## Clinical trial regulations in India

# Inundation of global clinical trials

**Strategic location, low costs and English-speaking population are some of the positives that attract the attention of foreign companies to conduct clinical trials in India. But all these require a sound regulatory environment in place. Thus, to take advantage of this opportunity, the regulations governing trials must be revised and amended, where necessary.**

Dr Shubhangi Desai &
Savitha Naik

India is one of the most strategic locations for global pharma companies to conduct their drug Research and Development (R&D). The country offers the advantages of lower trial costs, large English-speaking population, well-trained medical community, large population of qualified patients as well as a set of regulatory framework with guidelines.

In order to conduct a clinical trial in India, permission is primarily needed from regulatory authority of India, ie, Drugs Controller General of India (DCGI), and also from institutes where the trial will be conducted.

The DCGI is a body that falls under the Health Ministry and is responsible for regulatory approvals of clinical trials in India. Its functions include approval of trial, importing the drug for trial and sending biologicals overseas for testing. The DCGI follows Schedule Y of Drugs and Cosmetic Act, which was laid down in 1945, and was recently amended in January 2005. The change is promising and is supportive to the industry for clinical trials. Earlier, foreign drug trials could be conducted only in one phase below the highest phase of testing abroad. Parallel global clinical trials are now being conducted in India as well, ie, permission is granted for concomitant phase II and III trials.

As per the rules, the applicant has to submit details such as chemical and pharmaceutical data; generic & chemical name; dosage form; composition; animal pharmacology & toxicity data; animal toxicology and clinical data; as well as phase I, II, III & IV data to the DCGI. The protocol of the clinical trial with a consent form is also submitted. The authority also needs to know about the regulatory status of the drug in other countries, including names of countries where the drug is approved, and international package insert or the place where Investigational New Drug (IND) application is filed. Applicants have to report any Suspected or Unexpected Serious Adverse Reaction (SUSAR) from other

participating countries, if any. Further, it is necessary to submit an affidavit from the sponsor stating that the study has not been discontinued in any country. In case of discontinuation, reasons for the same must be communicated to the DCGI. The process of approval can take up to 10-12 weeks as compared to an average of 30 days in the US Food and Drug Administration (USFDA) and 60-90 days in Europe.

After the initial approval, it is mandatory to send safety reports in real-time and one annual report with all details of the study in India. After the study is complete, a detailed report must be submitted to the DCGI. The DCGI also undertakes inspections to ensure that trials are conducted as per protocol, ethics and the laid guidelines.

### Institutional Ethics Committee (IEC)/Institutional Review Board (IRB)

The IRB approval process can be conducted in parallel with the DCGI review. The provisions facilitate the process of having study protocols in place and quickly initiating trials. In order to comply with all applicable regulatory requirements and guidelines, each IRB must have the following records:

- Written Standard Operating Procedures (SOP) or charter
- Constitution and composition of the IRB
- Curriculum vitae of all IRB members
- Copies of all trial documents received for review
- All correspondence between IRB and investigator
- Agenda and minutes of all IRB meetings
- Final report of the study

After granting the approval for conducting clinical trial(s), it is the responsibility of IRB to have a review of the trial in progress. This includes but is not limited to:

- Review of safety reports (all serious adverse events and adverse drug reactions happening at the trial sites)
- Review and approval of amendment(s) in protocol or informed consent document
- Review of significant deviations or violations (if any)

The frequency of these reviews may vary from one institute to another, as specified in the respective IRB charters or SOPs, but is usually once in 4-8 weeks. The usual time for approval by the Ethics Commitee (EC) is 6-8 weeks.

### Bright future...

Despite several pitfalls, India is certainly gearing up to attract more and more researchers from around the world to conduct their clinical trial studies here. In this regard, the regulatory system is also being fine-tuned. Laws are being amended to facilitate entry of global clinical trials. Massive and concerted efforts are on to train research

professionals and increase the base of investigators and supporting staff. These initiatives will certainly improve the current situation. In brief, India is already off the starting blocks and gearing up for an inundation of clinical research trials. This will ensure timely completion of clinical trials and, at the same time, generate high-quality data for international submission.

## Recent regulatory reforms initiated by Central Drugs Standard Control Organization (CDSCO)

**Fast-tracking approval timelines:** In September 2009, the CDSCO revised timelines for various regulatory processes. If the application is complete, first response from the DCGI office can now be expected within 30 days for T licence and 45 days for approval of clinical trial applications. Moreover, applicants can check the status of their application since the approval letters sent out by the DCGI office are displayed on the CDSCO website under 'Daily Dispatch' section.

**Single-window clearance for export No Objection Certificate (NOC):** Indian regulators have recently introduced a single-window approval process through the DCGI for trial-related biological sample export NOC. Earlier, after obtaining permission from the DCGI for conducting a trial, an applicant had to apply separately to the Directorate General of Foreign Trade (DGFT) for an export NOC. This process has now been simplified and fast-tracked, so that an applicant can apply simultaneously for trial permission as well as export NOC to DCGI, without the need for a separate application to DGFT. As per revised timelines, export NOC can now be expected within 10 working days, in contrast to the previous 2-4 weeks timeline for DGFT approval.

**Stringent pre-approval review process:** Fast-tracking of the approval process does not imply that the DCGI has become lenient and will approve any or all applications. On the contrary, for global trials, the US IND number and US IRB approval letters need to be submitted along with trial application. The ethical and scientific aspects are closely scrutinised by the regulators, including protocol procedures, rationale for sample size, etc. Queries are being raised more frequently by the DCGI office and in the scenario of lack of appropriate justification by the applicant, a trial might even be rejected.

**Mandatory registration with Clinical Trials Registry-India (CTRI):** The National Clinical Trial Registry *(www.ctri.in)* launched by National Institute of Medical Statistics (NIMS) under the Indian Council of Medical Research (ICMR) has been operative for the last two years (since July 2007). However, until recently, the registration was voluntary, or at the most, advisory. Since June 2009, prospective registration with the CTRI has been made mandatory for all trials to be conducted in India. By making available in public domain all the important trial-related information (eg, inclusion exclusion criteria, protocol summary, site details, name of contact persons, total sample size, etc), CTRI ensures accountability and transparency in conducting trials that are the two essential demands of globalisation.

**DCGI inspection of trial sites:** Another welcome initiative by the DCGI is inspection of trial sites. Recently, the DCGI inspectors had visited an Indian site, which reported death of an infant participating in a vaccine trial by a foreign company and halted the trial, suspecting violation of regulatory norms. The process was expected to be in full swing starting December 2009, with trained teams of inspectors randomly visiting trial sites across India. The DCGI, in collaboration with the USFDA, has recently concluded an initial training session of 25 members to be designated as potential inspectors.

## Initiatives for future governance

DCGI is planning to initiate a system of registration and accreditations of Contract Research Organisations (CROs), to quality check their activities. A draft guideline on the CRO registration process has already been made and is proposed to be incorporated as new Schedule Y1 to Drugs and Cosmetics Rules, 1945. This draft includes the following:

- Registration of clinical trial sites
- Registration of EC/IRBs
- Opening doors to allow early (Phase I) phase trials for foreign molecules in India
- Creating environment for Phase 0 or microdosing studies in India
- Ensuring penal provision for fraud and misconducts in clinical research

The CDSCO also has a futuristic plan of implementing e-governance programme, which would enable companies to file, track and review trial applications online.

## Conducting quality trials

The Indian regulatory system has started adapting to the demands of quality, transparency and accountability of global trials. The recent initiatives underscore the fact that our national regulatory authority is in the process of becoming more pro-industry, more vigilant and more efficient, translating to a more USFDA-like regulatory system, which is the need of the hour. MPh

Dr Shubhangi Desai, PhD, Associate Director – Clinical Project Management, SIRO Clinpharm, is responsible for overseeing successful execution of SIRO's clinical trial operations. She is associated with the field of clinical research for over a decade. Her career in clinical research began with Ranbaxy Laboratories, and her last assignment was as Head-Clinical Operations, Wellquest.
Email: shubhangi.desai@siroclinpharm.com

Savitha Naik, Sr Executive – Regulatory Affairs, SIRO Clinpharm, is responsible for planning, managing, executing and overseeing the submission of applications to the regulatory body – The DCGI and all regulatory activities in clinical operations. She has over seven years of experience serving pharma companies and CROs in India.
Email: savitha.naik@siroclinpharm.com