

## Carrying out Clinical Trials in India

Jayasheel B G explains why India's regulatory environment supports the country as a favoured clinical trials destination and examines the associated advantages and challenges faced by sponsors in this market.

India is making a name for itself in the international pharmaceutical arena as a preferred destination for leading global companies to conduct clinical trials and it is a challenge for both the government and the private sector to create a balance between ethics and trade. The Indian government has played its part by standardising the regulations governing the conduct of clinical trials and the private sector, which includes pharmaceutical companies and contract research organisations, has succeeded in conducting global clinical trials in India.

Furthermore, an increased awareness of good clinical practice requirements and a stronger desire for international acceptability of research carried out in India have brought favourable changes in the attitude of Indian clinicians towards participation in clinical trials. Investigators are eager to take part in clinical trials that comply with GCP and are also willing to adhere to constraints of the protocol.

According to a joint study by international consultancy Ernst & Young and the Federation of Indian Chambers of Commerce and Industry, India now participates in over 7% of all global Phase III and 3.2% of all global Phase II trials<sup>1</sup>. Furthermore, a report by market research firm RNCOS says that the clinical trial outsourcing market in India is forecast to grow at a compound annual growth rate of over 30% during 2010-2012 to around \$600 million by 2012<sup>2</sup>.

In this context, this paper describes the changing regulatory framework for clinical trials in India as well as the advantages and challenges of carrying out trials in this market.

### Regulatory bodies and framework

In India, the central government, via the Central Drugs Standard Control Organization under the Ministry of Health and Family Welfare, largely works on developing standards and regulatory measures for drugs, diagnostics and devices; laying down regulatory measures by amending acts and rules; and regulating the market authorisation of new drugs – all in an effort to standardise clinical research in India and bring safer drugs to the market (see Table 1).

*India is making a name for itself as a preferred destination for clinical trials*

*The CDSCO's activities are carried out with a view to standardising clinical research*

*A number of government bodies and expert committees are involved in the pharmaceutical regulation*

Table 1. Regulatory bodies in India involved in pharmaceutical regulation		
	Body	Function
DCGI	Drug Control General India	Regulatory apex body under the government of India that oversees all clinical trials in the country
ICMR	Indian Council of Medical Research	Apex body that formulates, co-ordinates and promotes biomedical research
GEAC	Genetic Engineering Approval Committee	Consists of experts in the field of genetic engineering and molecular biology; clinical trials involving the use of biotech products would be referred by DCGI to GEAC for recommendations
DBT	Department of Biotechnology	Apex body that oversees the new impetus to develop the field of modern biology and biotechnology in India
AERB	Atomic Energy Review Board	Authority that exercises regulatory control over the approval of new types of radiation equipment, and for the registration/commissioning of new radiation equipment, inspection and decommissioning of installations
BARC	Baba Atomic Research Centre	Apex body that oversees and approves all radiation related projects in India. DCGI refers all clinical trials that involve the use of radiopharmaceuticals to BARC for its expert opinion
DCC	Drugs Consultative Committee	Provides technical guidance to the Central Drugs Standard Control Organization
CDL	Central Drugs Laboratory	National statutory laboratory of the Indian government for quality control of drugs
CLAA	Central License Approving Authority	Body within the CDSCO responsible for issuing "No Objection Certificates" for manufacturing licences
DTAB	Drugs Technical Advisory Board	Provides technical guidance to the CDSCO

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*The central government participates in the WHO's GMP certification scheme*

In its role as the regulator of imported drugs, the CDSCO works with the Drugs Technical Advisory Board and the Drugs Consultative Committee, while the Central Drugs Laboratory undertakes testing of such drugs. Other functions of the CDSCO include screening of drug formulations available on the Indian market, monitoring adverse drug reactions, participation in the World Health Organization good manufacturing practice certification scheme and screening of applications for granting "No Objection Certificates" for export of unapproved/banned drugs.

The State Drugs Control Organization is responsible for licensing drug manufacturing and sales establishments, licensing drug testing laboratories, approving drug formulations for manufacture, carrying out pre- and post-licensing inspections, and overseeing the manufacturing process, for drugs manufactured by respective state units and those marketed in the state. Furthermore, the state government is involved in investigations and prosecutions where there is contravention of the legal provisions, as well as in recalls of substandard drugs.

### Regulatory momentum

Apart from specific elements of the Indian market that attract global players (discussed in more detail below), the main aspect that has put the country at an advantage is the notable momentum adopted by the Indian Council of Medical Research and the CDSCO in tandem with global regulatory guidelines – considering India's involvement in global GCP has only happened in the past decade.

*Regulatory bodies recognise the need for a framework on par with global standards*

With the number of clinical trials being conducted in India increasing rapidly, the regulatory bodies recognised the need to frame guidelines and regulatory approval processes on a par with international standards.

The DTAB, for example, endorsed the adoption of GCP guidelines for streamlining clinical studies, which have been incorporated into Schedule Y (governing clinical trials legislative requirements) of the Drugs and Cosmetics Act. The CDSCO has made the guidelines available to the public on its website in order to ensure a level playing field<sup>3</sup>.

Furthermore, the ICMR has issued guidelines for ethical research in human subjects<sup>4</sup>. These are essentially based on the Declaration of Helsinki, WHO guidelines and International Conference on Harmonisation requirements for GCP. In addition, guidance for industry has been issued on biotechnological/biological products<sup>5</sup> which covers submission of clinical trial applications for evaluating safety and efficacy; requirements for permission of drugs approval; post-approval changes in biological products: quality, safety and efficacy documents; and preparation of the quality information for drug submission for drug approval.

As a result of these efforts, over the past two years, the regulatory approvals process in India has become progressively more streamlined, with median approval times reduced from 16 to ten weeks. Approval from local ethics committees at the site level is processed in parallel.

The CDSCO is now working with expert bodies to develop guidelines and introduce regulations for the mandatory registration of CROs and institutional review boards/ethics committees. The CDSCO is also working to develop guidelines and regulations for clinical trial site inspections and many more similar initiatives to strengthen and facilitate the conduct of clinical trials with highest quality and ethics.

### Timelines

With proper documentation, trial applications can be approved within a relatively short timeline (see Table 2). Making error-free submissions is the key to getting faster approvals from the DCGI.

*Clinical trials approvals can stretch to 14 weeks in certain cases*

Regulatory body	Approval	Timeline
DCGI	For conduct of clinical trials (all phases)	First response or approval within 45 working days
	For conduct of bioequivalence study for export	28 working days
IEC/IRB	IEC approval by various study sites	4-6 weeks (in parallel)
DCGI	Test licence to import supplies	2 weeks
Total (parallel processing)	Not applicable	14 weeks
Any file sent to referral bodies/sent for expert opinion	IND applications for rDNA products, radiopharmaceuticals, stem cells, etc	Additional 12 to 14 weeks

Any inadequacy found in the documents will lead to a query from the DCGI. The applicant's response to the query goes through a long queue and takes time to reach the concerned authority. Any discrepancy could thus delay the process by an additional 45 days.

## Clinical trials in India: advantages and challenges

In addition to the efforts mentioned above to align India's regulatory framework and guidelines with international standards, the main advantages of carrying out clinical trials are:

- strong availability of study subjects across major therapeutic segments;
- high level of ICH GCP and US Food and Drug Administration standards compliance (since 2001, the DCGI has implemented conformity to ICH GCP and good laboratory practice guidelines. Generally, most competent authorities, including the US FDA, will find the standards of Indian clinical trials acceptable);
- high quality of research professionals (India has a strong reputation for graduating students in the medical and scientific fields. The government is involved in curriculum development at major universities and students pursuing these fields of study are given financial incentives to study in India);
- a favourable regulatory environment that allows the conduct of global trials, duty-free imports of drugs intended for use in trials, bioequivalence studies for export of data, etc;
- cost competitiveness (depending on the number of patients and investigators, and the amount of analytical work completed in India, most sponsors will enjoy a 30-50% cost advantage over a similar trial in Europe or the US<sup>6</sup>); and
- increasing prevalence of diseases.

*India is continually introducing programmes to create a favourable regulatory environment*

Approval of clinical trial documents from both the IRB/IEC and the DCGI is mandatory to initiate a study. Because India's potential as a major hub for global clinical research has been acknowledged and thus, the regulatory bodies have to elevate themselves to meet international standards, they are facing some challenges. Some of the major issues that have been recognised as areas in need of improvement are discussed below.

### Lengthy approval timelines

International Phase I clinical trials with new chemical entities developed in a foreign country (first-in-human trials) are not allowed in India. For NCEs developed (or co-developed) in India permission can be granted, but the timelines for approval are approximately five to eight months, whereas the US FDA approves the same in 30 days. Increased one-to-one interaction between the regulatory authorities and the sponsor/CRO would help enhance understanding of the regulatory requirements and develop transparency in the relationship between the industry and regulators.

*More sponsor-regulator interaction would enhance understanding of the regulatory requirements*

Moreover, clinical trials applications submitted to the DCGI where the DCGI office does not have the competency to review such protocols are sometimes referred to outside agencies such as the ICMR, the BARC, the DBT, the AERB and/or the GEAC for their review and expert opinion, which results in longer review times. When this occurs, the additional time involved is unpredictable. At times, these referral bodies do not have the competency to review the submitted protocol. Therefore, expert committees are constituted to review the protocol and other submitted documents. Ample time is taken to constitute such committees.

The committee must overcome some other hurdles, for example: expert committee members must be available to meet at a joint forum; the decision is usually not taken during a single sitting, therefore multiple sittings are required; queries raised during such meetings take a long time to be drafted and circulated to the applicant; and after the applicant's response, the committee has to meet again to review the documents submitted to take the final decision.

### Inspections by health authorities

The number of clinical trials being conducted in India is on the rise and the data are being accepted by regulators across the world. Due to this, there has been an increase in the number of sponsor audits and inspections by other regulators to whom the data is being submitted. But, to date, there have been virtually no inspections for clinical trials by the DCGI in India. However, there is an ongoing effort to revise the regulations and guidelines to align India's requirements with those of other regulators. These could enter into force within a year or so.

*There have been virtually no inspections by the DCGI to date*

### Manpower crunch and application backlog

Though the number of clinical trial applications being submitted is increasing, there has been no increase in the review staff at the DCGI<sup>7</sup>. The DCGI office is facing a serious manpower crunch and this increases the timelines required to review and approve clinical trial applications, which is a hindrance to multinational/national companies wanting to conduct trials in India. The DCGI needs to delegate the required authority to the lower ranks, which would shorten the approval timelines. Presently, however, all files go through the higher ranking authorities notwithstanding their busy schedules, which directly results in the increased number of pending applications.

*All files go through the higher ranking authorities*

### **Lack of communication**

As there are no direct communication channels between industry and the DCGI's office, some applications are queried outright, without the regulator checking the information provided or due to misunderstandings. This puts the application back to the end of the queue.

### **Overcoming the challenges**

India is working hard to address the above obstacles. Below is the state of play on a number of efforts that are under way:

- a separate checklist of documents required to be submitted for the conduct of global clinical trials has been published on the CDSCO's website. As per these requirements, the applicant has to submit details on, among other things: the name of the applicant; the sponsor authorisation letter; the drug name; the regulatory status in other countries; the trial objective; the phase of study; participating countries and sites; details of patient enrolment globally and in India; IRB approvals; any reported suspected unexpected serious adverse reactions from other participating countries; and data as per Form 44 (clinical trial application) and Form 12 (application to import drugs for use in clinical trials);
- the DCGI has suggested simplifying the procedures for issuing test licences and to that end has published a guideline on its website;
- for serum samples, clinical trial and export applications are now issued by the DCGI, whereas previously, the Director General of Foreign Trade had to be approached for the export licence after the clinical trial was approved by the DCGI;
- the regulatory bodies in India are gearing up to meet the challenges in the global scenario by trying to increase qualified manpower and bringing in more academic expertise (other than in DTAB) to discuss necessary improvement strategies. Many initiatives are under way to ensure India meets its global regulatory requirements and creates an environment for effective interaction between regulators, industry and academia. For example, the DCGI office recently organised academia-regulator meetings to discuss various issues such as pharmacovigilance;
- the country's participation in global research networks and in efforts to support innovation should ensure fast track and fruitful approvals; and
- the government is working on upgrading the pharmacy curriculum, creating training programmes and focusing on consumer education, etc.

*There are initiatives under way to promote effective interaction between regulators, industry and academia*

Last but not least, there are plans to link the relatively new Indian clinical trials registry (CTRI) to the International Clinical Trials Registry Platform maintained by the WHO. The Indian government last year made the registration of all clinical trials conducted in the country mandatory, applicable to all trials that started after 15 June 2009<sup>8</sup>.

Through this, validity and accountability is being ensured. Now, all clinical trials are being registered on the CTRI website, which is maintained by the National Institute of Medical Statistics and funded by the ICMR, the Department of Science & Technology and the WHO. To date, about 1,000 trials have been registered in the CTRI. A total of 987 clinical studies are running at various centres in India, according to ClinicalTrials.gov, which is run by the US National Institutes of Health.

*Some 1,000 clinical trials have been registered in the CTRI*

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