading CRAMS providers for MNC innovator companies. Although CRAMS is still in its nascent stages in India, it represents a significant opportunity for medium-sized Indian pharmaceutical companies. Subcontracting in India has gradually moved up the value-added chain from intermediates and APIs to new drug discovery, clinical trials, marketing, and sales. There is need to have collaborations between Indian and foreign firms in the domestic market,

especially involving the biotechnology sector, in a wide variety of areas such as collaborative R&D (including drug discovery and clinical trials), co-marketing and manufacturing.

Facing lagging sales of patented drugs by MNCs in their home markets, declining R&D revenues, and rising costs, many MNCs have turned to India for contract manufacturing and research services, co-marketing alliances, outsourcing of research and clinical trials to reduce costs, increase development capacity, and trim the 'time to market' for new drugs. These strategies permit MNCs to focus on their core profit making activities, such as drug discoveries and marketing, rather than on manufacturing.

Western pharmaceutical companies are now outsourcing a wide range of activities including: the manufacture of APIs, chemical intermediates, and formulations; clinical research and clinical testing; and packaging and labeling. The Indian market for contract outsourcing has been driven by the need of leading MNC pharmaceutical companies to reduce production costs and increase revenues. These companies have shifted portions of the production, research & development, clinical trials, packaging and labeling, stability testing, and other types of drug development and discovery activities to India.

**RESEARCH AND DEVELOPMENT (R&D)**

Traditionally, the vast majority of India's pharmaceutical R&D spending was concentrated on reverse engineering and the adaptation of patented foreign drugs to the Indian market. Most of the industry's funding went to research rather than to new drug discovery and development. With the reintroduction of product patents, after 2005, Indian pharmaceutical should alter their business strategies by placing greater focus on R&D and the discovery of new chemical entities. Indian companies could not survive as global players without significant R&D capabilities.

Whereas new drug discovery costs between $100 million and $200 million in the West, the same process in India only costs approximately $10 million. MNCs have been attracted by India's low costs for new drug discovery and many of these firms have founded state-of-the-art research facilities in India. Driven by the dynamics of the market, leading foreign pharmaceutical companies have entered into R&D agreements with India's leading drug companies. Indian companies cannot fulfill their ambitions to become players on the world stage unless they make significant increases to their R&D expenditures.

India's comparative advantages lie in its cost competitiveness (development, manufacturing, R&D, clinical trials, and labor) and its reverse engineering experience. Because of this, India can become a hub for pharmaceutical research and development and clinical trials for many leading foreign pharmaceutical companies.

Europe, the world's third largest pharmaceutical market, behind the United States and Japan, had generic sales of approximately $100 billion primarily in the UK, Germany, and France. Indian pharmaceutical companies have made a number of acquisitions in Europe to gain a foothold in its markets. Use of generics is growing quickly in Europe, due to government price controls and other pro-generic measures. European generics markets considered to be under served include Spain, Italy, and France, and are expected to be important and growing markets for Indian exporters.
Indian pharmaceutical companies should look at the global market with potential to accelerate their growth including the regulated markets of the United States, Japan, and Europe; the semi-regulated markets of BRIC countries; and less regulated markets of Africa, Middle East, and Southeast Asia.

**BIOPHARMACEUTICAL**

Generic substitutes to original biologics are known as biosimilars. Biosimilars are drugs that are copies of biological agents and are approved through an abbreviated pathway. Global sales of biologics reached nearly $137 billion in 2009 and Biosimilars accounted for sales of just $1.23 billion less than 1% of the total biologics market in 2009. They have the potential to decrease hospital and health-system drug expenditures. Current biologic medicine costs are staggering, putting lifesaving treatments out of reach for many patients. There is considerable potential for growth as the patents on at least 48 biologics are due to expire over the next decade. Industry experts predict that the global biosimilars market could be worth more than $43 billion by 2020.

A Congressional Research Service (CRS) study of US completed in 2010 showed that the cost of biologics is often prohibitively high, both for patients and the government. The report found that average annual costs for the rheumatoid arthritis treatment Enbrel® was $26,000, Herceptin® for breast cancer averaged $37,000, Humira® for

Crohn's disease was more than $51,000 per year, and the annual cost for Cerezyme® to treat Gaucher's disease was $200,000 in US.

CRS concluded that spending on biologics will be unsustainable without the approval of biosimilars to enable market competition and reduction in prices. Competition from biosimilar versions of branded biologics will help reign in these escalating costs and deliver sizeable savings while providing affordable options to patients needing treatments for deadly diseases.

The proven track record of savings for consumers using traditional generic drugs can be duplicated in the biopharmaceutical market. The approval of biosimilars will inject the competition needed in the biologic market to lower costs and provide significant savings for patients in need of these lifesaving treatments.

The European regulatory agency (EMEA) has announced the guidelines for approval for biosimilars and has already approved a number of biosimilars. Comparatively, in the US, the market for biosimilars remains limited as of now as the FDA is still in the process of developing the regulatory pathway for biosimilars. It is possible that some biosimilars could reach the U.S. market in 2012. Whereas spending in US for traditional drugs grew 1.2 percent in 2011, spending for biologics grew more than 7 percent. And what is a $120 billion market in 2011 is projected to become a $200 billion market in 2015.

The research infrastructure, talent pool and academic network in India are at the nascent stage so far as biosimilars industry is concerned. The regulatory hurdles are both at domestic as well as global level. The costs and technology related challenges for biosimilar are also higher. Indian companies need to invest in R&D as the market for biosimilars will grow sharply in the coming years.

**US MARKET**

India has the largest number of U.S. Food and Drug Administration (FDA)-approved drug manufacturing facilities outside the U.S totaling 74. The Indian pharmaceutical industry accounts for the second largest number of Abbreviated New Drug Applications (ANDAs), is the world's leader in Drug Master Files (DMFs) applications with the U.S. Food and Drug Administration.

The US government's most recent National Health Expenditure Accounts (NHEA) report shows that total U.S. health care spending reached $2.6 trillion in 2010, which translates to $8,402 per person or about 18 percent of the nation's Gross Domestic Product (GDP).

NHEA further notes that the average annual growth in health care spending is expected to be 6.2 percent per year through 2018, outpacing annual growth in the overall economy (anticipated at 4.1 percent) by 2.1 percentage points per year. By 2018, according to government projections, national health care spending will reach $4.4 trillion and comprise over one-fifth of the GDP. At this rate of growth, within 15 years health care costs would amount to half of the nation's GDP.

The Indian Pharmaceutical industry's long-established position as a world leader in the production of high-quality generic medicines is set to reap significant new benefits as the demand for generic drugs is set to rise by looking at the above data by NHEA and considering the fact that patents on a number of blockbuster drugs are scheduled to expire over the next few years.

**ABBREVIATED NEW DRUG APPLICATIONS**

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act of the US. The Hatch-Waxman Amendments created section 505(j) of the Act. This section established the ANDA approval process, which allows lower-priced generic versions of previously approved innovator drugs to be approved and brought on the market.

An innovator drug applicant must include in its new drug application (NDA) information about any patents that claim the drug product that is the subject of the NDA, or the use of such drug product. The FDA publishes this patent information upon approval of the NDA or a supplemental NDA in Approved Drug Products with Therapeutic Equivalence Evaluations, which is generally known as the Orange Book.

The Hatch-Waxman Act allows generic manufacturers to file an ANDA demonstrating bioequivalence to an innovator drug, rather than an NDA, which is far costlier as it requires data establishing safety and efficacy. Under the Hatch-Waxman Act, a generic manufacturer may file an ANDA prior to the expiration of the innovator's patents. An ANDA applicant must include in its ANDA a patent certification as described in section 505(j)(2)(A)(vii) of the Act. The certification must make one of the following statements:

(1) That such patent information has not been filed;
(2) That such patent has expired;
(3) The date on which such patent will expire; or
(4) That such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted.

The fourth certification is known as a paragraph IV certification. The ANDA applicant must provide appropriate notice of a paragraph IV certification to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA refers. The first generic manufacturer to file a substantially complete ANDA with a paragraph IV certification may be awarded a 180-day marketing "exclusivity" period during which no other ANDA filers can market their version of the drug dose. Thus, the opportunity to be the sole competitor to the innovator for up to 6 months is aggressively pursued. Which results in windfall profit as there are restricted number of players, usually one (ie, the innovator) and in these 180 days the margins are very high. The company that wins this exclusivity can reap huge profits during the 180-day exclusivity period. In fact, the company can garner a market share, which is 5-10 times higher than the other generics players.

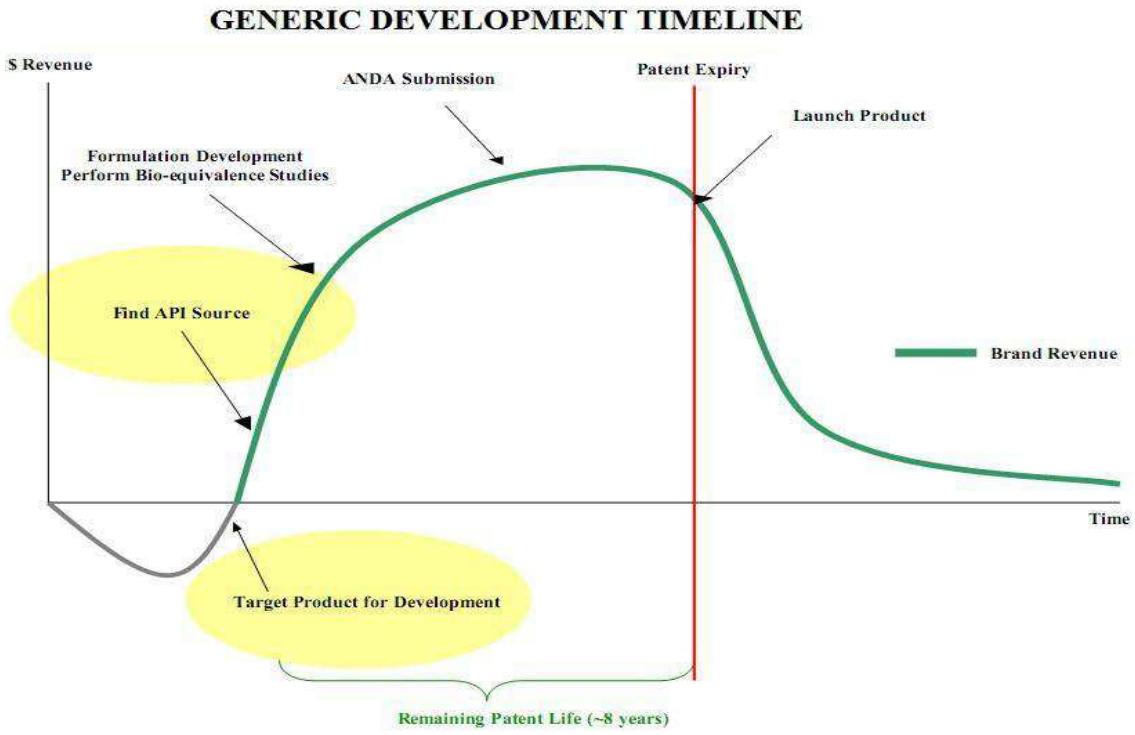
Hatch-Waxman Amendments grant generic manufacturers standing to mount a validity challenge without incurring the cost of entry or risking enormous damages flowing from any possible infringement. Generic company's liability may amount to litigation costs, but pales in comparison to the immense volume of generic sales and profits.

Invalidity could result due to several factors including public disclosure, lack of novelty, obviousness or other statutory requirements like enablement, written description or best mode. Sometimes, even priority issues can affect the validity of the patent - for instance, a patent originally filed in another country can be used to claim priority for the US application. If that priority is lost, the patent may become invalid due to intervening references. So, there are several possibilities to invalidate a patent.

However, at present only Ranbaxy and Dr Reddy's are aggressively using this strategy and have an impressive pipeline of Para IV filings. Indian companies can benefit from a greater acceptance of generic drugs among the U.S. public, tremendous pressure on healthcare providers to reduce costs With the rising competition in the global generics space coupled with the drastic reduction in the price of the drugs on expiry of the exclusivity period, the aggressive Para IV filing strategy will be one of the key determinants of the success of Indian generic companies.

Indian companies can manufacture pharmaceuticals for less than half what it costs to manufacture them in the United States, conduct clinical trials for approximately one-tenth the U.S. cost, and conduct R&D for less than one-eighth the U.S. cost. Indian pharmaceutical companies led by Glenmark, Aurobindo and Sun Pharma maintained their number one position in the US generics market, by bagging 33.17 per cent or 139 of 419 original Abbreviated New Drug Application (ANDA) approvals from the US Food and Drug Administration (FDA) in 2010. The Filing of ANDA with a Para IV certification by Indian companies is very less. It is a high risk - high reward growth strategy. Indian companies should challenge the patents of global companies via Para IV filings and India's share in the total Para IV filings is required to grow further.

This is clear from the below chart that if the generic company has to launch generic drug for the patented drug through ANDA then it has to start the work on the targeted product well in advance and has to find API source for the same at initial level and if the company want to file ANDA with a Para IV certification then extra caution is required because only first applicant gets the 180 days marketing exclusivity. Indian companies need to focus on this point and should start investment in research and development for successful ANDA Para IV filings.




The overall generic utilization rate in U.S. reached 80 percent in 2011, meaning that more than 3.2 billion of the approximate 4 billion total brand and generic prescriptions written in the U.S. last year were dispensed using generic versions of branded drugs.

Indian companies will be challenged by declining prices in the U.S. market, declining profit margins, growing competition from other low-cost countries, parallel launches of authorized generics by Western innovator companies, and the increasing power of large distributors in the U.S. and European markets so they have to prepare strategy for consistent achievement in generic drugs market. The Filings of ANDA with a Para IV certification by Indian companies is required for better prospects of Indian pharmaceutical companies.

**CHALLENGES**

Developing an innovative new drug, from discovery to worldwide marketing, now involves investments of around $1 billion, and the global industry's profitability is under constant attack as costs continue to rise and prices come under pressure. Pharmaceutical production costs are almost 50 percent lower in India than in Western nations, while overall R&D costs are about one-eighth and clinical trial expenses around one-tenth of Western levels. Clinical trials in India cost approximately $20 million while the cost abroad would ranges between $300 million and $350 million. Costs of pharmaceutical innovation in India are estimated as low as one-seventh of their levels in Europe.

India offers a large qualified and English-speaking workforce, low production costs, intellectual property rights, and judicial and quality standards which gives India an edge over other generics-producing nations, especially China and Israel. The government should take early decision on data protection to facilitate and encourage clinical trials in India.

India and China could potentially account for 35 percent to 40 percent of the outsourced market share for active pharmaceutical ingredients, finished dosage formulations and intermediates. Indian firms have embarked on an unprecedented shopping spree of overseas acquisitions to establish themselves in these highly lucrative markets and boost their capacities, as demand continues to grow.

India's long-established position as a preferred manufacturing location soaring costs of R&D and administration are persuading drug manufacturers to move more and more of their discovery research and clinical trials activities to the

subcontinent or to establish administrative centers there, capitalizing on India's high levels of scientific expertise as well as low wages. Previously, only process patents were granted, a situation that led to India's current role as a world leader in the production of high quality, affordable generics.

The surge in production has been driven by legislative reforms, the growth in contract manufacturing and outsourcing, value added foreign acquisitions and joint ventures, India's mastery of reverse engineering of patented drug molecules, and India's efforts to comply with its World Trade Organization (WTO) Trade Related Intellectual Property Agreement (TRIPs) obligations.

There is a need for regulatory reform in India to encourage leading global players to continue and accelerate the outsourcing of their R&D activities-beginning with discovery research-to the subcontinent. This is particularly urgent in the face of the strong competition from China, where the government has been particularly proactive in encouraging foreign investments in pharmaceuticals and biotechnology. Action is required soon, if India wants to be a significant player in the global pharmaceutical arena.

## CONCLUSION

India's pharmaceutical industry has evolved from almost non-existent to a world's leader in the production of high-quality, low-cost non-branded or generic drugs, accounting for nearly 20 percent of the world's production. Indian companies should focus on developing follow-on biologics, Challenging IPRs on regulated markets, investing in R&D for proprietary NCEs. Many mid-level Indian producers can turn to contract manufacturing, outsourcing, contract research, contract clinical trials, or other tie-ins with MNCs.

These alliances and millions of dollars spent on establishing domestic and foreign-based manufacturing facilities, acquiring foreign drug manufacturing firms, as well as marketing and sales networks, will enable India's leading pharmaceutical producers to re-direct large sums of their cash flow to R&D and move up the value-added chain. These foreign acquisitions will enable Indian companies to gain a foothold in Western regulated markets, diversify their portfolios, acquire recognized brands, and gain R&D capabilities.

The United States has some of the highest drug prices in the world and has attracted imports of generic drugs from India and a number of low-cost countries. However, severe price compression and growing competition from other low-cost countries is forcing Indian majors to offset their losses by shifting their attention to Western Europe.

India has the potential to become the region's hub for pharmaceutical and biotechnology discovery research, manufacturing, exporting and health care services within the next decade. India's continuing failure to provide data protection needs to be rectified urgently. Indian manufacturers cannot fulfill their ambitions to become players on the world stage unless they make significant increases to their R&D expenditures. There is need to increase R&D collaboration with MNCs to gain the advantage of the India's conducive environment for new drug discovery and development.

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