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UNIT-V

Indian regulatory requirements

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Abstract: Central Drug Standard Control Organization (CDSCO) and State Licensing Authority: Organization, Responsibilities, Certificate of Pharmaceutical Product (COPP), Regulatory requirements and approval procedures for New Drugs.

Keywords: Automation, Optimization, Process Control, Quality Assurance, Standardization validation.

1.1 Introduction

The majority of laws and regulations pertaining to medicines are created and enforced by the Drug Regulatory Authority (DRA). Its primary responsibility is to guarantee the efficacy, safety, and quality of medications as well as the correctness of product information. This is accomplished by establishing regulations that ensure that the production, acquisition, import, export, distribution, supply, and sale of pharmaceuticals, as well as the advertising and marketing of products and clinical studies, are conducted in compliance with predetermined criteria.

Functions of Regulatory Authority:

- Regulation of drug manufacture, importation, and distribution; regulation and control of drug marketing and information; and product registration (drug evaluation and authorisation, as well as monitoring of drug efficacy and safety).
- Monitoring adverse drug reactions (ADRs) and licensing individuals, facilities, and procedures.
- Ensuring the safety, effectiveness, and quality of pharmaceuticals is the primary objective

of drug regulation.

1.2 Central Drugs Standard Control Organization (CDSCO)-

The nation's declared medical devices, pharmaceuticals, and cosmetics are all subject to regulatory oversight by the Central Drugs Standard Control Organization. The primary regulatory body for clinical trials, pharmaceuticals, and medical devices in India is the CDSCO. In order to carry out the duties delegated to the Central Government by the Drugs and Cosmetics Act, it is the Central Drug Authority. It operates under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, and has its headquarters at FDA Bhawan, Kotla Road, New Delhi.

It is separated into zone offices that provide post-market surveillance, recalls where necessary, and inspections before and after licensing.

Vision: To safeguard and advance Indian health

Mission is to ensure the efficacy, safety, and quality of pharmaceuticals, cosmetics, and medical equipment in order to safeguard and enhance public health.

Drugs Controller General of India (DCGI)

- He or she is nominated by the federal government and will work under the DCGI, the state drug control organisation, and is in charge of approving new drugs, medical equipment, and clinical trials to be carried out in India.
- The Drug Consultative Committee (DCC) and the Drug Technical Advisory Board (DTAB) provide advice to the DCGI.

Clinical studies, new medicine introduction, import permits, and product approval and approval requirements are all under the DCGI's purview. Only once a medicine has received CDSCO approval may a state provide a manufacturing license.

Process of drug regulation

This entails assigning duties such as approving new medications, carrying out domestic clinical trials, establishing drug standards, managing the quality of imported medications, and generally supervising the SDRAs in addition to serving as an advisor to ensure uniformity in the DC Act's operation.

New drugs are approved by the Central Drugs Standard Control Organization based on a combination of non-clinical study results and clinical data studies conducted both

domestically and abroad, with an emphasis on safety and efficacy, while also taking the drug's regulatory status in other countries into consideration. Rules 122A, 122B, 122D, 122DA, 122DAA, 122DAB, 122DAC, 122DB, 122DD, and 122E supply the legislative requirements for new medication approval.

According to Schedule-Y DC Rules, a waiver of requirement for local clinical trials may be permitted if licensing authority determines that it is in public interest to make the new drug available for importation and manufacturing using data from other nations. Legislation allows Licensing Authority to compress, postpone, or waive clinical data completely under some circumstances, including those that are essential for the treatment of disorders or diseases that are particularly relevant to the Indian healthcare system. Formerly called the New Drug Advisory Committees, the 12 Subject Expert Committees (SEC)

Committees (NDAC), evaluate applications for the approval of new drugs. Experts from Government Medical Colleges and Institutes located around India usually make up these panels. These committees' recommendations serve as the basis for deciding whether to approve or deny such petitions. It has seriously clouded India's clearance and regulating procedure for new pharmaceuticals. The fact that the government, not CDSCO, ordered the prohibition makes it much worse and calls into question CDSCO's authority as a regulatory agency. In addition to approval, licensing and inspections play significant regulatory functions. The Drug Inspectors (DI) are authorized by Sections 22 & 23 of DC Act to examine establishments that produce or sell drug or cosmetic and to collect samples of any of these products in return for a written recognition and the drug's fair price. When a sample is obtained for testing or analysis, the DI is required to notify the property owner in writing of its intended use. Additionally, the requirements instruct the DI to extract as many units of the medicine or split samples into four (or three, if they were taken from the manufacturer) properly sealed pieces.

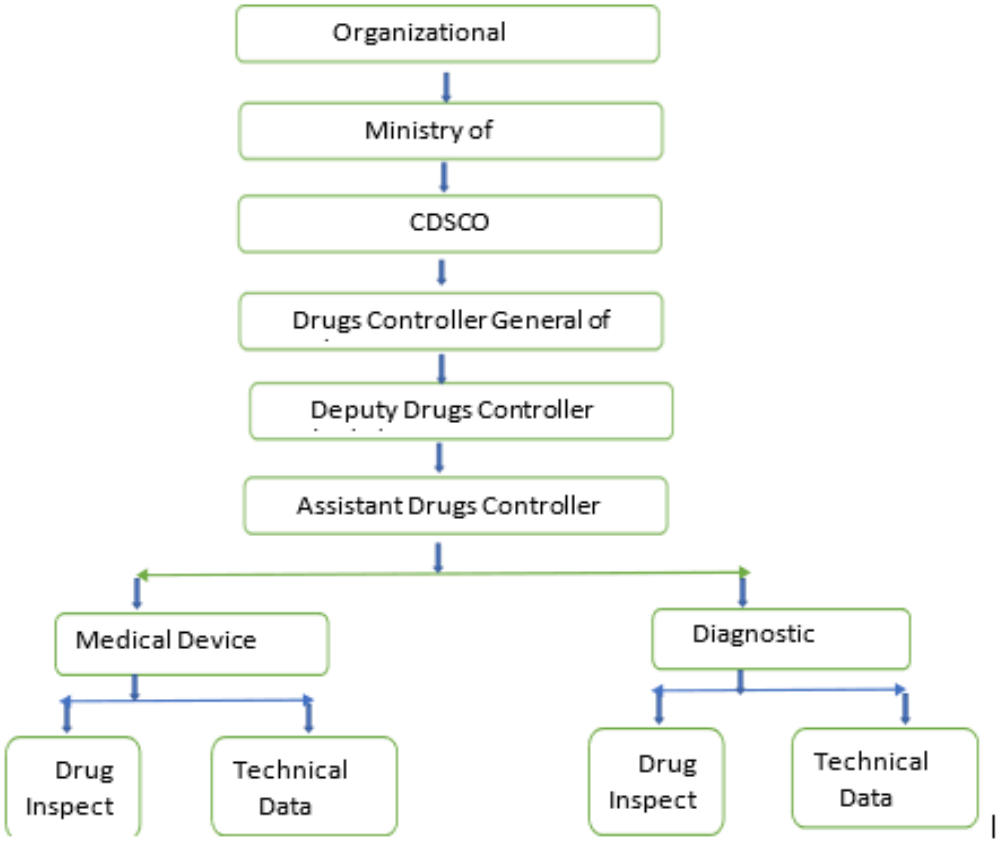
The Government Analyst should next create and sign a report in accordance with Section 25 of the DC Act, which is essentially a declaration of fact regarding the drug's quality level. These guidelines are further strengthened by the DC Rules, which provide comprehensive explanations of the roles of Government Analyst, Drug Inspector, and Licensing Authority.

It was changed in 2017 and now stipulates that before granting a manufacturing license, a joint inspection by a drug inspector from the federal government and the appropriate state governments is required. Additionally, the amendment stipulated that the aforementioned joint inspection of the production site must be conducted at least once every three years; if not, at any earlier period that is determined necessary by the risk

analysis. Recently, the DTAB suggested a change to the DC Act that would provide licensing authorities the authority to require drug merchants to halt sales. Until now, only the licensing authorities had the authority to impose stop-sale orders in the event of manufacturing non-compliances.

1.3 Organization of CDSCO

Organization of CDSCO



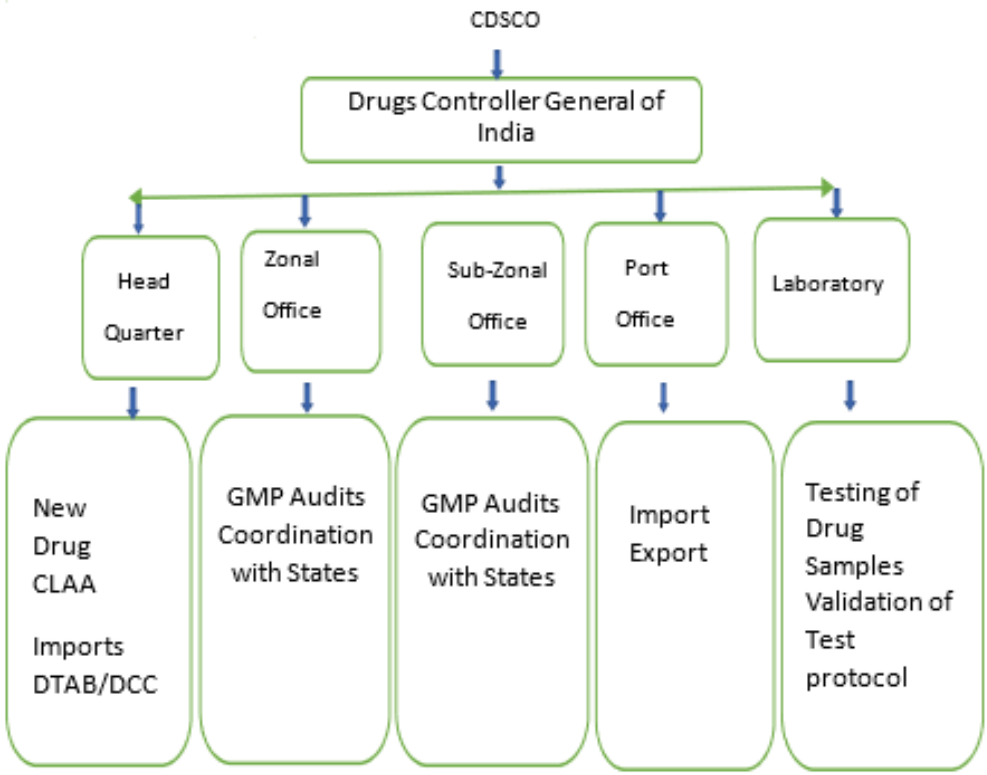


Fig. No.5.1: Organization of CDSCO

Zonal offices

- Mumbai
- Kolkata
- Chennai
- Ghaziabad
- Ahmedabad
- Hyderabad

The State Drug Control Administration and the zonal offices collaborate closely to ensure that the drug act and related laws are applied consistently throughout India. They participate in GMP audits and inspections of production facilities for significant quantities of blood, vaccine, serum, and parental goods.

Sub-zonal office:

- Chandigarh
- Jammu
- Bangalore

To ensure uniform standards of inspection and enforcement, these centers coordinate with the state drug control authorities within their purview.

Functions of Port Offices of CDSCO

- Examining bills of entry to make that imported medications adhere to the rules.
- To verify export shipping invoices for statistical information and maintain regulatory.
- To guarantee that no new drug is brought into the nation unless approved by the Drugs Licensing Authority in accordance with Rules 122 A and 30-AA.
- To make sure that modest amounts of medications imported for personal use or clinical studies are properly allowed under the applicable Permit License (12 B) or Test License (11 or 11-A), as applicable.
- Updating statistics on the import and export of pharmaceuticals and cosmetics.
- Working together with customs officials.
- Post-import checks are coordinated with Zonal Offices and State Drug Controllers.
- Monthly, quarterly, and yearly reports are prepared.
- To extract samples from re-import and import/export shipments

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 labs were set up in accordance with the Indian medication and Cosmetic Act of 1940 and are in charge of the nation's medication and cosmetic quality control.

Among the duties performed by these labs are:

1. Statutory functions:

a) Analytical quality monitoring of the vast majority of foreign medications sold in India.

b) Serving as an appellate body in cases involving disagreements over the quality of medications.
c) Establishing guidelines for medications, cosmetics, diagnostics, and equipment.
d) Establishing regulations and making changes to laws and regulations.
e) To control the approval of new medications for the market.
f) To control clinical research conducted in India.
g) As the Central License Approval Authority, to provide licenses to produce certain medicine categories, such as those for blood banks, vaccinations, sera, and big volume parenteral.
h) To regulate the quality of imported drugs.
i) Activities pertaining to the Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB).
j) Central Drugs Labs tests medications
k) The Indian Pharmacopoeia is published.

2. Other functions:

i. Gathering, preserving, and dispersing reference preparations of drugs and pharmaceutical chemicals that meet international standards.
ii. State Drug Control Laboratories and other organizations train their drug analysts.
iii. To provide the Central Drug Control Administration with advice on the toxicity and quality of drugs that are pending licenses.
iv. To determine the analytical requirements for creating monographs for the Indian Pharmacopoeia and the Indian Homoeopathic Pharmacopoeia.
v. Observation under the WHO GMP certification program.
vi. Examining medication compositions that are offered for sale in India.
vii. Reviewing and vetting applications for a NOC to export prohibited or unapproved medications.

Functions of CDSCO in Centre:

- The authorization of novel drugs and clinical research
- Import licensing & registration
- The licensing of vaccines, r-DNA products, blood banks, LVPs, certain medical equipment, and diagnostic agents.
- The D&C Act and Rules have been amended.
- Taking part in WHO GMP certification programs.
- Prohibition of cosmetics and narcotics.
- NOCs for export, personal licenses, and grants for test licenses.

- Central Labs tests medications.
- The Indian Pharmacopoeia is published.
- Keeping an eye on negative medication effects.
- Advice about technical issues.

Central Authority Responsibilities

CDSCO: To implement and update the same as periodically notified by the authority.

- In accordance with the provisions of the Drugs & Cosmetics Act 1940 and Rules 1945, begin draughting rules, regulations, and guidance papers to reflect current concerns.
- Assist in the uniform application of the 1940 and 1945 Drugs & Cosmetics Act requirements.
- Operate as the Central License Approving Authority in accordance with the 1940 Drugs and Cosmetics Act and the 1945 Regulations.
- Training Indian regulatory staff;
- collaboration with other similar international organizations.
- New drug approval;
- national clinical trials;
- drug standards establishment;
- coordination of State Drug CO operations;
- and expert advice with the goal of achieving uniformity in the Drugs and Cosmetics Act's enforcement

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 MedicalResearch;
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 carryout the other functions assigned to it by this Act.

The Drugs Consultative Committee (DCC)

Additionally, it is an advisory council established by the Constitution of the federal government:

- 2 representatives of the Central Government
- 1 representative of each State Government

Functions:

- To provide advice on any other issue pertaining to ensuring consistency in the implementation of this Act across India to Central Government, State Governments, & Drugs Technical Advisory Board.
- Section 33 D of the Act established a separate "Ayurvedic, Siddha & Unani Drugs Consultative Committee."

1.4 State Drugs Control Origination

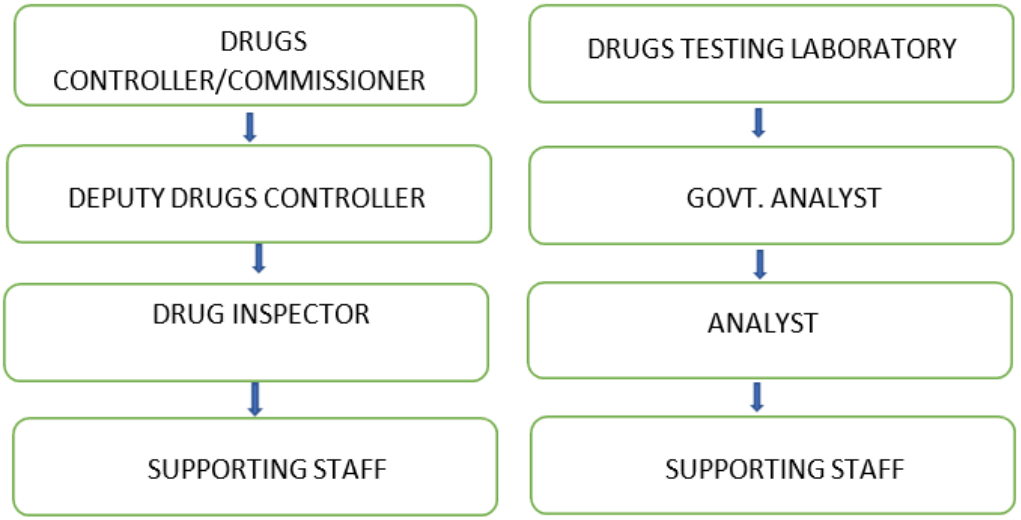


Fig. No.5.2: State Drugs Control Origination

State Drug Regulatory Authorities (SDRAs):

Entities created in accordance with the DC Act are in charge issuing licenses for manufacturing & sales locations, inspecting the aforementioned locations to make sure the licensing procedure is being followed, collecting samples for testing and maintaining high-quality drugs, suspending or cancelling licenses as necessary, keeping an eye on the sale of counterfeit and adulterated drugs, filing cases as needed, and controlling the advertising of drugs that might be deemed illegal.

The State Drug Regulatory Authority is led by the State Drug Controller. Reports are sent to the state government's health department's joint secretary. The Deputy Drugs Controller, who also serves as the state's licensing authority, receives reports from the Drug Inspectors who are part of a normal SDRA. In addition to these administrative responsibilities, state governments are in charge of departmental budgets, hiring people, training officials, and allocating funding for inspection. The aforementioned research claims that several SDAs were combined with FDA departments in other states, making it difficult to distinguish between SDA monies and resources in other states.

Function of State Licensing Authorities

1. Licensing facilities that manufacture & sell drugs

2. Drug testing laboratory licensing

3. Drug formulations are approved for manufacturing.

4. Quality control of medications and cosmetics produced by the appropriate state agencies and sold inside the state.

5. The investigation and prosecution of potential violations of the law.

6. Executive measures

Responsibilities of State Authority

- Producing, marketing, and distributing medications;
- granting licenses to drug testing facilities; and authorising drug formulations for production
- Conducting checks both before and after licensing
- Supervising the production of medications produced by the appropriate state entities and sold inside the state

1.5 Certificate of Pharmaceutical Product (COPP)

Definition-

A worldwide voluntary agreement, the World Health Organization's (WHO) Certification Scheme for a Certificate of Pharmaceutical Product (COPP) provides nations participating with assurances regarding the quality of pharmaceutical goods entering international trade. In response to requests from WHO Member States to promote international pharmaceutical product commerce amongst Member States, WHO created the Certificate of Pharmaceutical Product program. The plan was initially created in 1975. It has since undergone revisions in 1988, 1992, and 1997.

Purpose-

When creating a COPP, the WHO format is used. A special certificate that permits a specific pharmaceutical product to be registered and marketed in the exporting country of interest, as well as being a component of a marketing authorization application, requires the COPP in addition to the importing country for pharmaceutical products. This document details the qualities of the pharmaceutical product that has been authorized in the exporting nation, including details on the certificate applicant, and adheres to the World Health Organization's suggested model. The status of the stated

pharmaceutical, biological, radiopharmaceutical, or veterinary product as well as the GMP status of the product's manufacturer are established by this certificate, which was granted by the Inspectorate. A COPP should ideally not exist for nations with complete review capabilities. A COPP should be in place whenever a pharmaceutical product is subject to product licensing/marketing authorization or when administrative action is needed to renew, extend, or modify the license

Aim and Scope-

An affidavit known as the COPP certifies that the specific manufacturing company is allowed to trade its pharmaceutical product in the nation where it is produced. For instance, if someone wishes to register a pharmaceutical product overseas, the government agency in charge of approving the application often needs a COPP proving that the product is marketed as a commercial finished good in the nation where it is produced.

A Certificate of Pharmaceutical Product certifies that the imported drug satisfies the necessary requirements for effectiveness, safety, and quality in order to be sold in the designated market. It is evidence that the product has been examined and approved by the regulatory bodies of the exporting nation. Thus, it also demonstrates that appropriate guidelines and GMPs were followed, which improved the product's quality and safety even further. It is required by a COPP when a country of import plans to register or renew the product, which includes license, authorization, or extension, in order to facilitate the product's distribution or commercialization in that country. WHO has recommended certification to enable undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities in importing countries to evaluate pharmaceutical products' quality before registering or importing them.

Need & Importance of COPP:

The WHO-COPP recommendation is one of the essential documents needed to secure global approval for any pharmacological medical product, whether intended for people or animals. When a marketing authorization license or marking permission is being considered for entry and sale in the receiving state, or when regulatory action is needed, such as a renewal or extension, or when licensing or marking permits need to be altered or inspected, a COPP is issued by the licensing country's authority and made available to the importing country's authority for use within the importing country.

A COPP covers veterinary drugs for both food-producing and non-food-producing animals as well as pharmacological, biological, and radiopharmaceutical treatments for humans. Each pharmaceutical product (trade name, pharmaceutical form, and strength) has a certificate issued by the exporting nation.

These certificates are given to manufacturers who have a valid manufacturing authorization but no valid marketing authorization, to MAHs of pharmaceuticals with a valid marketing authorization, to their authorized representatives, or to wholesale distributors who have been given permission by the MAH to obtain information about the pharmaceutical or pharmaceuticals.

Types of COPP:

1. **WHO 1975 type COPP-**

   The 1975 WHO version is a certificate that must be issued by the regulatory body of exporting country & states:

a) Authorized product must be put on the market for use in the country along with the permit number and date of issue, or

b) No authorized product has been put on the market for use in the country along with the justifications for its necessity; Furthermore, as advised by the World Health Organization, the product's maker complies with GMP regulations. b) The items must only be sold or disseminated inside the nation of origin; or c) They must be shipped to the manufacturing facility where they are made, subject to inspections at appropriate intervals

2. WHO 1988 type COPP-

In contrast to WHO 1975 version, all labelling copies and product details should be in the exporting nation's responsible authorities there.

3. WHO 1992 type COPP-

This is meant to be used in two circumstances by the importing nation's appropriate authority:

a) When a query about an importation and sale license comes up

b) For a license renewal, extension, review, or modification.

The following information required for the certificate:

i. Whether or not a licensed product must be put on the market.

ii. In addition, if the applicant provided accurate information indicating the product's manufacturing was carried out by a third party,

iii. The product's maker has undergone inspection;

iv. Whether the certificate is temporary or permanent;

v. Whether the applicant or an independent business created dosage forms, packaging or labelling of a completed dosage form;

vi. lists the names of the nations that import and export (certify).

In addition to the three COPP kinds, there is another particular kind of U.S. FDA COPPs here. For the remaining goods that are neither exported nor produced in the US, the FDA issued "Pilot-COPP." Only when no other nation has approved the registration of the completed pharmaceutical product.

Content of the COPP

A CPP has two distinct parts: a) Evidence of quality, safety, and efficacy (QSE) Review and

a) Evidence of Compliance with GMP.

Content and format

- The nation of importation
- The nation that exports
- Product name, dosage form, and composition (API per unit dose).
- Information on registration (license)
- The product's state of marketing in the exporting nation.
- The product's license number (which includes the license holder's information and, if applicable, their involvement in manufacture), along with the issue date
- A synopsis of the technical foundation for the product's license, if mandated by the licensing body
- Information on the currently marketed product; applicant details for the product; and, if there are any gaps in the exporting nation, a description of the reasons must be included.

Key challenges of interpretation of COPP scheme

- Product names differ between certifying and seeking nations; the COPP verifies GMP status; further GMP certifications shouldn't be required.
- Since the COPP is a legally binding instrument, no further apostille or legalization should be sought.
- The term "country of origin" or "source country" has several meanings and needs to be defined because it could refer to any of the following: the pharmaceutical company's primary headquarters, manufacturing, packing, final release, or first clearance or marketing.
- The COPP offers proof that the issuing nation's QSE review was favorable. It is not appropriate to seek a complete dossier.
- Some importing nations need additional manufacturers to be included, but the scheme only pertains to the dosage form manufacturer.

Advantages of the scheme

- Pharmaceutical businesses must get COPP certificates in order to expand their operations in international countries. The Scheme offers the standard format that is anticipated to be utilized.
- Provides assurance on the product's QSE in the issuing country to recipient COPP countries.
- Facilitates patient access to high-quality medications by assisting the evaluation and approval process
- Requires certifying authorities to provide the importing nation with critical information.

  In order to support a regulatory filing, the COPP can be required. This can be provided concurrently with or at the start of the health authority's review. According to ICH rules, nations that can do a full QSE evaluation and require a comprehensive ICH CTD dossier would not need COPPs under the WHO Scheme. Only the certifying nation's authorized manufacturing sourcing path is reflected in the COPP.

The majority of recipient authorities anticipate receiving drug products that are identical to those authorized by the COPP issuing authority. Early in the planning stage, COPP criteria are taken into account while developing a worldwide submission strategy. To ensure that everything proceeds as swiftly as possible, HAs should, if needed, be available for pre-submission discussions to solicit feedback and come to a consensus on what will be submitted, including which forms the COPP will use.

Certificate of a pharmaceutical product

This certificate, which follows the format suggested by the World Health Organization, certifies the pharmaceutical products and the applicant's status in the exporting nation. Since authorized information and manufacturing arrangements for various dosage forms and strengths might change, it is only for a single product (Asit et al., n.d.; BP702T_IP_II, n.d.; BP702T_IP_III, n.d.).

The COPP provides the information of the following:

1. COPP certificate number: The COPP certificate number should be included in the format advised by the WHO.

2. Name of exporting country, also known as the certifying country: The name of the country (certified country) to which the products are being exported must be listed on the certificate.
3. Name of importing country, also known as the requesting country: The names of the countries (requesting countries) from whom the items are being imported from a certified country must be listed on the certificate.
4. **Name and dosage form of the product:**

Table No.5.1: 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 dosageform should be given on the certificate or be appended.
Complete composition includingexcipients	Details of quantitative composition are preferred but their provision is subject to the agreement of theproduct-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 ofthe 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 thelicense 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 independentcompany; or

c) is involved in none of the above.

- It should be noted that information regarding the site of production is part of the product license; if the production site changes, the license must be updated or it is no longer valid.

- The name and location of the company making the dosage form for categories b and c is Only with the product-license holder's or, in the case of unregistered products, the applicant's consent can this information be shared.

- Is a summary justification for approval attached? (Yes/no) This gives a summary of the technical basis for the product's license and makes reference to the document produced by some national regulatory agencies.

- Is the included legally authorized product information correct and in accordance with the license? (Given, no, or yes).

  This refers to product details, including Summary Product Characteristics (SPC), that have been authorised by the appropriate national regulatory body.

The certificate applicant, if their name and address differ from the licence holder's In this case, the product-license holder must give approval for the certificate to be issued. The applicant must provide the authorities this authorisation

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

- The following information was supposed to be included in the COPP if the certifying authority regularly inspected the manufacturing facility where the dosage form is made. Frequency of routine inspections (years):
- Has an inspection been conducted on the production of this kind of dosage form? (Yes/no)
- Do the operations and facilities follow World Health Organization's approved GMP? (Yes, no, or not relevant.

7. **The applicant's information satisfies the certifying authority about every facet of the product's manufacturing by a third party:**

When the applicant or product-license holder satisfies status (b) or (c) as stated in the preceding notice, this area must be filled out. It is especially crucial when the product is being manufactured by overseas contractors. the applicant must provide the certifying authority with information that identifies the contractual parties in charge of each step of the final dosage form's manufacturing process, as well as the kind and degree of any controls that were put in place over each of these parties.

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

- Certifying authority's address
- Telephone and Fax
- The authorised person name
- Date, stamp & signature

How to obtain COPP?

- The Marketing Authorization Holder (MAH) submits a request to the exporting nation's health authority in order to get a COPP.
- The COPP is issued by an authorized individual and given back to the MAH. A manufacturing license, proof of a GMP certificate (if applicable), an application for

an export certificate form, and the most recent authorized SPC (Summary of Product Characteristics) are additional papers needed to get a COPP.

Types of drugs for which COPPs may be issued

- Approved pharmaceutical items
- Products that are over-the-counter (OTC) that include active pharmaceutical ingredients (API)
- Unauthorised pharmaceutical items
- Homoeopathic medications

Who can apply for COPP?

- The person or business exporting the medicine must submit a full application for export certification;
- the certification is meant for a substance that satisfies the standards of the Food medicine and Cosmetic Act 801(e)(1) [21 U.S.C.381(e)(1)] or the appropriate Act requirements.

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:

Following receipt of a complete and correct COPP application, drugs compliance are typically provided within twenty (20) government working days.

Certificates may not be issued

- A note stating the missing information was attached to the returned application with missing information.
- Disapproved: production plants do not adhere to good manufacturing principles (GMPs).
- Refused: pharmaceutical items that do not adhere to regulations (

Expiration of COPP

- The certificate expires two years after the date of notarisation or as specified. A fresh COPP application must be filed after the expiration date.

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: ----------

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 theLicense? 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:

1. 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): ----------

1.2 Has the manufacture of this type of dosage form been inspected? Yes/no (key in asappropriate)

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

2. Does the information submitted by the applicant satisfy the certifying authority on all aspectsof 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

Any Indian business that wants to manufacture or import a new medication must apply for clearance, either by submitting Form 44 or by providing the necessary information. according to Schedule Y of the 1940 Drugs and Cosmetics Act and the 1945 Regulations. In order to prove its effectiveness and safety in the Indian population, clinical studies must be conducted in accordance with the requirements outlined in Schedule Y, and data must be provided in the appropriate manner. Before a drug product to be authorized for importation or manufacturing into a new drug by the Central Drugs Standard Control Organization (CDSCO), it must be safe and effective for human use. The details that must be included in an application for the importation or manufacture of a novel medicine for marketing are specified in the Drugs and Cosmetics Act 1940 and its regulations, 122A, 122B, and 122D, 1945. The sponsor of an experimental new medication must give the DCGI comprehensive information about:

1. A generic name
2. Status of patents
3. A succinct explanation of physico-chemical and biological
4. Technical details, such as: a) stability; b) specifications; c) manufacturing procedure; d) global regulatory status; e) studies on animal nutrition and toxicity
5. Reports from published clinical trials
6. The suggested procedure and pro forma
7. Trial length
8. While the master file
9. Making an effort to report adverse drug reactions that are serious or life-threatening.

It is also necessary to give information on the prescription, product monographs, labelling, samples, and testing procedures. In India, approving a clinical study typically takes three months. Clinical studies can be registered with the Clinical Studies Registry of India (CTRI), which provides information on the trials and the participants. The following guidelines must be adhered to under the 1945 Drugs and Cosmetics

1. Rules: 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.

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

Rule-122A of the Drug and Cosmetic Act 1940 and Rules 1945 states that the licensing authority may permit the importation of novel pharmaceuticals based on data from trials conducted in other nations if he determines that everything is in the public's best interests. Another clause in Rule 122A states that clinical trials may be permitted for any new medicine that has been licensed and has been in use for a long time in another country.

Similar to this, Rule 122-B permits applications for approval to import or manufacture fixed dosage combinations (122-D) and to create new medications other than those classified under Schedules C and C (1).

Purpose-

Protecting public health is the primary goal of regulatory authorities' regulation of all pharmaceutical items. The purpose of regulatory bodies is to ensure that pharmaceutical businesses adhere to all rules and guidelines in order to safeguard patients' health.

The Common Technical Document (CTD) guidelines for the US, EU, and Japan were created through the International Conference on Harmonization (ICH) procedure.

The CTD format has been accepted by the majority of nations. In order to meet the technical criteria for the registration of pharmaceutical goods for human use, CDSCO has likewise chosen to employ the CTD format.

It is obvious that the CDSCO will find it simpler to review and take the necessary actions with this application's well-structured contents that are comprehensive and reasonable. Additionally, it will facilitate the preparation of electronic submissions, which might soon be made at CDSCO.

New Drug Application (NDA)

A New Medication Application (NDA) is a request for permission to commercialize a novel product, such as a new medication, made to the relevant regulatory body. A sponsor must provide preclinical and clinical test results for analysis of the drug information and a description of the manufacturing processes in order to obtain this approval.

The NDA goes through a technological check when the agency receives it. This assessment makes sure that enough information and data have been provided in each section to support "filing" the application for formal FDA review.

Following FDA assessment of an NDA, the sponsor may get one of three possible actions:

• Not acceptable: outline the shortcomings and provide an explanation in this letter.

• Approvable: This indicates that the medication may be authorized with only minor flaws that may be fixed, such as labelling modifications or a potential request to do post-approval research.

• Approval: this indicates that the medication is authorized.

The FDA gives the applicant a chance to meet with the agency and go over the shortcomings if the action is deemed either acceptable or not.

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 Indiaare:

- 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

In accordance with the guidelines of the Drugs and Cosmetic Act 1940 and Rules 1945, the producer or sponsor must submit an application on Form 44 for approval to approve new drugs. With five modules, the document design complies with the Common Technical Document (CTD) international submission standards.

Module I: Administrative/Legal Information

Documents unique to each location, such as application forms or the suggested label for usage there, should be included in this module. The appropriate regulatory bodies can specify the structure and content of this module.

Module II: Summaries

Module 2 should start with a general introduction to the pharmaceutical, which should include its pharmacologic class, mode of action, and proposed clinical use. The

introduction should be no more than one page and should include the company name, the proprietary or nonproprietary name or common name of the drug substance, the dosage form or forms, the strength or forms, the route of administration, and the proposed indication or indications. The CTD summaries for quality, safety, and efficacy information are included in this module, which is very important because it offers detailed summaries of the various sections of the CTD, including: A very brief introduction; Quality overall summary; Non clinical overview; Clinical over view; Non clinical written and tabulated summaries for pharmacology, pharmacokinetics, and toxicology; and Quality overall summary.

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

The organized format outlined in the M4Q advice should be used for presenting quality information. The purpose of this document is to offer guidelines about the format of a drug substance and related drug product registration application. It includes all of the quality documentation pertaining to the drug substance's and product's chemistry, manufacturing, and controls.

Module IV: Non-clinical information

The organized framework outlined in the M4S advice should be used for presenting safety information. Presenting a critical evaluation of the non-clinical evidence relevant to the medication's safety in the target group is the aim of this section. All pertinent data, whether positive or negative, should be taken into account in the analysis, which should also explain how and why the findings support the suggested indication and prescription information. All of the final nonclinical study papers are provided in final copy

Module V: Clinical information

The organized framework outlined in the advice M4E should be used for presenting efficacy information. Clinical pharmacology studies, biopharmaceutics, pharmacokinetics, pharmacodynamics, clinical effectiveness, clinical safety, summaries of the individual studies, and final copies of comprehensive clinical research reports are all included in the clinical summary.

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.50000After 1yr of approval -Rs.15000

Approval of New claim, New Dosage form etc.Rs.15000

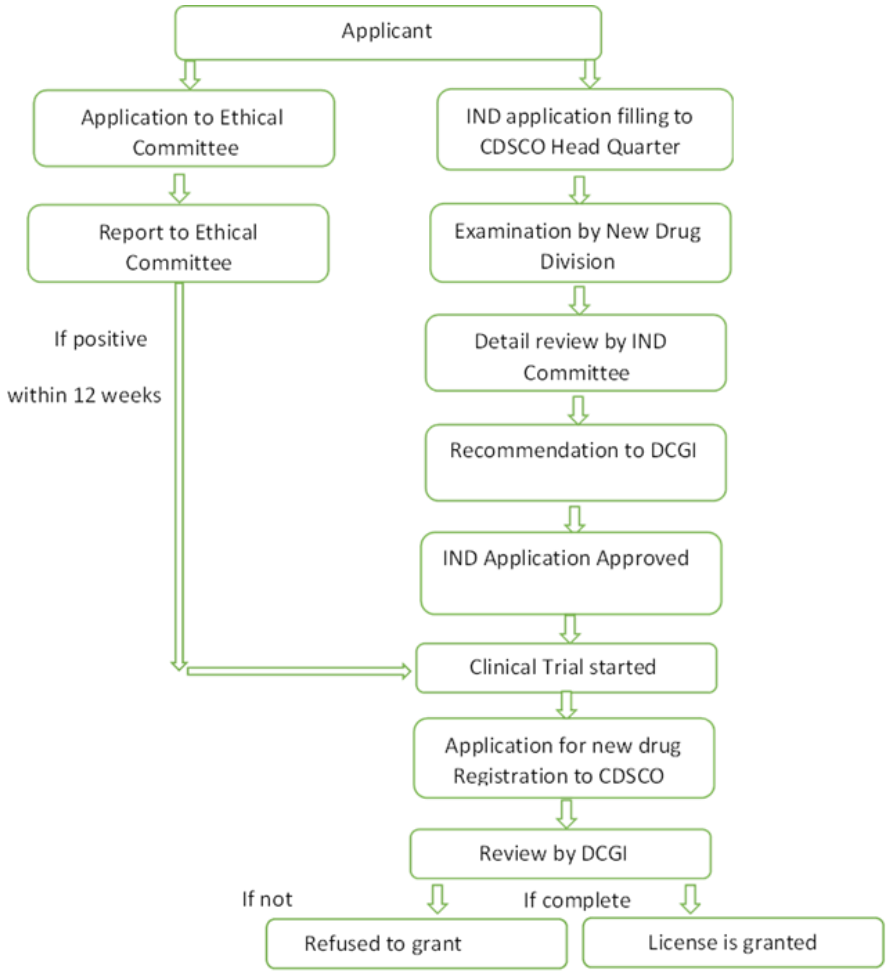


Fig. No.5.3: Drug Approval process in India

Review Questions

Short Answer 02 marks

1. Describe CDSCO's functions.
2. Explain the significance of CoPP.
3. What type of medications are eligible for CoPP?

Short Essay 05 marks

1. Describe the organization and duties of the State licensing authority.

2. Describe the organization and activities of CDSCO.

Long Essay 10 marks

1. Describe the several kinds of CoPP. Provide the CoPP certificate format.

References

Central Drug Standard Control Organization (CDSCO)

1. Kumari, M. (2022). Central Drug Standard Control Organization (CDSCO).

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Certificate of Pharmaceutical Product (COPP),

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4. Guarino, R. A. (2009). New drug approval process. *Drugs and the pharmaceutical sciences*, *100*.
5. Jawahar, N., & Lakshmi, V. T. (2017). Regulatory requirements for the drug approval process in US, Europe and India. *Journal of Pharmaceutical Sciences and Research*, *9*(10), 1943-1952.

Abbreviations:

ADR	Adverse Drug Reporting
AE	Adverse Events
APCTT	Asian And Pacific Centre For Transfer Of Technology
API	Active Pharmaceutical Ingredients
APLAC	Asia Pacific Laboratory Accreditation Cooperation
BCIL	Biotech Consortium India Limited
BE	Bioequivalence
BMR	Batch Manufacturing Record
CA	Corrective Action
CCP	Critical Control Point
CDSCO	Central Drug Standards
CFR	Code Of Federal Regulation
cGMP	Current Good Manufacturing Practices
COPP	Certificate Of Pharmaceutical Product
CPPs	Critical Process Parameter
CQAs	Critical Quality Attributes
CROs	Clinical Research Organizations
CTRI	Clinical Trial Registry-India
CTRI	Clinical Trial Registry India
DCC	Drugs Consultative Committee
DCGI	Drug Controller General Of India
DMF	Drug Master File
DPCO	Drug Cost Control Order
DQ	Drug Qualification
DRA	Drug Regulatory Authority
DTAB	Drug Technical Advisory Board
EMS	Environmental Management System
FAT	Factory Acceptance Tests
FAT	Factory Acceptance Test
FDA	Food And Drug Administration
FIFO	First In First Out
FMEA	Failure Mode Effect Analysis
FMECA	Failure Mode, Effects And Criticality Analysis
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
IB	Investigational Brochure

ICH	International Council For Harmonization Of Technical Requirements Of Pharmaceuticals For Human Use
ILAC	International Laboratory Accreditation Conference
IND	Investigational New Drug
IPC	In –Process Control
IQ	Installation Qualification
IRB	Institutional Review Board
ISO	International Organization For Standardization
ISPE	International Society For Pharmaceutical Engineering
MA	Marketing Authorization
MAAs	Marketing Authorization Applications
MAH	Marketing Authorization Holder
MFR	Master Formula Record
MHRA	Medicines And Healthcare Products Regulatory Agency
MOUs	Memoranda Of Understanding
MTD	Maximum Tolerated Dose
NABL	National Accreditation Board For Testing And Calibration Laboratories
NCEs	Novel Chemical Entities
NDA	Novel Drug Application
NDAC	New Drug Advisory Committees
NIMS	National Institute Of Medical Statistics
NIMS	National Institute of Medical Statistics
NRDC	National Research And Development Corporation
OOS	Out Of Specifications
OQ	Operational Qualification
OTC	Over-The-Counter
PD	Primary Pharmacodynamic
PISV	Preinvestigational Site Visits
PMDA	Pharmaceutical and Medical Device Agency
PQ	Performance Qualification
PTPs	Proficiency Testing Providers
PTPs	Proficiency Testing Providers
PvPI	Pharmacovigilance Program Of India
QA	Quality Assurance
QbD	Quality By Design
QC	Quality Control
QMS	Quality Management Systems

QRA	Quality Risk Assessment
R & D	**Research And Development**
RMPs	Reference Material Producers
RMPs	Reference Material Producers
RU	Receiving Unit
SCV	Study Close-Out Visits
SDRAs	State Drug Regulatory Authorities
SEC	Subject Expert Committees
SIDBI	Small Industries Development Bank Of India
SIV	Study Initiation Visits
SOPs	Standard Operating Procedures
SPC	Statistical Process Control
SU	Sending Unit
TBSE	Technology Bureau For Small Enterprises
TGA	Therapeutic Goods Administration
TIFAC	Technology Information, Forecasting And Assessment Council
TOT	Transfer Of Technology
TPQP	Target Product Quality Profile
TQM	Total Quality Management
TT	Technology Transfer
VMP	Validation Master Plan
VP	Validation Protocol
VR	Validation Report

Glossary

A

- **Active Pharmaceutical Ingredient (API)**
  The primary substance in a pharmaceutical product responsible for its therapeutic effect.
- **Analytical Method Transfer**
  Verification that analytical methods perform consistently across different laboratories or locations.
- **Acceptance Criteria**
  Predefined standards or specifications that must be met for a product, process, or material to be deemed acceptable.

B

- **Batch Record**
  A document containing the complete history of a manufactured batch, including raw materials, processes, and quality checks.
- **Biostatistics**
  The application of statistical methods to analyze and interpret data in pharmaceutical research and clinical trials.
- **Bracketing**
  A study design that evaluates only the extremes of certain variables to infer results for intermediate values.

C

- **Change Control**
  A systematic approach for managing and documenting changes to processes, equipment, or procedures to maintain compliance.
- **Clinical Research Protocol**
  A detailed plan describing how a clinical trial will be conducted, including objectives, design, methodology, and analysis.

- **Corrective Action (CA)**
  Steps taken to address and eliminate the cause of a detected nonconformity or quality issue.

D

- **Design Qualification (DQ)**
  Verification that equipment, systems, and facilities are designed to meet intended operational requirements.

- **Drug Development Team**
  A multidisciplinary group responsible for overseeing the development of a pharmaceutical product from discovery to commercialization.

E

- **Excipient**
  An inactive substance used as a carrier or to enhance the properties of the active ingredient in a formulation.

- **Emulsifying Agent**
  A substance that stabilizes an emulsion by reducing surface tension between two immiscible phases.

F

- **Failure Mode and Effects Analysis (FMEA)**
  A structured approach for identifying potential failures in a process and assessing their impact and likelihood.

- **Fluid Bed Dryer**
  Equipment used to dry solids, such as granules or powders, using a stream of heated air.

G

- **Good Laboratory Practices (GLP)**
  Standards ensuring the consistency, reliability, and quality of non-clinical laboratory studies.

- **Good Manufacturing Practices (GMP)**
  Regulations to ensure the consistent production of quality pharmaceutical products.

H

- **Hazard Analysis and Critical Control Points (HACCP)**
  A systematic approach to identifying, assessing, and controlling risks in production and processing.

I

- **Installation Qualification (IQ)**
  Documentation verifying that equipment and systems are installed according to design specifications.
- **Investigational New Drug (IND) Application**
  A request submitted to regulatory authorities to begin clinical trials for a new drug.

M

- **Master Manufacturing Record (MMR)**
  A comprehensive document detailing the standard procedures and materials required for manufacturing a product.
- **MoU (Memorandum of Understanding)**
  An agreement between parties outlining terms and conditions for collaboration.

P

- **Pilot Plant**
  A facility for scaling up manufacturing processes from laboratory scale to commercial production levels.
- **Process Analytical Technology (PAT)**
  Systems and technologies used for monitoring and controlling manufacturing processes in real time.

Q

- **Quality Assurance (QA)**
  Activities and procedures ensuring that products consistently meet specified quality standards.

- **Quality Control (QC)**
  The process of sampling, testing, and ensuring raw materials, intermediates, and final products meet quality specifications.

- **Quality Risk Management (QRM)**
  A structured process for assessing, controlling, and monitoring risks to product quality.

R

- **Regulatory Authorities**
  Government or independent agencies responsible for overseeing and enforcing compliance with pharmaceutical regulations.

- **Risk Analysis**
  The systematic evaluation of the likelihood and impact of potential risks in a process or system.

S

- **Scale-Up**
  The process of transitioning from laboratory-scale production to full-scale commercial manufacturing.

- **Standard Operating Procedure (SOP)**
  A written document providing step-by-step instructions for specific tasks to ensure consistency and compliance.

- **Stability Testing**
  Testing performed to evaluate how a product's quality changes under the influence of environmental factors like temperature, humidity, and light.

T

- **Technology Transfer (TT)**
  The process of transferring knowledge, processes, or technologies between development and manufacturing sites.

- **Total Quality Management (TQM)**
  A management philosophy focusing on continuous improvement in all aspects of quality.

V

- **Validation**
  Documented evidence demonstrating that a process, method, or system consistently produces the intended results.

- **Validation Master Plan (VMP)**
  A detailed document outlining the overall strategy for validation activities within a project.

- **Validation Protocol (VP)**
  A document specifying the steps and acceptance criteria for validating a specific process or system.

W

WHO Guidelines for Technology Transfer (TT)
Standards set by the World Health Organization for transferring processes and knowledge between facilities or organizations.