Generic Drugs Assessment and Approval Process in India

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Drugs fall under the Concurrent list of the Constitution

The Act is a Central Act, enforced by both Central and State Govt.

Extended to Whole of India
Implementing Authorities:

- **Central Government:**
  - Central Drugs Standard Control Organization (CDSCO)

- **State Governments:**
  - State Drug Licensing Authorities
Responsibilities

Central Responsibilities:
- New Drug Approvals/Medical Devices
- Import of Drugs/Medical Devices
- Clinical Trails
- Standards for Drugs
- Amendments to Act and Rules
- Pharmacovigilance

State Responsibilities:
- License for Manufacture, Sale and Distribution
- Monitoring quality of Drugs and Cosmetics
- Investigations and Prosecutions
• National Regulatory Authority of India

• Headed by Drugs Controller General (India)

• Headquarters at New Delhi
Central Drugs Standard Control Organisation

Drugs Controller General (I)

HEAD QUARTER
- New Drugs
- Clinical Trials
- Imports
- Biological
- Medical Devices
- Export
- QA
- Pharmco.Vig
- Legal etc

ZONAL OFFICE (6)
- GMP Audits
- Enforcement
- Draw drug Samples

SUB ZONAL OFFICE (4)
- GMP Audits
- Coordination with States

PORT OFFICE (13)
- Import
- Export

LABORATORY (7)
- Testing of Drugs
- Validation of Test protocols
CDSCO Offices

- **Zonal Offices**: (6)
  Ghaziabad, Mumbai, Chennai, Kolkata, Ahmedabad and Hyderabad

- **Sub Zonal Offices**: (7)
  Baddi, Bangalore, Goa, Guwahati, Indore, Jammu and Varanasi

- **Central Drugs Laboratories**: (7)
  Kolkata, Mumbai, Chennai, Hyderabad, Chandigarh, Guwahati and Kasuali

- **Port Offices**: (16)
  Import and Export
Regulatory Provisions

Drugs and Cosmetics Act 1940

- Drugs and Cosmetics Rules 1945
  - Import
  - Manufacture
  - Sales
  - Legal provisions

- New Drugs and Clinical trial Rules, 2019
  - Investigational new drugs
  - New drugs / Subsequent New drugs
  - Clinical Trials
  - Bioequivalence study and bioavailability study
  - Regulation of Ethics Committee

- Medical Device Rules, 2017
  - Import
  - Manufacture
  - Sales
  - Legal provisions
New Drugs and Clinical Trial Rules, 2019

• Before, 19.3.2019, clinical trials were regulated under Part X-A of the Drugs and Cosmetics Rules, 1945 and Schedule Y to the Rules.

• Now clinical trials are regulated under the New Drugs and Clinical Trials Rules, 2019, notified on 19.3.2019

• The new rules contain various provisions for improving transparency and accountability and also promoting ethical and scientific clinical research and development of new drugs.
These rules apply to NDs, INDs for human use, CT, BA, BE and regulation of ethics committee relating to CT, BA/BE study and biomedical health research.

Definition of new drugs has been modified to incorporate novel drug delivery system (NDDS), living modified organism, monoclonal antibody, stem cell derived product, gene therapeutic products and xenografts.
New Drug

• A modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority

• vaccine,

• recombinant Deoxyribonucleic Acid (r-DNA) derived product,

• monoclonal anti-body,

• stem cell derived product,

• gene therapeutic product or

• xenografts, intended to be used as drug

will always be considered as new drug
Explanation -

The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licencing Authority and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs;
Drugs Approval (within 4 year period)

Applicant for a drugs which is to be approved for the first time in the country (Innovator) and

Subsequent applicant for the same drug for approval within the period of four years from the date of permission granted by CDSCO

• Shall make an application to CDSCO as per the requirement of New Drugs and Clinical Trials Rules 2019 for permission to Import / manufacture of the drugs which fall under the definition of “new drugs”
Drugs Approval (within 4 year period)

Review process

- **Application**
- **Review - CDSCO**
  - Query reply BE / CT report
- **Evaluation IND/SEC Committee**
- **Recommendations**
- **Grant of Permission/ Rejection**
  - Query or BE / CT NOC
  - Presentation by Applicant
Approval of New Drug

• Disposal of New drug applications within a period of 90 working days.

• Provision for Accelerated approval with condition of requirement of Post Marketing Trial

• Provision for application by Sponsor for Expedited Review

• In case of modified or new claims and NDDS the non clinical and clinical data requirement may be relaxed omitted under certain conditions.

• Permission /Rejection/Query in 90 working days
Animal Toxicology Requirements

• Flexibility given to adopt between General Guidance under Rules or ICH
• Studies may be planned, designed and conducted as per the ICH
• To promote safe, ethical development of new drugs in accordance with
  - 3R (Reduce / Refine / Replace) principles.
waiver of Local CT for approval of new drug

• If the new drug is approved and marketed in countries specified under the Rules and no major unexpected serious adverse events have been reported

OR

• Global clinical trial which is ongoing in India

AND

• No evidence, of

  - difference in enzymes or gene, involved in metabolism
  - factor affecting PK/PD, safety and efficacy of the new drug
Waiver of local CT

Phase IV CT is required for such waivers. However the same may be relaxed under following conditions:

- Indicated in life threatening or serious diseases or diseases of special relevance
- For unmet need in India
  - XDR tuberculosis, hepatitis C, H1N1, dengue
  - Malaria, HIV, rare diseases
  - Orphan drug.
Accelerated Approval

• For serious/life-threatening condition or disease, unmet medical needs/No alternatives available for a disease, taking into account its severity, rarity, or prevalence

• Surrogate endpoint shall be considered which are reasonably likely to predict clinical benefit

• Marketing approval may be based on Phase II clinical trial data, if remarkable efficacy observed in Phase II CT

• Phase IV CT mandatory to validate the anticipated clinical benefit.
New Provisions for predictability of regulatory pathways

- Pre and Post- submission meeting

- The applicant can ask for Pre and Post-submission meeting with payment of fees.
Separate Schedules

- General principles and practices for clinical trial
- Requirements and guidelines for permission to import or manufacture of new drug for sale or to undertake clinical trial with special provisions for expedite review, accelerated approval process like in case of unmet medical need, etc.
- Conduct of clinical trial
- Formulae to determine the quantum of compensation in case of clinical trial related injury/permanent disability or death.
- Requirements and guidelines for conduct of bioavailability and bioequivalence study of new drugs or investigational new drugs.
- Post marketing assessment of new drugs
Post marketing Safety Assessment

Detailed guidelines in the Fifth Schedule Assessment may be carried out by different ways-

- Phase IV (Post marketing) trial

    ----As per recommendation of DCGI
    -----as per approved protocol by CLA
    ------All regulations of CT including compensation apply
-----Post marketing Safety Assessment

- Post marketing surveillance study or observational or non interventional study for active surveillance
  - regulatory provisions for CT of a new drug are not applicable
  - new drug supplied may not be free.

- Post marketing surveillance through Periodic Safety Update Reports in accordance with the procedures.
Application of grant of licence to manufacture drugs which are beyond the period of four years from the date of their permission granted by the Central Licensing Authority.

The applicant shall make an application to the State licensing authority appointed by the respective State Governments as per the requirements of Drugs and Cosmetics Rules.
Drugs Approval (beyond 4 year period)

Requirements:

• applicant shall submit the result of bioequivalence study along with the application for grant of manufacturing licence of oral dosage form of drugs falling under the Category II and Category IV of the Biopharmaceutical Classification System

• the applicants shall submit evidence of stability, safety of excipients etc. to the State Licensing Authority before grant of product manufacturing licence.
Requirements: (contd)

- before the grant of manufacturing license, the manufacturing establishment is to be inspected jointly by Drugs Inspectors of Central Government and State Government

- licensed manufacturing premises shall be inspected jointly by Drugs Inspectors of Central Government and State Government to verify the compliance with the conditions of license and the provisions of the Drugs & Cosmetics Act and Rules for not less than once in three years or as needed as per risk based approach.
Regulatory provision for Import and Registration of drugs in India
Import of drugs are regulated under the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945 made there under.

Bulk drugs (Active Pharmaceutical Ingredients) and Finished formulations are regulated under the said Act. Any substance falling within the definition of Drug (Section 3b of the Act) is required to be registered before import into the country.

Not only the drug but the manufacturing site also needs to be registered for import.
Regulations:

- Chapter III of Drugs & Cosmetics Act 1940, governs the import of Drugs & Cosmetics into India.

- The provision for grant of Import Registration Certificate and Import Licenses are prescribed under Part IV of the Drugs & Cosmetics Rules 1945.
Documents to be submitted - Registration Certificate

• Application in Form 40 to be filed online through SUGAM portal (www.cdscoonline.gov.in).

• Power of Attorney (POA)

• GMP certificate / COPP (as per WHO format) or WC issued by their NRA or certificate equivalent to WHO GMP guidelines issued by NRA of USA or Japan or Australia or Canada or the European Union for the purpose of marketing of the drugs in their country

• Countries where marketing authorization or import permission is granted

• Countries where marketing authorization or import permission is cancelled/ withdrawn
Schedule D (I): Information and undertaking required to be submitted by the manufacturer or his authorized agent with the application form for a registration certificate

- Plant Master File
- Plant Layout, HVAC system, Water system, etc.,
- List of Major equipments in Production and QC.
- List of key personals with qualification, experience and responsibilities.
- Distribution, Complaints & products recall SOP, List of Contract Manufacturing/analysis
Schedule D(II) : Information and undertaking required to be submitted by the manufacturer or his authorized agent with the application form for the registration of bulk drugs/formulations/special products for its import into India

• Drug Master File
  – General:
    – Name of the drug/formulation and its therapeutic class
    – Chemical and pharmaceutical information of drugs.
    – Chemical name, dosage, composition, source of API
• Biological and biopharmaceutical information of drugs
  – Pharmacological and toxicological information of drugs.
  – Clinical documentation
  – For new drug, permission to market in India (CT-19/CT-20), brief summary and clinical documentation.
  – Bio-equivalence data to be submitted for oral dosage form of drugs specified under BSC Class II and IV.
  – Labelling and packaging information of drugs.
  – Specific information required for the special Products.
Registration Fees

- Manufacturing premises - 10000 USD (or its equivalent to Indian Rupees),
- Drug - 5000 USD (or its equivalent to Indian Rupees) / per drug
  if manufacturing site remains the same.
- Inspection - 25000 USD (or its equivalent to Indian Rupees) in case of inspection of the manufacturing site.
Import Licence

Import Licence is required for import of drugs (Bulk Drugs and Finished Formulations) into India, under rule 23 and 27 of the Drugs and Cosmetics Rules;

Requirements:

- Application in Form 8
- A copy of Registration Certificate authenticated by Indian Agent
- Undertaking in form 9 from the authorized agent or from manufacturer duly verified by the Indian Embassy where the manufacturer is located
- Copy of sale license or manufacturing license
- Fees of Rs.10000/- for the first drug and Rs.1000/- for each additional drug
Post Approval Changes

➢ The manufacturer or authorized agent shall inform the licensing authority within 30 days in writing in the event of any change in manufacturing process, or in packaging, or in labeling or in testing, or in documentation of any of the drug pertaining to this Registration Certificate.

➢ In case of any major modification in such as change in constitution, addition of manufacturing site etc., manufacturer or authorized agent shall obtain necessary approval within 30 days by submitting a separate application along with the registration fee, as specified in clause (ii) of sub rule (3) of rule 24-A.
Exemptions for Registration

- In case of emergencies the licensing authority may with the approval of Central Government, issue an import license in Form-10 or 10-A as the case may be, without the issuance of Registration Certificate.
- Import of drugs required for personal use for any patient.
- Government hospitals can import drugs for their own patient.
- Drugs imported for clinical trials.
- Drugs imported for products/formulations development and data generation.
- Drugs not yet approved and marketed in the country and meant for export only.
Control Measures

– Drug complies with the standard set out in the Second Schedule of the Drugs and Cosmetics Act are imported.
– No drug, which is misbranded, adulterated or spurious, or which makes false or misleading claims about its true nature is permitted to be imported.
– Drug whose import has been banned is not permitted to be imported.
Memories…

13-15 September 2017 at Ahmedabad, Gujarat, INDIA
Memories…

Meeting with Japanese Delegation

Minoru Shimada
Yakult Danone India Pvt. Ltd
Thank you

ありがとうございました

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