

UNIT-V

CDSCO AND PHARMACOVIGILANCE



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- **D&C Act and Schedule Y**
- **Differences in Indian and global Pharmacovigilance requirements**

Schedule Y

The legislative requirements of pharmacovigilance in India are guided by specifications of Schedule Y⁷ of the DC Act and the DC Rules thereto.

Schedule Y sets forth, for example, regulations pertaining to preclinical and clinical studies for the development of a new drug, as well as clinical trial requirements for the import, manufacture and receipt of marketing approval for a new drug in India. To this end, Schedule Y includes the approval procedures for clinical trial and other documentation to be submitted with the sponsor's application, with attention to the responsibilities of the sponsor, requirements of informed consent, responsibilities of Ethics Committees and details of the four phases of trials. Schedule Y also requires compliance with Good Clinical Practice Guidelines issued by CDSCO, the Directorate General of Health Services and the government of India.

Schedule Y underwent thorough review several years ago. Its latest amendment, dated January 20, 2005, aimed to underscore the continued commitment of DCGI to ensure pharmaceutical companies' adequate compliance with pharmacovigilance obligations. The amended Schedule Y also attempts to better define the responsibilities of pharmaceutical companies for their marketed products, as well as responsibilities for reporting adverse events from clinical trials. For a complete understanding of reporting responsibilities specific to clinical trials conducted in India, Schedule Y should be read along with Rules 122A, 122B, 122D, 122DA, 122DAA and 122E of the DC Rules.

REQUIREMENTS AND GUIDELINES

- **FOR PERMISSION TO IMPORT AND / OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS**

Application for permission

- ▶ Form 44
- ▶ Chemical and pharmaceutical information as prescribed in item 2 of Appendix I; (ii) animal pharmacology data:
- ▶ Specific pharmacological actions
- ▶ General pharmacological actions
- ▶ Pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance
- ▶ Animal toxicology data
- ▶ Human clinical pharmacology Data
- ▶ Regulatory status in other countries
- ▶ Full prescribing information

Clinical Trial

- ▶ Approval for clinical trial
- ▶ Responsibilities of sponsor
- ▶ Responsibilities of the investigator
- ▶ Informed consent
- ▶ Responsibilities of the ethics committee
- ▶ Human pharmacology (Phase I)
- ▶ Therapeutic exploratory trials (Phase II)
- ▶ Therapeutic confirmatory trials (Phase III)
- ▶ Post marketing trials (Phase IV)

Approval for clinical trial

- ▶ Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee (s)
- ▶ All trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol
- ▶ Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee

Responsibilities of sponsor

- ▶ Sponsor is responsible for implementing and maintaining quality assurance systems
- ▶ Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity
- ▶ Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Licensing Authority
- ▶ The sponsor (whether a pharmaceutical company or an Institution) or his representative shall submit details of compensation provided or paid for clinical trial related injury or death, to the Licensing Authority within thirty days of the receipt of the order of the Licensing Authority

Responsibilities of the Investigator

- The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance
- Standard operating procedures are required to be documented by the investigators for the tasks performed by them.
- The investigator should ensure that adequate medical care is provided to the participant for any adverse events.
- Investigator(s) shall report all serious and unexpected adverse events
- He shall also inform/guide the subject for the purpose of making claims in the case of trial related injury or death.

Informed consent

- ▶ In all trials, a freely given, informed, written consent is required to be obtained from each study subject.
- ▶ The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject.
- ▶ The subject's consent must be obtained in writing using an 'Informed Consent Form'.
- ▶ Patient information sheet as well as the Informed Consent Form should be approved by the ethics committee and furnished to the Licensing Authority.

Responsibilities of the Ethics Committee

- ▶ To review and accord its approval to a trial protocol so as to safeguard the rights, safety and well being of all trial subjects.
- ▶ Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol
- ▶ In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so
- ▶ In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation

Human Pharmacology (Phase I)

- ▶ The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s)
- ▶ Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients.
- ▶ Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients.
- ▶ Phase I trials should preferably be carried out by Investigators trained in clinical pharmacology
- ▶ Maximum tolerated dose, pharmacokinetics, pharmacodynamics, early measurement of drug activity

Therapeutic exploratory trials (Phase II)

- ▶ To evaluate the effectiveness of a drug for a particular indication or indications in patients under study
- ▶ To determine the common short-term side-effects and risks associated with the drug.
- ▶ Studies should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population.
- ▶ An important goal is to determine the dose(s) and regimen for Phase III trials.

Therapeutic confirmatory trials (Phase III):

- ▶ Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s).
- ▶ Studies are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population.
- ▶ These studies should be intended to provide an adequate basis for marketing approval.
- ▶ Studies may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

Post Marketing Trials (Phase IV)

- ▶ Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s)
- ▶ These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition
- ▶ These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use
- ▶ Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc

Studies in special populations

- ▶ Geriatrics
- ▶ Paediatrics
- ▶ Pregnant or nursing women
- ▶ Post marketing surveillance
- ▶ Special studies: Bioavailability / Bioequivalence Studies

Geriatrics

- ▶ Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the Sponsor's option) in meaningful numbers, if-
 - ▶ (a) the disease intended to be treated is characteristically a disease of aging; or
 - ▶ (b) the population to be treated is known to include substantial numbers of geriatric patients; or
 - ▶ (c) when there is specific reason to expect that conditions common in the elderly are likely to be encountered; or
 - ▶ (d) when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient

Paediatrics

- ▶ The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments.
- ▶ For a drug expected to be used in children, evaluations should be made in the appropriate age group.
- ▶ It is usually appropriate to begin with older children before extending the trial to younger children and then infants.
- ▶ If the new drug has a potential for use in paediatric patients – Paediatric studies should be conducted.

Pregnant or nursing women

- Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant/nursing women or foetus/nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable. (ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required
- Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug

Post Marketing Surveillance

- ▶ The applicant shall have a pharmacovigilance system in place for collecting, processing and forwarding the report to the licensing authority for information on adverse drug reactions emerging from the use of the drug manufactured or marketed by the applicant in the country. (ia) The system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports. (ib) Subsequent to approval of the product, new drug shall be closely monitored for its clinical safety once it is marketed.

Appendices

- Appendix 1 Conduct clinical trials/import/manufacture of new drugs
- Appendix IA For grant of permission to import and / or manufacture a new drug
- APPENDIX II Structure, contents and format for clinical study reports
- APPENDIX III Animal toxicology (non-clinical toxicity studies)
- APPENDIX IV Animal pharmacology
- APPENDIX V Informed consent
- APPENDIX VI Fixed dose combinations (fdcs)

Appendices

- 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