Regulatory environment for clinical research: Recent past and expected future

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INTRODUCTION

India has the potential to contribute meaningfully to global clinical drug development. A critical enabler to achieve this potential is a balanced, predictable, and scientifically based regulatory review/approval for clinical trial applications. Safety of Indian patients participating in clinical trials is of utmost priority while ensuring the regulatory environment remains conducive for clinical research. This article will attempt to review the overall regulatory environment for clinical trials in the recent past and expected future trends in the country.

REGULATORY ENVIRONMENT IN THE PAST

The regulatory framework and guidelines that govern clinical research in India are as mandated in (a) Schedule Y of the Drugs and Cosmetic Rules revised in 2005, (b) Good Clinical Practices (GCPs) for Clinical Research in India established in 2002, and (c) Ethical Guidelines for Biomedical Research on Human Participants (Indian Council of Medical Research) published in 2006.

In the past, the regulatory path for clinical trials was fairly simple with a single tier approval process involving review at the Central Drugs Standard Control Organization (CDSCO) office only. Approval timelines ranged between 8 and 12 weeks. This regulatory scenario was conducive to conduct clinical trials and was an opportunity to have newer therapeutic options available for use in Indian patients at an earliest.

BACKGROUND TO THE CONSTANTLY EVOLVING REGULATORY ENVIRONMENT

The Parliamentary Standing Committee in their 2012 report questioned among other things the implementation of regulations governing review/approval of clinical trials.

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There was also a Public Interest Litigation petition filed in February 2012 on behalf of the nongovernmental organization Swasthya Adhikar Manch (SAM), seeking justice for “drug trial victims throughout the nation,” and sought to halt the conduct of clinical trials in India for new products that will not be sold or marketed in India. SAM alleged in the petition that weak regulatory controls on the conduct of clinical trials combined with poor enforcement of such controls has contributed to an unacceptable number of deaths and adverse events in the clinical trials conducted in the country.

Consequently, the Supreme Court directed the Union Government to come up with a new regulatory regime that would reflect the concern of all stakeholders.

In addition, the Prof. Ranjit Roy Choudhury Expert Committee was constituted by the Union Health Ministry in early 2013 to formulate a comprehensive policy and guidelines for all aspects related to approval of new drugs and clinical trials. A report finalized by this committee in July 2013 suggested practices that would be strengthening regulatory standards while ensuring safety of Indian patients participating in clinical trials and at the same time providing a conducive environment for the growth of clinical trial industry in India.

Various updates on policy and guidelines relevant to clinical trials were thereafter released. This article will review the most important changes that had maximal impact on clinical research in India.

MAJOR REGULATORY REFORMS IN THE RECENT PAST

Three-tier review process
In March 2011, CDSCO office constituted 12 New Drug Advisory Committees (NDACs) consisting of experts from Government Medical Colleges and eminent institutions from across the country for review of regulatory applications including clinical trials. Review included face-face presentations by applicants to NDAC members in the presence of CDSCO officials. Additional step of NDAC review led to longer review timelines. Presently, these committees are named as “Subject Expert Committees (SECs).” Since August 2014, there exist 25 panels of SECs across various therapeutic domains.

Further, effective February 2013, a three-tier review process has been implemented, wherein each clinical trial application is being referred for review to the Technical and Apex Committee after the proposal has been approved in SEC meeting as depicted in Figure 1. This three-tier review process adversely impacted clinical trial approval timelines. The delays in clinical trial approvals were worsened due to the unpredictable occurrence of SEC meetings and infrequently conducted Technical and Apex Committee meetings. Considerably delayed approval timelines of clinical trials made India less competitive in comparison with other emerging markets for the conduct of clinical trials.

However, in the recent past, SEC meetings are conducted more frequently followed by Technical and Apex Committee reviews, and average approval timelines of about 6–7 months are experienced for clinical trials in India. In addition, minutes of meetings of these committees are displayed on CDSCO website making the regulatory review process more transparent in the public domain.

There have been various suggestions given by stakeholders to CDSCO office about simplification of the three-tier review process. A few of them include simplified processes for review/approval of extension studies, postmarketing or phase IV studies, repeat phase III studies, protocol amendments, etc.

Compensation and free medical management
Another regulatory concern in India in the recent past was with regard to compensation in cases of trial-related injury or death as per G.S.R. issued in January 2013. Amendment vide Gazette Notification G.S.R. 53 (E) dated January 30, 2013,[4,5] specifies procedures to analyze the reports of serious adverse events occurring during clinical trials and procedures for payment of compensation in case of trial-related injury or death as per prescribed timelines in the new Rule 122DAB. This amendment required the sponsors to provide free medical treatment to the patients irrespective of whether the impairment was related or not related to a clinical trial. The objective was to improve (a) reporting timelines of serious adverse events including deaths during clinical trials, (b) patient safety, and (c) timely payment of compensation to patients. The amendment resulted in serious concerns for researchers and research organizations around the areas of financial compensation and liability of the trial researchers. Because of these changes in the regulatory framework, many clinical studies were either discontinued or moved out of India.
Need for financial compensation for injury arising due to: “Adverse effect of investigational product(s), use of placebo in placebo-controlled trials, or failure of investigational product to provide intended therapeutic effect” was issues, which warranted further discussion and debate. Clinical research is often exploratory in nature and is undertaken to test a hypothesis when there is a lack of adequate knowledge in the said domain. Industry associations had repeated deliberations with regulators expressing their concerns. Clarification of what is meant by “intended therapeutic effect” was requested as this clause essentially undermines the spirit of science. Similarly, the inclusion of a placebo arm in clinical trials is scientifically rational when there is nonavailability of an active comparator or in diseases with a high placebo reactor rate. Therefore, compensation for any injury to subjects participating in a placebo-controlled trial due to lack of therapeutic effect made little sense. Finally, compensation for adverse effects of an already approved marketed control drug should not have been made mandatory.

The Health Ministry later in December 2014 released a much better balanced 6th amendment in the form of G.S.R. 889 (E) effective June 2015\[3\] which clarified that “In case of injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or until such time it is established that the injury is not related to the clinical trial, whichever is earlier.” It additionally stated, “In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subjects.”

The compensation formulas to arrive at the exact compensation amount have been judiciously developed based on the Workman’s Compensation Act and have been implemented by researchers.

**Mandatory Ethics Committee registration**

The Ethics Committee (EC) has the prime responsibility of regulating clinical research at each individual study site and safeguarding the rights and safety of research participants. Despite the establishment of ethical guidelines since a long time, the ECs in our country were still grappling with basic issues including inadequate or no standard operating procedures, lack of trained manpower and enough administrative support, and noncompliance with Schedule Y recommendations.

In an attempt to make clinical trial approval procedures and monitoring mechanisms more accountable, the regulators in February 2013 issued an amendment to the Drugs and Cosmetic Rules vide G.S.R. 72 (E)\[4\] in the form of Rule 122 DD to make registration of EC with licensing authority mandatory before it reviews and accords approval to a clinical trial protocol. The registration is granted to ECs for a period of 3 years. The Drug Controller General of India (DCGI) Directorate also issued a notice in July 2013\[5,6\] allowing independent ECs registered by CDSCO to oversee only BA/BE studies. This meant all patient-based studies could be overseen by institutional ECs only.

With initial operational challenges being resolved, till date, more than 2000 ECs have been registered with licensing authority.

**Audio-video recording of informed consent process**

A gazette notification was issued as G.S.R. 364 (E) in June 2013\[7,8\] mandating audio-video (AV) recording of informed consent process of clinical trials. The AV recording increased the transparency and the conduct of the consent process and was aimed to safeguard the rights of the subjects involved in the trial. However, there were many practical challenges to this step from an operational perspective. The customs and traditions still prevalent in many parts of India made a tough job for the site management staff to convince patients to appear in front of the camera. This also appeared to impact recruitment in some pockets. Further, a single recording of such a long duration is difficult to logistically manage for many site personnel. In case of certain diseases such as sexually transmitted disorders and immunodeficiency syndromes, discussing the ailment over the camera made patients uncomfortable and at times they refused to do so.

Global counterparts of clinical research organizations raised genuine concerns over this mandate although most organizations effectively implemented the same in practice. Later, a Gazette Notification G.S.R. 611 (E) dated July 2015\[9\] was released modifying the audio-visual recording norms. It was clarified that audio-visual recording of informed consent process shall only be mandatory for cases where vulnerable population is involved, and the trial is with a new chemical entity or new molecular entity. While this clarification was welcomed by researchers, more understanding of which patients fall under the definition of “vulnerable” is necessary. Clinical trial permissions issued by CDSCO post this gazette still maintain the old formats and need to be amended to facilitate pragmatic implementation of the gazette notification.

**Tougher requirements for site selection**

In July 2014, tougher norms were mandated for clinical trial sites. Vide circular issued in July 2014,\[10\] it was mandated that no investigator could conduct more than three trials at any time. Fifteenth Technical Committee Meeting held on June 4, 2014, mandated that no clinical trial shall be conducted at sites with <50 hospital beds.\[11\] These requirements had a huge negative impact with sponsors being not able
to choose investigators with specific patient population or engaging a specialized center for a particular disease. Selection of investigator sites became extremely challenging. Further, in practice, it was mandated by CDSCO for most studies to include at least 50% government sites in each study. Many government sites did not even have adequate infrastructure (including registered ECs) to participate in global trials as per these requirements.

In August 2016, CDSCO office revoked some challenging norms including not more than three trials per investigator and minimum fifty bedded hospitals vide two circulars. Under the revised norms, the ECs have been empowered to decide whether a site is suitable for a trial irrespective of its bed capacity. It is also suggested that the site should have “emergency rescue and care arrangements.” Further, the cap on number of trials will now be decided after the EC examines the overall capabilities of a research site and also the risk and complexity involved in a particular study.

Further, a third circular issued in August 2016 mentioned that respective ECs after due diligence can approve addition of site(s) and investigators, and No Objection Certificate (NOC) from DCGI in the normal course should be necessary. Sponsor is expected to inform DCGI about such site addition/deletion, and thereafter, if no objection was received from DCGI, it would be deemed to have concurrence of CDSCO.

**Regulatory inspections**

Among various measures taken by regulators to strengthen regulations for clinical trials, an important one was an amendment issued vide Gazette Notification G.S.R. 63 (E) dated February 1, 2013, which specified various conditions for conduct of clinical trials, authority for conducting clinical trial inspections, and actions in case of noncompliance. A new Rule 122DAC has been inserted which mentions that authority of CDSCO is authorized for inspection of clinical trial sites of sponsors and investigators. In case of noncompliance, DCGI can recommend that the study may be rejected or discontinued; suspend or cancel the clinical trial permission, or debar the investigator(s); sponsor including his representative to conduct any clinical trial in future. Subsequent to the above gazette, regulators have conducted few inspections in 2014 of clinical trial sites and sponsors/CROs to supervise clinical research work in India.

CDSCO office has also issued GCPs inspection checklist recently in August 2016 and is helpful for sponsors and sites.

**Other recent regulatory updates**

G.S.R. 313 (E) released dated March 16, 2016, clarified regulators expectations about academic research studies. The said gazette mentioned that no permission for conduct of clinical trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration where the trial is approved by EC, and the data generated are not intended for submission to licensing authority. The EC, however, is expected to inform the licensing authority about the cases approved by it and also about cases where there could be an overlap between the clinical trial for academic and regulatory purposes and where the said authority does not convey its comments to the EC within a specific period of 30 days from the date of receipt of notification; it is presumed that no permission from the licensing authority is required. This can be seen as a facilitatory step to enable setup and conduct of genuine academic research.

Recently, a notification was issued in August 2016 by Directorate General of Foreign Trade under Ministry of Commerce and Industry followed by Gazette S.O. 2612 (E) regarding import/export policy for Human Biological Samples. Requirement of NOC for export of biological samples is no longer applicable. It was informed that customs authorities at the port of entry/exit shall permit export of biological samples without prior approvals from any government agency, provided the concerned firm submits an undertaking confirming adherence to rules for safe transfer, and disposal of biological samples. This is a positive step to facilitate ease of conducting clinical research in the country and has further simplified administrative process for study conduct.

**REGULATORY ENVIRONMENT - FUTURE TRENDS**

The Indian Clinical Research Industry went through a trying phase as already mentioned in 2013 and 2014. However, late in 2014 and in 2015 saw the Indian regulator take steps to mitigate the challenges posed by regulatory uncertainty, and concerns of stakeholders were addressed through amendments in regulations, new orders, and further guidance on existing ones. Figure 2 below clearly depicts rising trend of number of clinical trials being approved in India since 2014.

Among the notable future trends, CDSCO had decided in January 2015 to introduce a system of formal Presubmission Meetings of applicants with CDSCO officers and subject experts to discuss regulatory pathway in respect of a specific application. Although the proposal is currently only in the form of a notice, when implemented in future, the system is expected to bring more transparency, accountability, predictability, and speedy disposal of cases.

CDSCO has recently launched a new tool (SUGAM) for online applications as part of efforts to increase accountability,
transparency, and efficiency of processing applications with speed. Recently, three workshops or meetings have been conducted by CDSCO involving industry members to provide hands-on training and gather suggestions. This approach by CDSCO has been welcome by industry and research organizations. In fact, effective early October 2016,[22] this tool is functional for online clinical trial applications.

If review/approval processes are made simpler and less bureaucratic and consequently if approval timelines are further reduced, then it could be a definite enabler for more clinical studies to be conducted in India.

Seventieth DTAB Meeting held in August 2015[23] agreed to increase validity of test license of imported study drugs from 1 year to 3 years. This proposal if translated to an amended rule in future, the logistic and administrative burden on researchers as well as regulator's office will be further reduced.

As per DRAFT gazette G.S.R. 1011 (E) dated December 29, 2015,[24] fees for various applications was proposed to be hiked with fees for clinical trial application to be increased from current INR 25000 to INR 2.5 lakhs. In future, this fee hike may be expected to be released as a final gazette. While some researchers have expressed concerns over the proposed massive fee hike, stakeholders expect improvement in performance matrices of CDSCO functioning in response to the fee hike.

Internationally, the International Conference on Harmonization (ICH) GCP E6 guideline is being revised to keep pace with the scale and complexity of clinical trials. The ICH E6 (R2) is due to release by end 2016/early 2017. Industry experts already refer to it as an important milestone in driving adoption of Quality-by-design and Quality Risk Management principles and methodologies in clinical development.[25] The ICH GCP E6 (R2) takes this evolution of technology into consideration and encourages sponsors to pursue innovative approaches for conducting and monitoring clinical trials. It also emphasizes on establishing a risk-based quality management system and conducting and reporting centralized monitoring in lieu of traditional monitoring processes. Quality-by-design and risk-based quality management are now recommended as approaches of choice to sponsors of clinical trials. It is worthwhile to watch how Indian clinical research stakeholders adopt these guidelines.

Although there have been various regulatory reforms in the recent past, there are still some areas that require regulatory guidelines to ensure parity with clinical research environments in other countries and facilitate respond appropriately to special needs of the Indian environment, and these areas include stem cell, phase o-micro dosing, medical devices, etc. India now demonstrates that stem cell research and development is not confined to developed countries and has begun to harness stem cells to address its own health-care needs.[26] However, there are considerable scientific, operational, and regulatory gaps in stem cell research in India compared with the developed countries. Indian regulators are responding to these challenges in many ways including establishing regulated stem cell research units and creating task forces to establish guidelines and formalize relevant regulations.

The environment is certainly more positive, but rebuilding trust and confidence is a long and slow process. What has been extremely encouraging is the inclusive approach adopted by the Indian regulators, whereby stakeholder feedback has been actively sought and acted upon in many cases. We now have a regulatory system that is slowly getting more balanced appears to align with global trends and one that addresses our uniqueness as a country and society.

While the value of clinical research in India is being appreciated more, its full potential has yet to be realized. India has 17% of the global population and 20% of the global disease burden, yet its share of all clinical studies being done in the world is ~1.4%.[26] Given that, many of the regulatory challenges of the last 2 years have now been addressed through new amendments and orders; there is a need to rebuild the confidence of global and local stakeholders to strengthen clinical research in India. Based on the fact that the drug regulator has eased norms related to pharmaceutical research, it may boost the number of clinical trials by International Research Organizations for Indian patients.

The most important aspect to be considered for a balanced clinical research environment in India is that participation of Indian patients in clinical trials will only facilitate early approval of innovator drugs in India following its approval by major regulators worldwide.
CONCLUSION

Indian regulations have been evolving positively in the recent past and are expected to be much more conducive for clinical research facilitating faster approval timelines, increased transparency while fully ensuring patient safety. This will help bring newer innovative medicines to Indian patients at an earliest.

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Conflicts of interest
There are no conflicts of interest.

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