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New drug approval and Post Marketing Surveillance

CDSCO

Legal Provisions for permission to 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 D

Permission to import/manufacture of FDC

Rule 122 DB

Suspension / Cancellation of permissions

Rule 122 E

Definition of New Drugs

Legal Provisions for regulation of Clinical Trial



Drugs and Cosmetics Act, 1940 and Rules, 1945

Requirements and Guidelines - Schedule Y

Rule 122 DA

Permission to conduct clinical trial

Rule 122 DAA

Definition of Clinical trials

Rule 122 DAB

Compensation in case of trial related injury or death

Rule 122 DAC

Conditions of Clinical Trial permission & Inspection

Rule 122 DD

Registration of Ethics Committee

Rule 122 E

Definition of New Drugs

GCP Guidelines, 2001

Definition of New Drug



Rule 122E

- Any new substance proclaimed for therapeutic use
- An already approved drug with modified or new therapeutic claims, indications, dosage forms or routes of administration
- FDCs of drugs
- All vaccines and recombinant R-DNA derived products
- A new drug shall continue to be considered as new drug for four years

Schedule- Y

- It specifies the requirements and guidelines for permission to manufacture/import of New Drugs or to undertake clinical trial

- **Form 44**: Application for Permission to undertake clinical trial/Manufacture/Import of New Drugs with details of documents to be submitted along with prescribed fees
- Data required to be submitted
 - As per Appendix- I (For unapproved new molecules)
 - As per Appendix- IA (For approved new drugs)

New Drug Application

Data required

- Chemical and Pharmaceutical information
- Animal Pharmacology
- Animal Toxicology
- Phase I,II,III Clinical Trials
- Regulatory Status in other country
- COPP/FSC (in case of import)
- Label, Prescribing information

Fees for Clinical Trial/Approval of New Drugs

- Phase I (IND) Rs. 50000
- Phase II (IND) Rs.25000
- Phase III(IND) Rs.25000
- Approval of New Molecule Rs.50000
- Approved New Drug:
 - Within 1 yr of approval Rs.50000
 - After 1yr of approval Rs.15000
- Approval of New claim,
New Dosage form etc. Rs.15000

Requirements of Local Clinical Trial



- For New Drug substance discovered in India clinical trial is required to be conducted right from Phase I.
- For New Drugs approved outside India, Phase III studies need to be carried out to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information.

WAIVER OF LOCAL CLINICAL TRIAL REQUIREMENT



- **Rule 122 A (2) and Rule 122 B (3):**

“the requirement of local clinical trials may not be necessary if the drug is of such a nature that the Licensing Authority may, in public interest, decide to grant permission to import / manufacture the new drug on the basis of data available from other countries.

- **Clause 1 (3) of Schedule Y:**

“for drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority..

Waiver of Clinical Trial, can be considered only in cases of national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy.

Approval of new drugs already approved in other countries, based on clinical trial conducted in Indian patients as part of global clinical trial

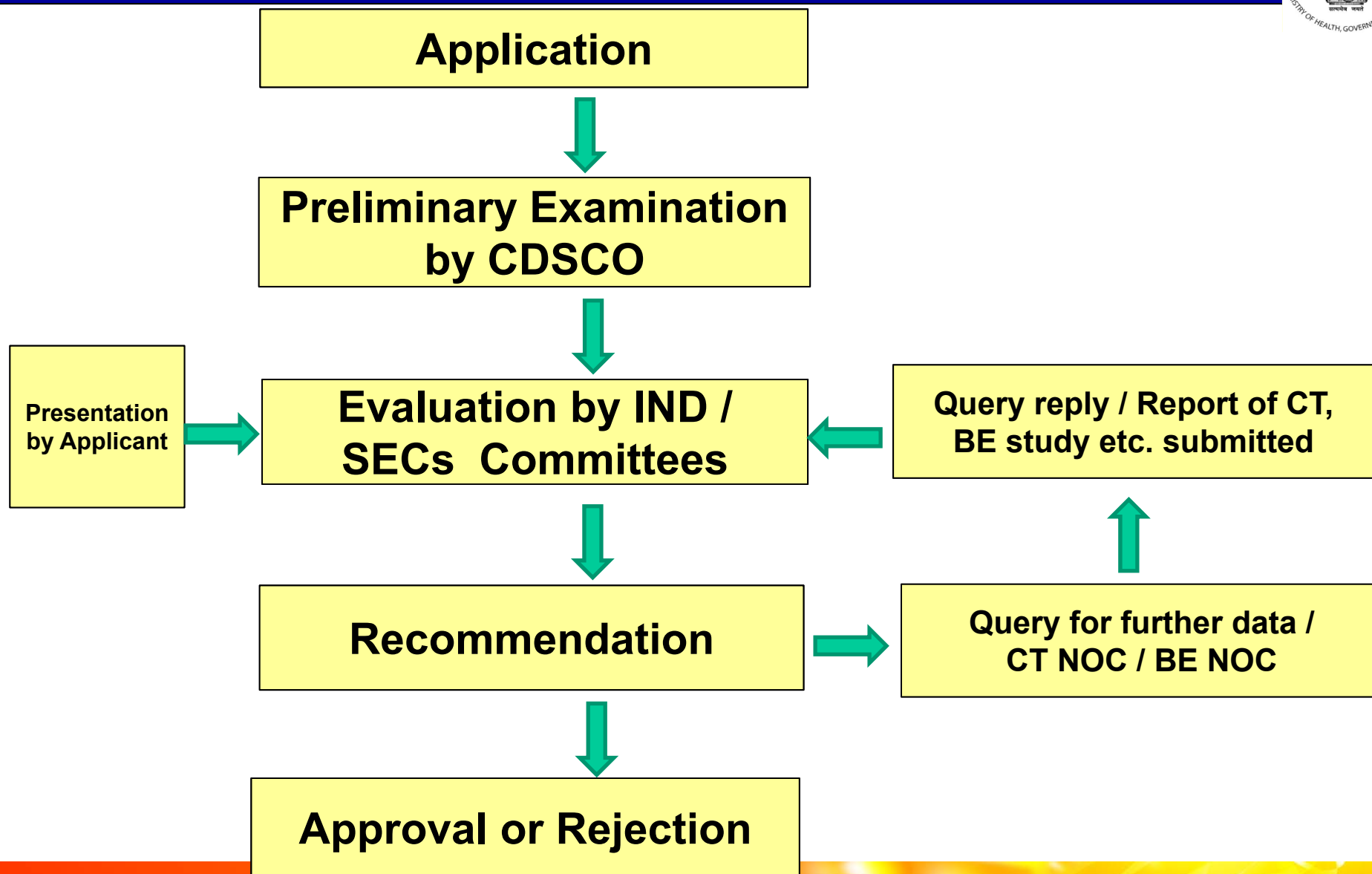
- If Indians have participated in phase III global trials, the number of Indians participated in phase III global clinical trial in India would have to be adequate for considering approval of drug in India.

Committees for Evaluation of Applications



- IND Committee – Evaluation of Investigational New Drugs (new molecules discovered in India). Chaired by DG, ICMR & Secretary, Department of Health Research.
- Subject Expert Committees (SEC) – 25 panels of about 350 various medical experts for evaluation of applications of clinical trial and new drug approvals except IND,
- Technical Committee (TC) – Separate committee of experts chaired by Director General Health Services to review proposals Clinical trials and cases of CT waiver for new drug approval.
- Apex Committee : Reviews recommendations of Technical Committee in cases of Clinical trial of NCEs including IND

Evaluation of Applications by IND/SECs



Recent initiatives



- Online submission and processing of CT and new drug applications through SUGAM Portal
- Interactive workshop for the SEC members and reviewers of CDSCO for streamlining the new drug evaluation process in collaboration with USFDA and ICMR
- Guidelines for SECs for review of clinical trial and new drug applications
- Comprehensive review of existing regulatory provisions and preparation of new rules to make them contemporary to meet the aspirations of the stakeholders are underway. The new rules will have new features for following:
 - pre-submission meeting,
 - Post trial access
 - waiver of local CT for new drugs already approved in certain other countries,
 - accelerated approval under certain conditions,etc. preparation

Post Marketing Surveillance (PMS)

Post Marketing Surveillance of a Pharmaceutical Product entails:

- ❖ Post Licensure **Safety Evaluation** by Marketing Authorisation holder through
 - Submission of Periodic Safety Update Reports
 - Active/Passive Surveillance
 - Structured Phase IV trial
 - Observational Study
- ❖ Pharmacovigilance Programme of India through 210 ADR monitoring Centres located in medical colleges and hospitals
- ❖ **Quality Monitoring** of the marketed product by MA holder and Regulatory system

Legal Provisions For Post Licensure Safety Evaluation as per Drugs and Cosmetics Act 1940 and Rules 1945 for New Drugs

- Amendment by Gazette notification vide GSR no. 287 (E) dated 08th March 2016 and as per Para 3(4) of Schedule Y of Drugs & Cosmetics Rules-1945.

Post Marketing Surveillance-

- ❖ 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.

- ❑ 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.
- ❑ Subsequent to approval of the product, new drug shall be closely monitored for its clinical safety once it is marketed.
- ❑ The applicant shall furnish **Periodic Safety Update Reports (PSURs)** in order to-
 - (a) report all relevant new information from appropriate sources;
 - (b) relate the data to patient exposure;

- (c) summarise the market authorisation status in different countries and any significant variations related to safety; and
 - (d) Indicate whether changes shall be made to product information in order to optimize the use of product
- ❖ Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR.
 - ❖ All relevant clinical and non-clinical safety data should cover only the period of the report (interval data).

Structure of PSUR

- (a) A title page stating: Periodic safety update report for the product, applicant's name, period covered by the report, date of approval of new drug, date of marketing of new drug and date of reporting;
- (b) Introduction,
- (c) Current worldwide market authorization status,
- (d) Update of actions taken for safety reasons,
- (e) Changes to reference safety information,
- (f) Estimated patient exposure,
- (g) Presentation of individual case histories,
- (h) Studies,
- (i) Other information,
- (j) Overall safety evaluation,
- (k) Conclusion,
- (l) Appendix providing material relating to indications, dosing, pharmacology and other related information.

- ❖ As per conditions 5 and 6 in Form 45 (permission for import of new drugs) and Form 46 (permission for manufacture of new drug)

Condition no.05

“The applicant shall submit PSUR every six months for the first two years. For subsequent two years, the PSUR shall be submitted annually.”

Condition no. 06

“All reported adverse event shall be intimated to Drugs Controller, India and Licensing Authority and regulatory conditions resulting from their review should be complied with.”

- ❖ As per condition 4 in Form 41 (Registration Certificate for import of Drugs into India)
- ❖ The manufacturer or his authorised agent in India shall inform the licensing authority in the event of any administrative action taken due to adverse reaction, viz. market withdrawal, regulatory restrictions, or cancellation of authorization, and/or not of standard quality report of any drug pertaining to this Registration Certificate declared by the Regulatory Authority of the country of origin or by any Regulatory Authority of any other country, where the drug is marketed/sold or distributed

Condition 4 in Form 41

- ❖ The dispatch and marketing of the drug in such cases shall be stopped immediately, and the licensing authority shall be informed immediately.
- ❖ Further action in respect of such stopped marketing of drug shall be followed as per the direction of the licensing authority.
- ❖ In such cases, action equivalent to that taken with reference to the concerned drug in the country of origin or in the country of marketing shall be followed in India also, in consultation with the licensing authority.
- ❖ The licensing authority may, however, direct any further modification to this course of action, including the withdrawal of the drug from Indian market within 48 hours time period

Post Marketing Surveillance under Schedule Y

- ❑ PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.
- ❑ If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.
- ❑ All cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant.

❖ As per Para 28 of Schedule M of Drugs and Cosmetics Act and Rules:

- All complaints concerning product quality shall be carefully reviewed and recorded according to written procedures.

- Each complaint shall be investigated/evaluated by the designated personnel of the company and record of investigation and remedial action taken thereof shall be maintained.

- Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority.

Post Marketing Trial (Phase IV)



- In certain cases of new drug approval, depending on the nature of the drug and disease for which it is indicated, the applicant is asked to conduct Phase IV clinical trial as per protocol approved by the LA.
- Such conditions generally include drugs for serious/ life threatening diseases for unmet need, rare diseases or diseases which has a special relevance to Indian health scenario, etc.
- In such cases, new drugs are approved with a condition requiring Phase IV CT

Pharmacovigilance Programme of India (PvPI)



- ❖ CDSCO, in collaboration with PvPI at IPC has initiated a nation-wide Pharmacovigilance programme.
- ❖ Adverse Drug Reactions are collected through 210 AMCs throughout the country.
- ❖ AMCs report the ADRs through VigiFlow
- ❖ In 2015 launched Android Mobile App and helpline No.18001803024 (Toll free) for ADR reporting
- ❖ PvPI collaborated with various National Health Programme like AEFI, RNTCP, NACO and NVBDCP
- ❖ Steering Committee monitor and supervise the Programme
- ❖ Working Group approve technical and policy issues
- ❖ Quality Review Panel, Core Training Panel and Signal Review Panel for quality review, training and assessment of ADRs for potential signals

Pharmacovigilance Programme of India (PvPI)



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- ❖ Working Group approve technical and policy issues
- ❖ Quality Review Panel, Core Training Panel and Signal Review Panel for quality review, training and assessment of ADRs for potential signals
- ❖ So far more than 2,50,000 ADRs reported to VigiBase in UMC, Sweden
- ❖ Started Active Surveillance for MDRTB drug Bedaquiline in 6 identified Centers across the country
- ❖ PvPI make recommendations to CDSCO for safety related issues
- ❖ Issued 37 drug safety alerts through SMS to create awareness in HCPs

Thank You