Regulations & Guidelines in India for Clinical Trials / Research

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Drug Regulatory Status In India

- Drug is in concurrent list
- Import, Manufacture, Sale and Distribution of Drugs in the country is regulated under Drugs & Cosmetics Act 1940 and Drugs and Cosmetics Rules, 1945 made there.
- Central Government through DCG (I) regulates imports, introduction of new drugs and making legislation.
- Manufacture/sale and monitoring of quality of drugs in the country is looked after by respective State Governments through their drug control organisation.
GOVERNMENT OF INDIA
MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health)
THE DRUGS AND COSMETICS ACT AND RULES
THE DRUGS AND COSMETICS ACT, 1940
(As amended up to the 30th June, 2005)
and
THE DRUGS AND COSMETICS RULES, 1945
(As amended up to the 30th June, 2005)
The Main Objectives of D&C Act 1940 :-

• The Drugs and Cosmetics Act provides the Central Legislation, which regulates import, manufacture, clinical trials, sale & distribution of drugs and cosmetics in the country.

• The Drug is also to ensure that the ‘Drugs’ available to the patient population are safe and efficacious for use.
Drugs & Cosmetics Act -

• Drug and Cosmetics Act 1940 is contain:
• Two Schedules - **First Schedule** for Names of the Books under Ayurveda & Siddha system.
• **Second Schedule** for Standards to be complied with by imported drugs and drugs manufacture for sale, stock or exhibited sale or distribution.
Drugs & Cosmetics Act

- The Act Contains Part –I - five Chapters which includes 38 different Sections.
- Part II of the Act is – **Drugs and Cosmetics Rules 1945**, The D&C **Rules** contains 19 parts (Part XIX).
- Part X-A is for ‘IMPORT OR MANUFACTURE OF NEW DRUG FOR CLINICAL TRIALS OR MARKETING.
- There are currently **172 Rules**, followed by Schedule A to Y
- **Schedule Y** is for” **Requirements & Guidelines for permission to import and /or manufacture of New Drugs for sale or to undertake Clinical Trials”**.
New Drug

- **122-E** New Drug Definition

- Not been used in the country under labeling conditions

- Approved but now proposed to be marketed with new claims – indications, dosage, dosage form, (modified) route of administration

- FDC individually approved drug and it is to be combined for the first time in a fixed ratio or if ratio is changed.

- Vaccines and r-DNA derived products are new drugs unless otherwise certified

- Considered new drug for 4 years from date of first approval or inclusion in IP
Different Categories of New drugs

- Investigational New Drug (IND)
- New Chemical Entity
- New Molecules Approved/Marketed Outside India
- New Dosage Form
- New Indication,
- New Route of Administration,
- New Strength,
- Modified Dosage Form of Approved Drugs
- New Fixed Dose Combination
- New Drugs Already Approved In the Country, Less than Four Years.
Investigational New Drug - IND

- New chemical entity (NCE) or a product having therapeutic indication but which has never been earlier tested on human beings
- All IND applications are reviewed and evaluated by IND Committee, under the Chairmanship of DG ICMR.
GCP

• A **standard** for clinical studies or trials that encompasses the **design**, **conduct**, **monitoring**, **termination**, **audit**, **analyses**, **reporting** and **documentation** of the studies.

• It ensures that the studies are implemented and reported in such a manner that there is **public assurance** that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects are protected.
Structure of GCP Guidelines

ICH E6
- Glossary
- Principles
- IRB/IEC
- Investigator
- Sponsor
- Protocol
- Investigators’ Brochure
- Essential Documents

Indian GCP
- Definitions
- Pre-requisites
- Responsibilities
- Records & Data
- Quality Assurance
- Statistics
- Special Concerns
- Appendices
GOOD CLINICAL PRACTICES

Guidelines for Clinical Trials on Pharmaceutical Products in India

Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health & Family Welfare, Government of India
New Delhi.
INDIAN GCP BOOKLET : 2001

CONTAINS

• Definitions, Pre-requisite of the Study,
• Protocol, Relevant components of Protocol,
• Ethical & Safety consideration,
• Inform Consent Process, Compensation for subjects,
• Responsibility-Sponsor, Monitor & Investigator,
• Record keeping & Data Handling,
• Quality Assurance, Statistics
• Special Concerns- C/T Vaccines, Contraceptives, Devices, Herbal Remedies & Medicinal plants;
• Five Appendices- Sch-Y, Decl. of Helsinki, r-DNA product requirement, IB and Essential Documents.
Current Regulations

**Schedule Y**
Requirements and Guidelines for clinical trial and approval of new drugs

**Indian GCP**

**Ethical Guidelines for Biomedical Research on Human Subjects (ICMR)**

**Related Rules**
Drugs & Cosmetics Act
What is regulated under the Act:

- Manufacture
- Distribution
- Import
- Sale

Act
What is regulated under Rules

- Clinical Trials
- New Drugs
- Exports
Functions of CDSCO

- Approval of New Drugs and Clinical Trials
- Import Registration and Licensing
- Licensing of Blood Banks, LVPs, Vaccines, r-DNA products & some Medical Devices
- Amendment to Drugs & Cosmetics Act and Rules
- Banning of Drugs and Cosmetics
- Grant of Test License, Personal License, NOCs for Export
- Testing of Drugs and Registration of Ethics Committee
Functions of State Licensing Authorities

- Licensing of Manufacturing Site for Drugs including API and Finished Formulation
- Licensing of Establishment for sale or distribution of Drugs
- Approval of Drug Testing Laboratories
- Monitoring of Quality of Drugs and Cosmetics marketed in the Country
- Investigation and prosecution in respect of contravention of legal provision
- Recall of sub-standard drugs
Approval of Clinical Trials, Import & Manufacture of New Drugs

Requirements and Guidelines - Schedule Y

Rule 122 A
Permission to import new drug

Rule 122 B
Permission to manufacture new drug

Rule 122 DAA
Definition of Clinical trials

Rule 122 E
Definition of New Drugs*

- New substance having therapeutic indication
- Modified or new claims, new route of administration for already approved drug
- Fixed Dose Combination
### Legal Provisions for regulation of Clinical Trials

- **Schedule Y- 2005**

<table>
<thead>
<tr>
<th>Rule 122 DA</th>
<th>Permission to conduct clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule 122 DAA</td>
<td>Definition of Clinical trials</td>
</tr>
<tr>
<td>Rule 122 DAB</td>
<td>Compensation in case of trial related injury or death</td>
</tr>
<tr>
<td>Rule 122 DAC</td>
<td>Conditions of Clinical Trial permission &amp; Inspection</td>
</tr>
<tr>
<td>Rule 122 DD</td>
<td>Registration of Ethics Committee</td>
</tr>
<tr>
<td>Rule 122 E</td>
<td>Definition of New Drugs</td>
</tr>
</tbody>
</table>

**GCP Guidelines, 2001**
Phases of Clinical Trials:

- **Phase I:** (Human Pharmacology) Small group [20-80] for 1st time to evaluate safety, determine safe dosage range (MTD) & identify SE in human.

- **Phase II:** (Therapeutic Exploratory Trials): New drug given to larger group [100-300] to confirm effectiveness, monitor SE, & further evaluate safety.
**Phases of Clinical Trials (cont.)**

- **Phase III:** (Therapeutic confirmatory trials): New Drug given to even larger group [1,000-3,000] to fulfill all of Phase II objectives & compare it to other commonly used approved new drug & collect data that will allow it to be used safely.

- **Phase IV:** (Post Marketing Trials): Done after new drug has been marketed - studies continue to test new drug to collect data about effects in various populations & SE from long term use.
What Is Schedule Y

• It is “Schedule under Part X-A of Drugs & Cosmetics Rule 1945” describe the information/data required for approval of Clinical Trial and/or to import or manufacture of new drug for marketing in India.

• It is also describe the pre-clinical, animal studies requirement, including toxicity studies.

• There are Template for Clinical Trial Protocol, Inform Consent, Trial Report Submission etc.
Salient Features of Schedule -Y

• Concurrent phase global clinical trials permitted,
• Phase I (first-in-human) study of New Drug substance discovered outside the country, not permitted (Repeat Phase I is permitted)
• Provides statutory support to Indian GCP Guidelines & ICMR- BIO-Ethics Guidelines.
• Stipulates responsibilities of EC, Investigators and Sponsor.
• Structure, contents and formats for CT protocols, reports, EC approvals, ICF, SAE reporting are incorporated.
• There are 12 Appendices.
Drugs And Cosmetics Act And Rules

• **Rule 122DA.** Application for permission to conduct clinical trials for New Drug/Investigational New Drug.

• **Rule 122DAA.** Definition of Clinical trial.--For the purpose of this Part, “Clinical trial” means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug.]

• **Rule 122DB.** Suspension or cancellation of Permission/Approval.
Drugs And Cosmetics Rules

• **Rule 122 DAB.** – Compensation in case of injury or death during clinical trial. (G.S.R. 53 (E) dated 30th January 2013).

• **Rule 122 DAC.** Permission to conduct Clinical trial. (G.S.R. 63 (E) dated 1st February 2013).

• **Rule 122 DD.** Registration of Ethic Committee, (G.S.R. 72 (E) dated 8th February 2013).

• **Amendment to Rule 122DAB** – G.S.R. 889(E) dt. 12-12-2014; Clarifications on the criteria for eligibility of compensation. (effective from 13th June 2015)
Important Appendices of Schedule Y

Appendix I:

Data to be submitted along with Form 44 to
- Conduct clinical trial
- Import and
- Manufacture of New Drugs for marketing in the country

( Rule 122 E is Definition of New Drugs)
Appendix I–A

Data required along with Form 44 for grant of permission

- To import and / or
- Manufacture new drugs already approved in the country (within period of 4 years, mainly for Subsequent Applicants)
Appendix II

- Structure
- Contents &
- Format for clinical study reports

Appendix-III (Animal toxicology-Non clinical toxicity studies)

- Systemic toxicity studies
- Male fertility study
- Female reproduction & Dev toxicity study
- Local toxicity, Dermal toxicity, Photo-allergy toxicity studies,
- Allergenicity, hypersensitivity
- Genotoxicity
- Carcinogenicity
Appendix IV
- Animal pharmacology

Appendix V
- Informed consent

Appendix VI
- Fixed Dose Combinations (FDCs)

Appendix VII
- Undertaking by the investigator

Appendix VIII
- Ethics committee

Appendix IX
- Stability Testing of new drugs
Appendix X
- Contents of the proposed protocol for conducting clinical trials

Appendix XI
- Data elements for reporting serious adverse events occurring in a clinical trial.

Appendix XII
- Compensation in case of injury or death during Clinical trial. (Rule 122 DAB) (GSR No. 53-E, 30th Jan 2013)
Subject Expert Committee (SEC)  
(Earlier NDAC)

• Since April 2011, **Twelve** New Drug Approval Committees (NDACs) (Now SEC) were constituted to advise DCG(I) in matters related to review and regulatory approval of clinical trials and new drugs {except INDs} of **12** different therapeutic categories.

• Details of the **SECs** along with the names of the committee members are posted at CDSCO website  [www.cdsco.nic.in](http://www.cdsco.nic.in)
Procedure for evaluation of Clinical trial & New Drug Applications at DCG(I) OFFICE:

• Since April 2011, as Min of Health Letter No.X-19029/5/2011-DFQC, it has been decided to constitute a NDAC, now “Subject Expert Committee” (SEC) (as per Order 3rd July 2014) to advise DCG(I) in matter related to review & regulatory approvals of clinical trials and new drug (except IND) of following categories:

1. SEC: Oncology & Hematology
2. SEC: Cardiovascular and Renal,
3. SEC: Metabolism & Endocrinology,

Contd:
Contd:-

4. **SEC**: Antimicrobial, Anti parasitic, Antifungal & Antiviral,
5. **SEC**: Reproductive & Urology,
6. **SEC**: Gastroenterology & Hepatology,
7. **SEC**: Dermatology and Allergy,
8. **SEC**: Pulmonary
9. **SEC**: Neurology & Psychiatry,
10. **SEC**: Analgesic, Anesthetic & Rheumatology,
11. **SEC**: Ophthalmology,
12. **SEC**: Vaccines.

( Details regarding names & addresses of subject Experts may be seen at [www.cdsco.nic.in](http://www.cdsco.nic.in) )
Recent Amendments:

- Since January 2013, CDSCO has announced following significant changes in form of laws & guidelines in clinical trial sector in India:- (http://www.cdsco.nic.in)
- **GSR 53 (E)**: Specifying the procedures for payment of compensation to the subjects of clinical trial in case of injury or death,
- Expert committee to advice CDSCO on compensation,
- Formula to determine the quantum of compensation in case of SAE of deaths occurring during C/T. (Guidance document at CDSCO web-site)
- **GSR 63 (E)**: Specifying various conditions for conduct & inspection of clinical trials;
- **GSR 72 (E)**: Specifying the detailed guidelines for Registration of Ethics Committee;
- Apex committee & Technical committee to supervise and monitor clinical trials,
- Expert committee to formulate policy, guidelines, SOPs, for approval of new drugs, clinical trials & banning of Drugs (Dr. Roychaudhary Committee)
Guidance Documents issued by CDSCO


- **Draft Guidance** - Requirements for permission of Drug Approvals - posted on 04-12-2008.


- **Draft Guidance** - Requirements for permission of Fixed Dose Combinations, posted on 20-08-2010.


- **Draft Guidance** - Requirement of Chemical & Pharmaceutical Information including Stability Study Data Before Approval of Clinical Trials / BE Studies, posted on 21-12 2011


(These above Guidance Documents are related to new drugs & GCP only and available at [www.cdsco.nic.in](http://www.cdsco.nic.in))
Ethics Committee Registration:

- As per Gazette Notification No. GSR 72 E dated 8th Feb 2013, and under Rule 122DD

“No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of Rule 21”, (i.e. DCG(I))
MCI Regulation 2002:

• **7.22 Research**: Clinical drug trials or other research involving patients or volunteers as per the guidelines of ICMR can be undertaken, provided ethical considerations are borne in mind.

• Violation of existing ICMR guidelines in this regard shall constitute misconduct.

• Consent taken from the patient for trial of drug or therapy which is not as per the guidelines shall also be construed as misconduct.
SAE Reporting (Rule 122 DAB)

- All serious adverse events should be reported by P.I. to CDSCO, Sponsor and EC within 24 hrs.
- The detailed report of SAE after due analysis, should be forwarded by the Sponsor to CDSCO, Chairman of Ethics Committee and Head of Institute where the trial has been conducted within 14 calendar days of occurrence of SAEs.
- Ethics Committee shall forward its report on SAEs, after due analysis along with its opinion on financial compensation to CDSCO within 30 calendar days.
- CDSCO shall decide the quantum of compensation to be paid, and shall pass orders as deemed necessary within 150 days of the occurrence of SAE.
- SAE reports submitted to the CDSCO should be in COLOR coded binding:
  - **RED** - for SAEs of Deaths, **Blue** - for SAEs of Injury, remaining cases of SAEs in **White** cover.

*(Ref: G.S.R. 292 (E) dated- 24th April, 2014)*
Clinical Trials Registration in India (CTRI)

To enhance – transparency
   - accountability &
   - accessibility of clinical trials,
   - made mandatory by the DCGI’s office from June 15th 2009.

• 20 data set points of the WHO, as well as details of Indian PI’s, ethics and DCGI approval (including submission or approval documents)
• For Global clinical trials, specific information regarding the number of patients being recruited and the date of first enrollment in India.
• Clinical Trials Registration (www.ctri.nic.in). Manage by ICMR, New Delhi. India.
A Way Forward:

• There are encouraging sentiments of upcoming positive changes in the regulatory environment will lead to more clinical trial work in India.

• With the advent of globalization, it is important to adhere to global standards and best practice respecting local norms and value at the same time look at innovative ways to provide affordable healthcare to patients in India.

• Collaborative work is required between regulators, industry and academia to support innovation.
Thank You