Firm Foundations

As India looks to cement its place as a key player on the clinical research scene, ensuring it has a robust regulatory framework in place to attract more business is proving increasingly important.

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In India, pharmaceuticals are governed by the Drugs and Cosmetics Act and the rules framed to implement the provisions in the Act. The history of these regulations in India dates back to the 1940s when the Drugs and Cosmetics Act was passed in order to regulate the import, manufacture, distribution and sale of drugs in India. The drug rules were framed in 1945 to give effect to the provisions of the Act. In 1985, the Narcotic Drugs and Psychotropic Substances Act was enacted by repealing the Dangerous Drugs Act, 1930, and Opium Act, 1878.

At present the following acts and rules regulate the manufacture, export and clinical research of drugs and cosmetics in India:

- Drugs and Cosmetics Act, 1940 (1)
- Drugs and Cosmetics Rules, 1945
- Pharmacy Act, 1948
- Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954
- Medicinal and Toilet Preparations (Excise Duties) Act, 1955
- Drugs (Price Control) Order, 1955 under Essential Commodities Act, 1955
- Narcotic Drugs and Psychotropic Substances Act, 1985

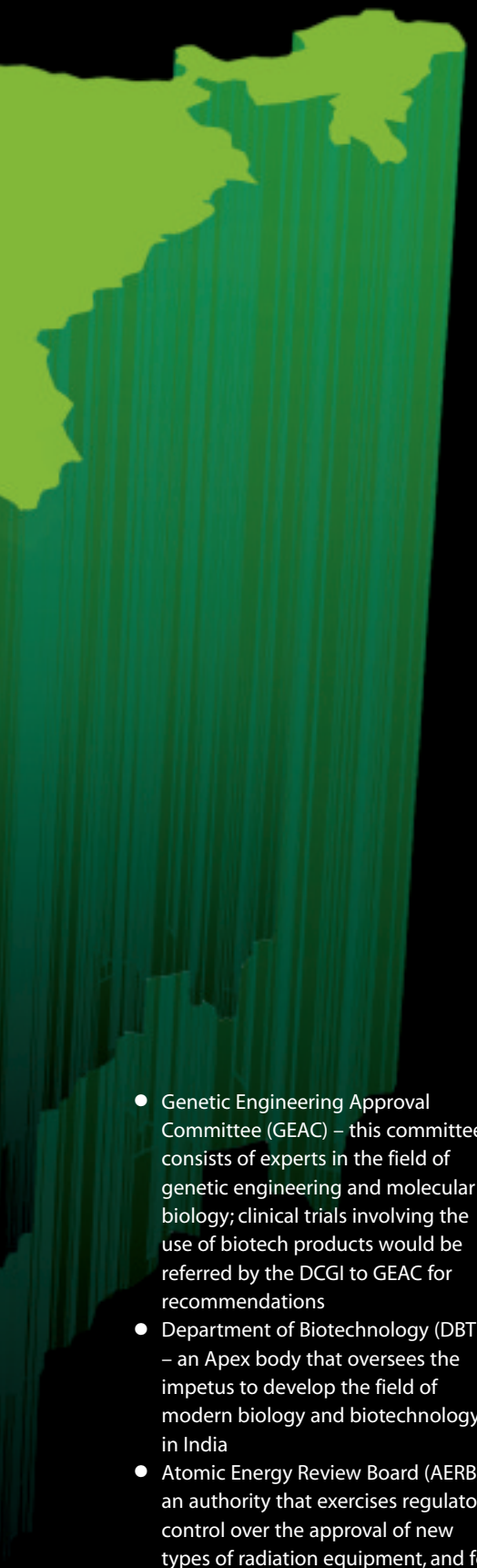
In India, the central government, via the Central Drugs Standard Control Organization (CDSCO) under the ministry of Health and Family Welfare, largely works on developing standards and regulatory measures for drugs, diagnostics and devices; laying down regulatory measures by amending acts and rules; and regulating the market authorisation of new drugs. 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 the screening of drug formulations available in the Indian market, monitoring adverse drug reactions, participation in the World Health Organization's good manufacturing practice certification scheme, and the screening of applications for granting 'no objection certificates' for export of unapproved or banned drugs.

The State Drugs Control Organization is responsible for licensing drug manufacturing and sales, 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. The state government is also involved in investigations and prosecutions where there is contravention of the legal provisions, as well as in recall of substandard drugs.

Regulatory Bodies

There are a number of regulatory bodies in India that are involved in the regulation of pharmaceuticals:

- Drug Controller General of India (DCGI) – the apex regulatory body under the Indian Government that oversees all clinical trials in the country
- Indian Council of Medical Research (ICMR) – an Apex body that formulates, coordinates and promotes biomedical research



- Genetic Engineering Approval Committee (GEAC) – this 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 the DCGI to GEAC for recommendations
- Department of Biotechnology (DBT) – an Apex body that oversees the impetus to develop the field of modern biology and biotechnology in India
- Atomic Energy Review Board (AERB) – an authority that exercises regulatory control over the approval of new types of radiation equipment, and for the registration and commissioning of new radiation equipment, inspection and decommissioning of installations
- Bhabha Atomic Research Centre (BARC) – an apex body that oversees and approves all radiation related projects in India. The DCGI refers all clinical trials that involve the use of radiopharmaceuticals to BARC for its expert opinion
- Drugs Consultative Committee (DCC) – this committee provides technical guidance to the CDSCO
- Central Drugs Laboratory (CDL) – a national statutory laboratory of the Indian government for quality control of drugs
- Central License Approving Authority (CLAA) – a body operating within the CDSCO responsible for issuing 'no objection certificates' for manufacturing licenses
- Drugs Technical Advisory Board (DTAB) – this board provides technical guidance to the CDSCO

Regulations Governing Clinical Trials in India

The Drug Controller General of India (DCGI) is the body governing the regulations for approval of clinical research in India. The DCGI falls under the CDSCO, which in turn operates under the health ministry and is responsible for regulatory approvals of clinical trials in India, and which includes approval of trial, importing the drug for trial and sending any biological outside the country for testing. The DCGI follows Schedule Y of Drugs and Cosmetic Act, which was laid down in 1945 and has been amended with the latest ruling in January 2005.

Apart from Schedule Y 2005, there are other guidelines which are also to be used for the conduct of clinical trials in India. These were formulated by a number of agencies over the years. A number of important guidelines have been given, including: the Indian GCP guidelines in 2001; and the ethical guidelines for biomedical research on human participants, ICMR, in 2006.

2005 proved to be an important year as India signed a product patent and also came out with an important amendment to schedule Y. The amendment to schedule Y was designed to serve as a hallmark – it allowed entry of concurrent global clinical trials and laid down requirements specifically for the industry relating to the conduct of trials such as the responsibilities of the investigators, sponsors and ethics committees. It also contained requirements and guidelines on clinical trials for the import, manufacture and marketing of a new drug. The marketing approval for a new drug would depend on the status of the drug in other countries. If the drug has been marketed in other countries, Phase 3 trials are deemed not to be required. If the drug has not been marketed in other countries, concurrent global trials are permitted in India depending on current available data. Phase 1 trials are generally not permitted in India for drugs discovered in other countries unless data from Phase 1 trials carried out in other countries are available, or if the drug in question is relevant to a health problem in India.

For new drug substances discovered in India, clinical trials must be carried out from Phase 1. Approval is given for each phase and it is dependent on the data emerging from the previous phase. Permission to conduct trials must be sought by applying for a test license to import or manufacture the drug. The application must be submitted along with data for each phase of the clinical trial, the protocol for proposed trials, the case report forms to be used and the names of investigators and institutions. The institution's ethical committee approval is also needed before the trial can be initiated. If the institution does not have an ethical committee, then the approval of independent ethical committee for the protocol needs to be sought. Permission for clinical trials in the paediatric age group is given only after Phase 3 trials in adults are completed, but if the drug is of value primarily in a disease affecting children, then permission for earlier trials in the paediatric age group may be given. Sponsors are required to submit an annual status report of each trial that is ongoing, completed or terminated. In case of termination, reasons should be

specified and any unexpected serious adverse event must be notified to the licensing authority within 14 calendar days. A formal written consent signed by the participant and the investigator is also required (2).

Ethical Guidelines for Biomedical Research on Human Participants

In 1980, the Indian Council of Medical research (ICMR) brought out the Policy Statement on Ethical Considerations involved in Research on Human Subjects and revised these guidelines in 2000, and later in 2006, as the Ethical guidelines for Biomedical Research on Human Participants (3). A detailed description of vaccine trials, herbal products, blood banking, stem cell research and so on has been provided to make the document reflect current ethical requirements, which can be applied to India from an ethical, legal and social angle.

Indian GCP

In order to develop Indian guidelines to ensure the uniform quality of clinical research throughout the country and to generate data for registration of new drugs before use for the Indian population, an expert committee set up by the CDSCO in consultation with clinical experts formulated GCP guidelines for the generation of clinical data on drugs. The Drug Technical Advisory Board (DTAB) – the highest technical body under D&C Act – endorsed the adoption of the GCP guideline for streamlining the clinical studies in India (2). These guidelines need to be followed when conducting any research in India.

Approval of Biological Drugs or Vaccines

The regulation of biologicals in India is controlled by the DCGI and Central and State Drugs Control departments such as CDSCO and drug regulatory authorities (DRAs). In India, all vaccines and drugs derived from recombinant DNA techniques are considered as new drugs and both approval and clinical trial requirements for them are very stringent. Biologicals may, at times, require clearance from the department of biotechnology and, in certain cases, for example, where the product is developed or manufactured using recombinant-DNA (r-DNA) technology, the approval of various other agencies of committees is essential. These include GEAC, the recombinant DNA Advisory Committee (RDAC), the Review Committee on Genetic Manipulation (RCGM) and the Institutional Biosafety Committee (IBSC). Presently, there are no special guidelines for approval of biosimilars in India (4).

Trials for Medical Devices

DCGI has defined medical devices depending on the category of risk and is responsible for regulating trials for medical devices. There are well-written guidelines defined by DCGI for clinical trial requirements (5).

Trials for BA/BE Studies

Approval is needed for BA/BE from DCGI and again, there are well-written guidelines available for the conduct and requirements of approval (6).

Trials for Stem Cells

ICMR has developed stem cell research and therapy guidelines which address adult, cord blood and embryonic stem cells in response to the support provided by the Indian Government in order to facilitate stem cell research in India to improve understanding of human health and disease, and evolve strategies to treat serious diseases.

These guidelines address both ethical and scientific concerns to encourage responsible practices in the area of stem cell research and therapy. Currently, approval is needed from various bodies including IC-SCRT, NAC, ICMR and DCGI for conducting clinical trials in stem cells (7). This area is relatively new and requirements placed on trials still lack clarity.

Regulatory Challenges

Three challenges still remain in terms of setting up and running trials in India:

Review and Approval Process

As the global market for conducting clinical trials in India continues to grow, the DCGI is facing an increasing numbers of clinical trial application submissions. Theoretically, the approval process should take about 14 weeks. However, these timelines often get extended due to a variety of reasons, which include the process of providing rationale for the number of patients to be recruited in India as part of a global trial, providing approvals of western countries participating in the study, providing justification for age of certain populations to participate in studies and so on.

Intellectual Property Protection

Though India has signed product patent in 2005, the risk of generic drugs is perceived to be quite high, and a number of European and US companies are still wary of conducting trials in India due to this perceived threat.

Guidelines for Compensation

The Indian laws relating to clinical trials have specified requirement for the provision of compensation of participants for research related injuries. There is still a lack of clarity about compensation, implementation, payment structure and so on. Members of ICMR-FERCI-ISCR have proposed a draft which is under consideration with the DCGI, and a final guideline is expected to be released shortly (8).

Positive Steps

A number of positive steps have been taken by DCGI:

Single Window Clearance

The DCGI now works as a single point of contact for receiving objections for a trial, for importing permits for drugs, and avoiding objection for exporting the clinical trial samples out of the country. This definitely has helped in reducing the timelines for the start-up of trials.

Mandatory Registration with Clinical Trial Registry of India (CTRI)

The CTRI was launched on 20 July 2007. Initially it was optional, but with effect from 15th June 2009 it is mandatory to register the clinical trial on the website before enrolment of the first patient in India. The CTRI website is maintained by

the National Institute of Medical Statistics and funded by the ICMR, the Department of Science & Technology and the WHO (9). This step has led to increased transparency, better awareness and greater access to information for the general public outlining the clinical trials being conducted in the country.

Inspections of Sites

The Indian Government has conducted inspections at many clinical investigational sites to ensure quality. The DCGI had two training sessions with USFDA regulators, conducted mock and stand-alone inspections across the country, and plans to do many more on a regular basis to maintain quality and ensure principals of GCP, ethics and country regulations are not violated. The DCGI also released a guidance document on Clinical Trial Inspection dated 1 November 2010. The objective of the document was to provide instructions for inspectors and CDSCO officers for conducting inspections of clinical trial sites, along with sponsor and CRO's facilities, and to provide information to investigators, sponsor and CROs about procedures for inspection and follow-up steps (10).

Guidelines on SAE Reporting

The safety of participants is of paramount importance, and the DCGI has implemented an initiative through a draft guidance document dated 11 May 2011 on reporting serious adverse events in clinical trials. This nine-page draft guidance requires a causality assessment by the investigator and the medical monitor of the sponsor or CRO, clearly mentioning whether the SAE is related or not related. Further, it requires the sponsor or the CRO to provide details of compensations provided for injury or death and, in the situation where no compensation is paid, the reason for this. This draft guideline is open for comments from the industry and is expected to be finalised soon (11).

Future Plans (2011-2015)

The DCGI is planning to initiate a system of registration and accreditations of CROs in an attempt to quality-check their activities. A 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 (12). Additional areas to discuss will include:

- The registration of clinical trial sites
- The registration of EC/IRBs
- Opening doors to allow early (Phase 1) trials for foreign molecules in India
- Creating an environment for Phase 0 or microdosing studies in India
- Ensuring penal provision for fraud and misconducts in clinical research

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

Conclusion

The Indian pharmaceutical industry is the third largest in volume terms in the world and the 14th in terms of value. The clinical research industry was valued at about $140 million in 2006, and has subsequently grown to $350 million in 2009-2010; currently it is valued at about $400 million. India is emerging as an important player in the clinical research and pharmaceutical field, but to maintain this growth and to emerge as a key player on the global market, a strong and supportive regulatory framework is essential or the advantage gained so far would be lost.

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