Schedule Y in India - A Review Article

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ABSTRACT

International Conference on Harmonisation (ICH) coming into existence in 1991, there is a strong trend towards globalization of regulatory and scientific requirements pertaining to safety, efficacy and quality issues. Regulatory control in India, sovereign function of the government to ensure safety, efficacy and quality of drugs supplied to public, Central Drugs Standard Control Organisation (CDSCO), DGHS, Ministry of Health and Family Welfare With the Drug Controller General of India (DCGI) as the executive head. Requirements of data submission on animal testing for permission to undertake Phase I, Phase II and Phase III clinical trials laid down in Schedule ‘Y’ of Drugs & Cosmetics rules. The relevant data submitted to DCGI is evaluated with assistance of expert clinicians/scientists. For registration and approval of new drugs, which have already been registered and used in the country of origin, Phase III trials in about 100 patients is usually insisted upon by DCGI before allowing such products to be marketed in India. Normally new drug approval is initially granted for a period of 2 years.

Keywords: ICH, CDSCO, DCGI, Schedule ‘Y’

I. INTRODUCTION

• International Conference on Harmonisation (ICH) coming into existence in 1991
• There is a strong trend towards globalization of regulatory and scientific requirements pertaining to safety, efficacy and quality issues

Drug Control

An endeavour - legislative, executive and judicial- by the Government to:

• Regulate
• Import,
• Manufacture,
• Sale and
• Standards of drugs.
• USA: Federal Food, Drug and Cosmetics Act, 1968
• UK: Medicines Act, 1968
• India: Drugs and Cosmetics Rules, 1945
Regulatory control in India
Sovereign function of the government to ensure safety, efficacy and quality of drugs supplied to public.

This function is performed by:

- Central Drugs Standard Control Organisation (CDSCO),
- DGHS, Ministry of Health and Family Welfare
- With the Drug Controller General of India (DCGI) as the executive head

DCGI and Drug Control in India

- Requirements of data submission on animal testing for permission to undertake Phase I, Phase II and Phase III clinical trials
- Laid down in Schedule ‘Y’ of Drugs & Cosmetics rules
- The relevant data submitted to DCGI is evaluated with assistance of expert clinicians/scientists
- For registration and approval of new drugs, which have already been registered and used in the country of origin,
- Phase III trials in about 100 patients is usually insisted upon by DCGI before allowing such products to be marketed in India
- Normally new drug approval is initially granted for a period of 2 years

Definition of New Drug
A new substance of

- Chemical, biological or biotechnological origin
- In bulk or prepared dosage form Used for prevention, diagnosis or treatment of disease in man or animal
- Which except during local clinical trials, has not been used in the country to any significant extent; &
- Which except during local clinical trials, has not been recognized in the country as effective and safe for proposed claim

- Already approved drug for certain claims, now proposed for new claims (indications, dosage, dosage form, and route of administration)
- FDC of 2 or more drugs, individually approved earlier for certain claims, now proposed to be combined for first time in a fixed ratio
- Considered as new drug for 4 years from the date of its first approval or its inclusion in the IP whichever is earlier

Vaccines

Implants

New drugs

Medical Devices

SCHEDULE ‘Y’
Provides requirements and guidelines for:

- Permission to import &/ or manufacture of new drugs for sale or undertake clinical trials
- Application to be made in Form 44

For new substances discovered in India:

- CT in India right from Phase I
- New substances discovered in other countries:
- Submission of Phase I data generated outside India, permission for repeat Phase I, Phase II and Phase III

Definition of Clinical Trial

- A systematic study of new drug(s) in human subject(s):
- To generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects
- With the objective of determining safety and/or efficacy of the new drug
**Forms for Application**

<table>
<thead>
<tr>
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</tr>
<tr>
<td>Application for import of drugs for the purpose of examination, test or analysis</td>
<td>Form 12</td>
</tr>
<tr>
<td>Import license granted for drugs for examination, test or analysis</td>
<td>Form 11</td>
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<tr>
<td>Application for grant of license to manufacture drugs for the purpose of examination, test or analysis</td>
<td>Form 30</td>
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<td>Form 29</td>
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**APPENDIX I**

Data to be submitted along with application for conducting clinical trials/ import/ manufacture of new drugs for marketing in the country

**Introduction**

Should contain a brief description of the drug and the therapeutic class to which it belongs

**Chemical and Pharmaceutical information:**

Drug Information on active ingredients
Drug Information (Generic name, Chemical Name or INN)
Physicochemical data

**3. Animal pharmacology:**

- Summary
- Specific pharmacological actions
- General pharmacological actions
- Follow up and Supplemental Safety Pharmacological Studies

- Pharmacokinetics

**4. Animal Toxicology:**

- General aspects
- Systemic toxicity studies
- Male fertility study
- Female reproduction and developmental toxicity studies
- Local toxicity
- Allergenicity/ Hypersensitivity
- Genotoxicity
- Carcinogenicity

**5. Human/ Clinical Pharmacology (Phase I):**

- Summary
- Specific pharmacological actions
- General pharmacological actions
- Pharmacokinetics
- Pharmacodynamics/ early measurement of drug activity

**6. Therapeutic Exploratory Trials (Phase II):**

- Summary
- Study report given in Appendix II

**7. Therapeutic Confirmatory Trials (Phase III):**

- Summary
- Individual study reports with listing of sites and investigators

**8. Special studies:**

- BA/BE
- Other studies (Geriatric, Paediatrics etc.)

**9. Regulatory Status in other countries:**

- Countries where the drug is marketed, approved, approved as IND, withdrawn
- Restrictions on use, if any

**10. Prescribing information, Drafts of labels and cartons**

**11. Samples and testing protocols**

**12. Protocol with investigators consent**

**13. Consent letter of the supplier**
APPENDIX I-A
Data required to be submitted by an applicant
For grant of permission to import &/or manufacture a
new drug already approved in the country

1. Introduction
2. Chemical and Pharmaceutical information
   • Chemical/ generic name, structure etc.
   • Dosage form and composition
   • Test specifications
   • Tests for identification
   • Method of manufacture
   • Stability data
3. Marketing information:
   • Proposed package insert
   • Draft of label and carton
4. Special studies:
   • BA/BE and comparative dissolution studies for
     oral dosage forms
   • Sub-acute animal toxicity studies for
     injections

APPENDIX II
Provides information on structure, contents and
format for clinical study reports

1. Title page
2. Study synopsis (1-2 pages)
3. Statement of compliance
4. List of abbreviations and definitions
5. Table of contents
6. Ethics Committee
7. Study team
8. Introduction
9. Study objective
10. Investigational plan
11. Trial subjects
12. Efficacy evaluation
13. Safety evaluation
14. Discussion and overall conclusion
15. List of references

APPENDIX III
- Provides format for Animal toxicology (Non-
  Clinical Studies)
- Toxicity studies should comply with the norms of
  Good Laboratory Practice (GLP)
1. Systemic toxicity studies
   • Route of administration
   • Oral /Parenteral/transdermal
   • Inhalation
2. Special toxicity studies:
   • Male fertility studies
   • Female reproduction studies
   • Allergenicity / Hypersensitivity
   • Photo-allergy/ dermal Photo-toxicity
   • Genotoxicity
   • Carcinogenicity

Laboratory parameters to be included in toxicity
studies:
• Haematological parameters
• Urinalysis
• Blood Biochemistry parameters
• Gross and Microscopic Pathology

APPENDIX IV
Animal Pharmacology
Specific and general pharmacological studies should
be conducted to support use of therapeutics in
humans
Data on the following needs to be submitted:
• Specific pharmacological actions
• General pharmacological actions:
  • Essential safety pharmacology
  • Effect on CVS, CNS & respiratory system
  • Follow-up and supplemental pharmacological
    studies
  • Timing of safety pharmacological studies in
    relation to clinical development
  • Prior to first administration in man
  • During drug development
  • Before applying for Marketing approval
  • Application of Good Laboratory Practices
APPENDIX V

- A checklist of essential elements to be included in the study subject’s informed consent document &
- Format for the Informed Consent Form for study Subjects is given in Appendix V

Informed Consent

Check list:

Essential elements:

- Statement that study involves research and explanation of purpose of research
- Expected duration of subject’s participation
- Description of procedures to be followed, including invasive procedures
- Description of any reasonably foreseeable risks or discomforts to the subject
- Description of any benefits to the subjects/others expected for the research
- Disclosure of specific appropriate alternative procedures or therapies available to subject
- Statement describing extent to which confidentiality of records identifying subject will be maintained and who will have access to these records
- Trial treatment schedules and probability for random assignment to each treatment (for randomized trials)
- Compensation and/or treatment(s) available to the subject in the event of a trial-related injury
- Explanation about who to contact for trial related queries, rights of subjects and in the event of an injury
- Anticipated prorated payment, if any, to the subject for participating in the trial
- Subject’s responsibility on participation in the trial
- Statement that participation is voluntary
- Subject can withdraw at any time for the study & refusal to participate will not involve any penalty or loss of benefits to which subject is otherwise entitled
- Any other pertinent information

- Statement of foreseeable circumstances under which the Subject’s participation may be terminated by the Investigator without the subject’s consent
- Additional costs to the subject that may result from participation in the study
- Consequences of a subject’s decision to withdraw for the research procedures for orderly termination of participation by subject
- Statement that the Subject or Subject’s representative will be notified in a timely manner
- If significant new findings develop during the course of the research which may affect the Subject’s willingness to continue participation will be provided.
- A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable
- Approximate number of Subjects enrolled in the study

APPENDIX VI

FIXED DOSE COMBINATIONS

One/more of the ingredients is a new drug
- Data required for any new drug (including clinical trial)

Active ingredients already approved/marketed individually - combined for first time:
- CT carried out in other countries: Report to be submitted
- FDC marketed abroad: Regulatory status

Combination not marketed but drugs already in use concomitantly for the said claim:
- Chemical and Pharmaceutical data
- Stability data

For any other such FDCs:
- Clinical trial required
- Pharmacological, toxicological and clinical data on the individual ingredients and rationale for the combination.
• LD50 and pharmacological data on the individual ingredients and their combination in the proposed ratio

FDCs already marketed, but change in ratio of active ingredient proposed or for new therapeutic claim:

• Rationale including published reports

FDCs with individual ingredients widely used in a particular indication for years, concomitant use often necessary and proposed for convenience only:

• Stability of dosage form and no drug interaction

Undertaking by the investigator:
1. Full name, address and title of Principal Investigator (or Investigator(s) when there is no principal Investigator)
2. Name and address of Site where Clinical trial will be undertaken
3. Name and address of all clinical laboratory facilities to be used in the study
4. Name and address of the Ethics Committee responsible for approval and continuing review of the study
5. Names of the other members of the research team
6. Protocol title and Study number of the clinical trial to be conducted by the Investigators
7. Commitments of the Investigator
8. Signature of the Investigator with Date

APPENDIX VIII
• Ethics Committee Clearance is provided in this format

APPENDIX IX
• Data regarding Stability testing of the proposed new product is submitted in this appendix

APPENDIX X
• Contains the contents of Proposed Protocol for conducting Clinical Trials
  • Essential Elements:
    1. Title page
      • Table of Contents

2. Background and Introduction
3. Study Rationale and Objectives
4. Study Design
5. Study Population
6. Subject Eligibility
7. Study Assessments
8. Study Conduct
9. Study Treatment
10. Adverse events
11. Ethical Considerations
12. Study Monitoring and supervision
13. Investigational Product management
14. Data analysis
15. Undertaking by Investigator
16. Appendices

APPENDIX XI
• Format for reporting Serious adverse events
• Essential Elements:
  1. Patient Details
  2. Suspected Drugs
  3. Other Treatments
  4. Details of Suspected Adverse Drug reactions
  5. Outcome
  6. Details about the Investigator
  7. Signature of the Investigator

Schedule Y guidelines at a glance

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II. REFERENCES


phase of clinical trial

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Studies in Special population Appendix I


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