

# **INDIA PHARMACEUTICAL REGULATORY REPORT 2013**

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## **I. OVERVIEW OF INDIA'S ECONOMY**

From 1950 to 1980, India's economy grew at an average rate of 3.5%. However, after past economic reforms, India is now the world's fourth-largest economy, after the US, China and Japan. India's total GDP in 2010 purchasing power parity was \$4 trillion, equivalent to 30% of the GDP in the US and 40% the GDP in China during the same period. Between 2006 and 2010, India's GDP annual growth averaged 8%. Its 2010 GDP growth of 9% was significantly higher than the OECD countries' average of 3.0%.

India's economic landscape is transforming rapidly. Migrants are flocking to its burgeoning megacities. Hundreds of thousands of college graduates enter the labor market each year. Thanks to the Internet and low-priced communication means, India has become a prime destination for services such as information technology, call centers, and business process outsourcing. India's manufacturing base is also growing rapidly. As competition for skilled workers intensifies, many Indians in the urban areas are seeing rapid income growth, and increasing their consumption accordingly.

India's demographics indicate its growth potential may stretch even farther than China's in the long term. At current estimates, China will see a population slowdown in the future (that is similar to current Japan and Europe) much sooner than India. By the year 2050, it is predicted that India's population of 1.2 billion people will exceed China's current 1.3 billion.

Although India is a huge, diverse country, over half of Indians are in agriculture and farming. With 70% of India's population residing in rural areas, it will be a long time before economic growth brings its benefits to the entire population. Rural development still lags behind urban development. More than a third of India's population is still classified as "poor". Nevertheless, this is a vital moment for Western pharmaceutical companies to expand their presence in the Indian market in order to capture the country's next development boom.

## **II. OVERVIEW OF INDIA'S HEALTHCARE SYSTEM**

India boasts a large network of free public hospitals and clinics, which had past successes in improving public health. However, the public healthcare system is severely underfunded and has limited capacity to provide quality, modern healthcare to Indians. Currently, the demand for better healthcare is almost entirely supplied by private providers. However, India's private healthcare sector is also largely under-regulated, leading to discrepancies in healthcare quality control.

### **A. History**

In 1952, after becoming independent, India embarked on creating a comprehensive public healthcare system. The country also commenced several intensive campaigns against specific diseases. Between 1951 and 2010, average life expectancy increased from 36 to 65 years. Diseases like smallpox and guinea worm have been eradicated. However, the public health system is still poorly funded, and in many ways, has failed to meet the standards it was set up for.

In most countries, as the economy develops, government healthcare spending usually increases in tandem with GDP growth. This is due to an expanding public healthcare expenditure to provide more services. This has not been the case in India. Although Indian healthcare spending has increased in absolute terms, its growth rate is still slower than GDP growth. According to the World Health Organization (WHO), as a percentage of GDP, public healthcare spending actually fell from 1.3% in 1991 to 0.9% in 2005. As of 2009, however, this percentage climbed up to about 1.4% of its GDP. This is still lower than in China and even its smaller neighbor Sri Lanka, where public healthcare spending to GDP ratios were respectively 2.3% and 1.8% in the same year. However, India's public healthcare spending is expected to further increase to 2.5% of GDP in 2012. In terms of healthcare facilities, India only has about 900 hospital beds per million people, much lower than 3,000 hospital beds per million people in China. Moreover, high poverty levels in India continue to lead to poor health conditions in both urban and rural areas. Infant mortality in India is one of the highest in the world, at about 46 deaths per 1,000 live births. This is at least eight times higher than that in the US, at six deaths per 1,000 live births. Even though healthcare demand has increased and medical technology has progressed, India's public healthcare system still does not have the resources to cope with its rapid population growth.

### **B. India's Healthcare System: Goals and Challenges**

The Indian government is in the midst of finalizing the country's 12<sup>th</sup> Five-Year Plan (12<sup>th</sup> Plan). The 12th Plan outlines India's strategy to further develop the country over the next five years, between 2012 and 2017. Economic and social development milestones are set through this Plan. The 12<sup>th</sup> Plan was presented by the Planning

Commission to the Indian Prime Minister by the end of April 2011. After it was reviewed by the Prime Minister, it was approved by the National Development Council, comprising India's state chief ministers. "An approach to the 12<sup>th</sup> Five Year Plan" was published in October 2011.

Although the 12<sup>th</sup> Plan has yet to be finalized, India's Ministry of Health and Family Welfare issued a Results-Framework Document and a Strategy Development Plan, which outlined the government's healthcare development goals for 2012-2017.

The key development goals to be achieved by India by the end of 2017 are:

- To provide accessible and affordable quality healthcare to all Indian citizens, including improvement in maternal and child health
- To establish a comprehensive primary healthcare delivery system
- To reduce communicable diseases and to alleviate the cost of non-communicable diseases
- To promote the rational use of pharmaceuticals in India
- To develop skilled labor in India's healthcare sector

These goals, however, are not new. They were previously highlighted in India's National Health Policy 2002 (NHP). The NHP had aimed to achieve these development goals through the creation of new health care infrastructure in underdeveloped areas. In the more developed areas, the upgrading of existing medical infrastructure had been undertaken. In 2005, the National Rural Health Mission (NRHM) was also launched to significantly improve the health system of India's rural population.

Unfortunately, weak finances, low service quality and inefficient allocation of resources in the public sector led to ineffective implementation of India's healthcare development. Under the Indian Constitution, the responsibility for public health is shared by the Central, State, and local levels of government. As for 2010, private healthcare spending accounted for almost 68% of India's total (private and public) healthcare spending, compared to 53% of China's.

## **C. Healthcare Providers**

### *Public Providers*

India has a wide network of over 160,000 public hospitals and clinics in urban and rural areas. Institutions run by state or local governments are intended for the general public. Some national healthcare networks also exist to serve specific groups.

The state healthcare networks are arranged in three tiers. In the first tier are sub-centers, which are outpatient only, together with primary health centers, with 5-6 beds each. There are around 150,000 sub-centers in India as of March 2011. In the second tier are primary health centers. As of March 2011, there are about 24,000 primary health centers

in India. In the third tier are community health centers, with 30 beds each. There are about 5,000 community health centers in India as of March 2011. Outside the three-tier public rural healthcare system, there are district hospitals, comparable to Western hospitals in size, which provide specialist services. Other public institutions include urban health centers, family health centers, dispensaries (outpatient clinics which focus on drug treatments), and specialized state-level hospitals.

The Ministry of Health and Family has spearheaded the National Rural Health Mission (NRHM), which is being implemented by state governments. It aims to improve access to quality healthcare in poor rural areas, especially for women and children, with the long-term goal to provide universal public healthcare. Major provisions of the NRHM include increasing public health expenditure and devising plans for public-private cooperation in the health sector. The NRHM has already been implemented in 18 states across India.

There are also public hospital networks set up by the national government. This includes the Employees State Insurance Scheme, a social security scheme that includes hospital care for covered industrial workers. There are also hospitals for the armed forces, civil service, and railway workers. Overall, state-level funding, not federal, makes up about 85% of total healthcare spending by the government.

Recent studies conducted by India's National Sample Survey Organization (NSSO) showed a decline in the use of public health facilities for inpatient care. This trend was seen in India's rural and urban areas. On the other hand, there was an increase in the use of health facilities in the private sector, in both rural and urban areas. This was despite the higher costs of private sector treatment. The patients' switch to private healthcare was mainly due to long waiting times, lack of medical staff and poor medical infrastructure in public medical institutions.

Because of their shortage of funding, public institutions tend to be low-quality, poorly equipped, and overcrowded. Doctors are scarce in India to begin with, with about 0.6 doctors for every 1,000 people, compared with about 2.6 in the US. In addition, private sector salaries quickly draw doctors out of public hospitals. This means health professionals in the public sector have an extremely heavy workload: doctors often attend to as many as 100 outpatients in a single shift. Moreover, although state and municipal hospitals are theoretically free, patients must often pay for drugs, some medical supplies, and even amenities like bed sheets.

Because of this, virtually all healthcare consumers choose to attend private hospitals if they can afford them. Doctors in public hospitals will even refer their patients to private hospitals for more reliable specialist treatment.

Being aware of these problems, lower-income Indians sometimes choose to stay away from the public healthcare providers when they suffer minor conditions. They often choose to self-medicate or use traditional remedies instead. However, for more serious conditions, such as rare or chronic diseases, they have no alternatives.

### *Private Providers*

More than 68% of India's healthcare delivery is currently provided by the private sector. However, for much of India's history since its independence, private healthcare providers were mostly limited to small-scale, often individual practices. There were a few large companies which maintained private hospitals to treat their own employees exclusively. These began to change in the mid-1980s. The first corporate for-profit hospital was founded in 1983 in Chennai, and was the first site of what is now the Apollo Hospitals Group. The private sector growth sped up in the 1990s as India's economy boomed. The government also established policy incentives to expedite the growth of private hospitals, including favorable terms on occupying public land, tax deductions on capital gains from hospital investments, and low or zero tariff rates on imported medical products by hospitals.

In 2008, the government's budget included a five-year tax holiday for new hospitals. This extended to all of India, with the exception of the greater metropolitan areas of Mumbai, Delhi, Kolkata, Bangalore, Chennai, Ahmedabad, Hyderabad, and six other major cities. Private medical providers welcomed this benefit as it enabled the establishment of many more hospitals in India's growing medium and small-sized cities.

As of 2008, over 10,000 of India's 16,000 full-sized hospitals were privately owned. The Apollo Hospitals Group has grown to become one of the leading Indian chains, with 50 hospitals in India, and a foreign branch hospital in Mauritius. Other well-known names in healthcare include Wockhardt, Fortis, Max, and Escorts. There are more than 150 corporate groups involved in providing private healthcare in India. Indian government officials estimate that 60% of inpatient care and 80% of outpatient care are given by private hospitals or clinics.

Although it is widely perceived that private Indian healthcare providers are superior to public ones, the private system was not without its problems. Prior to the Clinical Establishment Act 2010, there was no public system of supervision or accreditation of private hospitals. This led to concerns about their accountability and quality control.

To overcome issues of malpractice in the private healthcare sector, the Clinical Establishment Act 2010 was enacted in August 2010. The Act applies to all public and privately-owned medical institutions involved in the diagnosis (including laboratory work) and treatment of illnesses and diseases. Under this Act, all entities providing medical services need to be registered with the Indian government.

The Clinical Establishment Act 2010 also led to the establishment of a National Council for Clinical Establishments. The National Council was set up for the following tasks:

- Compile and publish a National Register of Clinical Establishments by August 2012
- Classify clinical establishments into various categories

- Develop minimum standards for clinical establishments and conduct periodic reviews
- Determine a set of standards for the provision of healthcare by clinical establishments by August 2012
- Collect statistics pertaining to clinical establishments

The National Council will follow a consultative process in determining the standards and classification of clinical establishments in India.

Following from this, a State Council for Clinical Establishments has also been set up in each state. The State Council is responsible for the collection of statistics and registration of clinical establishments in their respective states, which will then be forwarded to the National Council. In addition, the State Council performs the following tasks:

- Represent the State in the National Council for Clinical Establishments
- Handle appeals by clinical establishments
- Annually publish the State's progress in implementing the clinical establishment standards

#### **D. Healthcare Spending**

The vast majority of India's private healthcare spending comes directly from patients' personal or family funds, and not through health insurance or other sources. Out of the total healthcare spending in India, about 71% comes directly from patients. This compares to 61% in China and 54% in Sri Lanka. Among the out-of-pocket spending by Indian patients, 70% is used to purchase drugs. As of 2011, total spending on drugs in India was \$14.3 billion. This includes \$3.3 billion spent on brand-name drugs. Total expenditures on drug are predicted to at least double to about \$29 billion by the year 2016.

Without other sources of payment, access to good healthcare is strongly determined by income. For example, the average price of a heart operation in India is US\$7,000. Although this is less than a fourth of the price of a similar operation in the US, it is almost ten times the average Indian income. According to a 2005 WHO survey, over 40% of Indians who received critical medical treatment had paid their bills through borrowings. Due to these cost issues, Indians are more likely to undergo curative treatment, and not preventative treatment such as checkups or routine diagnostics.

Although the Indian private health insurance industry is growing rapidly, its market is still under-developed. As of 2009-2010, around 300 million Indians (or 25% of India's population) are insured under some forms of health insurance (public and private). Expenses on commercial insurance account for less than 1% of the total health expenditures in the country.

Some skilled urban employees have their hospitalization costs for medical care reimbursed directly by their employers, because there are tax advantages to providing compensation in that form.

Public health insurance was further developed by the government in April 2008, when the Ministry of Labour and Employment launched the National Health Insurance Scheme for families living below the poverty line. The Scheme protects poor households from liabilities arising from hospitalization costs. Beneficiaries under the Scheme are entitled to up to Rs. 30,000 (\$675) to cover most diseases that require hospitalization. The insurance coverage extends to five family members, including the head of the family and spouse, as well as up to three dependents. The registration fee to enroll into the Scheme is about \$1. The Indian central and state governments will pay the health premiums (on behalf of the beneficiary family) to the insurer, which is selected by the state government. Beneficiaries are allowed to choose between public and private hospitals. According to WHO, more than 55 million people in India were covered under this Scheme in 2010.

The Indian government has also introduced a health insurance scheme for central government employees and pensioners. The insurance scheme is on a voluntary-cum-contributory basis for existing government employees and pensioners, except for recruits after early 2011, who are on a mandatory-cum-contributory basis instead. This Central Government Health Scheme covers for death, disablement, sickness and maternity of the beneficiaries in the course of employment, including instances where occupational accidents happen. The beneficiaries include central government employees, public servants, and their family members. Free medicines are provided under the scheme, as well as cashless hospitalization subject to certain conditions. The government has selected a number of hospitals (including private ones) in which the insurance scheme is implemented. The government has an agreement with these hospitals that specify the rates and terms for reimbursement.

Generally, traditional health insurance plans in India, such as the MediClaim policies offered by state-owned insurance companies, cover inpatient care but not outpatient care or prescriptions. However, plans have been moving in a more Western direction, as plans with outpatient and other coverage emerge. Change has also been spurred by expected regulatory changes to allow more foreign investments in the healthcare insurance sector. Starting from late 2009, two insurance companies in India - Apollo DKV and ICICI Lombard - started to cover outpatient expenses. However, to prevent misuse, insurance companies have decided to cap the outpatient expenses. Also, the insured can claim outpatient charges only once throughout the policy term. Additionally, the insured cannot claim outpatient costs within 90 days of commencement of the policy.

The government had other recent, but less successful attempts to balance the healthcare accessibility between India's rich and poor. In February 2011, the Indian Federal Government announced a 5% tax charge for patients using medical services provided by air-conditioned hospitals, with a capacity exceeding 25 beds. This formed part of India's initiatives under the national budget for 2011/2012 to reallocate funds to the poor via healthcare taxes on the more affluent. The tax charge was not applicable to government

hospitals. However, the proposal drew strong protest from opposition political parties, healthcare industry players and the general public. Subsequently, in March 2011, the tax plan was withdrawn by the government due to overwhelming pressure. Critics of the plan claimed that the real cost of medical treatment for Indians would have risen by about 10% with the implementation of the tax charge.

## **E. Conclusion**

Like those of many fast developing countries, India's healthcare system appears disorderly. At the same time, it is also dynamic and full of potential. The government's inability to provide quality healthcare services to the Indian population has given rise to the private sector's strong emergence. Even if the government makes the huge undertaking of providing basic medical services universally, the private sector will continue to play a leading role in higher-level and more sophisticated treatments, including providing pharmaceuticals of Western origin.

### **III. INDIA'S PHARMACEUTICAL INDUSTRY**

#### **A. Market Profile**

With economic and social development, Indians' consumption of pharmaceuticals is increasing rapidly. The new skilled, salaried class has quickly become more health-conscious and brand-aware. According to official Indian statistics, India accounted for 8% of global pharmaceutical production in 2008, making it the world's fourth-largest pharmaceutical producer. In 2009, the Indian pharmaceutical market was worth about \$11 billion (compared to China's \$38 billion), and grew at a rate of 10%. Growth rates of 8-12% are projected through 2015.

India's most prominent pharmaceutical categories are monoclonal antibodies and vaccines. With persistent public health shortcomings, "diseases of poverty" like malaria and tuberculosis are not yet under control. However, with the growing economy, lifestyle changes are also affecting the disease profile. As Indians become wealthier, they are eating more, smoking more, and leading less active lifestyles. They are also becoming better-protected against traditional sicknesses. This leads to a greater incidence of the more "modern," non-transmissible diseases such as cardiovascular disease and cancer.

Cardiovascular disease cases are predicted to increase from 29 million in 2000 to 64 million in 2015, rising from 20% of all deaths to 34%. Cardiovascular health has already become a key pharmaceutical product area.

As of 2012, it is estimated that there are 2.8 million cancer patients in India. The number of cancer patients in India grows an average of 1.2%, or 1 million people each year. This is just slightly lower than the number of new cancer patients in the US, at 1.5 million each year. However, from the year 2020 onwards, India will add more than 2 million new cancer patients every year. Cancer is India's fourth largest killer, behind cardiovascular, respiratory and childhood diarrhea diseases. The current Indian cancer drug market is estimated at \$280 million. The market will grow about 16% annually by the year 2014, when the market value is expected to reach \$560 million. This rapid rate of growth can be attributed to a burgeoning Indian population, most of which continues to live in unhealthy and polluted conditions.

Other diseases which have rising incidence and whose treatments have high projected sales growth include HIV/Aids and mental illnesses. The drug categories enjoying the highest sales growth in 2009 included cardiovascular, anti-diabetic, and dermatological.

#### **B. Industry Profile**

For a long time, India was an unpopular destination for foreign pharmaceutical companies, primarily because of unfavorable patent laws that enabled copying. The general business environment was also difficult, with regulations restricting foreign investment. In 2005, its patent laws were finally amended to protect pharmaceutical

intellectual property rights according to international standards. Now, foreign pharmaceutical companies have a much-improved legal foundation for releasing new products. General policies toward foreign investment have also improved significantly. These structural changes have come at the same time when Indians need newer classes of drugs and are more able to afford them at international prices. Therefore, recently-developed foreign drugs are now increasingly able to take advantage of India's drug demand growth.

However, the pharmaceutical market in India is still heavily marked by the old patent regime, where copying was legal. It is highly fragmented, with at least 10,000 manufacturers. Only about 250 of these are large-scale. About 97% of India's pharmaceutical market value is made up of generic substances.

In 2012, India's Patent Office granted the country's first ever compulsory license to Hyderabad-based Natco Pharma, who was authorized to sell the generic version of Bayer's patented drug Nexavar, which is used for treating renal and liver cancers. Natco Pharma was allowed to sell one month's supply of the drug for \$175, while the price of the same amount of Bayer's patented version was \$5,500. In other words, Natco Pharma was allowed to sell the generic drug at a discount of 97%, which would effectively put an end to Bayer's monopoly over the cancer drug. Compulsory licenses are recognized by international laws as a way to provide affordable drugs to the general population. According to the WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights, if the patent holder fails to make its drug affordable, compulsory licenses may be granted to another manufacturer three years after the drug has been patented. Natco Pharma's landmark case may just be a precedent for more compulsory license approvals to come. Pharmaceutical companies that invest heavily in R&D may be discouraged from making further investments in India.

Domestic firms tend to spend very little on research and development (R&D). Some of the major domestic firms, such as Dr. Reddy's Laboratories, Ranbaxy, Nicholas Piramal, and Cipla, are counting on the new patent system to change the industry landscape. To adapt, they have greatly increased investments in R&D from about 1% to 3-5% of sales, and as much as 12% in some cases. However, they still value generic drugs in their business strategies. They are even engaging in acquisitions of Western generic firms, especially in Europe. For example, in 2006, Dr. Reddy's Laboratories purchased Betapharm, a major German generic pharmaceutical company, for about \$572 million. The weakening of the rupee in 2008 has slowed this trend, however. Sales of foreign drug manufacturers also increased. AstraZeneca, for example, saw its India sales grow by 13% in 2007, and Merck's India sales rose 25% in the same period. However, between 2005 and 2008, although multinational companies saw growth, their share of the total Indian pharmaceutical market did not greatly increase, hovering at one-fifth.

A strong trend in the industry is the outsourcing of R&D. Despite the domestic industry's emphasis on generics, the country's population of trained, English-speaking researchers and doctors has made R&D a practical option. GlaxoSmithKline, for example, has a long-running R&D alliance with Ranbaxy, which started in 2003, and expanded in scope in

2007 from early-stage laboratory testing to Phase I and II clinical trials. Other global pharmaceutical firms with substantial India partnerships include Amgen, Eli Lilly, and Bristol-Myers Squibb. Many Indian partner firms are not just acting as low-cost contractors but also sharing in the financial risk and reward as they search for new blockbusters. One example is Merck's October 2008 alliance with Orchid Chemicals & Pharmaceuticals to search for new drugs to treat bacterial and fungal infections and develop them through Phase IIa. In addition to royalties, the agreement also enables Orchid to receive as much as \$100 million in milestone payments from Merck.

India's huge patient base, combined with the availability of expertise, also makes clinical trials a popular target for outsourcing. In 2002, the total clinical trial market in India was about \$20 million; by 2008, this had shot up to about \$300 million. In pursuit of cost savings and easier subject recruitment, foreign pharmaceutical companies are making use of Indian contract research organizations, or setting up their own clinical sites.

Pharmaceutical manufacturing through subsidiaries, joint ventures, or contract manufacturers is growing as well, making use of India's low labor costs and the improving quality of its manufacturing base. For example, GlaxoSmithKline, which already has two manufacturing sites in India, is in the process of expanding its operations further. Sandoz, the generic branch of Novartis, now manufactures leprosy and tuberculosis drugs on a large and increasing scale in India.

Drugs in India are among the cheapest in the world. In addition to granting compulsory licenses, the Indian government has also introduced price ceilings to ensure supply of affordable drugs (*see Part E under Section VII for more background information on price control in India*). 20% of drugs are currently under price control, but the Indian government plans to bring an additional 45% of drugs under price control by the end of 2012. Most of these additional drugs are essential medications, such as cancer and anti-HIV drugs. The average prices of the three top-selling drugs in each category will be set as the price cap. Opponents of the price ceilings argue that current drug prices are already low enough due to competition among drug manufacturers. However, proponents suggest that pharmaceutical companies often make deals with doctors, who push for expensive patented drugs as opposed to the more affordable generics.

In a move to further extend affordable public healthcare to the underprivileged, India's Ministry of Health and Family Welfare is poised to provide essential drugs for free at state-run hospitals over a period of five years, starting August 2012. This is part of India's 12<sup>th</sup> Five-Year Plan. The entire free drug program will cost around \$4.8 billion, out of which \$3.6 billion will be paid for by the central government, and the state governments will be requested to contribute \$1.2 billion. In fact, two states – Rajasthan and Tamil Nadu – have already been giving out free drugs at public hospitals. About 350 essential drugs will be on the list of the essential medicines, which the Indian government is to purchase in bulk from local generic drug manufacturers, including Lupin, Ranbaxy and Cipla. The Indian government may also buy drugs from large-scale Western pharmaceuticals which have acquired Indian generic drug manufacturers, such as Abbott Laboratories. However, the essential drug list will not include brand-name drugs

produced by the same Western pharmaceutical companies, such as Lipitor and Plavix. As of July 2012, the “free drugs for all” scheme was yet to be finalized and approved.

The free drug initiative will be a further challenge to big Western pharmaceuticals, following the Patent Office’s decision to grant Natco Pharma a compulsory license to produce the generic version of Bayer’s patented drug, as mentioned above (*for further information on intellectual property issues in India, see Section IX*). However, India still offers promising opportunities for Western pharmaceutical companies, because of India’s growing middle and upper-middle classes, who prefer to go to private clinics and use foreign made brand-name drugs.

### **C. Conclusion**

India has specific advantages for all stages of the drug life cycle – R&D, clinical development, manufacturing, and sales. Sales may be the more challenging of these, since price competition is high. Nevertheless, now that legal changes have secured better rights for innovative companies, global pharmaceutical players have realized that the market’s potential over time is too strong to be ignored.

## **IV. REGULATORY OVERVIEW**

### **A. Governing Legislation**

India's *Drugs and Cosmetics Act* (DCA) governs the registration, import, manufacture, testing, and sale of drugs and cosmetics. It was first passed in 1940, and is still the primary law today after many amendments. Its provisions are implemented in detail in the administrative *Drugs and Cosmetics Rules* (DCR), first issued in 1945. The latest update was passed in 2008, providing deterrent penalties for offences relating to the manufacturing of spurious or adulterated drugs. The penalty has increased to at least 10 years of imprisonment and liability for fines.

As of July 2012, India's Ministry of Health and Family Welfare has renewed a Bill to add an amendment to the DCA, which would define and regulate medical devices in the country. At present, medical devices are regarded as drugs in India. As a result, thousands of medical devices remain unregulated. Under the proposed Medical Devices Regulation Bill, a separate definition would be effective for medical devices. Clinical trials, risk-based classification, and conformity assessment for medical devices would also be detailed in the amendment. The Bill has already been pending for more than four years, due to opposition from some states. However, the Bill appears to have gained momentum recently, and the Ministry is expected to push the Bill through Parliament during the monsoon session (August-September) of 2012.

One area the DCA does not cover is drug advertising. This is regulated by a separate law, the *Drugs & Magic Remedies (Objectionable Advertisements) Act* of 1954 (see chapter X below). Finally, some addictive drugs are controlled by the *Narcotic Drugs and Psychotropic Substances Act* of 1985.

### **B. Agencies**

Like the United States, India has a federal political system with both state governments and a national government. Unlike the US FDA, however, its medical regulatory system has separate agencies at the state and national levels. This has created significant problems with coordination and division of labor between different parts of the system.

The main national pharmaceutical oversight agency is the Central Drugs Standard Control Organization, or CDSCO. This body is based in New Delhi and has some regional offices and testing laboratories in other cities. It reports to the cabinet-level Ministry of Health and Family Welfare. CDSCO is commonly referred to by the title of its head official, the Drugs Controller General (India), or DCGI.

State-level agencies have different names depending on their state. For example, in the state of Gujarat, it is the Food and Drugs Control Administration. However, they are generically referred to as "state food and drug administrations," "state FDAs," or "state drug controllers."

Generally, the DCGI handles important regulatory work, such as approval of new drugs, clinical trial oversight, and import licensing. The state FDAs handle more everyday matters such as licensing of drug manufacturers and distributors, as well as most inspection activity. In other words, when a new drug is filed for approval, it is first reviewed by CDSCO. After CDSCO has issued approval, the drug manufacturer can apply for a manufacturing license from the state drug authorities. However, the division of labor between the national and state drug agencies is not always clear-cut in practice. According to a Parliamentary Report published in May 2012, drug authorities in some states have issued manufacturing licenses for many fixed dose combinations (FDCs) without CDSCO's approval. *(Note: when two approved drugs are combined for the first time in an FDC, the FDC is considered a new drug and has to undergo the same approval process as other new drugs. See Part B under Section V on pp. 20-25 for information on new drug registration).* This unlawful practice by state drug authorities was first documented in 2000. Since then, the DCGI has requested the state drug authorities to stop issuing new manufacturing licenses and suspend old licenses that were not authorized by the CDSCO. However, almost no concrete steps have been taken and enforcement is very limited.

Although most activity relating to drug imports is overseen by the CDSCO, it is understaffed for the purpose. As pointed out by the 2012 Parliamentary report, out of 327 sanctioned posts at the CDSCO, only 124 are occupied. There were plans to add 1,045 posts within the CDSCO, but given that the average recruitment process takes 12 months, the plans may not materialize.

In addition, its employees often lack full technical training for their broad range of duties. Perhaps, the most stunning example is that, according to the DCA, the minimum qualification for the most important position of DCGI is only a Bachelor degree in pharmacy, pharmaceutical chemistry, or medicine with specialization in microbiology or pharmacology. On the other hand, for the lower-ranking position of Deputy Drugs Controller, the requirement is a post-graduate medical qualification. Moreover, the DCGI is required to have at least five years of experience in the manufacture of testing of drugs or in the enforcement of the DCA. This effectively excludes highly qualified professionals with clinical and research experience, such as those with MD or PhD degrees, from assuming the role of DCGI.

Nevertheless, since the beginning of 2012, there have been new developments regarding the recruitment of DCGI. In addition to the requirements listed in the DCA, the CDSCO has been looking for applicants with a post-graduate degree in chemistry, biochemistry or pharmaceutical chemistry to fill the position of DCGI, after Surinder Singh left office in late 2011. However, this apparent attempt to raise the qualification of the DCGI has been met with opposition from an Indian pharmacist association. When the CDSCO appointed G. N. Singh as the new DCGI in February 2012, the pharmacist association filed a lawsuit against the appointment for contempt of court, because the association claims that, as opposed to adhering to the DCA, the CDSCO has tailor-made the recruitment requirements of DCGI for G. N. Singh. Although the lawsuit is still being reviewed by

the court, in the meantime, the CDSCO has already extended G. N. Singh's term to August 2012. However, since his term is still temporary, there is uncertainty about the stability and continuity of the CDSCO in the future.

Applications for drug and medical device approvals can experience long, unexpected delays. A number of regulatory requirements are still vague, and can be applied inconsistently. Finally, the federal and state bodies do not share information systematically. For example, state FDAs have difficulty verifying import licenses from the DCGI or manufacturing licenses from other states.

A proposal by policymakers to unify the DCGI and state FDAs into a single body called the "Central Drugs Authority of India" (CDA) was approved by the Union Cabinet in January 2007. However, after extensive hearings in 2008, a parliamentary committee eventually decided that a proposed healthcare system modernization was needed, but that the proposed new agency was not. The bill is now being re-drafted. It is unclear at this stage whether the CDA will still come into existence, or if the DCGI will simply be reorganized.

To surmount the system's many barriers, it is crucial to make use of qualified regulatory personnel. Such people should have experience not just with drug regulations but with helping *foreign companies* with drug regulations, since that task can pose different problems. They should be able to spend a significant amount of time in New Delhi following up on submissions. It is preferable to have discussions with regulators over the phone or in person rather than by mail.

Industrial policies to develop the pharmaceutical industry are under the control of the Ministry of Chemicals and Fertilizers, not the health bureaucracy. Under this department is the National Pharmaceutical Pricing Authority (NPPA). The NPPA collects information on production, receives applications for pricing, and regulates prices for some drugs (see chapter VI below).

In March 2011, the Ministry of Health and Family Welfare formed a Task Force to develop a long-term strategy for addressing the various issues faced by India's pharmaceutical industry.

The 12-member Task Force, comprising members from the NPPA, DCGI, Indian Drug Manufacturers Association and other industry bodies are responsible for the following:

- Develop short-term, medium-term and long-term policies and strategies to make India a research and development hub for drug discovery.
- Develop strategies to enhance the interests of the Indian pharmaceutical industry in the light of issues related to Intellectual Property Rights. The Task Force will also recommend strategies to capitalize on the \$60-80 billion business opportunity of off-patent drugs over the next 5 years.

- Develop policy measures to ensure National Drugs Security, i.e.:
  - Promote indigenous production of bulk drugs in India
  - Prevent the over-dominance of MNCs in India's pharmaceutical industry
  - Overcome drug pricing issues
  - Promote generic drugs and recommend measures to ensure adequate availability of affordable, quality generic drugs to the public
- Recommend measures to overcome the problem of spurious drugs
- Review and advise on any other industry-related issue
- Devise roadmaps for the implementation of all the above recommended measures.

The Task Force has been requested to submit a status report on the above by the end of June 2011.

*Note to readers: Since some regulatory functions may be performed by either a state FDA or by the DCGI, this report will sometimes use the term "Licensing Authority" to refer to whichever body is relevant.* Contact Information for Regulatory Bodies:

**Central Drugs Standard Control Organization**

Directorate General of Health Services  
 Ministry of Health and Family Welfare  
 Government of India  
 FDA Bhavan, ITO, Kotla Road, New Delhi - 110002,  
 India  
 Phone: +91-11-23236965/ +91-11-23236965  
 Fax: +91-11-23236973

**Central Drugs Laboratory**

3, Kyd Street  
 Kolkata - 700016, India  
 Phone: +91-33-2299541  
 Fax: +91-33-2299380

**National Pharmaceutical Pricing Authority**

3<sup>rd</sup>/5<sup>th</sup> Floor, YMCA Cultural Centre Building  
 1, Jai Singh Road  
 New Delhi - 110001, India.  
 Phone: +91-11-23345116  
 Fax: +91-11-23345119 / 23746652  
 Email: [nppa@hub.nic.in](mailto:nppa@hub.nic.in)  
 Website: <http://nppaindia.nic.in/index1.html>

## V. DRUG REGISTRATION AND IMPORT

### A. Overview

Generally, all the requirements and guidelines for the permission to import and/or manufacture new drugs for sale, as well as clinical trials, are prescribed under Schedule Y of the Drugs & Cosmetics Rules, 1945.

Getting approval for the import of drugs into India consists of up to three main phases. To begin with, new drug approval must be received from the DCGI, not necessarily for new drugs only. Once the new drug registration has been obtained, or for drugs not needing it, an import registration certificate can be received from the DCGI. Finally, the importing party uses the import registration certificate to obtain an import license from the DCGI.

For a visual representation of the key steps, see Appendix I.

### B. New Drug Registration

Under Indian law, many products which are not “new” by Western standards may still have to go through the new drug application process. The categories that require new drug registration are:

- A. A drug which has not been marketed in India before.
- B. A drug with a new therapeutic purpose or dosage that has not been marketed in India.
- C. A new fixed-dose combination of two or more drugs, if they have not been approved in such a combination before.
- D. A drug or formulation which received its first new drug approval (of any of the types listed above) less than four years ago. This does not apply if the drug has been included in the Indian Pharmacopoeia since then.
- E. Any vaccine, unless certified otherwise by the DCGI.

The DCGI typically requires **phase III trials to be performed in India** before it will approve a foreign new drug for marketing. Other phases may be performed outside India. However, this only applies fully to category A (“true” new drugs).

New drug application content varies based on the category of new drug. For any category, **all new drug applications** must have the following information:

1. Drug name
2. Dosage form
3. Composition of formulation
4. Test specifications for:
  - a. Active ingredients
  - b. Inactive ingredients
5. Pharmacological classification
6. Indications
7. Manufacturer(s) of raw materials
8. Applicable patents, if any

To register new drugs for marketing which have **never been registered** before (type A above), the following items are required in addition to 1-8 above:

1. Introduction (brief description of drug and its therapeutic class)
2. Chemical and pharmaceutical information
  - a. Active ingredient(s) (generic name, chemical name, or INN)
  - b. Physiochemical data
  - c. Analytical data
  - d. Complete monograph specification
  - e. Validations
  - f. Stability studies
  - g. Formulation data
3. Animal pharmacology data
  - a. Summary
  - b. Specific pharmacological actions
  - c. General pharmacological actions
    - i. Essential safety pharmacology
      1. Cardiovascular system
      2. Central nervous system
      3. Respiratory system
  - d. Follow-up and supplemental safety pharmacology
    - i. Follow-up essential safety
      1. Cardiovascular system

- 2. Central nervous system
      - 3. Respiratory system
    - ii. Supplemental safety
      - 1. Urinary system
      - 2. Autonomic nervous system
      - 3. Gastrointestinal system
      - 4. Other organ systems (where there is cause for concern)
  - e. Pharmacokinetics
    - i. Absorption
    - ii. Distribution
    - iii. Metabolism
    - iv. Excretion
4. Animal toxicology data
- a. General aspects
  - b. Systemic toxicology
  - c. Male fertility
  - d. Female reproduction and developmental toxicology
  - e. Local toxicity
  - f. Allergenicity and hypersensitivity
  - g. Genotoxicity
  - h. Carcinogenicity

*Note:* Requirements in this category may be relaxed on a case-by-base basis if a drug has been marketed in other countries for several years and the other submitted safety evidence is considered sufficient.

5. Human Phase I data
- a. Summary
  - b. Specific pharmacological effects
  - c. General pharmacological effects
  - d. Pharmacokinetics
  - e. Pharmacodynamics
6. Human Phase II data
- a. Summary
  - b. Study report, following format in Schedule Y, Appendix II
7. Human Phase III data (in India)
- a. Summary
  - b. Individual study reports listed by site and investigator
8. Special studies
- a. Summary
  - b. Bioavailability and bioequivalence

- c. Other studies as needed: geriatrics, pediatrics, pregnant or nursing women, etc.
9. Comprehensive information on regulatory status in other countries
- a. In which countries the drug is:
    - i. Marketed
    - ii. Approved
    - iii. Approved as investigational new drug
    - iv. Withdrawn (describing reasons)
  - b. In which countries the drug's use is approved but restricted; information on restrictions, if any
  - c. Free Sale Certificate (or certificate of analysis, depending on country of origin)
10. Prescription information
11. Samples and testing protocols
- a. Samples of:
    - i. Pure drug substance
    - ii. Finished product (equivalent of at least 50 clinical doses)
  - b. Testing protocol(s)
  - c. Full impurity profile
  - d. Release specifications
12. Marketing information
- a. Proposed product monograph
  - b. Drafts of labels and cartons
13. Application for test license (to import drug provisionally for testing purposes [see page 31 below])

Some drugs already approved in India still require registration as new drugs. Their applications are divided into four types: formulations or bulk drugs approved less than four years previously (type D); new fixed-dose combinations of approved drugs (type C), and a new indication or dosage for an existing drug (type B). **All** of these drugs (types B-D) require the following information as well as items 1-8 (above, page 21):

- 1. Introduction (brief description, therapeutic purpose)
- 2. Chemical and pharmaceutical information
  - i. Chemical name, code name, number; generic name; structure; physiochemical properties
  - ii. Dosage form, composition
  - iii. Test specifications
    - 1. Active ingredients
    - 2. Inactive ingredients

- iv. Tests for identification of active ingredient(s)
  - v. Outline of manufacturing method of active ingredient(s)
  - vi. Stability data
3. Marketing information
    - i. Package insert, promotional literature
    - ii. Draft of label and carton
  4. Special studies depending on mode of administration
    - i. Oral:
      - a. Bioavailability and bioequivalence data
      - b. Comparative dissolution studies
    - ii. Intravenous infusion or injection:
      - a. Sub-acute animal toxicity data

The following additional information requirements for previously-approved “new drugs” depend on the category of the drug being applied for:

**Formulations** (same dosage and indications as recently approved new drug):

1. Bioavailability and bioequivalence protocol
2. Name of investigator/center
3. Raw material source and stability data

**Bulk drugs** (same as recently approved new bulk drug):

1. Manufacturing method
2. Quality count parameters and/or analytical specifications, stability report
3. Animal toxicity data

**Fixed-dose combinations:**

1. Therapeutic justification (must cite peer-reviewed journals or textbooks)
2. Pharmacokinetic/pharmacodynamic data on combination
3. Any other data generated by the applicant relating to safety and efficacy (can vary depending on preferences of DCGI)

### **New indication/dosage:**

1. Date, number of previous new drug approval
2. Therapeutic justification for modification to claim or dosage
3. Safety, efficacy, quality data (can vary depending on preferences of DCGI)

### *Fee Schedule*

- In most cases.....Rupees 50,000 (US\$1,125)<sup>1</sup>
- If the same applicant submitted another NDA less than 12 months previously.....Rs. 15,000 (US\$340)
- For new claims or new dosage for an approved drug.....Rs. 15,000 (US\$340)

After a new drug application is approved, a certificate is issued by the DCGI. The government does not promise to give approval within a particular time period. Review can last several months to a year. At the other extreme, one new drug, strongly desired for public health reasons and backed up by plentiful clinical data, was once approved in four weeks.

### *Similar Biologics*

India's Health Ministry published updated guidelines for the registration of similar biologics in June 2012. For a drug to be considered a similar biologic, its quality, preclinical and clinical production processes should be comparable to the reference product. For example, the similar biologic should have the same "route of administration, strength and dosage" as its reference product. Also, the active ingredient of the similar biologic should be proven to be similar to the reference biologic.

For a drug to be considered a reference biologic, it should be approved in India with a complete dossier as an innovator drug, i.e. a similar biologic cannot be considered a reference biologic for another drug. If the drug is not licensed in India, it should have been approved and widely marketed as an innovator drug in a country with a well-established regulatory mechanism for at least four years.

The acceptance of an innovator drug as the reference biologic for a similar biologic does not imply CDSCO's approval of the similar biologic. Although the preclinical and/or clinical requirements for the application for a similar biologic may be lower than that for the reference biologic (depending on the similarity between the two), the Health Ministry stressed that only similar biologics which fulfill the "safety, efficacy and quality" requirements would be approved. The new guidelines are scheduled to go into effect starting August 15, 2012.

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<sup>1</sup> (Based on 4/11 exchange rate of US\$1 = Rs. 44.4)

### C. Import Registration

Registration for the import of Western drugs, not homeopathic or traditional Indian medicines, is standardized in Form 40 and two schedules of additional information. Since the two schedules were added at different times, they overlap in some requirements.

This registration is only required for drugs to be imported, not manufactured. It should also not be confused with the import *license*, which actually lets a shipment pass through customs.

Import registrations are submitted to the DCGI, rather than to state FDAs. The DCA states that the government will generally issue an import registration certificate within 9 months of application. However, the process has been known to go on for longer than this, with further requests for clarification or information.

When submitting a non-new drug for import registration, it is important in practice to reference a predicate substance that is already marketed in India. If the DCGI mistakenly demands new drug registration, it may severely delay approval.

An import registration certificate remains valid for 3 years from its issue. However, if the license-holder applies for renewal at least 9 months before the license's expiration date, the license will remain valid past its expiration date, until renewal is approved or denied. If an application is rejected, the aggrieved party has the right to appeal the decision administratively within 30 days.

#### *Standing as Applicant*

The applicant for an import registration certificate cannot simply be an Indian agent or consultant to the manufacturer. It must be an entity which is licensed to either sell wholesale or manufacture drugs. The following cases illustrate what kind of applicant is required, depending on the situation. In all of these cases, a copy of the relevant license must be attached to the import license application.

<i>In the case that...</i>	<i>The applicant should be...</i>
Indian agent or distributor receives drugs directly and distributes	Holder of wholesale license
Indian agent or distributor receives drugs directly, repacks or reprocesses before distributing	Holder of manufacturing (repacking) license
Manufacturer's India office (usually a branch, subsidiary, or JV) receives drugs and sells to Indian distributors	Manufacturer's India office with distribution license

#### *Combining import registrations*

Technically, import registrations are issued per manufacturing site rather than per drug. This means that multiple drugs can be registered at once if they come from the same factory. The following chart illustrates how this works.

	<i>Making one drug</i>	<i>Making multiple drugs</i>
<i>One factory</i>	Single license	Single license (each drug specified)
<i>Multiple factories</i>	One license per factory	One license per factory (each drug specified)

*Exceptions to import registration requirements*

The following types of pharmaceutical substances do **not** need to be registered for import under the DCA:

- i. Substances not intended for medicinal use (this must be clearly labeled)
- ii. Substances imported to Special Economic Zones (SEZs) for manufacture and export (provided they are not diverted for sale in India)
- iii. Inactive bulk substances to be used to make drug formulations

*Factory inspection*

Since import registration is attached to the drug’s actual manufacturing site, the DCGI reserves the right to inspect the site if necessary. In these cases, the site is evaluated against Indian GMP standards (see chapter VI on manufacturing), and an extra fee of US\$5,000 is charged. However, the DCGI will usually trust GMP certification from an advanced country such as the US or Europe. Inspections are more likely for drugs produced in other low-cost countries such as China.

**Submitted on form:**

- 1. Applicant’s name and full address
- 2. Foreign manufacturer’s name, full address, telephone, fax, e-mail
- 3. Drug name
- 4. Full address, telephone, fax, e-mail of actual manufacturing premises

**Submitted attached to form:**

Schedule D(I):

1. Particulars of manufacturer
  - a. Name and address (including telephone, fax, e-mail) of manufacturing premises
  - b. Names and addresses of manufacturer's directors, partners, or proprietors
  - c. Name and address of manufacturer's authorized agent in India (see page 26 above for requirements)
  - d. Brief profile of activity of manufacturer, in India and internationally
  - e. Notarized copy of Plant Master File
  - f. Approval of manufacturing premises by national regulator in country of origin
  - g. Brief profile of manufacturer's research activity
2. Particulars of drug(s) to be registered
  - a. Notarized copy of drug marketing approval in country of origin
  - b. Notarized copy of GMP approval certificate for manufacturing site, issued by national regulator in country of origin
  - c. Domestic price to be charged in India, in currency of country of origin
  - d. Clarification of which drug(s) in application were products of original research by manufacturer
3. Undertakings (standard form promising to follow laws, accommodate inspectors, etc.; not included)

Schedule D(II):

1. General information
  - a. Name, brief description, therapeutic class of drug(s)
  - b. Free Sale Certificate (FSC) or Certificate of Pharmaceutical Product (CPP) issued by national regulator in country of origin
    - i. FSCs or CPPs from other major countries where drug is marketed, if any
  - c. Notarized Drug Master File
  - d. Notarized copy of GMP approval certificate for manufacturing site, issued by national regulator in country of origin
  - e. List of countries where marketing and/or import has been approved, including authorizations and dates
  - f. List of countries, if any, where marketing and/or import has been withdrawn or cancelled, with date of such action
  - g. List of countries where marketing and/or import is pending, with date from which it is pending
  - h. Domestic price of drug in country of origin
  - i. List of countries where drug is patented
2. Chemical and pharmaceutical information

- a. Chemical information
    - i. Chemical name
    - ii. Code name or number (if any)
    - iii. Nonproprietary or generic name
    - iv. Chemical structure
    - v. Physico-chemical properties
  - b. Dosage form and composition
    - i. Qualitative and quantitative composition in terms of active substance(s) and excipients
    - ii. List of active substance(s) separately from constituents of excipients
  - c. Specifications of active and inactive ingredients, with pharmacopoeial references
  - d. Source of active ingredient(s), with name and address
  - e. Tests for identification of active ingredient(s), including method of assays and tests for impurity profile with reference standards for impurity
  - f. Outline of drug manufacturing method and process
  - g. Detailed testing protocol, based on pharmacopoeia or in-house specifications with regulatory approval in country of origin
  - h. Stability data
    - i. Documentation on pack size
    - j. Numerical expression on EAN barcode
    - k. Safety documents on containers and closures
    - l. Storage condition documentation
  - m. Three samples of product, in packaging, with batch certificates
  - n. Five consecutive batch testing certificates from manufacturing site
  - o. Labeling
  - p. Package insert
  - q. Safety handling procedures
  - r. Postmarketing study report (data spanning up to five years, if existing)
3. Biological and pharmaceutical information
    - a. Biological control tests on starting material
    - b. Biological control tests on intermediate product
    - c. Biological control tests on finished product
    - d. Stability of finished product in terms of biological potency
    - e. Sterility tests, with specification and protocol
    - f. Pyrogen tests, with specification and protocol
    - g. Acute and sub-acute toxicity tests, with specification and protocol
    - h. Bioavailability and bioequivalence data
    - i. For r-DNA products only: Environmental risk assessment data
    - j. Other relevant information

*Note:* All items in this section are required only if applicable to the product.

4. Pharmacological and toxicological information. This can be provided in summary form only. It must mention:
  - a. Specific pharmacological actions
  - b. General pharmacological actions
  - c. Acute, sub-acute, and long-term toxicity studies
  - d. Also, if possible:
    - i. Reproductive toxicity
    - ii. Local toxicity
    - iii. Carcinogenic activity
5. Clinical information, for new drugs only. The full procedure for clinical data approval is part of the new drug approval procedure (see part B above). Therefore, this section only requires a brief summary of clinical data and documentation, accompanied by proof of new drug approval.
6. Labeling and packaging information to demonstrate compliance to relevant regulations (see page 51 below).
7. For certain classes of drugs, product dossiers containing details on:
  - a. **Blood products:**
    - i. Source plasma, viral screening, storage and transport from collection centers to fractionation centers, with regulatory status on collection centers
    - ii. Fractionation centers, their regulatory status, method of fractionation, control processes
    - iii. Viral inactivation process and viral validation studies; must include details on kits used in testing and their sensitivity and specificity
    - iv. Bulk filtration prior to pharmaceutical packaging, including any micro-filtration or nanofiltration
    - v. Pharmaceutical processing and utilization (complete details)
    - vi. Test protocol including specifications and pharmacopoeial method and batch test reports for at least 3 batches, including each testing parameter
    - vii. Pack size and labeling
    - viii. Product inserts
    - ix. Specimen Batch Release Certificate issued by national regulator of country of origin  
*Specific processes to be highlighted:* safe handling, material control, area control, pasteurization, stability studies, storage at various stages
  - b. **Vaccines:**
    - i. Seed strain information:
      1. History
      2. Source
      3. Date of receipt

4. Storage
5. Identity
6. Characterization
- ii. Manufacturing process, including:
  1. In-process toxicity controls
  2. Potency study and stability data of final bulk and final finished product
  3. Storage temperature
- iii. Complete chemical and pharmaceutical information:
  1. Composition and dosage form
  2. Method of manufacture with detailed flow chart
  3. Control of starting material, intermediate product, finished product
  4. Certificate of analysis of finished product
  5. Validation of critical manufacturing steps
- iv. Test protocol, showing specification and method of testing with pharmacopoeial specification
- v. Batch reports of at least 3 consecutive batches, specifying each testing parameter
- vi. Detailed test reports of all components used or packed in finished vaccine
- vii. Pack size and labeling
- viii. Product insert
- ix. Evaluation report by national regulator of country of origin
- x. Summary of pre-clinical and clinical data:
  1. Prescription information
  2. Pharmacological and toxicological data from animal testing
  3. Immune response and safety data from human testing
- xi. Samples of 3 consecutive batches, with test protocols and specifications for each quality control parameter  
*Specific elements to be highlighted:* seed strain source, characterization, and inactivation, processes of safe handling, material control, area control, process control, stability studies, storage at various stages, packaging

*Fee schedule*

Unlike most other fees in the regulatory system, import registration fees are denominated in US dollars rather than Indian rupees. The fee schedule is as follows:

- For manufacturing site.....\$1,500 (waived in future applications for drugs from the same site)
- For each drug applied for.....\$1,000
- For factory inspection, if necessary.....\$5,000

- For duplicate copy of certificate.....\$300

### *Reporting of changes*

The holder of an import certificate is obligated to report all material changes to the DCGI within 30 days. These include changes to:

- Manufacturing site
- Manufacturing process
- Packaging
- Labeling
- Testing
- Documentation

Notification of these changes can be done in simple letter form, specifying the appropriate import registration certificate number. However, it must come from the Indian agent, distributor, or subsidiary actually holding registration, not the manufacturer at its foreign address.

Major changes may require re-registration instead of notification. What makes a change “major” is not well-defined, and the DCGI makes decisions on a case-by-case basis. Changes to product composition or manufacturing site always require re-registration. When re-registration is required, the application should be submitted within 30 days of the change.

### **D. Import License**

The final step for a foreign company to bring a drug into India is to receive an import license. Import license application forms can differ depending on the type and purpose of the drug.

At the border, the import license is the only regulatory permission needed to bring in shipments besides general customs requirements. Officials may conduct testing to verify that a shipment’s contents and quality adhere to the license terms. Because of this requirement, drugs may only enter India via cities with appropriate testing facilities. They may enter by sea through Chennai, Kolkata, Mumbai, Kochi, Nhava Sheva, or Kandla, or by air through Chennai, Kolkata, Mumbai, Delhi, Ahmedabad, or Hyderabad.

Tariff levels range from as high as 28% to as low as 0% (for specified “life-saving” products). A common level for many products is 12.5%. This is calculated from the cost, insurance and freight (CIF) value given on the invoice. There is also a “countervailing duty” of 8%, which is equivalent to the internal excise tax. Life-saving drugs may also be exempt from the countervailing duty. On April 1, 2008, the internal excise tax rate on drugs was lowered from 16% to 8%. Since the countervailing duty is equivalent to the internal excise tax rate, tariffs on imported drugs dropped 8% as a result.

Import licenses are issued by the DCGI directly, not by state FDAs.

The types of drugs as distinguished in the import licensing process are as follows:

1. All drugs not listed below (general import license)
2. Drugs listed in Schedule X  
(Abusable sedatives and stimulants. For the full list, see Appendix XIX.)
3. Drugs imported in small quantities for personal use
4. Drugs imported in small quantities by a public hospital
5. Drugs for examination, testing, or analysis (including clinical trials)

The informational requirements to apply for import licenses are as follows:

*General import license*

1. Full address of applicant with telephone, fax, and email
2. Full address of manufacturer with telephone, fax, and email
3. Name(s) of imported drug(s)
4. Undertaking to follow relevant laws and regulations, signed by manufacturer
5. Copy of import registration certificate for drug, with its number, name and address of license-holder, and expiration date
6. Copy of applicant's license to distribute or manufacture drugs (see page 26 above).

*License to import drugs listed in Schedule X*

- 1 through 5. (Same as above)
6. Copy of applicant's license to distribute or manufacture drugs listed in schedule X (different type of license)

*License to import drugs in small quantities for personal use*

1. Applicant name, address, occupation
2. Name(s) of imported drug(s)

3. Origin of drug(s)
4. Prescription from licensed medical practitioner

*Note 1:* The Licensing Authority will determine if the quantity is appropriate for personal use.

*Note 2:* Drugs may also be imported for personal use during personal travel without this license if all of the following conditions are met:

- a) They are included in a passenger's baggage, and the passenger is the only user
- b) They are declared to Customs
- c) The quantity does not exceed 100 doses

*License to import new drugs in small quantities by a public hospital*

1. Applicant (must be representative of hospital)
2. Applicant designation
3. Name of importing hospital
4. Disease to be treated
5. Name and address of hospital treating disease
6. Name and quantity of drug(s)
7. Certificate stating that drug is urgently required for treatment and is not available in India, signed and sealed by Medical Superintendent of treating hospital

*Note:* Drug import and use must meet the following conditions:

- a) Approved in country of origin
- b) Quantity must not exceed 100 doses per patient treated

*License to import drugs for examination, testing, or analysis ("Test License")*

1. Applicant name, address, occupation
2. Testing site
3. Testing dates
4. Name, class, quantity of drug(s)

*Note 1:* Must be signed or countersigned by head of medical institution or firm conducting actual testing.

*Note 2:* For convenience, this application is often submitted attached to a new drug application. See page 23 above.

#### *Fee schedule*

1. All drugs not listed below.....Rs. 1,000 (US\$20)
2. Drugs listed in Schedule X.....Rs. 1,000 (US\$20)
3. Drugs imported in small quantities for personal use.....--
4. Drugs imported in small quantities by a public hospital.....Rs. 100 (US\$2)
5. Drugs for examination, testing, or analysis.....Rs. 100 (US\$2)

Multiple drugs can be registered with the same import license application. The fee for the first drug in the application is Rs. 1,000, and each additional drug costs Rs. 100. For later import licenses, if the drug is from the same manufacturing site as before, the first drug also costs Rs. 100. However, drugs in Schedule X cannot be mixed with other drugs on the same import license application.

#### **E. Adverse Event Reporting**

Legally, any firm applying for new drug registration undertakes to provide the DCGI with post-marketing safety reports. This reporting should be in the form of a Periodic Safety Update Report (PSUR). The PSUR is submitted twice a year for the first two years of marketing and once a year during the third and fourth years. It should include all new data received from post-market surveillance, any regulatory changes in other countries, and a recommendation on any necessary changes to the product. If any new studies are commissioned, these should also be concluded. Besides the PSUR, all serious unexpected adverse events in India known to the license-holder should be reported within 15 days.

However, from the viewpoint of establishing a modern system of monitoring drug safety, it is publicly recognized as inadequate to collect data only from recent new drugs. The Parliamentary Report of 2012 points out a few controversial drugs that should have been withdrawn from the market in India due to adverse events and subsequent regulatory changes in other countries. For example, Analgin was first banned in the US in 1977. The drug was then banned in about 20 other countries, following reports of agranulocytosis. However, Analgin is still allowed to market in India.

In 2004, India formed a national adverse event reporting body, the National Pharmacovigilance Center, which is housed in the All India Institute for Medical Sciences (AIIMS). AIIMS is India's national coordination center for monitoring adverse drug reactions (ADR) in the country. 33 regional and local reporting bodies were also established under the National Pharmacovigilance Center. These entities gather safety reports from hospitals and medical professionals. A 16-member National Pharmacovigilance Advisory Committee periodically evaluates the data and may recommend regulatory responses. Between 2006 and 2008, a total of 11,633 cases of ADRs were reported under the National Pharmacovigilance program. Nevertheless, none of the ADRs led to any restriction/prohibition on any drug in India. In July 2010, a

revised Pharmacovigilance Program was initiated with AIIMS to compliance to Schedule Y requirements.

Currently there are 22 Indian ADR monitoring centers under the revised Pharmacovigilance Program. The list of ADR monitoring centers can be found in Appendix XXIII of this report.

Nevertheless, India is still at an early stage in adverse event reporting. At this stage, an important goal of these pharmacovigilance bodies is simply to encourage doctors and patients to develop the habit of reporting adverse events. In gauging drug safety, India still tends to rely on data collected abroad.

## **VI. MANUFACTURING**

### **A. Overview**

Since the 1970's, manufacturing has been the foundation of India's pharmaceutical development. Today, the country has over 10,000 drug factories, which produce at least 6,000 brands. Although many of these are small and generic-focused, others aim to be good contract manufacturing partners for the Western industry. The country has more US FDA-approved plants than any other country outside the US. With new deals being made constantly, the value of the drug manufacturing industry is predicted to grow an average of 10% each year over the 2012-2015 period. Multinational pharmaceutical companies that manufacture in India include GlaxoSmithKline, Sanofi-Aventis, Pfizer, and Abbott.

### **B. Licensing**

Manufacturing licenses in India are usually issued by the state FDAs. New drugs, blood products, large volume parenterals, sera, and vaccines must receive their manufacturing licenses from the DCGI.

Most regulatory requirements for manufacturing have been integrated to a GMP standard under Schedule M of the DCA. Compliance is enforced by inspections by state FDA officials. However, some remaining manufacturing requirements are specific to India. Some of these provisions mandate particular college degrees and levels of experience for production heads and testing heads.

Although most manufacturing licenses are granted on the state level, receiving the license gives a manufacturer legal permission to sell its product anywhere in India. There was an excise tax of 16% on domestically manufactured drugs, though this was reduced to 8% in April 2008. In February 2011, as part of the national budget for 2011/2012, the Indian government set the excise duty on medicines and medical equipment to 5%. As outlined in the national budget for 2012/2013, six life-saving drugs and vaccines and the bulk drugs used in their production will be completely exempted from excise duty.

Manufacturing licenses are divided into a number of categories depending on the type of drug being made. The categories are:

1. Drugs not listed below
2. Drugs in Schedule C or C(I)  
(Biological products. For complete list, see Appendix XIV. Items in (4) below are included in the schedule, but licensed separately.)
3. Sera, vaccines, or large volume parenterals (sterile solutions with over 100ml per container)

#### 4. Blood products

A license may be for general manufacturing, only for repacking, or for manufacturing for testing purposes. Another category is the “loan license.” In loan licensing, a firm without manufacturing facilities (for example, a drug’s patent-holder) obtains permission to make a drug through a contract manufacturer, which must have a regular manufacturing license. This allows flexibility in choosing a contract manufacturer.

A license to manufacture for testing is only needed for a site that does not already have a manufacturing license. It has a significantly smaller fee and less stringent requirements. The DCA mostly waives requirements of drug quality and accurate claims for such licenses. However, the drug must be made in small quantities and be labeled as not for resale.

#### *Licensing Requirements*

The items to be assessed by a Licensing Authority for manufacturing licenses are given below, divided by type of license. For specific staff requirements, please refer to the following section.

Requirements for each license are described in two parts. Part (A) is the actual informational items that need to be submitted in an application. Part (B) is what the Licensing Authority is required to assess based on the information provided and on-site inspections.

State FDAs are required to assess information on drugs to be manufactured, when they are patented or proprietary. This requirement focuses on confirming that the planned dosages, formulations, and excipients are appropriate to claims *as stated*, rather than assessing the claims themselves. However, the documentary requirements are much more vaguely defined than the requirements for new drug or import registration. They can also vary from state to state. In these cases, one should consult with the relevant state FDA to determine how much information is necessary.

Multiple drugs can be registered for manufacture at the same site. The application should list them divided by category. The categories are:

1. Sterile products, parenteral preparations, and sterile ophthalmic preparations
2. Oral solid dosage forms (tablets and capsules)
3. Oral liquids (syrups, elixirs, emulsions, and suspensions)
4. Topical products (creams, ointments, pastes, emulsions, lotions, solutions, dusting powders, etc.)
5. Metered dose inhalers

6. Active pharmaceutical ingredients (bulk drugs)
7. Blood products

*General manufacturing license:*

A. To be submitted in application:

1. Applicant name, address
2. Manufacturing premises address
3. Names of drugs, by category
4. Names, qualifications, experience of production and testing staff
5. Plan of manufacturing premises
6. Information on patent or proprietary medicines used, if any. Evidence proving that the product(s):
  - a. Are in ingredients and quantities appropriate to claims or conditions recommended for use or claimed to be useful
  - b. Are safe with relevant excipients and formulation
  - c. Are in stable storage conditions
  - d. Are with therapeutically justified ingredients and quantities
  - e. If new drugs, have new drug approval

B. Points to be assessed (same for all manufacturing licenses; omitted below)

1. Qualified production staff
2. Compliant with Schedule M in terms of:
  - a. Premises
  - b. Space, plant, equipment
  - c. Practices
3. Testing unit:
  - a. Qualified supervisor
  - b. Adequate testing lab equipment
  - c. Testing unit must be separate from manufacturing unit
4. Adequate arrangement for storage of drugs

*Manufacturing license for drugs in Schedule C or C(I), sera, vaccines, large volume parenterals, or blood products:*

A. To be submitted in application:

1. Applicant name, address
2. Manufacturing premises address
3. Drug name(s)
4. Names, qualifications, experience of production and testing staff
5. Date premises will be ready for inspection
6. Plan of premises
7. Documentation for proprietary medicines

B. Points to be assessed (same as above)

*Repacking license:*

A. To be submitted in application:

1. Applicant name, address
2. Repacking premises address
3. Names of drugs to be repacked, by category
4. Names, qualifications, experience of staff
5. Plan of repacking premises

B. Points to be assessed:

1. Hygienic conditions
2. Qualified supervisor
3. Compliant with Schedule M in terms of:
  - a. Premises

4. Adequate arrangements to carry out testing at separate unit (may be contracted out to properly licensed operation)

*Loan license:*

A. To be submitted in application:

1. Names of proprietors, partners, or managing director of applying firm
2. Name of applying firm
3. Name and address of manufacturer to be used
4. Manufacturing license number of manufacturer to be used
5. Names of drugs, individually
6. Names, qualifications, and experience of production and testing staff at manufacturer
7. True copy of letter from applicant to manufacturer, authorizing manufacture to make drug
8. True copy of letter from manufacturer to applicant, agreeing to lend use of premises, equipment, and expert staff, to test every batch produced, and to keep records of raw material, finished products, and analysis reports
9. Specimens of labels and cartons for products

B. Points to be assessed:

1. Documentation on proprietary medicines, if any.

*Manufacturing license for examination, testing, and analysis:*

A. To be submitted in application:

1. Name, address of applicant
2. Manufacturing site address
3. Drug name(s)

B. Points to be assessed:

1. That drug(s) are recognized by experts as safe for use.

*Note:* If the drug is not recognized as such, prior permission to conduct tests must be obtained in writing from the Licensing Authority.

2. That drug is only used for examination, testing, and analysis
3. That records are kept of drugs produced and to whom they are administered

*Qualifications for Staff*

This section details staffing requirements for manufacturing licenses. There is no staffing verification for holders of *loan* licenses, since they do not do any manufacturing themselves.

Where “adequate” experience is required, the adequacy of an employee’s experience is determined by the Licensing Authority.

<i>Graduate in...</i>	<i>Experience in drug manufacture (if not stated otherwise)</i>
1. Manufacturing license (drugs not listed below, including Schedule X):	
a. Production supervisor (must be full-time)	
Pharmacy.....	18 mos.
Pharmaceutical Chemistry.....	18 mos.
Science (Chemistry as ..... principal subject)	3 yrs.
Chemical Engineering.....	3 yrs.
Chemical Technology .....	3 yrs.
Medicine.....	3 yrs.
Veterinary Science.....	18 mos.
(for veterinary drugs only)	
b. Head of testing unit (full-time)	
Pharmacy.....	Adequate
Pharmaceutical Chemistry.....	Adequate
Science .....	Adequate
Medicine.....	Adequate
2. Manufacturing license (drugs in Schedule C or C(I))	
a. Production supervisor (full-time)	
Pharmacy.....	18 mos.
Pharmaceutical Chemistry.....	18 mos.
Science (Chemistry..... or Microbiology as principal subject)	3 yrs.
Chemical Engineering.....	3 yrs.
Medicine.....	3 yrs.

- Veterinary Science.....3 yrs.  
(for veterinary drugs only)
- b. Head of testing unit (full-time)
- |                               |          |
|-------------------------------|----------|
| Pharmacy.....                 | Adequate |
| Pharmaceutical Chemistry..... | Adequate |
| Science.....                  | Adequate |
| Medicine.....                 | Adequate |
3. Manufacturing license (blood products)
- a. Production supervisor (full-time)
- |  |       |
|--|-------|
| MD in Microbiology,.....                             | 1 yr. |
| Pathology, Bacteriology,<br>Immunology, Biochemistry |       |
| Post-grad. degree in.....                            | 1 yr. |
| Science (Microbiology)                               |       |
| Post-grad. degree in.....                            | 1 yr. |
| Pharmacy (Microbiology)                              |       |
- b. Head of testing unit (full-time)
- |   |         |
|---|---------|
| Post-grad. degree in.....   | 18 mos. |
| Science or Pharmacy<br>(Chemistry, Microbiology,<br>Biochemistry) |         |
| MD in Microbiology,.....  | 18 mos. |
| Pathology, Biochemistry   |         |
4. Repacking license
- a. Repacking supervisor
- |   |        |
|---|--------|
| Diploma in Pharmacy.....                        | None   |
| Passed Intermediate.....                        | None   |
| examination (Chemistry as<br>principal subject) |        |
| Passed Matriculation Exam.....                  | 4 yrs. |
| (for college entrance)                          |        |

### Recent Updates

The CDSCO plans to put together an official national list of pharmaceutical manufacturers that are licensed in India in a computer database. There are presently over 10,000 drug manufacturing companies in India. But reliable and specific information on these factories are unavailable.

In March 2011, the CDSCO provided further clarification on the guidelines for new drug manufacturing and sales. These pertained to:

- Trial batches of new drugs

- “Significant change” in drug attributes
- Details of manufacturing site address
- Submission of data for new drugs under Loan License
- Co-packaging products
- Submission of stability data

*Trial batches of new drugs:*

Stability testing of new drugs substances and formulations are required to be carried out on at least 3 primary batches at the time of the application submission. These batches should be manufactured to a minimum of pilot scale\*.

For drug substances, the batches are required to be manufactured to a minimum of pilot scale by the same synthetic route. In addition, the manufacturing method should simulate the process used for full production.

For formulations, two of the three batches should be at least pilot scale and the third one may be smaller.

***\*Note on Pilot scale:***

*For solid oral dosage forms, a pilot scale is generally at a minimum of one-tenth of a full production scale, or 100,000 tablets or capsules, whichever is larger.*

*The batch size may be kept less than 100,000 tablets or capsules for drugs indicated in life threatening or serious diseases.*

*For oral liquid, topical preparations and sterile preparations, pilot scale is a minimum of one-tenth of a full production scale. This must be manufactured by a procedure that is representative of the full production-scale batch.*

*Significant change in drug attributes:*

“Significant change” for an API is defined by the CDSCO as the “failure to meet its specification”. If a significant change in the drug occurs during the 6 months of testing under the accelerated storage condition, additional testing under intermediate storage condition is required.

The CDSCO laid out the following criteria for “significant change”:

- a. 5% or more change in assay from its initial content of APIs, or failure to meet the acceptance criteria for potency under biological/immunological procedures
- b. The extent of degradation of the product goes beyond the acceptance criteria
- c. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test

- d. Failure to meet the acceptance criterion for pH level
- e. Failure to meet the acceptance criteria for dissolution for 12 dosage units

Details of manufacturing site address:

The applicant is required to mention the address of the actual manufacturing facility on Form 44 (the official form for registering new drugs), where simulated batches are also manufactured.

In addition, if the simulated batches are used for clinical trials, including BA/BE study purposes, these batches need to be manufactured in GMP facilities.

Submission of data for new drugs under loan license

This is with respect to the data submission for new drugs by applicants who intend to manufacture the drugs under the Loan License.

The Loan Licensee is required to establish and submit comparability data of the minimum pilot scale batch with the marketed product of the original licensee. The product would have to be the same as the original manufacture's, in the same facility with the same equipment used when obtaining the Form 46.

Co-packaging products

If the manufacturer already has market authorization for each component of the co-packaged product, the required information of the pharmaceutical products will be limited to the stability of the products in the co-packaging.

Submission of stability data

As stated in Schedule Y, an applicant needs to submit 12-month long term stability studies and 6-month accelerated stability studies. However, if the applicant submits both accelerated and real-time stability data for only 6 months, an initial expiry period of only 1 year may be considered. This expiration period can be increased after submission of adequate stability data and permission from the Directorate of General Health Services. In addition, extension of shelf-life will be made based on the submission of real-time stability studies.

### **C. Good Manufacturing Practice**

Schedule M, or Indian GMP, was amended to its current form in 2001. It was scheduled to be implemented in 2003, but political pressure from small businesses delayed this. It was finally imposed as a requirement for manufacturing licenses in July 2005. It was recognized at the time that although it would improve the domestic drug industry as a whole, its high standards would also drive some smaller drug manufacturers out of business. Although implementation was originally slow, it has accelerated over time. As of November 2008, about 1,000 of India's small-scale pharmaceutical manufacturers had

been forced to shut down for lack of GMP compliance, and another 2,500 were in imminent danger of closure.

The Schedule's provisions are based on the World Health Organization's GMP guidelines as of 1992. They do not incorporate more current international standards or US FDA standards. About 80 drug manufacturers in India have been inspected and approved by the US FDA for compliance with US GMP standards as well.

The Schedule sets requirements in the following categories:

1. General Requirements
2. Warehousing Area
3. Production Area
4. Ancillary Areas
5. Quality Control Area
6. Personnel
7. Health, Clothing and Sanitation of Workers
8. Manufacturing Operations and Controls
9. Sanitation in Manufacturing Premises
10. Raw Materials
11. Equipment
12. Documentation and Records
13. Labels and other Printed Materials
14. Quality Assurance
15. Self Inspection and Quality Audit
16. Quality Control System
17. Specification
18. Master Formula Records
19. Packing Records
20. Batch Packaging Records
21. Batch Processing Records
22. SOPs and Records
23. Reference Samples
24. Reprocessing and Recoveries
25. Distribution Records
26. Validation and Process Validation
27. Product Recalls
28. Complaints and Adverse Reactions
29. Site Master File

There are additional, more stringent requirements for some categories of drugs. These require specific equipment and mandate certain testing procedures. The classes that are divided up in this way are the same as 1-7 on page 34.

In October 2009, the Certificate of Pharmaceutical Products (COPP) and GMP under WHO certification were taken over by the DCGI. The COPPs will be issued after inspection of manufacturing facilities by CDSCO regulatory officials. Facilities must comply with WHO-GMP guidelines.

The application forms include details such as a product summary sheet, site master file as per WHO-GMP requirements, a list of master documents such as quality manuals and master validation plan, manufacturing layout, personnel list, etc. The main purpose of the COPP is to establish the status of the pharmaceutical product and of the applicant in the exporting country.

## VII. DISTRIBUTION

### A. Overview

India has a three-tiered system of distributors. First are drug retailers, of which there are over 300,000. They range from traditional small neighborhood pharmacists to in-hospital pharmacies to modern chain stores. Second are wholesalers, or “stockists,” who sell to retailers. Third and last are “clearing and forwarding agents,” which are the local agents of a manufacturer or importer, about one per state. Each of these firms, including the carrying and forwarding agent, assesses a markup, usually adding up to about 30-40% of the original price. There is also a value-added tax of 4-12%.

India’s geographic and linguistic diversity, as well as its sheer size, makes it difficult for one distribution partner to have competence across the country. It is common for Western companies to sign several distributors for better coverage across India’s different regions.

Most purchases by public-sector hospitals are made on a tender system. This includes phases of supplier qualification, publishing of tenders, and seeking the lowest qualified bid. Large medical purchases are sometimes arranged at the national level to obtain more favorable terms, even when the states are supplying the funds.

Private hospitals are not required to publish tenders or accept the lowest bidder. However, in practice, they often use tender systems similar to the government’s.

In November 2010, the Ministry of Health and Family Welfare proposed to establish a professional Central Procurement Agency (CPA) for medicines. The main purpose of the CPA is to improve India’s existing drug distribution system. The agency will procure, store and distribute healthcare products for various national health programs under the Ministry, especially the Reproductive and Child Health Program. The CPA is proposed to be registered as a society under the Societies Registration Act, 1860.

Via the CPA, the Indian government hopes to accomplish the following:

- To establish a transparent and efficient procurement system so that pharmaceutical products are procured at competitive prices.
- To establish and manage an efficient national pharmaceutical supply chain.
- To establish a Management Information System to prevent stock-outs and to reduce wastage due to excess inventory.
- To improve India’s quality control system, so that quality products are distributed to the Indian citizens.

As of May 2012, the process of setting up the CPA was in “an advanced stage”, according to India’s Health Minister Ghulam Nabi Azad. A society has already been registered for the purpose of the CPA, and a search committee has been set up to look for the Chief Executive Officer for the CPA. Currently, drugs, medical devices, contraceptives and vaccines are purchased through different procurement agencies for the Health Ministry’s different disease prevention programs. However, upon its establishment, the CPA will be a centralized, autonomous society responsible for the procurement for all disease prevention programs.

## **B. Licensing**

A manufacturing license or import license includes permission to sell the licensed drugs in India. However, a company needs a wholesaling license to distribute any drugs it did not import to or make in India.

According to the law, a license is required for “exhibiting” or “offering to sell” drugs, not just for selling them. It is common for a manufacturer working through an importer to also set up a small representative office in India which cannot sell products but can help promote them. Without having a license for sale, activities like displaying a drug at trade shows could theoretically be construed as illegal.

Licenses to sell drugs, whether retail or wholesale, are always issued by state FDAs, rather than the DCGI. They fall into different types based on the drug category: general drugs, biological drugs (Schedule C or C(I)), abusable sedatives and stimulants (Schedule X), and homeopathic drugs.

The information to be submitted to receive a wholesale license is as follows:

1. Applicant name
2. Address of sale premises
3. Categories of drugs to be sold
4. Names of drugs to be sold (only if drugs are in Schedule X)
5. Details of special storage accommodations (if required)

A license is valid for 5 years, and renewal should be applied for 6 months before expiration. An expired license for which renewal has been applied will stay valid until the Licensing Authority accepts or rejects it. Each license applies to only one site, so a distribution operation with two warehouses needs two licenses.

The Licensing Authority must be allowed to check proof of ownership or lease of the premises, as well as any issues related to proper storage and handling. However, its

standards on storage and handling are applied case-by-case and are not based on international standards.

*Fee schedule*

- To sell drugs not otherwise listed..... Rs. 1500 (US\$34)
- To sell drugs in Schedule C or C(I)..... Rs. 1500 (US\$34)
- To sell drugs in Schedule X..... Rs. 500 (US\$11)
- To sell homeopathic medicines..... Rs. 250 (US\$6)
- Duplicate copy of license..... Rs. 150 (US\$3)

**C. Record-Keeping**

The DCA requires licensed distributors and retailers to keep sale records in some detail for inspections by the Licensing Authority. The records requirements are broken down as follows.

*To be made and kept by wholesaler seller for at least 3 years:*

1. Date of sale
2. Buyer information:
  - a. If government, medical institution, or doctor:
    - i. Name and address
  - b. All other buyers:
    - i. Name and address
    - ii. Drug retail or wholesale license number
3. Drug name, quantity, batch number
4. Drug manufacturer
5. Signature of competent person who supervised sale

*To be made and kept by wholesale buyer for at least 2 years:*

1. Date of purchase
2. Seller information:
  - a. Name and address
  - b. Drug wholesale license number
3. Drug name, quantity, batch number

#### 4. Drug manufacturer

### **D. Packaging and Labeling**

Generally, drugs packaged and labeled according to international standards will be compliant with Indian law. English is fine for the label's language; no native Indian languages are required. However, conflicts can arise, and some additions may need to be made. The DCA requires compliance with the following standards:

#### *Labeling*

1. Drug name (generic name must be printed before and more conspicuously than trade name)
2. Net content, expressed in metric system
3. Active ingredient content
4. Name of manufacturer, premises at which drug was manufactured
5. Distinctive batch number
6. Manufacturing license number under which drug was manufactured (if in India)
7. For drugs in Schedule C(I) or Schedule P, including preparations made from them:
  - a. Date of manufacture
  - b. For drugs in Schedule P, date of expiration of potency (should correspond to periods specified in Schedule P)
  - c. For imported drugs in Schedule C(I), import license number
8. For drugs to be distributed to physicians free of charge, the text: "Physician's Sample – Not to be sold"
9. Alcohol quantity by volume (if at least 3%)
10. For drugs specified in Schedule G, the text: "Caution: It is dangerous to take this preparation except under medical supervision."
11. If a prescription drug (specified in Schedules H, X, or the Narcotic Drugs and Psychotropic Substances Act), the text: "Schedule [] Drug - Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only."

12. A conspicuous red vertical line running completely through left of label for all the following categories of drugs:

- a. Narcotic analgesics, hypnotics, sedatives, tranquilizers
- b. Corticosteroids, hormones
- c. Hypoglycemics
- d. Antimicrobials
- e. Antiepileptics
- f. Antidepressants
- g. Anticoagulants
- h. Anti-cancer drugs
- i. All drugs in Schedules G, H, or X

*Note:* Not required for veterinary drugs, preparations for external or parenteral use, ophthalmic preparations, or ear drops.

13. The “Maximum Retail Price” (MRP) of the drug, including wholesale and retail markups, as well as all taxes.

Any license number issued by a foreign country may not be included in the label, because it could have a misleading effect.

For the drugs listed in Schedules C, G, H, P, and X, see Appendices.

### *Packaging*

The DCA mandates packaging and dosage sizes for certain types of drugs. Most of these are in Schedule P(I), which lists substances ranging across various categories, such as aspirin, vitamins, and an anti-psychotic drug. The full list is given in Appendix XVII.

Drugs listed in Schedule X are also restricted to 100-unit doses (tablets or capsules), 300 milliliters (oral liquid preparations), or 5 milliliters (injections).

These dosage requirements do not apply to drugs supplied directly by hospitals to patients, even if the drug is listed in one of the Schedules.

In most cases, imported proprietary drugs are required to cross the border in packaged retail form. Otherwise, they may be stopped at the border. They may be allowed in bulk form only if the importer has a manufacturing license, meaning they are qualified to reprocess or repackage them for sale. However, in this case the importer must do this reprocessing or repackaging within 12 months of receiving the import license.

The Indian government is expected to implement a new packaging regulation on Indian drug and pharmaceutical exports by the middle of 2011. 2-dimensional (2D) barcodes will be required on the packaging label of each drug and pharmaceutical product that is exported from India. The new packaging regulation came from the Directorate General of Foreign Trade (DGFT) following quality concerns raised against Indian pharmaceutical products by some countries in Africa.

Each barcode will contain a unique product identification code (GTIN), a batch number, the expiration date and the serial number of the product. Tertiary packaging (shipper or carton) for drugs and pharmaceuticals, on the other hand, have been required to use 1D barcodes to encode the same information starting from October 1, 2011. Secondary packaging of drugs and pharmaceuticals are also required to be encoded with the same information, using either 2D or 1D barcodes, starting from January 1, 2012. The same barcode requirement for primary packaging has been effective since July 1, 2012. The DGFT will also require Indian drug and pharmaceutical exporters to include in their shipments a copy of the Certificate of Analysis. This Certificate is issued either by the drug manufacturer, or by the approved laboratory of the importing country, or by a laboratory approved by the Indian Drugs Controller. The new packaging and certification requirements may make it easier for the authorities to track fake drugs (*for further information on intellectual property issues in India, see Section IX*).

## **E. Price Controls**

Indian law fixes prices for a wide range of drugs. The National Pharmaceutical Pricing Agency (NPPA) implements these price controls, based on the Drugs Price Control Order (DPCO) of 1995. Only 74 out of over 400 bulk substances are controlled, but these represent about 40% of the bulk drug market.

The NPPA is subordinate to the Ministry of Chemicals and Fertilizers, which sets industrial policy for the pharmaceutical industry.

Price control operates on two levels: first, fixing the prices of bulk drugs (active pharmaceutical ingredients); and, second, fixing the prices of formulations based on those bulk drug prices.

Manufacturers of bulk drugs must submit forms annually to the NPPA describing many financial details of their operations. This data is to help the NPPA analyze the results of its policies. This submission is still required even for non-controlled bulk drug makers, for informational purposes only. The NPPA uses the data to try to set prices that create the “right” (that is, restricted) returns on investment for manufacturers.

Formulation prices are fixed on the basis of their bulk drug price, if that is initially fixed. The formula to calculate retail price is based on costs of materials, manufacturing, packing, distribution, and excise duties. For imported drugs, on the other hand, the formula begins from the landed cost (cost to get the drug into India) plus distribution and importer’s profit.

Prices are set separately for each dosage level sold. This means that a manufacturer can apply for a new fixed price by creating a formulation with a novel dosage. Therefore, the marketing of many different dosage levels has become common, especially for popular drugs such as aspirin.

A large proportion of bulk drugs with controlled prices are antibiotics, but the list also includes drugs such as pain relievers, anti-hypertension drugs, and psychiatric drugs.

Currently, India is in the midst of establishing a mechanism to regulate the prices of cancer drugs. India had been mulling over the decision to control cancer drug prices since 2008. Soaring cancer drug prices in India have crippled the affordability of this treatment among cancer patients in the country. In a study conducted by the NPPA, the government found that prices ranged widely for similar cancer drugs sold in India.

Price controls for cancer drugs in India will not be easy. Currently, the Indian government can fix prices of commonly used drugs, but not prices of imported medicines, including cancer drugs and other patented drugs. However, there is a policy that allows the government to intervene in drug prices out of public interest. Nevertheless, this provision is only applicable to drug prices which have increases exceeding 10% a year. It is less effective for controlling drug prices which are initially set at high prices since the products' launch.

Generally, India's price control regime does have the potential to significantly impact some drug producers' revenues. The drugs that are controlled are generally older and off-patent even in the West, so companies that specialize in newly discovered drugs rather than ones in common use are less likely to be affected.

The Indian drug industry and the price control regulators have a confrontational relationship. The NPPA is a small agency with many enforcement problems. A common tactic for larger drug companies is to challenge any rectification orders in court. Since judicial procedures are lengthy in India, this tactic often delays enforcement by years.

Changes are on the horizon to address the price control system's problems. A working group in 2005 suggested wide-ranging changes. These included deregulating bulk drug prices, setting ceilings rather than requiring prices, and basing prices on the "essentialness" of drugs rather than production costs. The proposed changes could ease the burdens of the current system. On the other hand, the proposal also suggested negotiating the prices of patented drugs prior to their marketing approval, with price controls an option if negotiations fail. This was strongly opposed by the industry, but has support within the Ministry of Chemicals and Fertilizers. Nevertheless, in 2007, the Ministry of Chemicals and Fertilizers also pressed to put more drugs listed as essential under price control.

Socially, the Indian public generally has a negative perception of global pharmaceutical firms for pricing their lifesaving drugs too high in India. In response, many global firms have charitable programs which give their products away to low-income people. For example, Novartis runs the "Glivec International Patient Assistance Program," which claims to provide 7,000 Indians with the cancer drug Glivec.

Differential pricing has also become an emerging trend in India's drug market. In this setup, drug companies sell patented drugs in India at lower prices than in developed Western countries. Though this strategy was not widely adopted in the past by major pharmaceuticals, Merck & Co launched new vaccines with differential pricing in April 2008. GlaxoSmithKline also promise to negotiate down prices of patented drugs in 2009.

However, such programs do not seem to have significantly softened public opinion. Also, from a business point of view, Western-derived prices are often unrealistic considering Indian incomes. (For example, when it does not give it away, Novartis prices Glivec in India at over \$2,000 per month, which is about half the average Indian income.) Now, global firms are considering differential pricing for countries like India. In April 2008, Merck started selling the diabetes drug Januvia (sitagliptin) in India at a cost of about \$25 per month, roughly one-fifth its cost in the US. If this strategy is adopted more widely, it could simultaneously increase sales and reduce the likelihood of future price control action by the government.

## **F. Prescription Management**

The over-the-counter market has been steadily growing in India over the past several years as pharmaceutical companies and drug retailers promote products with modern advertising and branding. However, prescriptions are the traditional method of access to drugs in India, and some drugs which could easily be dispensed over-the-counter (OTC) are not.

Legally, all drugs can be sold OTC if they are not listed in Schedules H or X. Schedule H is a wide-ranging list of several hundred drugs or, in some cases, drug categories. Although most of the items listed are prescription medicines in the West as well, some are not. Members of Schedule H include ibuprofen, cimetidine (Tagamet), and all antibiotics and corticosteroids. (Topical preparations are excluded.) All drugs need to be sold by holders of drug retail licenses, even if a pharmacist's presence is not needed.

Schedule K is also relevant to prescription management. It includes some basic "home remedy" products, including aspirin, paracetamol, and antacids, which can be sold without a license in small villages (with a population under 1,000, and where there is no other licensed retailer). An official committee proposed in 2003 to lift those restrictions in place. This change would make the home remedies fully "over-the-counter," sellable even at grocery stores.

Similarly, multinational pharmaceutical companies in India proposed in 2005 to relax prescription regulations by adding a number of product categories to Schedule K, liberalizing their sale in the same way. Their proposed categories included antiseptics, vitamins, natural laxatives, topical anti-bacterials, topical anti-fungals, and topical pain relievers. However, their effort was not successful.

Indian pharmacist associations, wishing to preserve the OTC market for themselves, are one source of opposition to these proposals. However, the proposals' failure also reflects a more general consensus. Many Indians in the government and the medical community are concerned about the current level of self-medication. Already, many pharmacists dispense medicines freely without required prescriptions, and the government does not monitor this well. In addition, only about 60% of adult Indians are literate, so reading and following label instructions is not always a reasonable expectation. At the moment, it appears that much of the country is opposed to significant expansion in OTC drugs.

For Schedules H, K, and X, see the Appendices.

## VIII. CLINICAL TRIALS AND R&D

### A. Overview

Clinical studies are taking off as an industry in India. Over 150 contract research organizations have sprung up to serve Western pharmaceutical companies remotely, as well as local Indian companies. This is possible partly because of the large savings available in the local wage environment. Low income levels can make costs as low as a fifth of the cost of similar trials in developed countries.

In addition, the ease of subject recruitment in India would be a key advantage for some Western companies even if there were no cost savings. Recruiting problems can mean dangerously long delays in some drugs' development. India's huge population makes it relatively easy to recruit subjects, even for rare diseases or with very specific admission criteria.

Laboratory testing services needed in clinical trials, such as blood tests, do not have as much cost savings as recruitment and other overhead. This is because testing equipment is commonly imported at international prices. Also, Indian subjects are often treatment-naïve, meaning they have never used Western medicine, which can affect trial results.

It should be noted that although India has a large number of medical professionals, experienced clinical trial professionals trained up to Western standards are in short supply, since demand is rising so quickly. Relatively high salaries (by Indian standards) may be required to get seasoned professionals, and there is an increased risk of turnover.

An aid to the clinical trial industry has been the government implementation of GCP standards. These outlined the proper conduct of clinical trials service providers in recent years. The guidelines and requirement for conducting clinical trials are specified in Schedule Y of the Drugs & Cosmetics Rules, 1945, as amended in December 2001, and are drawn from the GCP guidelines of the International Conference on Harmonization, World Health Organization, US FDA, and EU. The standards are compliant with ICH standards. In most cases, studies compliant with Indian GCP are now acceptable to the US FDA.

It should be noted that GCP standards according to Schedule Y are required not only for clinical data to receive Indian product approval. In fact, the law sets these standards for all clinical trials in India, no matter where the data will be submitted.

Not all CROs in India are yet compliant with Schedule Y. In July 2008, the Indian government began disbursing low-interest loans of Rs. 10 million (about \$200,000) to small and medium-sized CROs to help them implement Schedule Y.

The national budget for 2008/09 included a new stimulus for clinical research, allowing 125% of payments for R&D services to be deducted from a company's taxes. This is an incentive for Indian companies, as well as India subsidiaries of foreign companies, to outsource their R&D activities.

Clinical research organizations (CROs) are required to register with the Licensing Authority in order to conduct clinical trials in India. Where permission by the DCGI has been granted for clinical trials in India, companies are required to register these clinical trials in the Indian Council of Medical Research (ICMR) clinical trial registry at [www.ctri.in](http://www.ctri.in) before the initiation of the trial.

In January 2011, the Ministry of Health and Family Welfare issued a notification to amend the Drugs and Cosmetic Rules, 1945, with the following minor proposals (draft rules) on clinical trial establishments. These form part of the *Drugs and Cosmetics (First Amendment) Rules, 2011*. These proposals were made after consultation with the Drugs Technical Advisory Board.

- The registration of the CRO will be valid for 5 years from the date of issue, unless it is suspended or cancelled earlier.
- CROs whose registration has been suspended or cancelled by the Licensing Authority may, within 90 days of receiving the suspension/cancellation order, appeal to the Central Government to reverse or modify the order.

There were also proposed additions to Schedule Y, which are labeled as "Schedule Y-1". These additions stressed on the quality of clinical trials, the need for proper procedures as well as the requirements for skilled CRO staff. Specifically, Schedule Y-1 contains the following:

- The CRO shall implement quality assurance and quality control measures. Each CRO should have well-documented Standard Operative Procedures. CROs are required to maintain complete and accurate data and documentation on the conduct of clinical trials and related investigations.
- All documentation and communication records are required to be dated, filed and preserved for 5 years after the completion of study, or submission of data to CDSCO. Strict confidentiality is to be maintained when accessing and retrieving clinical trial information.
- CROs shall implement education programs to assist its investigators in carrying out research studies according to the clinical trial guidelines and regulations. Training should include protocol adherence, GCP guidelines, informed consent process and investigators' responsibilities for GCP compliance.

## **B. Restrictions on Clinical Trials**

For political reasons, India continues to put some restrictions on clinical trials in addition to GCP standards. One conspicuous example is that in most cases, Phase I trials are not allowed for foreign drugs. This stems from a desire to prevent Indians from being used as “guinea pigs” for unsafe drugs by foreigners. Indian CROs and multinational companies have lobbied to remove this restriction, but action on this front may be delayed or cancelled due to a controversy in 2008 over infant deaths in foreign companies’ clinical trials.

Clinical trials are divided between trials for foreign-discovered and domestically-discovered products. If they are discovered domestically, they are required to have Phase I, II, and III trials within India. If they are discovered internationally, Phase II and III trials may be conducted in India after a Phase I trial outside India, with Phase III trials in India being mandatory.

Despite these restrictions, there are two methods for conducting Phase I trials of foreign drugs in India. The first is to submit existing Phase I data from foreign trials, where Indian trials are meant to supplement existing trials elsewhere. The second is if the drug is “of special relevance to health problems of India.” This could be a situation in which the disease or condition treated is prevalent in India, especially if it is an official priority.

## **C. Global Clinical Trials**

The Indian government has developed an interest in promoting global clinical trials, in which trials are performed simultaneously in different sites around the world. In an October 2006 meeting with industry representatives, they announced a new procedure for approving these trials, designed to encourage the industry by cutting approval times.

Previously, trials of foreign drugs had to remain one phase behind foreign trials. For example, Phase II trials could only be carried out in India if foreign Phase II trials were already complete. However, this requirement has been mostly abolished, allowing most trials to run concurrently with their counterparts abroad, except for Phase I trials.

In the system being developed, global clinical trial applications are divided into two classes: A and B. A global clinical trial will be Category A if its protocol has been approved by advanced countries such as the US, Canada, the UK, Germany, Switzerland, South Africa, Japan, Australia, etc. Otherwise, it will be Category B. Drugs in both of these categories will be entitled to expedited approvals.

## D. Licensing and Monitoring

Only the DCGI has authority over clinical trials, not the state FDAs. The national DCGI does all application receipt, review, and approval.

An application to perform a clinical trial in India is made with Form 44. There is a possibility of confusion, since this is the same form used to apply for permission to market a new drug. However, less information needs to be submitted in a clinical trial application than in a new drug application. Besides the standard identifying information (same as 1-8 for new drug registration, see page 18 above), the required attachments are:

1. Introduction (brief description of drug and its therapeutic class)
2. Chemical and pharmaceutical information
  - a. Active ingredient(s) (generic name, chemical name, or INN)
  - b. Physiochemical data
  - c. Analytical data
3. Animal pharmacology data
  - a. Specific pharmacological actions
  - b. General pharmacological actions
  - c. Pharmacokinetics
4. Animal toxicology data
  - a. Acute toxicity
  - b. Long-term toxicity
  - c. Reproduction studies (if drug is to be used in women of childbearing age)
  - d. Local toxicity (if drug is to be used topically)
  - e. Mutagenicity and carcinogenicity (if drug is related to carcinogen or drug action suggests carcinogenic/mutagenic potential)
5. Previous clinical trials (conducted inside or outside India)
  - a. Phase I (required)
  - b. Phase II (if conducted)
  - c. Phase III (if conducted)
  - d. Postmarketing studies (if conducted)
6. Clinical plans
  - a. Investigator's Brochure (IB)
  - b. Proposed protocol and study objective
    - a. Rationale for proposed dose in trial
    - c. Case record form
    - d. Informed consent documents
    - e. Investigator's undertaking
    - f. Ethics committee clearance (if available)
    - g. List of clinical study locations in India
    - h. Number of patients enrolled in India

- i. Authorization letter from trial sponsor
- j. If trial protocol is also approved anywhere outside India:
  - i. Number of patients enrolled in trial worldwide
  - ii. Number and listing of sites worldwide
  - iii. Regulatory approval status (Investigational New Drug / marketing approval) in other participating countries
  - iv. Current status of trial in other participating countries
  - v. All Serious Adverse Events (SAEs) reported in other participating countries
  - vi. Affidavit from sponsor that:
    - 1. Study has not been withdrawn in other countries
    - 2. If study is withdrawn in the future, DCGI will be notified promptly
  - vii. If IB contains information from foreign trials, affidavit that summary of this information is based on facts
- k. Details on biological samples to be exported, if any

7. Comprehensive information on regulatory status in other countries

*Reporting*

In clinical trials approved by the government, periodic reports need to be made to the Licensing Authority every six months. However, it should be noted that India regulations require reporting to the Licensing Authority within 14 days of all unexpected SAEs. This is in contrast to other countries, where all suspected unexpected adverse reactions (SUSARs) need to be promptly reported.

When a study is terminated prematurely, a summary report must be submitted within 3 months of termination.

*Fee schedule and timing*

The fee to apply for clinical trial permission is Rs. 50,000 (US\$1,125).

There is no official time frame for the processing of applications. However, where an application is submitted with all necessary data, a normal period is 12-14 weeks for approval. This is significantly shorter than the several months needed in some other countries.

*Monitoring and Compensation*

For the approval of global clinical trials, the government has said it will speed up the process by accepting trial protocols based on their foreign approval (see list of countries, page 59). Drugs in Category A (protocols approved by developed countries) are supposed to be expedited to 2-4 weeks. Category B will only be expedited to 8-12 weeks, because

of the need to review their protocols more carefully. However, these numbers are based on the stated intentions of the government, rather than experience.

The CDSCO will hire more new inspectors to monitor clinical trials with surprise visits to ensure safety and quality control. In addition, it is enforcing stricter regulations on clinical trials. In July 2012, the CDSCO drafted guidelines on how pharmaceutical companies should compensate volunteers who have died or have been injured in clinical trials. The draft suggests that the compensation would be calculated based on the age and income of the deceased/injured, the possibility of permanent disability for the injured, and the severity of the disease that the subject was experiencing during the trial. For example, the younger the subject is, the higher the compensation will be. According to the proposed draft, within 30 days of the death or injury, the pharmaceutical company would have the opportunity to prove that the death or injury was not caused by the drug used in the clinical trial. In case the pharmaceutical company failed to do so, it would have to pay compensation to the victim within 90 days of the death or injury.

However, according to the Ministry of Health and Family Welfare, between January 2008 and October 2010, 31 new drugs were approved without clinical trials on local patients in India. As pointed out by the Parliamentary Report of 2012, the actual figure could be higher, because at least two other drugs (ademetionine and pregabalin) were not included on the official list. The Parliamentary Report stresses that those 33 drugs are not scientifically proven to be effective or safe in Indian patients.

In addition, the Parliamentary Report also criticizes “a nexus” between drug manufacturers and experts who participate in reviewing clinical trial applications at CDSCO. An example of the nexus involved a fixed dose combination of drotaverine and aceclofenac, which is not allowed in North America or Europe. In December 2007, an official from the CDSCO unlawfully authorized the drug manufacturer, Themis Medicare (based in Mumbai, India), to handpick which experts to review the drug. The CDSCO official even allowed Themis to deliver the experts’ opinion directly to the DCGI’s office. This is only one of the examples where recommendation letters sent from different locations in the country were written in identical language. The Parliamentary Report notes that CDSCO does not have a directory of drug experts. Nor does the CDSCO have guidelines on how to identify experts and obtain their opinions.

### *Ethics Committees*

In July 2012, the DCGI made it mandatory for ethics committees to register with the CDSCO. Ethics committees are independent organizations which review applications for clinical trials sponsored by pharmaceutical companies and/or CROs. Approval from the ethics committees is essential, because without it, the DCGI will not authorize the clinical trial. In the past, only the clinical trials themselves were required to be registered with the DCGI. However, following widespread criticism that many ethics committees were not truly independent, the DCGI decided to begin monitoring the ethics committees, such that the no ethics committees shall review or approve a clinical trial application unless they are registered with the licensing authority.

The application to register an ethics committee with the licensing authority shall be filed in accordance with Schedule Y-1. If the registration is granted, the ethics committee will be required to review clinical trial applications according to Schedule Y, the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable requirements. The registration will be valid for five years, unless it is suspended or canceled early. If the registration is not granted, the ethics committee will be notified and it will have 90 days upon the receipt of the notification to file an appeal to the central government.

### *Clinical Trials Registry – India*

Any clinical trials initiated after June 2009 require registration through the Clinical Trials Registry – India (CTRI). CTRI was set up by the Indian Council of Medical Research's National Institute of Medical Statistics (NIMS).

All interventional clinical trials conducted in India and involving Indian patients need to be registered. An interventional clinical trial is any research study that prospectively assigns people to one or more health-related interventions (e.g., preventative care, drugs, surgical procedures, behavioral treatments, etc.) to evaluate their effects on health-related outcomes. Early and late trials, trials of marketed or non-marketed products, and randomized or non-randomized trials should all be registered.

CTRI is an online register of clinical trials being conducted in India. Applicants would declare not only the twenty items of the Trial Registration Data Set as required by the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP) but also a few additional items. These include ethics committee approval status, regulatory clearance by the DCGI, etc. before the enrollment of the first patient. Then, the Registry will collect information on all prospective clinical trials to be undertaken in India and make this information available to the public.

To register a study, applicants will submit information including the basic data required by the ICTRP and will receive a WHO assigned unique identification number. In addition, CTRI will encourage the investigators to include subsequent protocol amendments and give regular updates on the status of the trial. The person responsible for registering the trial is either the principal investigator or the primary sponsor, to be decided by an agreement between the parties.

Information needed for the registration include sponsor and PI information, target sample size, outcomes, phase of trial, method of allocation concealment, blinding and masking, etc. The application is all online at [ctri.in](http://ctri.in)

Large quantities of drugs for clinical use will need to be registered and approved through the CDSCO.

## **E. Good Laboratory Practice**

From November 1, 2010, India's GLP standards were made mandatory through the revised Schedule L-1 under the Drugs and Cosmetics Rules, Third Amendment, 2008. The GLP standards include detailed requirements on personnel skills, equipment, chemicals and reagents, good housekeeping and safety procedures, as well as, quality system audits, amongst others.

Appeals have been made by the smaller laboratories to comply with the newly mandated GLP standards, which also require the setting up of capital-intensive machines such as FTIR (Fourier Transform Infrared Spectroscopy) machines in every pharmaceutical laboratory unit. This requirement was to ensure that all Indian pharmaceutical companies have calibrated and validated equipment in their laboratories.

In early April 2011, India's Department of Pharmaceuticals invited expression of interests from consulting companies to advise the government on setting up GLP compliant chemical testing laboratories and GLP compliant biological testing laboratories. The consultants will be responsible for assessing existing facilities in India vis-à-vis the requirements of the current pharmaceutical industry. Subsequently this assessment will be used by the Indian government to outline schemes for establishing new laboratories or upgrading existing facilities to be GLP compliant.

Before the GLP standards were mandated in November 2010, Schedule Y was relied upon to lay out a number of standards for the conduct of pre-clinical research for pharmaceutical R&D laboratories. In order for a new drug to be registered, its pre-clinical development inside or outside India needed to have followed those standards. Most of them have to do with animal toxicology and animal pharmacology. They set very specific requirements on how many animals should be tested, in what manner, for what periods of time, etc. They also described the circumstances which call for specific tests, such as carcinogenicity tests. (For the full text, see Appendix X.)

GLP is supervised by the National GLP Compliance Monitoring Authority (NGCMA). This body has a full accreditation system based on OECD principles for GLP. However, few Indian research sites have obtained this accreditation. In addition, though the body is an observer to the OECD's GLP working group, its accreditations are not yet recognized by OECD members. Some Indian laboratories have obtained GLP accreditation from foreign bodies instead of the NGCMA.

## **F. Accreditation of Testing Laboratories**

The National Accreditation Board for Testing and Calibration Laboratories (NABL) accredits testing laboratories on a voluntary basis. The NABL is an autonomous organization, founded in 1998, under the authority of the Department of Science and Technology. Although its scope is laboratories in general (divided into testing, calibration,

or medical laboratories), some pharmaceutical CROs have applied it, as well as laboratories that specialize in services for CROs.

NABL accreditation is designed to be internationally compliant. Its standards are according to ISO 15189:2003 for clinical or medical laboratories. Its process to test these involves pre-qualification through proficiency testing, internal auditing, submission of a Quality Manual, and multiple on-site assessments.

The NABL is a member of International Laboratory Accreditation Cooperation (ILAC), and is a full signatory to ILAC's Mutual Recognition Arrangement. This means that NABL accreditation can be recognized fairly easily by equivalent bodies in the US or Europe.

However, NABL accreditation has not been taken up as an industry standard. Nevertheless, in a recent notice posted by the Ministry of Health and Family Welfare, NABL accreditation will soon be required for all diagnostic laboratories in India. This will be compulsory for diagnostic laboratories to be eligible for insurance reimbursements under the Central Government Health Scheme. Laboratories cite high costs, time-consuming documentation, and equipment traceability requirements as making NABL accreditation troublesome. According to NABL, as of March 31, 2011, there were 360 accredited calibration laboratories and 779 accredited testing laboratories in India. These laboratories formed just a fraction out of thousand others which have yet to receive such accreditation. Although NABL accreditation is an impressive credential, lacking it does not mean a site has not met international standards.

## **IX. INTELLECTUAL PROPERTY PROTECTION**

### **A. History**

Indian drug laws were a thorn in the side of the international pharmaceutical industry. They favored generic producers at the expense of the interests of more innovative drug producers. However, this situation has now turned around with key changes to patent law.

In 1950, virtually no Western drugs were produced by Indian companies. Instead, foreign corporations dominated the small market. In 1970, aiming to develop the local industry, the government amended its Patents Law. After the amendment, pharmaceutical products could no longer be patented, only pharmaceutical processes. With this protection, many Indian companies reverse-engineered Western-developed drugs and sold them at low prices, thwarting the hopes of rights-holders.

India joined the World Trade Organization in 1995. This obligated the country to implement IP laws in accordance with the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). As a developing country, it was given a ten-year extension to comply with TRIPS requirements for pharmaceuticals.

In 1999, the Patents Law was amended to allow a temporary kind of patenting. In this system, a company could submit its *intention* to apply for a drug patent, and receive exclusive marketing rights (not patents) until 2005, when drug patents were to become possible. Although this was similar in practice to the new system, companies still waited for the full change to feel secure.

Political pressure from the domestic drug industry, much of which relied on copying, was strong. Widespread popular concerns also remain about balancing intellectual property rights with the need to protect public health. But in early 2005, product patents, rather than process patents, were finally enabled by Parliament.

The amendment to the Patents Law has been sufficient for most purposes of global pharmaceutical companies. It is thanks to the new law that various companies have gained the confidence to re-enter or expand operations in India.

### **B. Patent Applications**

Patents are supervised by the Controller General of Patents, Designs, and Trademarks, a central government authority. The Patent Office has its main offices in Kolkata, and receiving branches in New Delhi, Mumbai, Chennai, and Geneva, Switzerland.

A patent's term is 20 years from the date of application. The review process generally takes between a few months and one year. It includes searches by foreign patent authorities and a three-month period to file for notices of opposition.

Substances patented provisionally before 2005 can still be manufactured generically, if manufacture began before 2005 and “reasonable royalties” are paid. Substances discovered before 1995 cannot be patented, and remain open to all generic use.

### **C. Remaining Restrictions**

Although the Patents Law allows new drugs to be patented, it is not yet equivalent to Western laws. In particular, it appears difficult to patent new uses or changes to existing products, according to the following clause, which bars:

“...the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.” (Patents Law, Section 3(d))

In other words, this clause prohibits the patenting of new “forms” of drugs that do not increase their efficacy, as well as new uses of existing drugs. “New forms” are defined broadly as “salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives.”

This difference has been a headache for some global pharmaceutical companies. In particular, Novartis markets the drug Glivec (Gleevec in the US) to treat a form of leukemia. It received exclusive marketing rights provisionally in 2003. However, when it actually submitted its patent application in 2005, it was rejected on the grounds of being a derivative of a known substance. It appealed this decision to the judicial system, arguing that Section 3(d) violates TRIPS, but lost its last appeal in August 2007.

Now that the status quo seems to be for letting Section 3(d) stand, other legal challenges are underway. In January 2008, Roche sued the Indian pharmaceutical company Cipla for marketing generic erlotinib, marketed as Tarceva by Roche, which holds Indian patent rights on it. Cipla then challenged Roche’s patent in court on the basis of erlotinib being “derivative” of an earlier product, gefitinib. This case may help clarify how the term “derivative” in Section 3(d) is interpreted in the future. Although this case has not yet been resolved, in September 2008, Cipla also began marketing a generic version of Roche’s anti-infective Valcyte (valganciclovir hydrochloride). Legal proceedings are underway on this issue as well.

Under the new patent law, the government has also retained the right to issue compulsory licenses to allow generic manufacturing of patented drugs, as allowed in article 31 of TRIPS. This could be used in cases of a demand for drugs to treat HIV/AIDS or other public health crises, as well as to supply less developed countries lacking sufficient manufacturing capabilities. The first ever compulsory license was granted in early 2012 to Hyderabad-based Natco Pharma for Bayer’s patented drug Nexavar (*as mentioned in Part B under Section III*).

#### **D. Prosecution of IP Violations**

Since India's accession to the WTO, its government has stepped up efforts to stamp out counterfeit and IP-violating drugs. In October 2008, India's Parliament significantly increased penalties for "fake and spurious drugs." Previously, the basic fine for selling such drugs was only Rs. 10,000 (about US\$225); now, it has been raised to Rs. 1 million (about US\$22,500). In addition, the minimum jail sentence has been increased from 5 years to 10 years, going all the way up to life imprisonment depending on how dangerous the product is. However, the enforcement capabilities of the Indian government remain in question, since the DCGI has few personnel compared to other countries' regulatory authorities.

## **X. DRUG ADVERTISING**

India has relatively strict regulations on the advertising of drugs. Such advertisements are governed by the Drugs and Magic Remedies (Objectionable Advertisements) Act of 1954. This law was a dead letter for many years, virtually forgotten. However, it has come into attention recently with new acts of enforcement.

The creation of this act was strongly influenced by the prevalence of spurious drug claims. Its restrictions generally work by listing prohibited claims. The types of diseases it lists are generally chronic diseases, which can be palliated but not cured. With the advancement of modern medicine, though, some of the diseases in the list may be less chronic than previously thought. The law is still not enforced strongly. For example, the inclusion of “sexual impotence” did not keep Viagra and its successors off the Indian market. On the other hand, in 2007, the Tamil Nadu Drugs Control Administration raided Cipla, a large Indian drugmaker, for advertising an emergency contraceptive drug. Cipla had about Rs. 200,000 (US\$4,000) worth of products seized.

Besides the list of prohibited claims, the law also bans making false claims for a drug, giving false impressions about the drug directly or indirectly, or being false or misleading in any material particular.

The law does not apply to scientific works, advertisements to medical practitioners, doctors advertising treatment, or advertisements by the government. There is no system for examination and review of advertisements before they are published. Although it is a national law, it is enforced by the states. It also does not cover advertising in TV or other new media, although some places, such as New Delhi, have extended its coverage to TV on their own initiative.

There was a legislative proposal in 2007 to update the law to cover more media and increase penalties, but this proposal has not moved forward.

Some of the conditions for which cures cannot be claimed are listed below. These are a selection of those on the list with higher possibilities of confusion with current standards.

1. AIDS
2. Arteriosclerosis
3. Cancer
4. Diabetes
5. Diseases or disorders of the brain
6. Diseases or disorders of the uterus

7. Heart diseases
8. High or low blood pressure
9. Menstrual disorders in women
10. Obesity
11. Premature aging
12. Sexually transmitted diseases

The law also prohibits advertising drugs for contraception, to cause miscarriage, or to treat impotence (the last broadly defined as “the maintenance or improvement of the capacity of the human being for sexual pleasure”).

## **XI. CONCLUSION**

Opportunities in the Indian pharmaceutical market come with many challenges. The unique cultural and business landscape and the unpredictable regulatory system mean that market entry needs patience and care. An existing corporate strategy cannot be simply transplanted to India. As in most Asian countries, developing personal connections with reliable people is key in starting business. Nevertheless, in the big picture, the market has become much more open to foreign competition, in both regulatory and practical terms.

Today, epidemics and infections are still predominant diseases in India. But as Indians become healthier, modern treatments to cover more conditions are becoming more necessary to them. Since many of these drugs are researched and produced by Western companies, and they are now more easily protected, Indians are increasingly bound to turn to them.

In addition, India's entrepreneurs are developing more and more services to offer the pharmaceutical industry. Capacities in R&D, clinical trials, manufacturing, and distribution are expanding daily. Many Indian pharmaceutical businessmen are also quickly realizing the value of adhering to international quality standards. It is important to look at all of India's possibilities in combination. For example, if a drug is too expensive to sell well in India, contract manufacturing might help moderate the price.

India is not a place to make quick money. Before entering the market, it is vital to research and prepare for the regulatory and business hurdles that will appear. But the Indian pharmaceutical industry is a growing market that is here to stay.

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