Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Drug regulatory framework in India and its differences from Food and Drug Administration, United States

Indra Bhadu[1], Shekhar Goyal[1], Akhil Kapoor *[2], Surender Beniwal[3]

1 Department of Clinical Operations, SIARAM Clinical Research P Ltd., Bikaner, Rajasthan, India.
2 Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical College and AG of Hospitals, Bikaner, Rajasthan, India.
3 Department of Medical Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical College and AG of Hospitals, Bikaner, Rajasthan, India.

ARTICLE HISTORY

Received: 09.08.2014

Accepted: 27.09.2014

Available online: 30.11.2014

Keywords:

Drug regulatory framework, US-FDA, Indian regulatory board.

*Corresponding author:

Email : kapoorakhil1987@gmail.com
Tel.: +91-9950482121

ABSTRACT

Presently the Indian industry is gripped with rising allegations of unethical trials and time-consuming regulatory approvals. Governing intellectual property protection regulatory processes are currently being updated to harmonize with United States 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. This article reviews the differences and similarities between present Indian regulatory board and the internationally acclaimed agency of Food and Drug Administration, United States.

INTRODUCTION

Presently the Indian industry is gripped with rising allegations of unethical trials and time-consuming regulatory approvals. The Indian government has told the apex court of the country that a new law is being framed to regulate clinical trials. The National Institutes of Health (NIH), US, had recently cancelled 40 ongoing clinical trials in India. NIH had blamed the cancellations of the trials on the regulations that the Indian Government has formulated for its clinical studies. Some new amendment makes it mandatory in guidelines for investigators and sponsors to address issues of serious adverse events such as death of subjects involved in trials and mandates grant of adequate compensation in such cases. Claims were made that the Central Drugs Standard Control Organization (CDSCO), which is India's equivalent of the US Food and Drug Administration (FDA), had been too laid back on the issue of compensation in the case of trial-related injuries and deaths until the controversies erupted. This led to turmoil within and outside the India, showing bad impression around the globe, finally facing financial losses.[(1)] [1]

Need for regulatory framework in India

Governing intellectual property protection regulatory processes are currently 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.

Issues in India

SAE (Serious Adverse Event) Compensation

In the last seven years, 2,868 deaths were reported in India during the clinical trials. This brought to light a whole host of issues related to the regulatory system in the country and one of them was the issue of compensation, similarly amended the guidelines and regulations. The Government of India, in an attempt to make reforms in the regulatory environment, formulated new rules to execute clinical trials through the proper way in the country. The amendment made to Schedule Y of the Drugs and Cosmetics Rules, 1945, now makes it mandatory for investigators and sponsors to address issues of serious adverse events such as death of subjects involved in trials and mandates grant of adequate compensation in such cases. It specifies that in case the sponsor fails to provide the proper medical treatment or financial compensation as per the regulatory orders, then the authority may cancel or suspend the license of the sponsor to carry out the clinical trials and may even debar it from carrying any clinical trial in future in India.[(2)] [2]

A need was, however, felt to develop Indian Guidelines to

ensure uniform quality of clinical research throughout the country and to generate quality of data for registration for new drugs before use in the Indian population & community.

Ethical Committee Monitoring

According to DCGI rules 122DD & appendix VIII of schedule Y, every ethical committee (Institutional or Independent) should be registered themselves in DCGI to further review the each & every clinical trials. It has been applied for all industry sponsored or academic projects review purpose. Each & every EC got the unique EC registration number from Indian regulatory bodies. These new rules also highlight that an independent ethics committees would be set up either under medical institutes to monitor ongoing drug trials or coordinate the other studies (Bioavailability or Bioequivalance studies) according to their registration given by CDSCO. This would be helpful to ban the unethical work as well as monitor that EC would follow GCP guidelines and maintain the quality, adequate & accurate data.

Following points are legislative framework governing of India to conduct Clinical research

- Drugs and Cosmetics Act 1940 (Schedule Y guidelines)
- Drugs and Cosmetics (II Amendment) Rules,
- 2005 ICMR guidelines (ICMR bioethics Guidelines).
- DBT Guidelines.
- Medical Council of India Act 1956 (amended in the year 2002)
- Central Council for Indian Medicine Act 1970.
- Guideline for exchange of Biological Material (MOH order,1997)
- Right to Information Act 2005.
- The Biomedical research on Human Subjects (regulation, control and safeguards).
- Acts, rules and codes of ethics of professional bodies regulating the practice of medicine in India, such as the MCI, Department of AYUSH.

The DCGI is responsible for regulatory approvals of clinical trials in India, apart from these legislation's all clinical trials in India should follow the ICMR guidelines of 2000. A clinical trial can only be initiated after obtaining written permission from DCGI and an IEC/IRB.

Drug Regulatory Authority of India

The central drugs standard control organization (CDSCO), headed by the drug controller general (India) (DCGI), discharge the functions allocated to the central government (similar to the US Federal Government) under the Drugs and Cosmetic Act of 1940. The act's main objective is to ensure that available human drugs are safe and efficacious and confirm to prescribe quality standards and marketed cosmetics are safe for use.

The DCGI has statutory authority under the Act with port offices, zonal offices and drug testing laboratories. The DCGI's office is primarily responsible for:

- Approval of new drugs to be introduced in the country.
- Permission to conduct clinical trials.
- Developing regulatory measures and amendments to acts and rules.
- Establishing standards for drugs, cosmetics, diagnostics and devices and updating the Indian pharmacopeia.
- Decide the SAE compensation & management for clinical participant cases
- Inspection or audit the registered Ethics Committee to review the clinical trials data.
- Passed the amended audio video guidelines to every clinical trial participants in India.
- 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.
- To assess the global clinical trial by various committees.
- Monitoring the national or international sponsor agencies which conduct clinical trial in India.
- Coordination the activities of the States/ region and simultaneously advising them on matters relating to uniform administration or management of the Act and Rules in the Country.

Schedule Y in India

Clinical trials in India are regulated by schedule Y of the Drug and Cosmetic Rules 1945,the rules were revised in 2005. Schedule Y defines the requirement and guidelines for import and/or manufacture of new drug for sale or for clinical trials.

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.[3] [3]

- 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.

Table 1. Comparison between Regulatory frame work of India and USA

CONTENTS	INDIA	USA
Authority	CDSCO (Central Drug Standard Control Organisation) /SDSCO (state Drug standard Control Organisation) (responsibilities is divided on centralized and state authorities)	Food Drug and Administration (FDA) (single body regulates the drugs and responsible for all regulatory tasks)
Guidelines	Schedule Y and ICMR bioethics guidelines.	ICH-GCP
Legal framework	Indian directives applicable to all members.	Federal status and regulations applicable to all 50 states.
	National Laws apply.	Individual state laws apply.
	Legal representative required DCGI written approval required to commence Clinical trials	Authorized representative required IND written approval not required to proceed commences Clinical trials.
	Approval time frame varies, before that Clinical Trials not proceeds further.	May proceed 30 days after FDA receives IND unless notified otherwise.
	Progress report required to submit every six month.	IND annual report required
	Schedule Y Format paper or electronic (CTD format is optional)	It is mandatory that the dossier prepared in CTD format
	Fees apply	No fees apply
IRB/IEC (Institutional Ethics Committee)	Single review process Registered IEC approval required EC appointed or authorized	2 review process : Normal and accelerated review process IRB (Institutional Review board) approval required IRB registration required
EC Composition	-At least 5-7 members. - The quorum should have a minimum 5 members. - Member secretary belongs to the same institution.	- At least 5 members. - Not detailed. - Not recommended.

Conduct of Clinical trials	Undertaking by the Principal Investigator as per Appendix VII of Schedule Y of Drug and Cosmetic Rules.	Form FDA 1572 is required to be signed by the PI, if study is conducted in US and submitted to IND.
	Form 44, 12, Certification of Analysis, PIS & ICF as per Appendix V of Schedule Y.	Form FDA 3674 certification that all requirements of section 402 (j) of PHS Act are met.
	Protocol amendment implementation varies. Protocol waivers considered a breach of GCP (Good Clinical Practice).	Protocol amendments may be implemented once received by FDA, with exceptions (eg. safety issued or protocol study design issues). Protocol waivers are acceptable under certain circumstances.
Informed Consent Process	Patient & Investigator's should sign in the consent form. Investigator, subject & subject's LAR audio video consent recording would be mandatory.	Any one designated by the investigator to conduct and to sign the consent form.
Record Retention	Record retention for at least 3 years.	Record retention 2 yrs after marketing application is approved. Record retention 2 yrs after last shipment and delivery of Investigational Manufacturing Product if marketing application is not approved.[4]
IMP requirement	Label language requirement varies between states.	Label must be I English, except for Puerto Rico.
	Label should include the name and contact numbers of investigator and name of the institute.	The following statement is required "Caution: New drug united by federal law to investigational use."
Regulatory Compliance	Schedule Y (Refer to Rules 122A, 122B, 122D, 122DAA & 122E)	All clinical trials must comply with 21 CFR parts 50, 54, 56, 58 and 312.
Time for Regulatory Approval of Clinical Trial Agreement/ IND Application	Category A: 2-4 Weeks Category B: 8-12 Weeks.	30 days
Time for Evaluation of MAA (marketing authorisation application)	8-12 weeks	180 days
MAA Fee	50,000 INR	$217,787

- A separate application or documents is required for shipping biological / genetic samples collected during the trial (e.g., body fluids) out of India.

- 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 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 one month of implementation.

- All unexpected serious adverse events (SAEs) must be communicated to the DCG(I), EC and sponsor by study investigators within 24 hrs. 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. Detailed report would be submitted to DCGI and EC within 10 days as per new guidelines.

- In India every clinical trial should be audio video consenting of the informed consent process along with written consent of each trial subject. Audio video consent is another best mechanism intended to improve the quality of ICF. An audio video consent of the informed consent process will protect both the subjects and the investigators.

- 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.

Schedule Y includes format and examples of all documents to be submitted to the DCG(I). Table 1 compares the regulatory frame work of India and USA.[4] [4]

CONCLUSION

The regulatory boards play a key role in the safe and orderly conduction of clinical trials in any country. There are few important differences between the constitution and methodology of various regulatory boards across the world. These must be considered while formulating international trials so that they can comply with the regulations of all the authorities.

REFERENCES:

1. Biospectrumasia.com [Internet]. Singapore: BioSpectrum Bureau. Indian government framing new clinical trial law. Cyber Media (India) Ltd. Published online on 26/07/13. Available from: http://www.biospectrumasia.com/biospectrum/news/192428/indian-government-framing-clinical-trial-law

2. Biospectrumasia.com. India: Sukhija S. India's regulatory framework needs lot more work. Cyber Media (India) Ltd. Published online on 29/08/13. http://www.biospectrumasia. com/biospectrum/analysis/194395/india-suffers-adverse-effect-clinical-research/page/2?WT.rss_a=india+suffers+adverse+effects+of+clinical+research&WT.rss_f=home

3. Regulatory Considerations for conducting clinical trials in India, by Mukesh Kumar,PhD & Surinder Kher, MD. 26 March 2007 Read on: http://www.readbag.com/amarexcro-articles-docs-raps-focus-mar2007

4. Clinical trial requirements: similarities and differences. By Anita Fenty, Covance, Inc; available at http://www.slideshare.net/RETIRE/clinical-trial-requirements-us-vs-eu-similarities-and-differences