UNIT –V INDIAN REGULATORY REQUIREMENTS

POINTS TO BE COVERED IN THIS TOPIC

- INTRODUCTION
- CENTRAL DRUGS STANDARD CONTROL ORGANIZATION (CDSCO)
- LICENSING AUTHORITY
- CERTIFICATE OF PHARMACEUTICAL PRODUCT (COPP)

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.

• Its quality is critical to patient health and poor quality can lead to–

✓ Treatment failure

✓ Adverse effects

✓ Prolonged illness

✓ Distrust in healthcare system

✓ Waste of limited financial resources

✓ Death

➤ 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 headquarter is located at FDA Bhawan, **Kotla Road,** New Delhi 110002 and also has **six zonal offices, four sub zonal offices, thirteen Port offices and seven laboratories** spread across the country. 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**.**

➤ Objective

• Prescribes standards and measures to ensure the **safety, efficacy and quality of drugs,** cosmetics, diagnostics **and** devices in the country.

• Regulates the **market authorization of new drugs and clinical trials** standards.

• Supervises drug imports and approves licenses to manufacture the drugs by acting as central license approving authority **(CLAA).**

➤ Functions of CDSCO

i. Approval of **new drugs and clinical trials**.

ii. Import Registration **and Licensing.**

iii. Licensing of **Blood banks, LVPS, Vaccines, Pie-DNA products and some medical devices and diagnostic agents**.

iv. Amendment of **D and C Act** and Rules.

v. Banning of drugs and cosmetics.

vi. Grant to Test license, Personal License, NOC's for export.

vii. Testing of drugs by Central Labs.

viii. Publication of **Indian Pharmacopoeia**.

ix. Monitoring adverse drug reactions.

x. Guidance on **technical matter**.

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.

• 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.

• 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.

• 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.

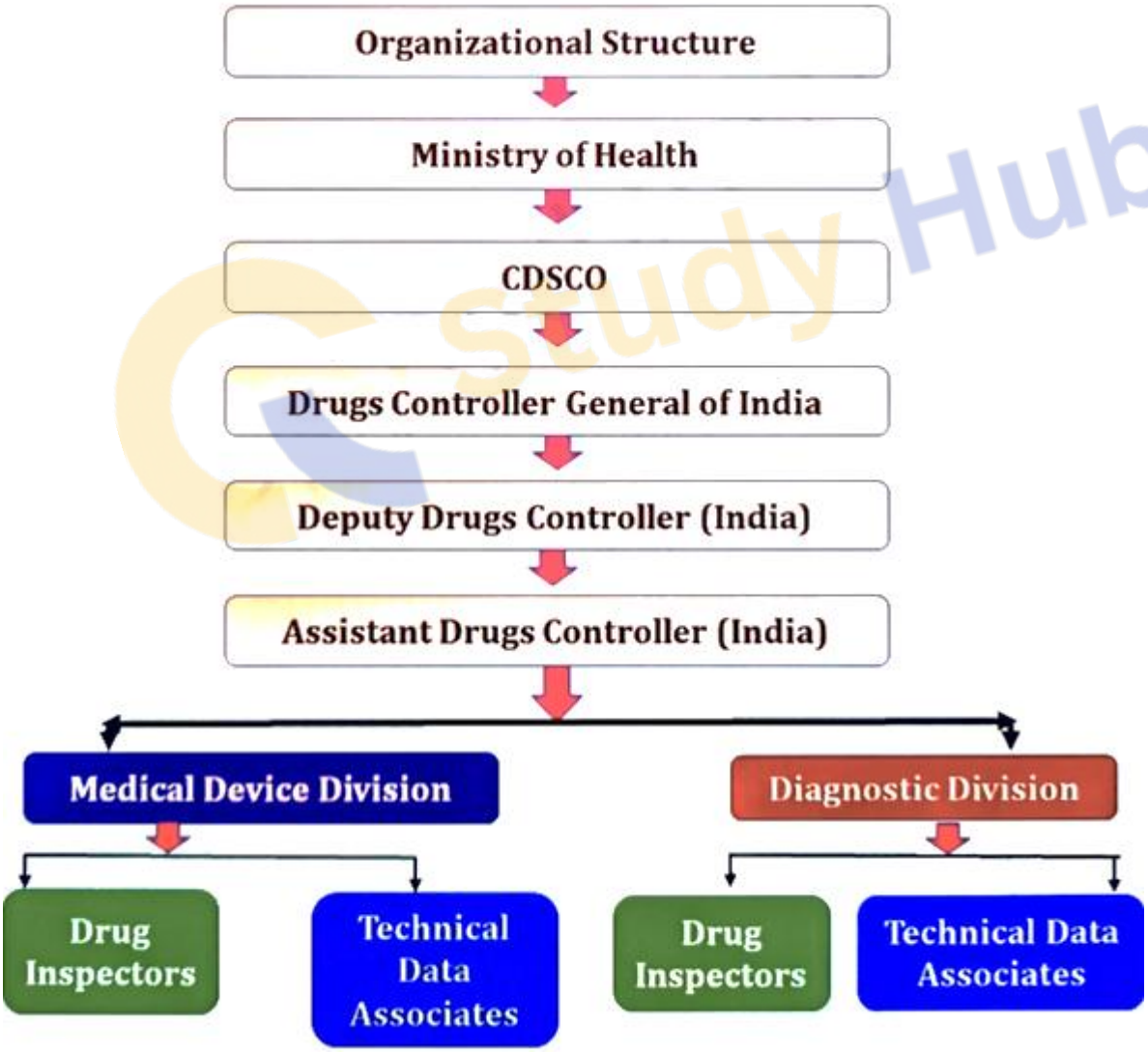
• The provisions also direct the **DI to divide the samples into four** (three, if taken from the manufacturer) properly sealed portions or take as many units of the drug. The Government Analyst under **Section 25** of the DC Act must then prepare a signed report which is then taken to be a conclusive fact upon the standard of quality of the drug.

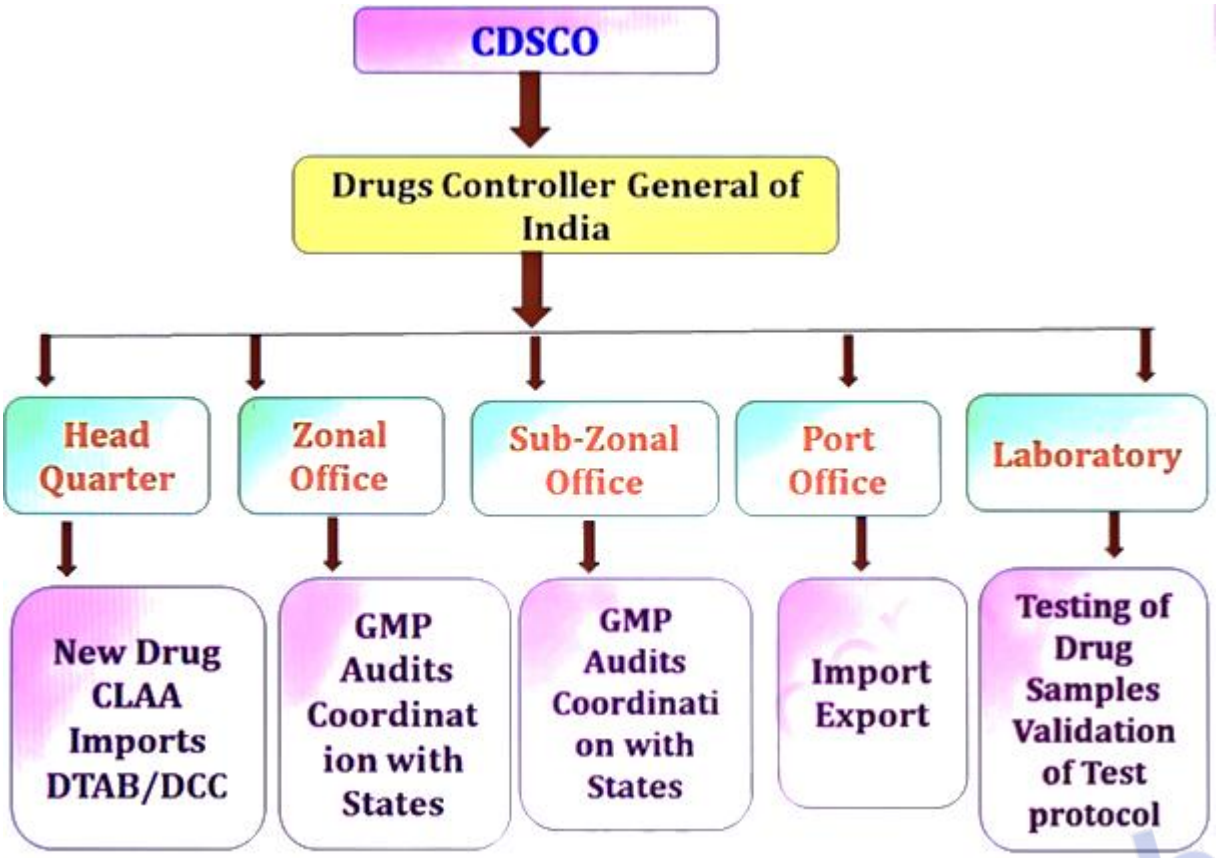
• These provisions are complemented by the DC Rules which elaborate on the duties of the Government Analyst, the Drug Inspector and the Licensing Authority.

• 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 than **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**.

Organization of CDSCO





Head Quarter	FDA Bhawan, Kotla Road, New Delhi
Zonal Office	Mumbai ,Kolkata , Chennai , Ghaziabad , Ahmedabad , Hyderabad
Sub-Zonal Office	Chandigarh , Jammu , Bangalore
Port Office	13
Laboratory	7

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 **(12 B)** as the case may be.

• Maintenance of statistics regarding **import and export of drugs and cosmetics**.

• Coordination with customs authorities.

• Coordination with **state 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**.

Drugs Controller General of India (DCGI)

• He/she is responsible for approval of **New Drugs,** Medical devices **and** Clinical Trials 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.

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**.

Functions of These Laboratories Include

STATUTORY FUNCTIONS	OTHER FUNCTIONS
• Analytical quality control of majority of the imported drug available in Indian market. • Acting as an Appellate authority in matters of disputes relating to quality of Drugs. • Laying down standards of drugs, cosmetics, diagnostics and devices. • Laying down regulatory measures, amendments to Acts and Rules. • To regulate market authorization of new drugs	• Collection, storage and distribution of International Standard reference preparations of **Drug & Pharmaceutical substances.** • Training of Drug Analysts deputed by State Drug Control Laboratories and other Institutions. • To advise the Central Drug Control Administration in respect of quality & toxicity of drug awaiting license. • To work out analytical specifications for preparation of Monographs for the Indian Pharmacopeia & the Homeopathic Pharmacopeia of India. • Monitoring in the WHO GMP certification scheme. • Screening of drug formulations available in Indian market. • Evaluation /screening of applications for granting NOC for export of unapproved /banned drugs.

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

(v) Director of the Central Research Institute, Kasauli

(vi) President of Medical Council of India

(vii) President of the Pharmacy Council of India

(viii) Director of Central Drug Research Institute, Lucknow

➤ Nominated

i. Two persons by the Central Government.

ii. One person by the Central Government from the pharmaceutical industry.

iii. Two persons holding the appointment of **Government Analyst** under this Act.

➤ Elected

i. One person, to be elected by the **Executive Committee of the Pharmacy Council of India**.

ii. One person, to be elected by the **Executive Committee of the Medical Council of India**.

iii. One pharmacologist to be elected by the **Governing Body of the Indian Council of Medical Research**.

iv. One person to be elected by the **Central Council of the Indian Medical Association**.

v. 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.

LICENSING AUTHORITY

❖ Central Authorities

• Approval of **new drugs**

• **Clinical trials**

• Lays down the **standards**

• Control over the **quality imported drugs**

• Co-ordination of the activities of **state drug control organizations**

Central Licensing CLAA approval and grant of license – Manufacture

⬇

State licensing Authorities

(license prepared by state licensing authority)

⬇

Joint Inspection by State and Central Inspectors

⬇

Examination of Report for

• biological

• Large volume parenteral (LVP)

• Blood Bank and blood products

• some medical devices

❖ **State Authorities**

• State Licensing Authority means the **state agency responsible for the issuance, renewal, or reinstatement of a state license**, or the state agency authorized to take disciplinary action against a state licensee.

• Issue licenses for **manufacture of approved drugs**

• **Monitor quality control**

• **Distribution and sales of drugs**

❖ State Drug Regulatory Authorities (SDRAs)

• Established under the **D & C Act**

• Responsible for licensing of **manufacturing establishments and sale premises**

• Undertaking **inspections** to ensure compliance with **license conditions**

• **Drawing samples for testing and monitoring quality of drugs**

• Taking actions like **suspension / cancellation of licenses**

• Surveillance over **sale of spurious and adulterated drugs**

• Instituting **legal prosecution** when required

• 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** fall 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.

➤ Function of State Licensing Authorities

i. Licensing of drug manufacturing **and sales establishments**.

ii. Licensing of **drug testing laboratories**.

iii. Approval of drug formulations for manufacture.

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

v. **Investigation and prosecution** in respect of contravention of legal provisions.

vi. Administrative actions.

vii. **Pre- and post- licensing inspection**.

viii. 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)

• The certificate of pharmaceutical product **(COPP)** is a certificate issued in the format recommended by the World Health Organization **(WHO)**, which establishes the **status of**

the pharmaceutical product, about the quality of pharmaceutical products moving in **international commerce**.

• The CPP supports the review in countries without sufficient capability to conduct a full review themselves. Ideally, a CPP should not be required in countries that have the capabilities to conduct full reviews.

• It was first developed in **1975**. Since then it has been revised in **1988, 1992 and in 1997**.

➤ Purpose

• A COPP is in the **format recommended by the** WHO.

• COPP for the pharmaceutical product is a special type of **certificate** which enables a given **pharmaceutical product** to be registered and **marketed in the exporting country of interest** and forms part of the marketing authorization application.

• This certificate describes the **characteristics of the medicinal product** approved in the **exporting country**.

• 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 license / marketing authorization**.

• when administrative action is required **to renew, extend or vary such a license.**

➤ 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.

➤ 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 COPP, which has been recommended by the WHO.

• A COPP is issued by the **authorized body of the exporting country**.

• It 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**).

• 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

i. WHO 1975 type COPP

ii. WHO 1988 type COPP

iii. WHO 1992 type COPP

➤ WHO 1975 type COPP

• The **WHO 1975 version** is a certificate to be issued by exporting country regulatory authority stating :

✓ The authorized product has to be placed on the market for its use in the country also, the permit number and issue date.

✓ That the non authorized product has placed on the market for its use in the country and also add the reasons why it is needed.

✓ As recommended by **world health organization**, the manufacturer of product conforms to requirements.

✓ Only within the country **GMP** of origin the products to be sold or distributed.

✓ To be exported to manufacturing plant where the product is produced and at suitable intervals subject to inspections.

➤ **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.

➤ **WHO 1992 type COPP**

• This is intended for use by the competent authority of an importing country in **two situations**:

i. When the question arises related to **importation and sale license**.

ii. For **license renew, extend, review or changes**.

➤ **COPP Application**

• The application for grant of WHO GMP Certificate of Pharmaceutical Product shall be made to respective **zonal/sub zonal officers** as per the requirement.

• The COPP will be issued by **zonal/sub zonal officers** on behalf of **Drugs Controller General (India)** after inspection and satisfactory clearance by CDSCO officers as per WHO–GMP guidelines.

➤ General requirements for submission of application for issue of COPP

• A forwarding application shall be addressed to **DDC(I)/ADC(I)** of respective **CDSCO zonal/sub zonal offices** with **copy of covering letter & product summary sheet to DCF(I)** by authorized person only.

• Application should clearly indicate for fresh certification **(Grant)** or **reissue of products** applied, accordingly it will be scrutinized for the products applied.

• Applications will be reviewed by CDSCO officers and completed applications in all respects would be accepted for **inspection on first come first serve basis**.

• The forwarding **letter/application** shall be accompanied with list of products applied for **grant of COPP**, along with a product permission copy (**manufacturing license issued by the SLA**) & notarized product summary sheet, site master file as per WHO-GMP requirement.

• List of major/master documents like **master validation plan, quality manuals / master formula records** maintained by firm and list of **SOP's**.

• **Manufacturing layout**

• List of personnel (with qualification and designation).

• List of **equipment's, instruments**.

➤ Procedure for accepting the application for issue of COPP

• All applications received will be scrutinized by CDSCO Officials after receipt and **query letter will be sent to applicant**, if any or otherwise will be considered for **inspection**.

• Inspection will be carried out by CDSCO Officers as per WHO GMP guidelines of

✓ TRS 823/908 for non sterile products.

✓ TRS 822/902 for Sterile Products and other relevant guidelines in **TRS937, TRS 929, TRS 863** etc. as applicable from time to time.

• Self appraisal checklist should be **filled and submitted to CDSCO officer before inspection**.

• Inspection team verify the checklist at the time of inspection.

• Inspectors brief the **inspection findings at the exit meeting**.

• The report should clearly define deficiencies as per **WHO GMP guidelines**.

➤ Content of the COPP

• A CPP has **two distinct parts**

i. Evidence of **quality, safety, and efficacy (QSE) Review**

ii. 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 **apostle 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
    - main headquarters of the pharmaceutical company

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**.
- 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 (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 (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**

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:

i. **Number of product license and date of issue**

- Indicate, when applicable, if the license is provisional, or the product has not yet been approved.

ii. **Product license holder (name and address)**

iii. **Status of product license holder**

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

  a) Manufactures the dosage form

  b) Packages or labels a dosage form manufactured by an independent company

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.

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

- 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

Types of drugs for which COPPs may be issued

i. Approved drug products

ii. Active pharmaceutical ingredients (API)

iii. Over the counter drug (OTC) products

iv. Unapproved drug products

v. Homeopathic drugs

➢ **Process to apply for a COPP**

a) Submit Form no. 3613b

Located on the FDA internet

www.fda.gov/downloads/AboutFDA/ReportsManualsForms/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 DETAILS

- **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. PERIODIC INSPECTION DETAILS

- **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?

Yes / No (key in as appropriate)

3. APPLICANT COMPLIANCE

- **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:**

CERTIFICATE OF A PHARMACEUTICAL PRODUCT (COPP)

(WHO GMP Guidelines Format)

Office of the State Drugs Controller (Controlling & Licensing Authority)

Food and Drug Administration, Haryana (India)

- **No. of Certificate:** COPP/WHO-GMP/_____/____

- **Exporting (Certifying) Country:** INDIA

- **Importing (Requesting) Countries:** Nepal, Bangladesh, Myanmar, Nigeria, Sudan, Angola, Burundi, Philippines, Vietnam, Chad, Congo Brazzaville, Congo DMR, Mali

1. NAME & DOSAGE FORM OF PRODUCT

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

- Each uncoated tablet contains:
  - Lopinavir IP — 200 mg
  - Ritonavir USP — 50 mg

1.2 Is this product licensed to be placed on the market for use in the exporting country?

Yes / No

1.3 Is this product actually on the market in exporting country?

- If the answer to 1.2 is yes, continue with section 2A and omit section 2B
- If the answer to 1.2 is no, omit section 2A and continue with section 2B

2A

- **Number of product license:** _____
- **Approval Date:** _____
- **Product License holder (Name & Address):**

  Mencell & Argus Pharmaceuticals Ltd.

  100, Rampur Sanshri Road,

  Ambala Cantt – 133001 (India)

- **Status of Product License Holder:** A / B / C
- **For Categories B & C name & address of manufacturer producing the dosage form:**
- **Is summary basis of approval appended?** Yes / No
- **Is the attached, officially approved product information complete and consonant with the License?**

  Yes / No / Not provided

- **Application for Certificate if different from License Holder:**

  Not Applicable

2B

- **Applicant for Certificate (Name and Address):** _____
- **Status of Applicant:** A / B / C / D
- **For Categories B & C name and address of the Manufacturer producing the dosage form:**
- **Why is marketing authorization lacking?**
- **Remarks:** _____

3. INSPECTION DETAILS

- **Does the certifying authority arrange for periodic inspection of the manufacturing plant?**

  Yes / No / Not Provided
- **Periodicity of routine inspection:** ONCE A YEAR
- **Has the manufacture of this dosage form been inspected?** Yes / No
- **Do the facilities and operations conform to GMP as recommended by WHO?** Yes / No

CONTACT DETAILS

- **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 must apply for permission from the **Licensing Authority** **(DCGI)** by filing **Form 44**, submitting data as per **Schedule Y of Drugs and Cosmetics Act, 1940 and Rules 1945**.
- To prove **efficacy and safety in Indian population**, clinical trials must be conducted as per **Schedule Y**, and reports submitted in prescribed format.
- Demonstration of **safety and efficacy** is essential before approval for import/manufacture by **Central Drugs Standard Control Organization** **(CDSCO)**.

INFORMATION REQUIRED FOR INVESTIGATIONAL NEW DRUG

1. Generic name
2. Patent status
3. Brief description of physico-chemical / biological
4. Technical information:
    - Stability
    - Specifications
    - Manufacturing process

- Worldwide regulatory status
- Animal pharmacology and toxicity studies

5. Published clinical trial reports
6. Proposed protocol and proforma
7. Trial duration
8. Drug master file
9. Undertaking to report serious or life-threatening adverse drug reactions

RULES UNDER DRUGS & COSMETICS RULES, 1945

Rule	Description
Rule 122 A	Permission to import new drug
Rule 122 B	Approval to manufacture new drug
Rule 122 D	Import/manufacture fixed dose combination
Rule 122 DA	Permission to conduct clinical trials
Rule 122 E	Definition of new drugs

NEW DRUG APPLICATION (NDA)

- NDA is an application submitted to the regulatory authority to authorize marketing of a **new innovative drug**.

- Sponsor submits **preclinical and clinical data**, drug analysis, and manufacturing details.

NDA Decision Types:

- **Not approvable:** Lists deficiencies and reasons
- **Approvable:** Minor deficiencies; labeling changes or post-approval studies required
- **Approval:** Drug approved

➤ **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**

➤ **Rules & guidelines that should be followed for regulation of drugs in India are:**

i. Drugs and Cosmetics Act 1940 and its rules 1945

ii. Narcotic Drugs and Psychotropic Substances – 1985

iii. Drugs Price Control Order 1995

iv. Consumer Protection Act – 1986

v. Factories Act – 1948

vi. Law of Contracts (Indian Contract Act – 1872)

vii. Monopolistic & Restrictive Trade Practices Act – 1969

viii. ICH GCP Guidelines

ix. Schedule Y Guidelines

x. ICMR Guidelines

xi. Registry of Trial

➤ Stages of Approval

i. Submission of Clinical Trial application for **evaluating safety and efficacy**

ii. Requirements for **permission of new drugs approval**

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

iv. 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

• 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**.

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.

Module II – Summaries

The introduction should include proprietary name, non-proprietary 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**.

Module III – Quality Information

(Chemical, pharmaceutical and biological)

This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products.

It contains all of the quality documents for the chemistry, manufacture, and controls of the drug substance and the drug product.

Module IV – Non-clinical Information

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**.

Module V – Clinical Information

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

i. Phase I (IND) – Rs. 50,000

ii. Phase II (IND) – Rs. 25,000

iii. Phase III (IND) – Rs. 25,000

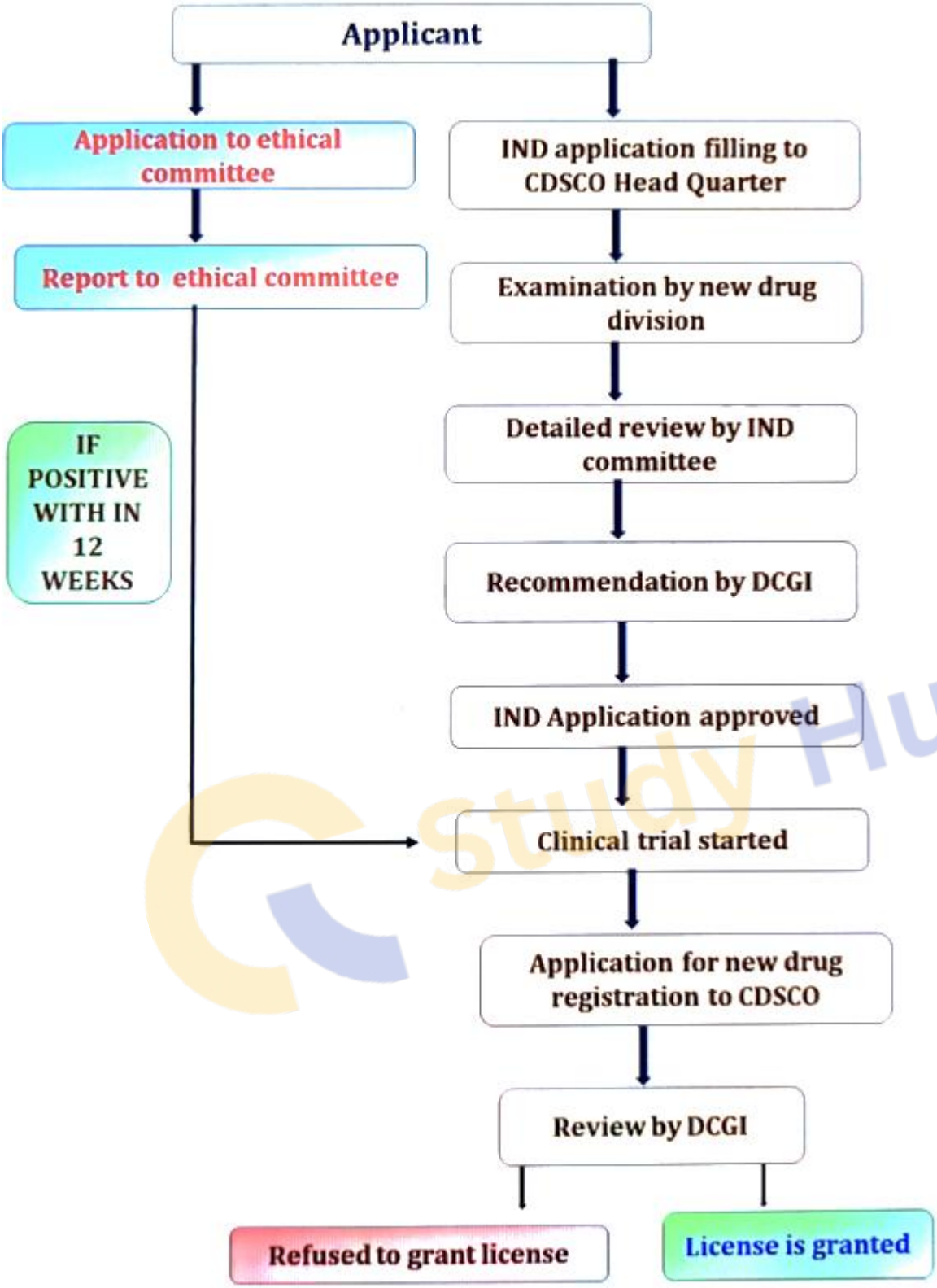
iv. Approval of New Molecule – Rs. 50,000

v. Approved New Drug:

- Within 1 year of approval – Rs. 50,000
- After 1 year of approval – Rs. 15,000

vi. Approval of New claim, New dosage form etc. – Rs. 15,000

➤ DRUG APPROVAL PROCESS IN INDIA


Applicant
Application to ethical committee
Report to ethical committee
IF POSITIVE WITH IN 12 WEEKS
IND application filling to CDSCO Head Quarter
Examination by new drug division
Detailed review by IND committee
Recommendation by DCGI
IND Application approved
Clinical trial started
Application for new drug registration to CDSCO
Review by DCGI
Refused to grant license
License is granted