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"New Drugs and Clinical Trials Rules-2018" (GSR-104 E) by CDSCO: It's Impact on BA/BE Studies in India

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Abstract

India is the largest provider of generic drugs globally with the Indian generics accounting for 20% of global exports in terms of volume. Comparative pharmacokinetic data under the regulatory framework of bioavailability and bioequivalence (BA/BE) study data is widely accepted by the developed countries regulatory agencies over last 4 decades to establish the efficacy of the generic products. Ministry of Health and Family Welfare, Government of India recently published the 'New Drugs and Clinical Trials Rules-2018' vide gazette notification (GSR-104E) dated 01/02/2018. An elaborate and streamlined regulations for conducting clinical research (CT and BA/BE studies) in India has been provided in the said draft rule. It was available in the public domain for the responses of different stakeholders which will be wrapped up in near future. In the present paper, significance of the new clinical trials rules-2018 particularly in the field of BA/BE studies have been tried to capture.

Keywords: Drugs; Pharmacokinetic; Plasma drugs

Abbreviations: CDSCO: Central Drugs Standard Control Organization; DCGI: Drugs Controller General of India; CLA: Central Licensing Authority; SLA: State Licensing Authority; DTAB: Drug Technical Advisory Board; BA/BE: Bioavailability/Bioequivalence; CT: Clinical Trial; CRO: Contract Research Organizations; BCS: Biopharmaceutical Classification System; API: Active Pharmaceutical Ingredients.

Overview

India adores a very significant position in the global pharmaceuticals market. With 1.2 billion people and wide variety of diseases and patient pool makes this country very attractive to the pharmaceutical companies for conducting clinical research (Clinical trials, BA/BE studies). Besides large and diverse patient pool, we also have a large pool of pharmacist, scientists and engineers who are potential enough to steer the pharmaceutical industry to a higher level. India is the largest provider of generic drugs globally with the Indian generics accounting for 20% of global exports in terms of volume [1]. But in recent past (5/6 years back), numerous discrepancies were brought into public and government notice which compelled them to become strict and frame stringent regulations for the testing of new drugs in India to ensure the safety of the patients or subjects [2]. As a result various pharmaceutical companies moved their research to some other counties which led India a potential loss in every aspect. This compelled Indian regulators as well as the members of Drug Technical Advisory Board (DTAB) for framing of "New Drugs and Clinical Trials Rules-2018". The gazette notification on first February, 2018 by the Ministry of Health and Family Welfare of Government of India via GSR-104 (E) was released as a draft for the responses addressed by different stake holders [3]. Preamble of said notification clearly indicates that the Part-XA and Schedule-Y of the Drugs and Cosmetics Rules-1945, and section 12 and 33 of the Drugs and Cosmetics Act-1940 are going to be abolished after its final publication [3]. Indian regulatory board, Central Drug Standard Control Organization (CDSCO) plans to start a single-window facility to provide consents, approvals and other necessary permissions. This move is aimed for giving a push to the widely chatted 'Make in India' initiative which is a part of the 'Pharma Vision 2020' by the Indian Government [4,5]. The Drugs Controller General of India (DCGI) is also trying to reduce the approval time required for reviewing trial applications to boost investments.

Highlights of the draft CT Rules- 2018

The draft notification of the rule contains 12 chapters and 8 schedules. This will be applicable to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study as well as ethics Committee. Previously, proper definitions were lacking which was properly addressed in the present rule and clear definitions as well as features were provided for academic study, the role of central licensing authority, trial protocol, biomedical and health research. Clinical research has to be carried out in humans to generate safety, efficacy and tolerance data for a new drug or investigational new drug covering the pharmacology, interactions, adverse events, pharmacokinetics, pharmacodynamics etc. the comprehensive power to review, permit or inspect clinical trial has been abridged to the Central Licensing Authority (CLA) or Drugs Controller general of India (DCGI). The CLA denotes to the Central Drugs Standard Control Organization (CDSCO). Pharma companies conducting clinical trials in India will no longer be able to escape form their accountability in case of injury or death of the trial participants. According to new draft rules for clinical trials and new drugs, if the sponsor fails to provide "medical management" to trial participants, not only will the trial be cancelled, but the company will also be restricted from holding any more trials. The stringent steps has also been proposed like debarring the CRO, blacklisting the site, investigator, penalty along with imprisonment etc [6,7]. But, if we consider the positivity, a smooth and time bound frame was proposed for the permission of clinical trials like below---

Proposed timeline for processing of application:

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- Clinical trial (in general): 90 days
- CT (innovated in India): within 45 days
- CT (if drug is already approved by other country): within 60 days
- New drug: within 90 days
- Processing of Import License: 7 days
- If the central licensing authority fails to communicate, the "permission to conduct the clinical trial shall be deemed to have been granted".

Conceptual Overview of BA/BE Studies

Availability of the generic products in the market has been gained serious public consideration in respect of their safety and efficacy with the innovator products. Bioequivalence (BE) studies with a view to demonstrate therapeutic equivalence between two drug products (test and reference or innovator) can able to answer this public concern internationally. The concept of BA/BE study was developed and accepted by the developed countries regulatory agencies over last 4 decades. In the early 1970's, the "United States Food and Drug Administration" (US-FDA) became interested in biological availability of new drugs. They formed a committee to establish the pharmaceutical and therapeutic equivalence relationships of drugs which later on implemented as the Code of Federal Regulations (CFR) for the regulations of bioavailability [8,9]. Pharmacokinetics is the application of mathematical calculation and modeling techniques to the time course of absorption, distribution, metabolism, and excretion of drugs in the body. It is primarily concerned with the analysis of concentration and rate of drug availability to the required receptor site. Analysis of plasma samples will target concentration of drug as time progresses, resulting in the production of a 'plasma drug concentration-time curve'. Plasma drug concentration time curve can be obtained after a single oral dose of a drug by measuring concentration of drug in plasma samples taken at various intervals of time and plotting the concentration of drug in plasma *vs*. corresponding time at which plasma samples were collected. BE study can be coined as the comparative pharmacokinetic study, where the bioequivalence was established based on the following parameters of test and innovator drug product-- maximum plasma concentration (Cmax), time to reach the maximum plasma concentration (Tmax), half-life ($t_{½}$): time taken for the plasma concentration to fall by 50% and area under the plasma concentration curve (AUC): a calculation to assess the bodies total exposure to a drug over a given time [10,11]. There are many generic products are available in the markets and it has become a public concern that these products are similar to that of innovator in terms of safety and efficacy. Therefore a valid evaluation is necessary to guarantee the quality of these products. The use of BA/BE studies can save a lot of time required for the drug discovery as well as the huge cost for the developments of the drug molecules used to spend by the pharma companies. These intensified the importance of such studies to the pharmaceutical industry, contract research organizations (CRO) as well as regulators.

CROs Conducting BA/BE Studies: Indian Scenario

In India, as per CDSCO requirements, BE study reports are required in the case of subsequent generic versions of an approved new drug (oral formulation) if it falls within a period of four years. No bioavailability or bioequivalence study of any new drug or investigational new drug shall be conducted in human subjects by any person or institution or organization except in accordance with the provisions of the Act and these rules. The study protocol also has to be cleared by the ethics committee and prior approval is required form the CDSCO office before initiation of the study.

As on date (May, 2018), CDSCO approved only 82 bioequivalence study center in India [12]. A state wise summery is depicted in Figure 1. The approval of the BE study center is based upon the clinical facility and analytical facility which is clearly mentioned in the approval letter of each and individual center in India. It is evident form the Figure 1 and Table 1, that the majority of these study centers are situated in Gujarat and Maharashtra (40 out of 82). The southern part of India is also having 31 centers mainly in 3 states- Karnataka, Andhra Pradesh and Tamil Nadu. Other Indian states are lacking behind in numbers. Besides bioequivalence study centers, the Indian regulatory agency (CDSCO) also approved bio-analytical facilities. Though the number of such approved bio-analytical facilities is very handful, only 10 (Table 2) and mainly located in the western and southern part of Indian states (Figure 2). Under this circumstance, in 2013, expert committee headed by Prof. Ranjit Roy Choudhary had recommended to make bioequivalence studies compulsory for all generics irrespective of when they were approved [13]. But the recommendations were not implemented because of the infrastructure for conduct of such studies is not uniformly available in India. However the pressure compels the Indian Regulators to frame a scientific and universally considered approach based on Biopharmaceutical Classification System (BCS). Any drug molecule can be classified according to BCS as per Table 2 depending upon the dissolution, solubility and intestinal permeability [14]. As a result, Ministry of Health and Family Welfare, Govt. of

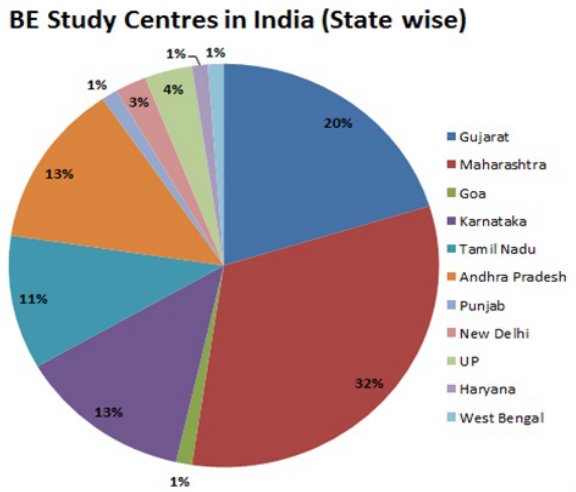

Figure 1: Sate-wise BE Study Centers in India.

CDSCO Zones	State	No. of Centers	
		BE	BA
West Zone	Gujarat	17	3
	Maharashtra	27	3
	Goa	1	Nil
South Zone	Karnataka	11	1
	Tamil Nadu	9	Nil
	Andhra Pradesh	11	3
North Zone	Punjab	1	Nil
	New Delhi	2	
	UP	3	
	Haryana	1	
East Zone	West Bengal	1	Nil
Total		**84/82**	**10**

Table 1: Approved Bioequivalence Study Centers (BE) and Bio-analytical Facilities (BA) in India.

India comes with an amendment of Drugs and Cosmetics Rules, 1945 via GSR-327(E) on 3rd April, 2017, which mandates the Indian drug manufacturers to submit the result of bioequivalence study for obtaining the license from CDSCO for the drugs categorized as BCS class-II and IV [15]. Such positives changes in Indian regulatory requirements encouraged the regulators for the conscripting of new draft clinical trials rules-2018. It was much needed to incorporate all the amendments published in recent past.

Salient Features of 'New Clinical Trials Rules-2018': Impacts on BA/BE Studies

Present paper is focused particularly on BA/BE study related part of the New Drugs and Clinical Trials Rules, 2018. Two important clause have been incorporated regarding the required documents dossier of BE study center for CDSCO registration. The center have to furnish the details written procedures (may be SOP or policy) to ensure impartiality, confidentiality, independence and integrity of the center. We have experienced a numerous cases of falsification of data, breaches of confidentiality, violation of existing rules and regulations under various pressures [16,17]. These also reflected in the allegations made by the whistleblowers as well as the regulators of other countries. An attempt was made in this rule to concrete the credibility of the generated data. Fundamental importance was given on identifying different divisions of a CRO (BE study center). Initially the approval is based on the clinical pharmacology unit and analytical unit [18]. But the present rule directs to specifies for separation and identification of the following units with properly qualified and trained staffs well versed with good clinical practice (GCP) guidelines besides CPU and analytical-- data management and statistics, documentation and report compilation as well as quality assurance of each and individual functional units of the study center. Clear documentation along with adequate facility for archival of the study data, reports along with retention of samples are prioritized in the present rule [3]. These requirements were not vibrant previously. However, the changes can be considered distinctly into two ways-a) Facility specific and b) Study specific.

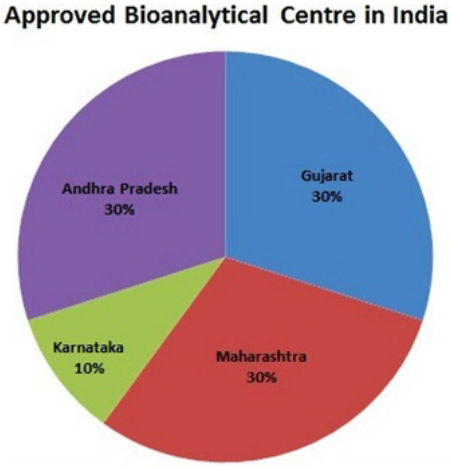

Figure 2: CDSCO approved Bio-analytical facilities in India.

Facility specific changes

- A definition had been provided as follows--"bioavailability and bioequivalence study center" means a center created or established to undertake bioavailability study or bioequivalence study of a drug for either clinical part or for both clinical and analytical part of such study.
- A BA/BE Study Centre has to be registered with the CLA. The center has to apply for the registration with the specified format. Form CT-08 has been introduced for the said purpose.
- Central Licensing Authority *i.e.* Drugs Controller General of India has been imposed a fees of Rs. 5 Lakhs for the approval of a BA/BE study center, which was nil previously.
- Reconsideration of application for registration of BA/BE study center will be charged of Rs. 1 Lakh.
- Validity Period of registration of a BA/BE Study Center will be five years from the date of its issue, unless suspended or cancelled.
- A BA/BE Study Center have to furnish the approval for renewal at least three months prior to date of expiry of its registration in form CT-08.
- BA/BE study Centre have to have a Registered Ethics Committee (may be Independent or Institutional). Ethics Committee registered with CDSCO will be played the role of the local regulators.
- If the center doesn't have any registered ethics committee, some other registered ethics committee, located within the same city or within a radius of 50 km of the center, can be approached to review and approve the study protocols of the center.
- BA/BE Study of investigational new drug shall be registered with the Clinical trial Registry of India (CTRI) before enrolling the first subject in the study.
- Archival have to be maintained for a period of five years after completion of study or for at least two years after the expiration date of the new drug or investigational new drug studied whichever is later.
- Representative of the State Licensing Authority (SLA) can accompanied with Central Licensing Authority for inspection purpose.

BCS	Permeability	Solubility	Remarks
Class I	High	High	Those compounds are well absorbed and their absorption rate is usually higher than excretion
Class II	High	Low	The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found
Class III	Low	High	The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
Class IV	Low	Low	Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

Table 2: Biopharmaceutical Classification System (BCS).

Study specific changes

- The sponsors have to apply to the CDSCO for obtaining permission to conduct BA/BE study. Different formats have been incorporated for different purposes as per specific requirements which are elaborated in the Table 3.
- Different fees structures as per the requirements of sponsors have also been provided in this new rule. As for example---

➢ Permission to conduct BA/BE study ---Rs. 2 Lakhs.

➢ Reconsideration of application of permission to conduct BA/BE study---Rs. 50,000/-.

➢ Permission to manufacture of new drugs or investigational new drugs for CT or BA/BE study--- Rs. 5,000 per product.

➢ Reconsideration of application to manufacture of new drugs or investigational new drugs for CT or BA/BE study- Rs. 2,000 per product.

➢ Permission to manufacture unapproved API for development of formulation for test or analysis or CT or BA/BE study -Rs. 5,000 per product.

➢ Reconsideration of permission to manufacture unapproved API for development of formulation for test or analysis or CT or BA/BE study-Rs. 2,000 per product.

➢ Import license processing of new drugs or investigational new drugs for CT or BA/BE study---Rs. 5,000 per product.

➢ Reconsideration of application for import of new drugs or investigational new drugs for CT or BA/BE study -Rs. 1,000 per product.

➢ No fees will be required for the institutions owned or funded wholly and partially by the Central/ State Government for conducting BA/BE study.

- The permission to conduct BA/BE study will be given within 90 days if the documents found satisfactory and the same will be valid for one year.
- The CLA can take the following steps if they are not satisfied with the documents or inspection--

➢ Suspend the BA/BE study

➢ Rejecting the study results

➢ Debarring the Principal Investigator

➢ Suspend the BA/BE study center

➢ Cancellation of registration of the study center

Forms	Purpose
CT-01	Application for Registration of Ethics Committee
CT-02	Grant of Registration of Ethics Committee related to CT or BA/BE study
CT-03	Grant of Registration of Ethics Committee relating to Biomedical Health Research
CT-04	Application for Grant of Permission to conduct CT of New drug or Investigational New Drug
CT-4A	Information to initiate CT of New Drug or Investigational New Drug
CT-05	Application for Grant of Permission to conduct BA/BE Study
CT-06	Permission to conduct CT of New Drug or Investigational New Drug
CT-07	Permission to conduct BA/BE Study of New Drug or Investigational New Drug
CT-08	Application for Registration of BA/BE Study Centre
CT-09	Grant of Registration of BA/BE Study Centre
CT-10	Application for Permission to Manufacture New Drug or Investigational New Drug for CT or BA/BE Study
CT-11	Permission to Manufacture New Drug or Investigational New Drug for CT or BA/BE Study
CT-12	Application for Grant of Permission to Manufacture Formulation of Unapproved Active Pharmaceutical Ingredient (API) for Test or Analysis or for CT or BA/BE Study
CT-13	Application for Permission to Manufacture Unapproved Active Pharmaceutical Ingredient (API) for Development of Formulation for Test or Analysis or CT or BA/BE Study
CT-14	Permission to Manufacture Formulation of Unapproved Active Pharmaceutical Ingredient (API) for Test or Analysis or CT or BA/BE Study
CT-15	Permission to Manufacture Unapproved Active Pharmaceutical Ingredient (API) for the development of Formulation for CT or BA/BE Study
CT-16	Application for Grant of License to Import New Drug or Investigational New Drug for CT or BA/BE Study
CT-17	License to Import New Drug or Investigational New Drug for the Purpose of CT or BA/BE Study
CT-18	Application for Permission to Import New Drug for Sale
CT-19	Permission to Import New Active Pharmaceutical Ingredient (API) for Sale
CT-20	Permission to Import Pharmaceutical Formulations of New Drug for Sale
CT-21	Application for Permission to Manufacture New Drug for Sale or Distribution
CT-22	Permission to Manufacture Active Pharmaceutical Ingredient (API) for Sale or Distribution
CT-23	Permission to Manufacture Pharmaceutical Formulation of New Drug for Sale
CT-24	Application for License to Import of Unapproved New Drug for Treatment of Patients of Life Threatening Disease in a Government Hospital or Government Medical Institution
CT-25	License to Import Unapproved New Drug for Treatment of Patients of Life Threatening Disease in a Government Hospital or Medical Institution
CT-26	Application for Permission to Manufacture Unapproved New Drug but Under CT for Treatment of Patients of Life Threatening Disease in a Government Hospital or Medical Institution
CT-27	Permission to Manufacture Unapproved New Drug but under CT for Treatment of Patients of Life Threatening Disease in a Government Hospital or Medical Institution

Table 3: Different forms for conducting clinical research [3].

Conclusion

The recommendations of the expert committee headed by Prof. Chowdhury and the gazette notification regarding report of BA/BE studies as per BCS classifications put the manufacturers into do or die situation. The mandatory requirement of safety and efficacy data of all the generic products manufactured is essential for the product registration. As a result the CRO's engaging in conducting BA/BE studies have experiencing a tremendous pressure. Moreover, the increasing number of products of Indian pharma companies for export made the situation more complex. Undoubtedly this boost helped the Indian CROs in growing their business. Under these circumstances the need for up gradation of the regulatory requirements was very much needed. The Indian Regulators had been in a process to strengthen the regulations of clinical research in recent past after reporting of some incidents---like as--subjects being enrolled into trials without informed consent, not being adequately compensated, not informed to the regulatory authorities, anomalies in ethical perspective etc. [19-21]. The rules were framed with a well-adjusted view in favor of the sponsors (Pharma Industry) as well as trial subjects. In spite of the commercial pressure, the Indian regulators are able to frame the draft guidelines which are really appreciated. The challenge will be to ensure that clinical research organizations engaged in conducting bioequivalence studies do not commit fraud in future as some scary incidents happened in recent past where they have been caught red-handed by foreign regulators. The role of the EC has also been expanded and has been made vital to any CT or BA/BE study.

Besides the massive positive moves, some lacuna was spotted, like--

- There were no specific guidelines regarding the selection of the reference product.
- Specific guidelines for the specific product may be introduced like US-FDA.
- The submission BE study data of the generic products become mandatory but what about after approval or product registration? It can be highly appreciable if the same has been instructed for every 3 years interval.

However, it is much simpler, well sequenced with comprehensive directives as well as instructions in comparison to the pervious rules and their subsequent amendments. The Indian government has taken many steps to reduce costs and bring down healthcare expenses. Speedy introduction of generic drugs into the market has remained in focus and is expected to benefit the Indian pharmaceutical companies. Discrepancies in the regulatory guidelines can able to make a negative impact on that. Therefore, in the proposed draft clinical trial rules attempts was made to recover the anomalies experienced in all possible aspects. This is able cover the full scale of clinical research activities (CT and BA/BE studies), functioning of ethics committees and manufacturing permissions to inspections, medical managements of the trial participants as well as compensation for injury or death. This streamlined draft guideline will surely able to retain the quality assurance of the clinical research conducted in India with ensuring the safety- wellbeing-ness of the trial participants and integrity of data after its official publication for implementation.

Conflict of Interest

None

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