

# Regulatory Considerations for Conducting Clinical Trials In India

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In the last few years, there has been increasing interest in the pharmaceutical industry in outsourcing drug discovery and clinical development programs to Asia, particularly India. Since clinical development accounts for about two-thirds of the total cost of developing a new drug, off-shoring clinical trials offers unique opportunities, especially in terms of access to study subjects, trained personnel, lower-cost infrastructure and labor pools. It has been widely recognized that India offers unique opportunities for conducting clinical trials due to a significant cost reduction and increased speed and productivity of all R&D phases required to bring a safe and effective drug to market. India has a large patient pool, well-trained and enthusiastic investigators, premier medical institutions, low per-patient trial cost and a highly favorable regulatory climate. It is estimated that as much as 20% of all global clinical trials might be conducted in India by 2010.<sup>1</sup> However, emerging opportunities in India for clinical development are not without challenges especially in terms of quality control measures, availability of trained professional resources, regulatory timeline predictability and data protection.

Despite being at the forefront of generic drug production for several years, being the world's



fourth largest producer of bulk drugs and home to the largest number of US Food and Drug Administration (FDA) approved manufacturing plants outside the US, India's clinical development industry is still in its infancy. Although some clinical trials have been conducted in India by and for global pharmaceutical industry and Indian academia for almost 15 years, the total number of clinical trials is significantly low compared to those conducted in the US and European Union. Regulations governing the conduct of clinical



trial have not been well defined and primarily focused on generic drugs. Universal regulatory guidelines like those published by FDA have not been adopted, leading to diverse interpretation of Indian regulations.

In the last two years, India's business and regulatory climate has undergone dramatic change. In December 2004, Indian patent law was modified to harmonize it with international laws governing intellectual property protection. Regulatory processes are also being updated to harmonize

with US and international standards, and plans are afoot to create a regulatory body in line with FDA, a central authority governing all drug development-related activities. Indian regulatory agencies are increasingly interacting with clinical development professionals to understand the caveats of old regulations and possible remedies. In addition to the primary concern about the safety of clinical trial subjects, Indian regulatory authorities need to address several other issues in developing regulatory guidelines, such as cultural

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differences, language considerations, investigator training, etc.

## History of Indian Drug Regulations

Various regulatory aspects related to drug import, manufacture, sale and advertising in India are covered under the *Drugs & Cosmetics Act* of 1940 and the ensuing *Drugs & Cosmetics Rules* of 1945, the *Pharmacy Act* of 1948 and the *Drugs & Magic Remedies (Objectionable Advertisements) Act* of 1954. Of these, the *Drug & Cosmetic Act (Act)* of 1940, which led to the *Drugs & Cosmetics Rules (Rules)* of 1945, is central legislation that regulates India's drug and cosmetic import, manufacture, distribution and sale. The *Act's* main objective is to ensure that available human drugs are safe and efficacious and conform to prescribed quality standards, and marketed cosmetics are safe for use. Over the years, the *Act* has been amended several times to address public concerns. The Central Drugs Standard Control Organization (CDSCO), headed by the Drugs Controller General (India) (DCG(I)), discharges the functions allocated to the Central Government (similar to the US Federal Government) under the *Act*. CDSCO is attached to the office of the Director General of Health Services in the Federal Ministry of Health and Family Welfare. The DCG(I) has statutory authority under the *Act* with port offices, zonal offices and drug testing laboratories. The DCG(I)'s office is primarily responsible for:

- approval of new drugs to be introduced in the country
- permission to conduct clinical trials
- registration and control of imported drug quality
- developing regulatory measures and amendments to acts and rules
- establishing standards for drugs, cosmetics, diagnostics and devices and updating the Indian Pharmacopoeia
- license approval as Central License Approving Authority for the manufacture of large volume parenterals, vaccines and biotechnology products and operating blood banks and also of such other drugs as may be notified by the federal government from time to time

- coordinating the activities of the States and advising them on matters relating to uniform administration of the *Act* and *Rules* in the country

Despite the *Act's* long history, nonuniformity in interpreting and implementing the provisions of laws have made it necessary to update the regulations to bring them up to par with international standards. Historically, regulations have developed mostly *de novo*, without much interaction with international regulatory agencies. The *Act* has been reviewed by several government advisory committees since the 1980s, who reached the conclusion that the legislation is reasonably well-drafted but its enforcement had been weakened by poor guidelines and variable regulatory personnel interpretation.

After several years of deliberations by various advisory committees, the Indian government plans to strengthen CDSCO and the office of the DCG(I) and considerably expand and reorganize CDSCO along the lines of FDA within the next year or two. DCG(I), along with the Indian Council of Medical Research (ICMR) have adopted international regulatory guidelines and issued Indian versions of the same. ICMR issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000 and Indian GCP guidelines were released by CDSCO in December 2001. The Drug Technical Advisory Board (DTAB), the highest technical body under the *Drugs & Cosmetics Act*, has endorsed adoption of GCP guidelines for streamlining clinical studies in India.

## Current Regulatory Processes

Clinical trials in India are regulated by Schedule Y of the *Drug and Cosmetics Rules*, 1945. The *Rules* were revised in 2005 and the current rules, the *Drugs and Cosmetics (II<sup>nd</sup> Amendment) Rules*, 2005, were released 20 January 2005. Under the updated *Rules*, the Schedule Y was extensively revised to bring the Indian regulations up to par with internationally accepted definitions and procedures.

Schedule Y defines the requirements and guidelines for import and/or manufacture of new drugs for sale or for clinical trials. These

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include details of the application process and components of the application for permission to conduct clinical trials, and the responsibilities of the sponsor, investigators, and the Independent Ethics Committee (IEC). A clinical trial can only be initiated after obtaining written permission from DCG(I) and an IEC. A clinical trial application utilizes Form 44, accompanied by documents pertaining to chemical and pharmaceutical information, animal pharmacology, toxicology data and clinical pharmacology data. Other trial-related documents that must be submitted for approval include the Investigator's Brochure, trial protocol, case report form, informed consent form, patient information sheet and investigator's undertaking. Some additional requirements exist for studies in special populations, e.g., children, pregnant women, nursing women, elderly patients, patients with renal or other organ system failure, and those on specific concomitant medication(s). In addition, the trial's regulatory status of the trial in other countries must be reported. The clinical protocol must be reviewed and approved by an IEC of, at minimum, seven members, including a medical scientist, a clinician, a statistician, a legal expert, a social scientist and a common person from the community. The Schedule Y application for permission to conduct a clinical trial must be accompanied by a filing fee which is either Rupees (Rs) 50,000 (~\$1200) for a phase I trial (called Human Pharmacology Study); or Rs 25,000 (~\$600) for a phase II (Therapeutic Exploratory Study) or a phase III study (Therapeutic Confirmatory Study). Initial phase I studies can only be approved for drugs developed in India; however, repeat phase I studies for other drugs can be approved.

When a Schedule Y application is filed, the office of the DCG(I) reviews it; the required review period depends upon the trial's regulatory status in other countries. To expedite the application process and avoid detailed and prolonged review of information for studies already approved by certain countries' regulatory agencies, on 22 November 2006, the office of the DCG(I) issued the following decisions. From 1 December 2006, all applications are divided into two categories: A and B. Category A includes clinical trials whose protocols have been approved by EMEA or regulatory agencies in the

US, UK, Switzerland, Australia, Canada, Germany, South Africa or Japan. Permission is granted for these drugs, accepting the protocol approval of those countries. Category A application review and approval are projected to take two to four weeks. Category B clinical trial applications, however, are reviewed under the previous system, by an expert committee, which takes eight to 12 weeks for approval. This review time does not include potential delays due to incomplete applications and time required for sponsor responses to queries. Once an application is considered under Category B, it cannot be shifted to Category A, even if the applicant produces an approval from a Category A country. For all applications, summarized information in the Investigator's Brochure, duly supported by an affidavit declaring the information furnished is based upon facts, may be acceptable in lieu of detailed pharmacology, toxicology and clinical experience data. The DCG(I) also can request guidance from such other independent government agencies as the ICMR or Department of Biotechnology (for biotech products) on a case-by-case basis, thus extending the review period.

Once written approval of the Schedule Y application is obtained from DCG(I) and an IEC, a clinical trial may be initiated. Products shipped from other countries require a separate import license, called the T-License (Trial license), for investigational drug products. Once the license is issued, it is valid for multiple shipments for one year. The T-License and Schedule Y applications may be submitted together, so the license is issued simultaneously with the application approval. A separate application is required for shipping biological samples collected during the trial (e.g., body fluids) out of India. This application also can be submitted simultaneously with that for the clinical trial. Once the clinical study is approved by the DCG(I), the import license and No-Objection Certificate (NOC) for shipping biological samples are granted within two to four weeks.

The protocol can be amended during the trial, as required. Protocol amendments fall into three categories: (a) minor administrative and logistical amendments that do not require any information or permission; (b) amendments that require DCG(I) to be informed but need not

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wait for permission, e.g., additional investigators, amended Investigator's Brochure or informed consent; and (c) those amendments requiring prior permission before implementation, e.g., change in principal investigator, increase in subject numbers or major changes in study design, dose or treatment options. Type (a) and (b) amendments should be communicated to the DCG(I) and IEC within 30 days of implementation. All unexpected serious adverse events (SAEs) must be communicated to the DCG(I) and all participating study investigators within 14 calendar days. SAE notification must be accompanied by proof that the same information has been submitted to the regulatory agencies in other countries where the study is being conducted. In addition, sponsors are required to submit progress reports on a format described in Schedule Y every six months. For studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within three months. The summary report should provide a brief study description, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions, if any, and the reason for discontinuing the study or not pursuing the new drug application. Schedule Y includes format and examples of all documents to be submitted to the DCG(I).

## **Practical Issues of Conducting Clinical Trials in India**

Clinical data generated by Indian clinical sites have been used successfully for drug approval applications in the US, EU and other countries over the last decade. However, India's indigenous pharmaceutical industry still conducts only a small fraction of the total clinical trials in the country. Most clinical studies in India are for foreign sponsors. This raises some India-specific issues that a sponsor with little or no physical presence in India should address.

### ***Partner selection***

Indian regulations require that foreign sponsors use a local agent as the lead contact for Schedule Y and other application filings. This prevents a

foreign sponsor having no presence in India from independently requesting clinical trial approval. This is easily circumvented by hiring one of the rapidly growing number of local clinical research organizations (CROs) to be responsible for complying with Indian regulations. Some global CROs also have an Indian presence. While providing an attractive opportunity for foreign sponsors to delegate their local regulatory responsibilities, selecting a suitable Indian CRO is a critical step for off-shoring clinical development. Many Indian CROs have personnel experienced in working on global clinical trials for major pharmaceutical manufacturers in both management and other levels. Almost all comply with ICH and FDA GCP guidelines. By incorporating some key elements into the CRO selection process, a sponsor can ensure quality clinical data. Items to review include:

- personnel training records
- SOPs
- QA documents
- previous investigators
- clinical trial type
- regulatory experience

Sponsors also should select an independent monitoring company with a good reputation in conducting clinical trials in the relevant therapeutic area.

### ***Timing the applications***

Since the Indian regulatory agencies require several distinct applications, the sponsor needs to develop a clear regulatory strategy prior to initiating the approval process. As noted previously, most of the applications can be filed simultaneously, thereby saving considerable time. If the study is being reviewed and/or conducted in any countries designated Category A by CDSCO, it would be wise to wait for at least one regulatory agency to approve the trial before filing with CDSCO to qualify for the faster approval time.

### ***Cost versus speed***

Another critical issue is the trial's cost. One key element attracting pharmaceutical companies to India is the lower clinical trial cost. However, such additional factors as the cost of obtaining Indian regulatory approval, additional quality

assurance monitoring costs, etc. mean that the direct savings may not be as large as expected for smaller studies or those for rare indications. Cost is a major advantage primarily in large studies with more subjects. Faster subject recruitment remains a strong motivation even when the cost factor is not as attractive since it can bring cost benefits by reducing the trial duration. Therefore, both cost and expected subject recruitment rate should be reviewed carefully when developing the Indian component of a trial strategy.

### **Investigator selection**

Although India has many doctors, several hundred hospitals and large pools of internationally acclaimed scientific professionals, those numbers do not directly translate into finding well-qualified and experienced clinical study investigators. India's medical infrastructure is very different from that in the US and EU; only 3-4% of patients carry any form of health insurance, most paying for medical expenses out-of-pocket. As a result, there could potentially be additional costs for meeting a subject's standard of care. There is also an acute need to create increasing appreciation among the Indian investigators of the benefits of participating in clinical studies for both personal professional development and patients. Another factor for sponsors to consider is the actual expense of the trials in Indian currency, to avoid any possibility of bias resulting from unreasonable financial benefits to investigators or study personnel. The local CRO should be able to assist the sponsor in establishing investigator compensation comparable to that in other countries.

### **Cultural issues**

In India, the personal physician strongly influences patient decisions, as do family and friends, which could raise potential ethical issues with patient recruitment. The Indian process leaves validating IECs to the sponsor (and, by delegation, the partner CRO). It is up to them to assure that the IEC meets membership requirements and utilizes the processes (SOPs, minutes, etc.) necessary to pass an audit by Indian and/or international regulatory agencies. Most major medical centers are located in urban locations relatively well-educated patient populations. While English is the major language of communication throughout India, the IECs require that informed consent forms and all other documents for subject review (e.g., study diary, questionnaires) be translated into local languages. This could mean translation into as many as 14 languages, with each translation adding to the

cost. Some specific documents, e.g., the quality of life questionnaire, might not have validated translations. Several organizations specializing in translation are available to help with this. All other study-related documents are in English and do not require translation. Some other issues, such as getting an unmarried female subject to meet birth-control requirements for the study, probably cannot be met and need to be addressed. Most such issues, however, can be addressed to the satisfaction of all regulatory agencies by IRB and IEC reviews and approvals.

### **Conclusion**

As its regulatory processes become more streamlined, India is poised to take the lead in the global clinical development process. The country has a strong reputation for meeting global professional parameters, as demonstrated by the information technology and service industries. The Indian government has a strong appreciation for pharmaceutical sector growth and its regulatory agencies are working closely with most international bodies to update the processes and smooth out kinks in the system. With more experience, the process will become more efficient and productive. India and the pharmaceutical services sector are working together to firmly position the country as a major global player. Its easier regulatory hurdles and the fact that English is one of the primary languages give India a distinct advantage over China, other countries in the region, and Eastern Europe. Sponsors around the world would be a prudent to consider India as an important element in the drive to lower drug development costs. With the proper strategy and partners, meaningful cost savings and quality data are possible.

### **REFERENCE**

1. Clinical Trials in India - Industry Report, CYGNUS Business Consulting & Research, Nov 2005

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