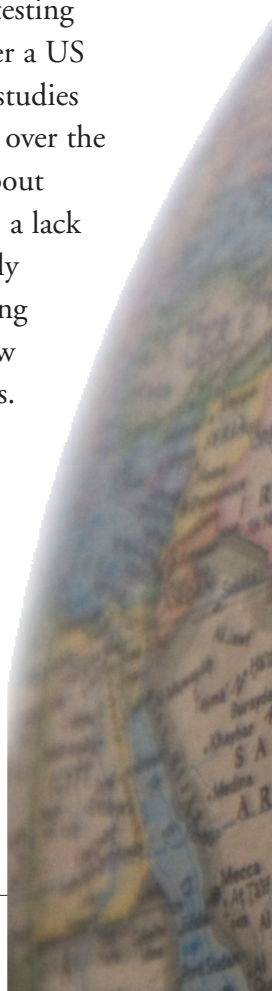
Regulatory Harmoniz
Keeping in Step With t

By Mukesh Kumar, PhD and Munish Mehra, PhD

The Indian pharmaceutical industry has established itself as a key player in the manufacturing arena, with almost half of the active pharmaceutical ingredients (APIs) worldwide being produced there. The double-digit growth rate of the pharmaceutical industry and the economic prosperity brought about by the enormous growth in the high-tech industry in the last 15 years, have transformed India's attractiveness as not only a location for cost-effective pharmaceutical product development but also a key market for finished products. Tremendous new opportunities have been created across all segments of the industry in India from generics to new product research and development (R&D) and contract research and manufacturing services.

Unlike the manufacturing and generics sectors, the R&D and clinical testing sectors are relatively new to India. Only about 1% of all clinical trials under a US IND are conducted in India, while the numbers for R&D and preclinical studies may be even lower. Despite extensive efforts by the Indian service industry over the last few years, the major reasons for this low growth have been concerns about intellectual property protection, outdated and unclear regulatory processes, a lack of innovative product development training, a business environment sharply tilted toward providing quality service to Western sponsors versus developing original products, and the increasing cost of doing business. For the last few years, Indian drug regulators have been working hard to resolve these issues. The regulatory processes are being updated to harmonize them with those in the US and Europe; clear guidelines have been released; and there are plans to create a new infrastructure comparable to the US Food and Drug Administration (FDA). This article lists the current status of, and future trends in, the Indian regulatory processes.



Clinical Trials with Drugs and Biologics

All clinical trials in India are carried out under Schedule Y of the *Drug and Cosmetics Act* of 1940 (Act) and the *Drug and Cosmetics Rule* of 1945 (Rule).[1] Both pieces of legislation have been amended several times over

zation Efforts in India:
the Globe

Medical devices are not defined in the Indian regulations and, when regulated, are treated as drugs.

the years; the most recent amendments to both were 30 June 2005.

A sponsor needs to file an Investigational New Drug (IND) application with the Central Drugs Standard Control Organization (CDSCO), the Indian equivalent of FDA. Foreign sponsors cannot file an IND directly, but must have an Indian agent, who could be a company Indian staff member or a contract research organization (CRO). An IND's contents, described in Schedule Y, are similar to those of a submission to FDA or the European Medicines Agency (EMEA). The sponsor needs to pay an IND review fee of about $1,000 (US) when filing an application. A clinical trial cannot be initiated until written permission from the chief of CDSCO, the Drug Controller General (DCGI), has been issued to the sponsor. An approval from an independent ethics committee is also required before trial initiation. In 2005, CDSCO also released the *Indian Good Clinical Practices* (*I-GCP*)[2] guidelines. These guidelines are similar to the ICH E6 guidance, with some minor additions based upon FDA regulations and the *Ethical Guidelines for Biomedical Research on Human Subjects* issued by the Indian Council of Medical Research (ICMR). The *I-GCP* guidelines describe in great detail the processes for conducting an acceptable clinical trial.

IND applications filed with CDSCO are reviewed by an expert committee convened by the DCGI from various Indian government agencies under the Ministry of Health and Family Welfare. This process takes a minimum of three to six months, much longer than the time required for similar FDA and EMEA reviews. To harmonize the Indian review process with that of FDA, the DCGI released a new policy about clinical trial approval in November 2006.[3] Under this policy, all clinical trials are divided into two broad categories, A and B, based upon information provided by the sponsor at the time of IND filing. Category A includes clinical trials whose protocols are approved by regulatory bodies in the US, UK, Switzerland, Australia, Canada, Germany, South Africa, Japan, or by EMEA. Category A applications are abbreviated submissions containing key information per a new format called "Requirement for Filing Applications for Global Clinical Trials."[3] Category A applications are approved within two-to-four weeks of filing. Clinical trials using drugs approved for marketing in India are also considered Category A studies and subject to expedited approval. All other trials are considered Category B studies and are reviewed as noted previously. Additionally, most phase 1 trials are reviewed as Category B applications. Once assigned, Category B cannot be changed to Category A.

Category A applications have become popular since the inception of the program, with the bulk of new IND applications submitted to CDSCO falling into this category and eligible for expedited approval. Recently, there have been discussions on extending the Category A process to global phase 1 trials; however, since phase 1 trials traditionally are smaller in terms of the number of both subjects and sites, true global phase 1 studies are rare. The only first-in-man studies currently premitted are for molecules discovered in India.

The Clinical Trials Registry

The National Institute of Medical Statistics, part of ICMR, established the clinical trial database called Clinical Trial Registry-India (CTR-I) in 2007.[4] The information required for CTR-I is based upon the World Health Organization's (WHO) International Clinical Trial Registry Platform dataset. Data from CTR-I is also available through the WHO clinical trial search portal. Registration is voluntary and free, and is recommended for all clinical trials conducted in India before enrolling any trial participants. Registration of trials conducted in other countries in the region is also permitted. Since its inception in late 2007, approximately 150 trials have been registered with CTR-I, most by academic centers and government laboratories. Due to its limited existence, it is too early to predict the clinical trial registry's impact on subject participation and dissemination of information.

Adverse Event Reporting in India

Under Schedule Y, all unexpected serious adverse events (SAEs) during a clinical trial, as described in the Indian GCP guidelines, must be reported to the DCGI's office within 14 calendar days. A sponsor is also required to submit an annual clinical trial status report containing all adverse events. In addition, investigators have to inform sponsors of all adverse events within 24 hours and relevant Ethics Committees within seven days. For Category A applications, the sponsor is required to furnish proof that it has informed all other regulatory bodies in countries where the trial is ongoing, including any comments from those agencies.

All manufacturers are required to conduct postmarketing pharmaco-surveillance. Every sponsor is required to submit Periodic Safety Update Reports (PSURs) that include all new safety information, marketing authorization status in other countries and suggestions for any labeling changes necessary for the product's optimal use by end users. PSURs must be submitted every six months for the first two years after approval, and annually for the subsequent two years. After that, no further PSURs are necessary unless deemed so in the interest of public health by CDSCO. In addition, all unexpected SAEs for approved products must be reported within 15 days of the manufacturer's initial receipt of information.

In July 2004, the Indian Ministry of Health and Human Welfare (MHHW) released the National Pharmacovigilance Program under CDSCO. Through this program, a National Pharmacovigilance Advisory Committee (NPAC) was created to oversee a network of National Pharmacovigilance Centers (NPCs). The main function of the NPAC and NPCs is to create an adverse drug reaction (ADR) data-capturing system. The database resides at CDSCO's headquarters. Since 2005, all safety reports submitted to CDSCO during the conduct of clinical trials and PSURs submitted during the initial four postapproval years have been added to the database to identify any safety-related trends. In addition, medical practitioners and members of the public can submit safety information directly to CDSCO using the ADR Reporting Form.[5] The ADR Reporting Form collects information similar to FDA's MedWatch Form. CDSCO plans to stay connected with regulatory agencies in other countries and exchange this safety database information with them. Safety information gleaned from analysis of these data can result in product label amendments, product withdrawals or suspensions. End users are informed via safety bulletins, drug alerts and media releases.

Drug Manufacturing

As noted earlier, India is the world's second-largest producer of APIs, not only in quantity but also in the variety of molecules. Indian API manufacturers have traditionally complied with US GMP regulations since the majority of the material produced is for export. However, in recent years, India has emerged as a large market for pharmaceutical products. The Indian middle class is estimated to be about 30% of the total population, making it, at more than 300 million strong, equivalent to the total US population. The middle class has been experiencing increasing incidences of indications traditionally considered diseases of the West (e.g., hypertension, cardiovascular indications, allergies, central nervous system indications, etc.) and has the economic means to afford expensive Western therapies. There is a trend for increasing local consumption of pharmaceutical products traditionally produced primarily for Western markets. In 2003, CDSCO released updated GMP guidelines harmonizing Indian GMP requirements with those of the FDA.[6]

Medical Devices

Medical devices are not defined in the Indian regulations and, when regulated, are treated as drugs. Until 2005, only disposable hypodermic syringes and needles, disposable perfusion sets, Copper T IUDs, tubule rings and condoms were regulated under the *Drug and Cosmetics Act*. Manufacture, sale or distribution of these devices only required a license from CDSCO. Manufacturers of certain low-technology devices could, on a voluntary basis, seek certification from the Bureau of Indian Standards (BIS) as proof of quality. The BSI seal is considered highly credible proof of quality in India. Imported high-technology devices, approved or cleared by the country of origin or by FDA, are permitted to be marketed in India, requiring only an import permit.

Before 2005, the cost of imported high-technology medical devices and lax intellectual property rules led to counterfeit products being sold without CDSCO's knowledge, due to the lack of regulatory authority. This raised serious safety concerns. Following a newspaper report in 2005, the use of unapproved, locally made cardiac stents was banned in one Indian state. The manufacturer challenged this ruling in the high courts, which subsequently ruled in favor of the regulators and mandated that DCGI should regulate 10 more types of devices. These are cardiac stents, drug eluting stents, catheters, intraocular lenses, IV cannulae, bone cements, heart valves, scalp vein sets, orthopedic implants and internal prosthetic replacements. A license is now required to manufacture, sell and distribute these devices. The establishment of a separate Indian Medical Device Regulatory Authority (IMDRA) under the CDSCO was also proposed.

Regulated devices need to be registered

with CDSCO, which requires information on design, testing, safety, use information, labeling and regulatory status in other countries. If the device is to be manufactured in India, a separate manufacturing license is required based upon the facility, documentation, quality control system and staff information. Several separate licenses might be required for each individual manufacturing step, e.g., import of raw material, pollution control, building permission, registration with the state where the facility is located, etc. The filing fees for a manufacturing license application are $1,500 per facility and $1,000 per product or family of similar products. All license applications are reviewed by an Expert Committee established by CDSCO, followed by GMP inspection. The medical device labels are required to meet Global Harmonization Task Force (GHTF) or ISO specifications.

India controls the prices of medical devices under the National Pharmaceutical Pricing Authority (NPPA). A differential pricing system is applied to critical devices to make them affordable to low-income patients. Manufacturers also need to negotiate and justify the prices of their devices when selling to state-run medical facilities such as hospitals, retail outlets and health projects. Since a majority of Indians use state-run medical facilities, this could be a huge portion of total sales.

Preclinical and Research & Development Activities

India offers a large pool of highly trained professionals in all of the biological sciences. To date, the pharmaceutical industry has not tapped into this potential to a great extent. While the manufacturing and clinical service industries have flourished, preclinical research and new drug discovery have lagged behind. It is well accepted that for the industry to grow in the long term, a robust drug discovery and preclinical infrastructure will be required. Industry's potential cost savings from using Indian providers in these sectors are much higher than for clinical trials. In the last few years, an increasing number of large global pharmaceutical companies have been moving front-end discovery and preclinical work to India. Similarly, Indian companies are investing more in new drug discovery and development. However, there is still much growth potential in these sectors.

Regulatory Infrastructural Changes

The Indian regulator agency, CDSCO, is heavily involved in all aspects of the pharmaceutical industry. It also works very closely with several other government agencies to execute its mandate.[7] For every review, committees are formed from across the several government organizations—Department of Biotechnology, Department of Science and Technology, ICMR, etc.—a process that takes time. With an exponential increase in the number of clinical trials in India over time, the need for a separate body to regulate clinicals was suggested.[8] As recommended by the Mashelkar Committee Report of 2003, the MHHW announced in mid-2007 that a new regulatory office will be created in the near future to regulate clinical research activities. This new body, called the Central Drug Authority (CDA), will be an independent entity within CDSCO. CDA will have a structure very similar to that of FDA, with offices to regulate different product types. IMDRA will be one of the offices within CDA. The new agency will have authority to conduct surprise audits of all parties involved in clinical trials and prosecute those who violate Indian regulations. Strict fines and other, stronger punitive measures for violations were recommended in the same bill. Technical expertise has been sought from FDA in helping India create CDA, which is expected to be fully operational by 2014.

Future Plans and Projections

India has made strides in harmonizing its regulatory processes with those of FDA and ICH. In all aspects of the biomedical industry, India has shown the desire and ability to undergo regulatory reforms to accommodate global industry while also fostering the growth of indigenous companies and trying to avoid ethical issues. The service industry, from drug discovery to clinical development, data management and statistical analysis, has seen exponential growth with practically all major, global pharmaceutical manufacturers invested in India. Several professional groups have established a presence in India and there has been an exponential increase in vendors offering training in the different aspects of the industry. FDA is considering opening an office in India similar to the one it is establishing in China, primarily to increase its safety inspections in the country. FDA is also in discussions with MHHW to provide

technical support in organizing CDA. However, concerns remain, due to the very high attrition rate (15%–30% by some estimates) for clinical trial professionals, a high inflation rate and saturation of the few clinical sites trained in GCP (there are approximately 300-500 GCP-trained clinical sites in India). These factors all lead to not only an increasing cost of doing business in India but also greater uncertainty about long-term projects. But, since India has a rich pool of highly educated, eager-to-learn, English-speaking younger professionals, these issues are expected to be resolved over time.

In the 2007-08 budget, the Indian Finance Ministry exempted all services carried out in the contract research and clinical trial industries from the service tax, a savings of 12.24%. This financial benefit, which would be transferred to the international sponsors, was expected to induce an added influx of international business to these sectors. The exact impact of this tax exemption has not been evaluated. With the US dollar losing approximately 15%-20% its value compared to the Indian rupee over the last year and the recession in the global economy, the impact might be smaller than expected. However, this exemption demonstrates the Indian government's strong commitment to the growth of this industry.

Conclusion

India's clinical research service industry has grown several hundred percent over the last five years. In the 1990s, only Eli Lilly, Pfizer and Quintiles were active in India; today almost 100 CROs are believed to be involved in the country. Since 2005, Indian intellectual property laws have been harmonized with those of other countries. That harmonization, coupled with developments in the regulatory environment, should make India a promising destination for drug development.

REFERENCES

1. *Drug and Cosmetics Act*, 1940. www.cdsco.nic.in/html/Drugs&CosmeticAct.pdf (page 503- 553)
2. Indian Good Clinical Practices, www.cdsco.nic.in/html/GCP1.html
3. CDSCO notification about global clinical trials, www.cdsco.nic.in/Global%20Trials.htm
4. Clinical Trial Registry, India, www.ctri.in
5. Adverse Drug Reaction Form, CDSCO, India, www.cdsco.nic.in/html/ADR_form_PDF_file.pdf
6. Indian Good Manufacturing Practices, www.cdsco.nic.in/html/GMP/ScheduleM(GMP).pdf
7. Kumar M. "Agencies Involved in Approving Clinical Trials in India." *Regulatory Affairs Focus.* 12(8):34-39, 2007.
8. Mashelkar Committee Report, www.cdsco.nic.in/html/Final%20Report%20mashelkar.pdf

AUTHOR

Mukesh Kumar, PhD, is a Senior Director, Regulatory Affairs, at Amarex Clinical Research, LLC, located in Germantown, MD, which is a full-service CRO offering strategic planning, trial management, data management and statistical analysis for global clinical trials, located in Germantown, MD. Kumar is a member of the RAPS Board of Editors for *Regulatory Focus* and can be reached at mukeshk@amarexcro.com.

Munish Mehra, PhD, is Managing Director at Global Drug Development, a Washington, DC-based company specializing in accelerating patient enrollment by adding experienced GCP-compliant sites with large patient populations in India, Central America, Eastern Europe and other select regions. Mehra has been involved in the design, conduct, analysis and reporting of global clinical trials for more than 22 years. He can be reached at mmehra@gddexperts.com.