BP 702 T (Industrial Pharmacy II) Theory

Unit V

Indian Regulatory Requirements

Central Drugs Standard Control Organization (CDSCO) and state licensing authority: Organization and Responsibilities, Certificate of Pharmaceutical Product (COPP), Regulatory requirements and approval procedures of New drugs.

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Abbreviations

DRA- Drug Regulatory authority
CDSCO- Central Drugs Standard Control Organization
DCGI - Drugs Controller General of India
DTAB- Drug Technical Advisory Board
DCC- Drug Consultative Committee
DC Act- Drug and Cosmetic Act
FDC- Fixed Dose Combinations
SEC- Subject Expert Committee
NDAC- New Drug Advisory Committees
SDRA- State Drug Regulatory Authorities
CDTL- Central Drugs Testing Laboratories
COPP- Certificate of Pharmaceutical Product
QSE- Quality, safety and efficacy
GMP- Good manufacturing practices
MAH- Marketing authorizations holders
API- Active pharmaceutical ingredients
OTC- Over the counter drug
ICH- International Conference on Harmonization

Introduction-

The drug regulatory authority (DRA) is the agency that develops and implements most of the legislation and regulations on pharmaceuticals. Its main task is to ensure the quality, safety and efficacy of drugs, and the accuracy of product information. This is done by making certain rules that the manufacture, procurement, import, export, distribution, supply and sale of drugs, product promotion and advertising, and clinical trials are carried out according to specified standards.

Functions of Regulatory Authority:

- Product registration (drug evaluation and authorization, and monitoring of drug efficacy and safety.
- Regulation of drug manufacturing, importation, and distribution.
- Regulation & Control of drug promotion and information.
- Adverse drug reaction (ADR) monitoring.
- Licensing of premises, persons and practices.
- Main goal of drug regulation is to guarantee the safety, efficacy and quality of drugs.

Central Drugs Standard Control Organization (CDSCO)-

Central Drugs Standard Control Organization (CDSCO) exercises regulatory control over the quality of drugs, cosmetics and notified medical devices in the country. The CDSCO of India is main regulatory body for regulation of pharmaceutical, medical devices and Clinical Trials.

It is the Central Drug Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act. Its Head quarter is located at FDA Bhawan, Kotla Road, New Delhi and functions under the Directorate General of Health Services, ministry of health and family welfare Government of India.

It is divided into zonal offices which do pre-licensing and post-licensing inspections, post-market surveillance, and recalls when needed.

Vision: To Protect & Promote Health in India

Mission: To safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices.

Drugs Controller General of India (DCGI)

• He/she is a responsible for approval of New Drugs, Medical devices and Clinical Trails to be conducted in India.

• He is appointed by the central government under the DCGI the State drug control organization will be functioning.

• The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC).

The DCGI is responsible for handling matters of product approval and approval standards, clinical trials, introduction of new drugs, and import licenses for new drugs. A drug may be licensed for manufacturing in a state only once it has been approved by CDSCO.

Process of drug regulation

The DC Act entrusts CDSCO with the responsibility for the approval of new drugs, and the conduct of clinical trials in the country, as well as laying down the standards for drugs, controlling the quality of imported drugs, oversight over the SDRAs, and an advisory role in ensuring uniformity in the enforcement of the DC Act itself.

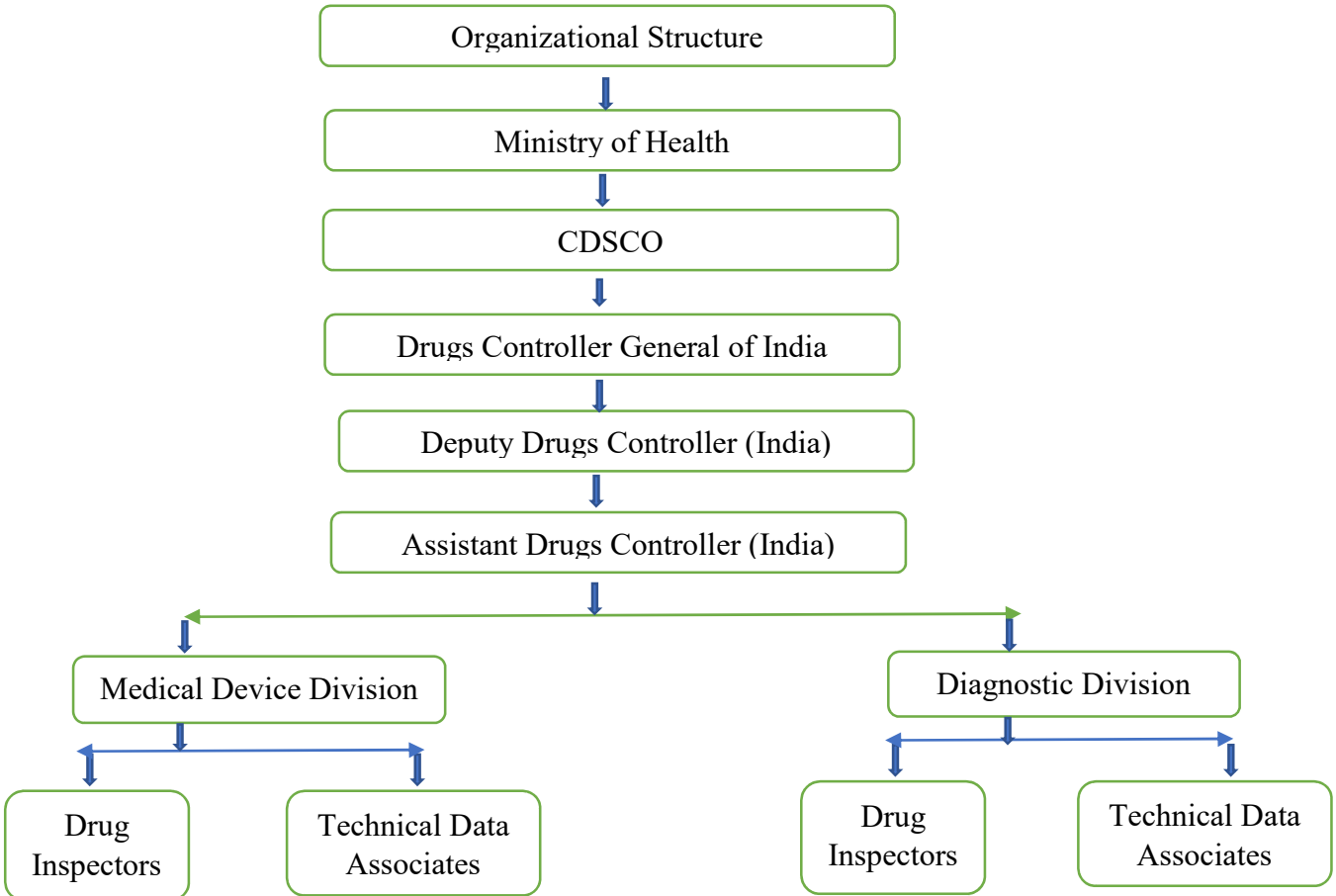
CDSCO approves new drugs based on a combination of non-clinical data, clinical trial data (focusing on safety and efficacy) from abroad as well as in India, and the regulatory status of the drug in other countries. The law around new drug approvals is contained in Rules 122 A, 122 B, 122D, 122 DA, 122 DAA, 122 DAB, 122 DAC, 122 DB, 122 DD and 122 E of Schedule-Y of the DC Rules. The law permits a waiver of requiring local clinical trials if the Licensing Authority decides it is in the public interest to grant permission to import / manufacture the new drug on the basis of data available from other countries. In special circumstances, such as drugs required in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the law permits the Licensing Authority to abbreviate, defer or omit clinical data requirements altogether.

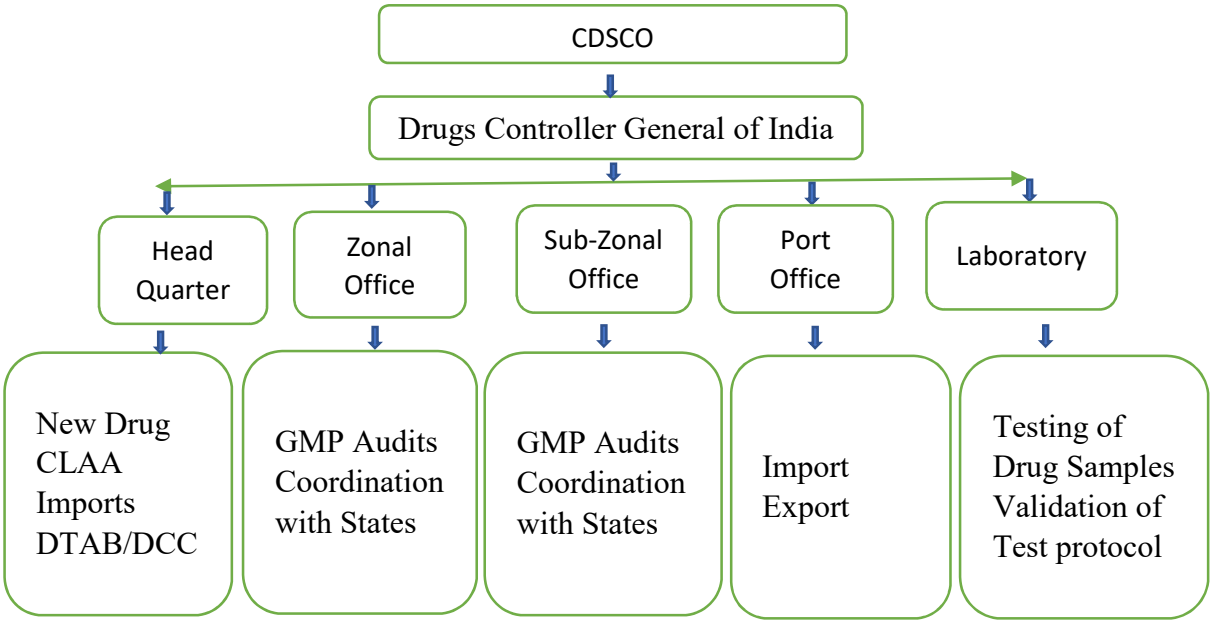
Applications for approval of New Drugs are evaluated by the 12 Subject Expert Committee (SEC) (formerly referred to as New Drug Advisory Committees (NDAC), consisting of experts usually drawn from Government Medical Colleges and Institutes across India. The approval or otherwise is granted based on the recommendations of these committees. Overall, this has put considerable cloud over the new drugs approval and regulatory process in India, and with the ban being issued by the government rather than by CDSCO, this particularly casts a shadow on the legitimacy of CDSCO as a regulatory body.

Besides approval, the other important regulatory roles are regarding licensing and inspections. Sections 22 and 23 of the DC Act give the Drug Inspectors (DI) the power to inspect premises manufacturing or selling drugs or cosmetics and take samples of any drug or cosmetic in exchange of its fair price and a written acknowledgement. Where the sample has been taken for testing or analysis, the DI must inform about its purpose in writing to the owner of the premises. The provisions also direct the DI to divide the samples into four (three, if taken from the manufacturer) properly sealed portions or take as many units of the drug. The Government Analyst under Section 25 of the DC Act must then prepare a signed report which is then taken to be a conclusive fact upon the standard of quality of the drug. These provisions are complemented by the DC Rules which elaborate on the duties of the Government Analyst, the Drug Inspector and the Licensing Authority.

In 2017, the DC Rules were amended, making it mandatory that before the grant of manufacturing license, the manufacturing establishment is to be inspected jointly by the Drug Inspectors of both the central government and the concerned state government. The amendment also made a similar joint inspection mandatory for manufacturing premises for not less that once every three years or as needed per the risk-based approach. Recently, the DTAB has recommended amending the DC Act to authorize Licensing Authorities to issue stop-sale orders for drug retailers. Earlier, this power to issue stop-sale orders was available to the Licensing Authorities in cases of manufacturing non-compliances only.

Organization of CDSCO





Zonal offices

- Mumbai
- Kolkata
- Chennai
- Ghaziabad
- Ahemdabad
- Hyderabad

The zonal offices work in close collaboration with the State Dug Control Administration and assist them in securing uniform enforcement of the drug act and other connected leistations, on all India basis. These are involved in GMP audits and inspection of manufacturing units of large volume parental, sera, vaccine and blood products.

Sub-zonal office:

I. Chandigarh
II. Jammu
III. Bangalore

These centre co-ordinate with state drug control authorities under their jurisdiction for uniform standard of inspection and enforcement.

Functions of Port Offices of CDSCO

•Scrutiny of bills of entry with a view to ensuring that imported drugs comply with the regulations. •To check the shipping bills for export for statistical data and keep control under the regulations

•To ensure that no New Drug is imported into the country unless its import is permitted by the Drugs Licensing Authority under Rules 122 A & 30-AA.

•To ensure that small quantities of drugs imported for clinical trials or for personal use are duly permitted under Test License (11 or 11-A) or Permit License as (12 B) as the case may be. •Maintenance of Statistics regarding import and export of drugs and cosmetics.

•Coordination with Customs authorities.

•Coordination with States Drugs Controllers and Zonal Offices for post-import checks. •Preparation of monthly / quarterly / annual reports.

•To draw samples from import/export and re-import consignments.

Central Drugs Testing Laboratories (CDTL)

• Central Drug Laboratory, Kolkata

• Central Drug Testing Laboratory, Mumbai

• Central Drug Testing Laboratory, Chennai

• Central Drug Laboratory, Kasauli

• Regional Drug Testing Laboratory, Guwahati

• Regional Drug Testing Laboratory, Chandigarh

These laboratories are established under the Indian Drug and Cosmetic Act, 1940 and responsible for quality control of drugs and cosmetics in the country.

The functions of this laboratories include:

1. Statutory functions:

a) Analytical quality control of majority of the imported drug available in Indian market.
b) Acting as an Appellate authority in matters of disputes relating to quality of Drugs.
c) Laying down standards of drugs, cosmetics, diagnostics and devices.
d) Laying down regulatory measures, amendments to Acts and Rules.
e) To regulate market authorisation of new drugs.

f) To regulate clinical research in India.

g) To approve licenses to manufacture certain categories of drugs as Central Licence approving Authority i.e. for Blood Banks, Large Volume Parenteral and Vaccines & Sera.

h) To regulate the standards of imported drugs.

i) Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC).

j) Testing of drugs by Central Drugs Labs

k) Publication of Indian Pharmacopoeia.

2. Other functions:

i) Collection, storage and distribution of International Standard reference preparations of Drug & Pharmaceutical substances.

ii) Training of Drug Analysts deputed by State Drug Control Laboratories and other Institutions.

iii) To advise the Central Drug Control Administration in respect of quality & toxicity of drug awaiting licence.

iv) To work out analytical specifications for preparation of Monographs for the Indian Pharmacopeia & the Homeopathic Pharmacopeia of India.

v) Monitoring in the WHO GMP certification scheme.

vi) Screening of drug formulations available in Indian market.

vii) Evaluation /screening of applications for granting NOC for export of unapproved /banned drugs.

Functions of CDSCO in Centre

- Approval of new drugs and clinical trials.
- Import Registration and Licensing
- Licensing of Blood Banks, LVPs, Vaccines, r-DNA products and some Medical devices and Diagnostic agents.
- Amendment to D&C Act and Rules.
- Participation in WHO GMP certification schemes.
- Banning of drugs and cosmetics.
- Grant to test license, personal license, NOC's for export.
- Testing of drugs by Central Labs.
- Publication of Indian Pharmacopoeia.

- Monitoring adverse drug reactions.
- Guidance on Technical matters.

Responsibilities of Central Authority

CDSCO: For implementing and to revise the same as notified, from time to time by the authority.

• Initiate in framing of rules, regulations and guidance documents to match the contemporary issues in compliance with the requirements of Drugs & Cosmetics Act 1940 and Rules 1945.

• Facilitate in Uniform implementation of the provisions of the Drugs & Cosmetics Act 1940 and Rules 1945.

• Function as Central license Approving Authority under the provisions of Drugs and Cosmetics Act 1940 and Rules 1945.

• Collaboration with other similar International agencies. • Providing training to the Indian regulatory personnel.

• Approval of New Drugs

•Clinical Trials in the country

•Laying down the standards for Drugs

•Control over the quality of imported Drugs

•Coordination of the activities of State Drug CO

• Providing expert advice with a view of bringing about the uniformity in the enforcement of the Drugs and Cosmetics Act

Drug Technical Advisory Board (DTAB)

Ex-Officio:

(i) Director General of Health Services (Chairman)
(ii) Drugs Controller, India
(iii) Director of the Central Drugs Laboratory, Calcutta
(iv) Director of the Central Research Institute, Kasauli
(v) President of Medical Council of India
(vi) President of the Pharmacy Council of India

(vii) Director of Central Drug Research Institute, Lucknow

Nominated:

1) Two persons by the Central Government.

2) One person by the Central Government from the pharmaceutical industry

3) Two persons holding the appointment of Government Analyst under this Act,

Elected:

1) One person, to be elected by the Executive Committee of the Pharmacy Council of India,

2) One person, to be elected by the Executive Committee of the Medical Council of India,

3) One pharmacologist to be elected by the Governing Body of the Indian Council of Medical Research;

4) One person to be elected by the Central Council of the Indian Medical Association;

5) One person to be elected by the Council of the Indian Pharmaceutical Association

Function:

To advise the Central Government and the State Governments on technical matters. To carry out the other functions assigned to it by this Act.

The Drugs Consultative Committee (DCC)

- It is also an advisory body constituted by central government.

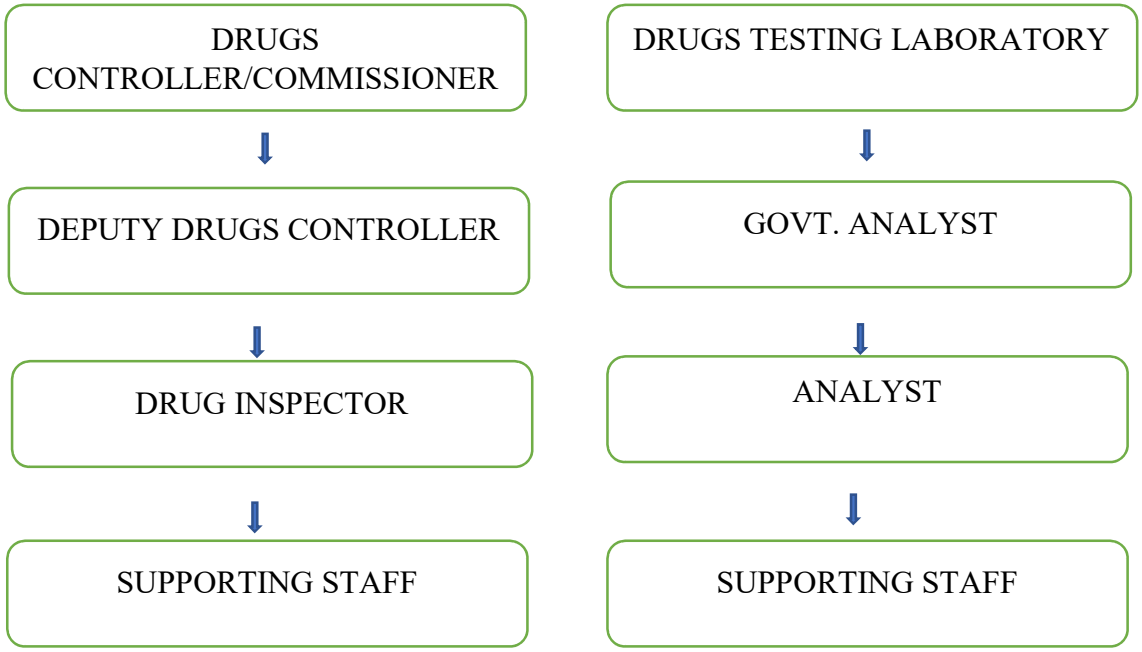
Constitution:

- Two representatives of the Central Government
- One representative of each State Government

Functions:

- To advise the Central Government, the State Governments and the Drugs Technical Advisory Board on any other matter tending to secure uniformity throughout India in the administration of this Act.
- There is separate "The Ayurvedic, Siddha, & Unani Drugs Consultative Committee constituted under sec 33 D of the Act.

STATE DRUGS CONTROL ORGINATION



State Drug Regulatory Authorities (SDRAs) established under the DC Act are responsible for licensing of manufacturing establishments and sale premises, undertaking inspections of such premises to ensure compliance with license conditions, drawing samples for testing and monitoring of quality of drugs, taking actions like suspension/cancellation of licenses, surveillance over sale of spurious and adulterated drugs, instituting legal prosecution when required, and monitoring of objectionable advertisements for drugs.

The State Drug Controller (SDC) heads the SDRA and reports to a joint secretary in the health department of the state government. A typical SDRA has Drug Inspectors reporting to the Deputy Drugs Controller who also acts as the Licensing Authority for the state. Administrative matters such as departmental budgeting, appointments, training of officers, and allotment of funds and resources for inspections, falls under the jurisdiction of the state governments. This report found that a number of SDRAs were conjoined with the food regulatory departments (FDAs) of the state, making it difficult to clearly demarcate the available funds and resources between the two.

Function of State Licensing Authorities

1.Licensing of drug manufacturing and sales establishments

2. Licensing of drug testing laboratories.

3. Approval of drug formulations for manufacture.

4. Monitoring of quality of Drugs & Cosmetics, manufactured by respective state units and those marketed in the state.

5. Investigation and prosecution in respect of contravention of legal provisions.

6. Administrative actions.

7. Pre- and post- licensing inspection

8. Recall of sub-standard drugs.

Responsibilities of State Authority

• Manufacturing, sales, distribution of Drugs licensing drug testing laboratories.

• Approving drug formulations for manufacture

• Carrying out pre- and post-licensing inspections

• Overseeing the manufacturing process for drugs manufactured by respective state units and those marketed in the state

Certificate of Pharmaceutical Product (COPP)

Definition-

The WHO Certification Scheme for a Certificate of Pharmaceutical Product (COPP) is an international voluntary agreement to provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce.

Certificate of pharmaceutical product is a scheme developed by the WHO in response to the request of WHO Member States to facilitate international trade in pharmaceutical products between Member States. It was first developed in 1975. Since then it has been revised in 1988, 1992and in 1997.

Purpose-

A COPP is in the format recommended by the WHO. It is the importing country who requires the COPP for the pharmaceutical product and a special type of certificate which enables a given pharmaceutical product to be registered and marketed in the exporting country of interest and forms parts of the marketing authorization application.

This certificate describes the characteristics of the medicinal product approved in the exporting country, includes information about the applicant of the certificate and is according with the model recommended by the World Health Organization. This is a certificate issued by the Inspectorate establishing the status of the pharmaceutical, biological, radiopharmaceutical or veterinary product listed and the GMP status of the fabricator of the product.

Ideally, a COPP should not be required in countries that have the capabilities to conduct full reviews. The COPP should be used when a pharmaceutical product is under consideration for a product licence/marketing authorisation or when administrative action is required to renew, extend or vary such a licence.

Aim and Scope-

The COPP is the legal document that declares a certain manufacturing company is legally allowed to sell their pharmaceutical product in the country they are producing. When registering a pharmaceutical product overseas, the Government body in charge of approving the application will usually require a COPP to ensure that the product is being sold as a commercial finished product in the country that is producing it.

A COPP demonstrates in question that the imported medicine is of the appropriate standard of quality, safety and efficacy to allow marketing in their market, having undergone rigorous testing and examination to Regulatory Authorities in the exporting country and also demonstrates that it follows the correct guidelines and procedures of Good Manufacturing Practice (GMP), increasing the level of quality and indeed safety of the product. The COPP is needed when the product tends that it is intended for registration or its renewal (licensing, authorization or prolongation)) by the importing country, with the scope that the product is distributed or commercialized in that country.

Certification has been recommended by WHO to help undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities in importing countries to assess the quality of pharmaceutical products as prerequisite of registration or importation.

Need & Importance of COPP:

To obtain global marketing approval for any pharmaceutical product (whether intended for animal/human use) one of the key documents required is a COPP, which has been recommended by the WHO. A COPP is issued by the authorized body of the exporting country and is intended for use by the competent authority within an importing country: when a pharmaceutical product is under consideration for a product license/marketing authorization that will authorize its importation and sale in the importing country; when administrative action is required to renew, extend vary or review such license.

A COPP is issued for human drugs (pharmaceutical, biological and radiopharmaceutical) as well as for veterinary drugs (food producing animals and non-food producing animals). For each medicinal product (Trade Name / Pharmaceutical Form / Strength) is issued a certificate stating the country to export. These Certificates are issued to the marketing authorizations holders (MAH) for medicinal products (with valid Marketing Authorization) or their representatives, manufacturers (without Marketing Authorization and with manufacturing authorization valid) or wholesale distributor authorized by the MAH to consult the information for the medicinal product(s)

Types of COPP:

1)WHO 1975 type COPP-

The WHO 1975 version is a certificate to be issued by exporting country regulatory authority stating: a) the authorized product has to be placed on the market for its use in the country also,

the permit number and issue date, or b) that the nonauthorized product has placed on the market for its use in the country and also add the reasons why it is needed; Also, that; a) As recommended by World Health Organization, the manufacturer of product conforms to GMP requirements. b) only within the country of origin the products to be sold or distributed; or c) To be exported to manufacturing plant where the product is produced and at suitable intervals subject to inspections.

2) WHO 1988 type COPP-

Unlike the WHO 1975 version, the competent authority of the exporting country should have: all labelling copies and product detailed information in the country of origin.

3) **WHO 1992 type COPP-**

This is intended for use by the competent authority of an importing country in two situations: a) When the question arises related to importation and sale license; and b) For license renew, extend, review or changes.

The following information required for the certificate:

i) Whether a licensed product is required to be placed on the market or not.
ii) Also if the satisfied information submitted by the applicant that the certifying authority of the manufacture of the product undertaken by another party
iii) iii) Inspection have been carried out of the manufacturer of product;
iv) If the certificate is provisional or permanent;
v) Is the dosage forms, packages and/or labels of a finished dosage form manufactured by an independent company or by the applicant;
vi) states the names of the importing and exporting (certifying) countries

Here besides three types of COPPs also we have another specific type of the U.S. FDA COPPs. The U.S. FDA issued "Pilot- COPP" for the remaining products which are neither exported nor manufactured in the United States. It is only when no other country has given an approval for the finished medicinal product registration.

Content of the COPP

A CPP has two distinct parts: a) Evidence of quality, safety, and efficacy (QSE) Review and b) Evidence of Compliance with GMP.

Content and format

- Importing country:
- Exporting country:
- Name, form of dosage and its composition of the product (API per unit dose).
- Registration Information (licensing)
- Marketing status of the product in the exporting country.
- license no. of product (containing license holder details; involvement of license holder in manufacturing if any) and also add date of issue,
- Summary of technical basis on which the product has been licensed (if required by the issuing authority)
- Currently marketed product's information
- Details about the product's applicant
- If lacking is there in the exporting country, need to mention the information about reasons.

Key challenges of the interpretation of the COPP scheme

- Difference in product names between certifying and requesting countries.
- The COPP confirms GMP status, additional GMP certificates should not be necessary.
- The COPP is a legal document, additional apostille and/or legalization should not be requested.
- Requirements for the 'country of origin' or 'source country' have multiple definitions and should be clarified as it could refer to the country of any one of the following: first approval or marketing, manufacture, packaging, final release, or main headquarters of the pharmaceutical company.
- The COPP provides evidence of a positive QSE review in the issuing country. A full dossier should not be requested.
- The scheme refers only to the manufacturer of the dosage form but some importing countries require additional manufacturers to be listed.
- The COPP issued is a snapshot of the Market Authorization (MA) in the issuing country and may not necessarily reflect the entire situation in the importing country.

Advantages of the scheme

- To grow business in foreign country, necessary to obtain the COPP certificates by pharmaceutical companies.
- The Scheme provides the standard format that is expected to be used.

- Enables recipient COPP countries to gain assurance on the QSE of the product in the issuing country.
- Obliges certifying authorities to disclose important information to the importing country.
- By supporting the review and approval process it facilitates patient access to quality medicines.

The COPP may be required to support a regulatory submission. This can be submitted at the beginning of, or during the health authority review. According to the WHO Scheme, COPPs should not be required in countries that require full ICH CTD dossiers and have the capability to conduct full QSE reviews.

The COPP only reflects the approved manufacturing sourcing route of the certifying country.

Most recipient authorities expect that the drug product they will receive mirrors that which has been approved by the authority issuing the COPP. When developing a global submission strategy COPP requirements are considered early during the planning phase. If required HAs should be open to discussion in advance of the regulatory submission to give advice and agree on the content of the submission including the COPP to move forward as quickly possible.

Certificate of a pharmaceutical product

This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

The COPP provides the information of the following:

1. **Certificate number of COPP**: The certificate number of COPP should be enclosed in the specified format recommended by WHO.

2. **Name of exporting country i.e. (certifying country):** The name of the country (certified country) to which the product is being exported must be mentioned in the certificate.

3. **Name of importing country i.e. (requesting country):** The name of the countries (requesting countries) from which the product is being imported from certified country must be mentioned in the certificate.

4. **Name and dosage form of the product:**

Table No.1: Essentials of Product

Active ingredient	International Non-proprietary Names (INNs) or national non-proprietary names
Amount per unit dose	The formula (complete composition) of the dosage form should be given on the certificate or be appended.
Complete composition including excipients	Details of quantitative composition are preferred but their provision is subject to the agreement of the product-license holder.
Is this product licensed to be placed on the market for use in the exporting country?(yes/no)	When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product license.

5. **Status of the product actually on the market in the exporting country**:

If the product is actually marketed in the exporting country, the COPP should be provided with the following details:

- Number of product license and date of issue: Indicate, when applicable, if the license is provisional, or the product has not yet been approved.
- Product license holder (name and address):
- Status of product license holder:

  Specify whether the person responsible for placing the product on the market:

a) manufactures the dosage form;

b) packages and/or labels a dosage form manufactured by an independent company; or

c) is involved in none of the above.

- **For categories b and c** the name and address of the manufacturer producing the dosage form is This information can only be provided with the consent of the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product license. If the production site is changed, the license has to be updated or it is no longer valid.
- Is a summary basis for approval appended? (yes/no)

This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

- Is the attached, officially approved product information complete and consonent with the license? (yes/no/not provided)

  This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC).

- Applicant for certificate, if different from license holder (name and address)

  In this circumstance, permission for issuing the certificate is required from the product-license holder. This permission has to be provided to the authority by the applicant.

6. **Periodic inspection of the manufacturing plant by the certifying authority:**

If the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced, the following details were to be included in the COPP.

- Periodicity of routine inspections (years):
- Has the manufacture of this type of dosage form been inspected? (yes/no)
- Do the facilities and operations conform to GMP as recommended by the World Health Organization? (yes/no/not applicable)

7. **The information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party:**

This section is to be completed when the product-license holder or applicant conforms to status (b) or (c) as described in note above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

8. **Other details of Manufacturing premises:**

The following details which is to be enclosed in the COPP are,

- Address of certifying authority
- Telephone and Fax
- Name of authorized person
- Signature

- Stamp and date

How to obtain COPP?

- To obtain a COPP, a request is made to the exporting country's health authority by the Marketing Authorization Holder (MAH).
- An authorized person issues the COPP and returns it to the MAH. Also other documents required to obtain a COPP including an application for Export Certificate form, evidence of a GMP certificate (if applicable), Manufacturing License and the last approved SPC (Summary of Product Characteristics).

Types of drugs for which COPPs may be issued

- Approved drug products
- Active pharmaceutical ingredients (API)
- Over the counter drug (OTC) products
- Unapproved drug products
- Homeopathic drugs

Who can apply for COPP?

- A complete application for export certification must be submitted by the person/company who exports the drug.
- The certification is intended for a drug which : meets the applicable requirements of the Act or Food Drug and Cosmetic Act 801(e)(1) requirements [21 U.S.C.381(e)(1)]

Process to apply for a COPP

a) Submit Form no. 3613b– Located on the FDA internet www.fda.gov/downloads/AboutFDA/Reports Manuals Forms/Forms/UCM052388

b) Requirements for COPP application:

- Applicant Contact Information
- Trade name (the drug product's brand name)
- Bulk Substance Generic Name
- Name of Applicant
- Status of Product License holder
- Listing of manufacturing location on COPP
- Complete Manufacturing Facility Address
- Facility Registration Number
- Importing countries

- Authorization to Release Information
- Number of certificates requested
- Certification Statement
- Billing contact
- Marketing Status in the Exporting Country

Process Time of COPP:

- Drugs in compliance are normally issued within twenty (20) government working days of receipt of complete and an accurate COPP application.

Certificates may not be issued

- Returned – missing information application with a letter identifying the missing information.
- Rejected – manufacturing facilities are not in compliance with good manufacturing practices (GMPs).
- Denied – drug products are not compliance as per regulation (e.g., misbranded drug)

Expiration of COPP

- Certificate expires on 2 years from the notarization date or as noted. After expiry date, a new COPP application has to be submitted.

Format of Certificate of Pharmaceutical Products (COPP) (as per WHO GMP guidelines)

No. of Certificate: ----------

Exporting (certifying) country: ----------

Importing (requesting) country: ----------

Name and dosage form of product: ----------

Active ingredient(s) and amount(s) per unit dose: ----------

1.Is this product Licensed to be placed on the market for use in the exporting country? If Yes, complete Box A. If No complete Box B.

A.

Product -license Holder (name and address): -

Status of license Holder- a/b/c (key in appropriate category)

Number of product License and date of issue: ----------

Is an approved technical summary appended? Yes/ No

Is the attached, officially approved product information complete and consonant with the License? Yes/no/not provided (key in as appropriate)

Applicant for certificate, if different from License holder (name and address): ----------

B.

Applicant for certificate (name and address): ----------

Status of applicant: a/b/c (key in appropriate category)

Why is marketing authorization lacking?

Not required/not requested/under consideration/refused (key is as appropriate)

Remark: ----------

2. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? Yes/no/not applicable (key in as appropriate)

If no or not applicable proceed to question 3.

2.1 Periodicity of routine inspections (years): ----------

2.2 Has the manufacture of this type of dosage form been inspected? Yes/no (key in as appropriate)

2.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization? 15 Yes/no (key in as appropriate)

3. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? Yes/no (key in as appropriate)

If no, explain: ----------

Address of certifying authority: ----------

---------- ----------

Telephone number: ---------- Fax number: ---------- ----------

Name of authorized person: ----------

Signature: ----------

Stamp and date: ----------

Approval of New Drug in India

If any company in India wants to manufacture or import a new drug, they need to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data

as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945.To prove its efficacy and safety in Indian population they need to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central Drugs Standard Control Organization (CDSCO). The regulations under Drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D describe the information required for approval of an application to import or manufacture of new drug for marketing. For an investigational new drug, the sponsor needs to provide detailed information to the DCGI about:

1. Generic name
2. Patent status
3. Brief description of physico-chemical/biological
4. Technical information like
   a) Stability b) Specifications c)Manufacturing process d) Worldwide regulatory status e) Animal pharmacology and toxicity studies
5. Published clinical trial reports
6. Proposed protocol and pro forma
7. Trial duration
8. During master file
9. Undertaking to Report Serious or Life-threatening Adverse Drug Reactions.

The information regarding the prescription, samples and testing protocols, product monographs, labels must also be submitted. It usually takes 3 months for clinical trial approval in India. The clinical trials can be registered in the Clinical Trials Registry of India (CTRI) giving details of the clinical trials and the subjects involved in the trials. The rules to be followed under The Drugs and Cosmetics Rules 1945 are:

1. Rule 122 A -: Application for permission to import new drug
2. Rule 122 B- Application for approval to manufacture new drug other than the drugs specified under Schedule C and C (1).
3. Rule 22 D- P Application for permission to import or manufacture fixed dose combination.

4. Rule 122 DA- Application for permission to conduct clinical trials for New Drug/Investigational New Drug
5. Rule 122 E - Definition of New Drugs*

There's a provision in Rule-122A of Drug and Cosmetic Act 1940 and Rules 1945, that if the licensing authority finds out that if everything is in the interest of public health then he may allow the import of new drugs, based on the data of the trials done in other countries. Another provision is Rule-122A is that clinical trial may be allowed in any new drug case, which are approved and already being used for many years in other countries.

Similarly, in Rule 122-B, application for approval to manufacture New Drug other than the drugs classifiable under Schedules C and C (1) and Permission to import or manufacture fixed dose combination (122-D).

Purpose-

The main purpose of regulating all the medicinal products by regulatory agencies is to safeguard public health. Regulatory agencies work is to make sure that the pharmaceutical companies comply with al, the regulations and standards, so that the patient's well-being is protected.

Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States.

Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use.

It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessary actions in a better way and would also ease the preparation of electronic submissions, which may happen in the near future at CDSCO.

New Drug Application (NDA)

New Drug Application (NDA) is an application submitted to the individual regulatory authority for authorization to market a new drug i.e. innovative product. To gain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing procedures.

After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application that is FDA formal review.

At the conclusion of FDA review of an NDA, there are 3 possible actions that can send to sponsor:

- Not approvable- in this letter list of deficiencies and explain the reason.
- Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labelling changes and possible request commitment to do post-approval studies.
- Approval- it state that the drug is approved.

If the action taken is either an approvable or a not approvable, then FDA provides applicant with an opportunity to meet with agency and discuss the deficiencies.

Different Phases of clinical trials:

- Pre- clinical study - Mice, Rat, Rabbit, Monkeys
- Phase I - Human pharmacology trial - estimation of safety and tolerability
- Phase II - Exploratory trial - estimation of effectiveness and short-term side effects
- Phase III - Confirmatory trial - Confirmation of therapeutic benefits
- Phase IV - Post marketing trial - Studies done after drug approval

Some of the rules & guidelines that should be followed for regulation of drugs in India are:

- Drugs and Cosmetics Act 1940 and its rules 1945
- Narcotic Drugs and Psychotropic Substances -1985
- Drugs Price Control Order 1995
- Consumer Protection Act-1986
- Factories Act-1948
- Law of Contracts (Indian contract Act-1872)
- Monopolistic & Restrictive Trade Practices Act-1969
- ICH GCP Guidelines
- Schedule Y Guidelines
- ICMR Guidelines

- Registry of Trial

Stages of approval-

1. Submission of Clinical Trial application for evaluating safety and efficacy.

2. Requirements for permission of new drugs approval.

3. Post approval changes in biological products: quality, safety and efficacy documents.

4. Preparation of the quality information for drug submission for new drug approval.

1. Submission of Clinical Trial Application for Evaluating Safety and Efficacy:

All the data listed below has to be produced.

(a) Phase-I & phase- II clinical trial:

I. General information
   - Introduction about company: Brief description about company
   - Administrative headquarters: Provide address of company headquarters
   - Manufacturing Facilities: Provide address of company headquarters
   - Regulatory and intellectual property status in other countries.
   - Patent information status in India & other countries

II. Chemistry manufacturing control
   - Product Description: A brief description of the drug and the therapeutic class to which it belongs.
   - Product Development
   - Strain details
   - Information on drug substance
   - Information on drug Product

III. Non-clinical data: References: schedule – Y, amendment version 2005, Drugs and Cosmetics Rules, 1945

IV. Proposed phase-I / II studies: protocol for phase-I / II studies

(b) Phase-III clinical trial:

All the information is as same as phase-I & phase- II clinical trial

- General information
- Chemistry manufacturing control

- Non-clinical data
- Proposed phase-III studies

2.Requirements for permission of New Drugs Approval

The manufacturer / sponsor have to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945. The document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

Module I: Administrative/Legal Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module II: Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action and proposed clinical use. In general, the introduction should not exceed one page. The introduction should include proprietary name, nonproprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It contains the CTD summaries for quality, safety, efficacy information. This module is very important, as it provides detailed summaries of the various sections of the CTD. These include: A very short introduction. Quality overall summary, Non clinical overview, Clinical over view, Non clinical written and tabulated summaries for pharmacology, pharmacokinetics, and toxicology.

Module III: Quality information (Chemical, pharmaceutical and biological)

Information on quality should be presented in the structured format described in the guidance M4Q. This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products. It contains of all of the quality documents for the chemistry, manufacture, and controls of the drug substance and the drug product.

Module IV: Non-clinical information

Information on safety should be presented in the structured format described in the guidance M4S. The purpose of this section is to present a critical analysis of the non-clinical data

pertinent to the safety of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. It gives final copy of all of the final nonclinical study reports.

Module V: Clinical information

Information on efficacy should be presented in the structured format described in the guidance M4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacology studies, clinical efficacy, clinical safety, synopses of the individual studies and final copy of detailed clinical study reports.

3. Preparation of the quality information for drug submission for new drug approval

1) Drug substance (name, manufacturer)

2) Characterization (name, manufacturer)

- Physicochemical characterization
- Biological characterization

3) Drug product (name, dosage form)

4) Control of drug product (name, dosage form)

5) Appendices

- Facilities and equipment (name, manufacturer)
- Safety evaluation adventitious agents (name, dosage form, manufacturer).

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

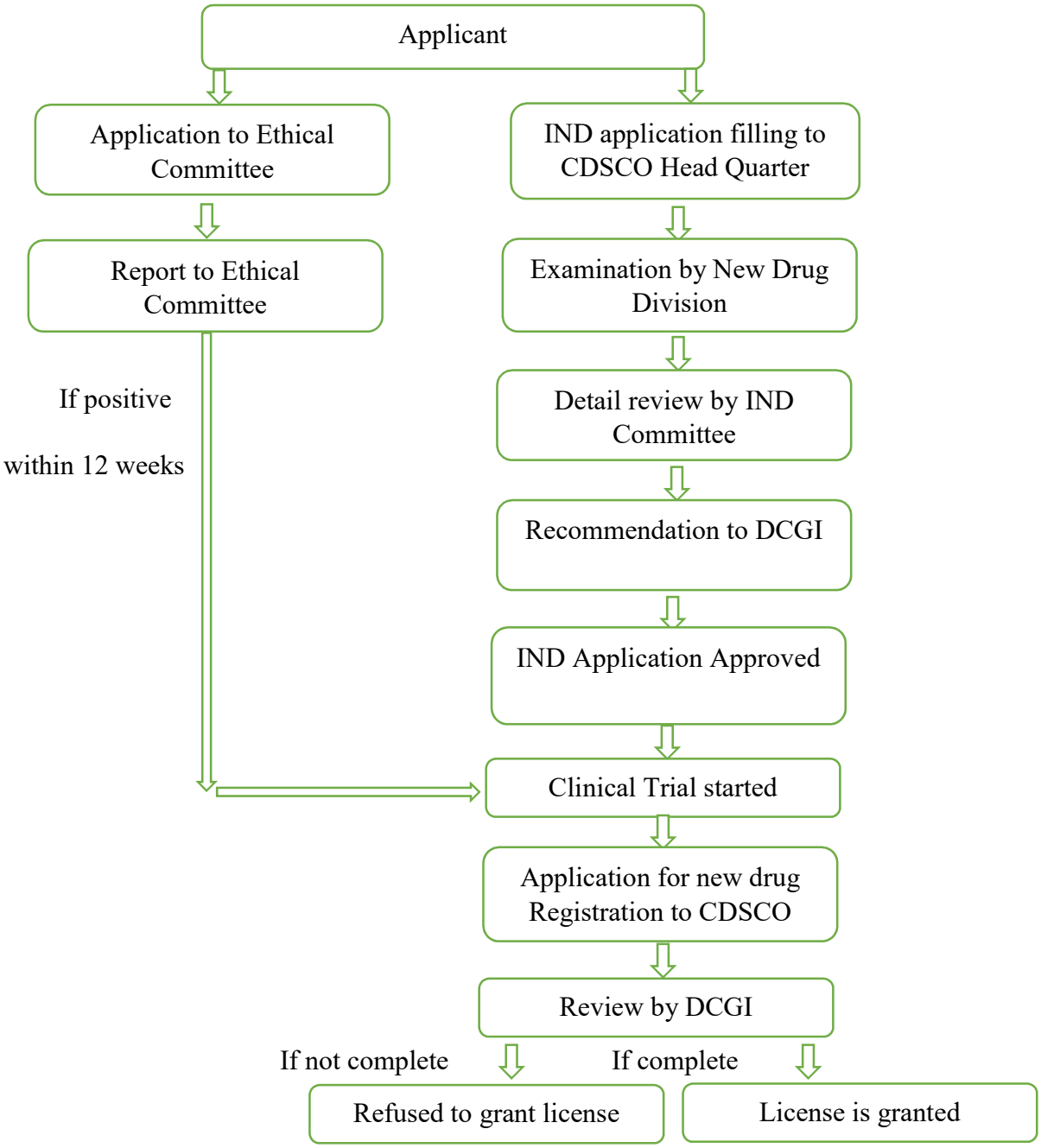


Fig. 1. Drug Approval process in India

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