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A Review on: Indian Pharma Regulatory System and List of New Drugs Approved By Central Drugs Standard Control Organization in the Year 2021 Till Date

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Abstract

Regulatory authorities and organizations play a crucial part in responding to the requirements of regulatory proceedings related to drug development in a region. Each country has its owned regulatory body, that is, liable for implementing laws and regulations, as well as offering guidance to control the evolution, grant/licensing, and registration of drugs. The Indian pharmaceutical industry is one of the most organized industries in the country. Knowing the scenario of regulatory bodies plays a vital importance because of the fast and continuous change and because of the pressure placed on regulators to maintain a steady availability of quality medicines at an economical price to the Indian masses. Current article focuses on the drug approval process and regulatory requirements according to the Central Drugs Standard Control Organization.

Keywords: Central Drugs Standard Control Organization approved drugs, Common technical document filing, Drug approval process, Regulatory bodies

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Introduction

The Indian Parliament approved the 1940 D and C Act and 1945 standards to control imports, manufacturing, sale, and distribution of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), the Drug Controller General of India (DCGI), and office of its leader were set up.[1]

The Indian government established Schedule Y to the D and C rules 1945 in 1988, which contains several requirements and guidelines for clinical studies. In India, a firm must apply to the Licensing Agency (DCGI) if it intends to manufacture or import a novel drug.[2] To verify the safety and efficacy of a novel medicine in the Indian population, clinical trials must be conducted in compliance with the schedule Y guidelines and a report of clinical trial must be submitted in a specific format.[3]

An effective regulation involves variety of results such as:

- Assure the safety, efficacy, and quality of drugs
- Provision of license of premises, person, and practices
- For product assessment and registration of products
- Supports the inspection of distribution channels and production facilities
- For evaluation and registration of the product
- Monitoring of ADRs
- Quality control.[4]

Pharmaceutical Regulatory Bodies in India

- CDSCO
- Ministry of Health and Ministry of Family Welfare
- Drug Technical Advisory Board (DTAB)
- Indian Council for Medical Research (ICMR)
- Indian Pharmaceutical Association (IPA)
- Indian Pharmacopoeia Commission (IPC)
- National Pharmaceutical Pricing Authority (NPPA)
- Central Drug Testing Laboratory.

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According to the D and C Act, the governance of the manufacture, marketing, and trading of drugs and medicines correspond mainly to the national authorities, and the central authority is liable for

- Approval of new drugs
- Conduct and development of clinical trials
- Formulation of drug standards and
- Quality control of imported drugs and country coordination.

Cdsco

The CDSCO is National Regulatory Agency of India, which is headed up the General Directorate of Health Services, Ministry of Health and Family Welfare (MHFW), Government of India. It is

headquartered in FDA Bhawan, Kotla Road, New Delhi (110002), and it has six regional, four subsidiary or subzonal offices, 13 port offices, and seven laboratories nationwide.[5]

In terms of regulatory, it is led by the DCGI and is mainly responsible for harmonizing State Drug Regulatory Authorities activities, formulating policies, and ensuring the unified implementation of D and C Act across the country.[6] DCGI is responsible for handling product approval requirements, clinical trials, introduction of new drugs, new drug import licensing, and other matters. [7,8] A drug can only be manufactured in a state with a license after it has been approved by CDSCO.[9]

DTAB

It provides consultations to the state government and central governments on scientific and technical issues originating of the legislation of "Drugs and Cosmetics Act," and performs the duties conferred by this act.

The newly constituted DTAB has 18 members. The committee is the highest decision-making body under the Union Ministry of Health on technical issues. The term of DTAB is 3 years.

ICMR

The ICMR, New Delhi, is India's foremost body for formulating, coordinating, and promoting biomedical research and one of the oldest medical research institutions in the world.

ICMR has been trying to meet the growing demand for scientific progress in biomedical research, on the one hand, and the need to find practical solutions to the country's health problems, on the other.[10]

IPA

Founded in 1939, IPA is the oldest pharmaceutical professional union in India, with over 13,000 members across the country. IPA functions in India through more than 46 local branches and 20 state branches. Members serve all aspects of the pharmaceutical industry, namely, hospital and community pharmacy, industry, regulatory, and pharmaceutical education. As a member of the DTAB of India, IPA is intently involved in urging the government on matters of professional importance.[11]

IPC

IPC is a self-governing (autonomous) agency run by the MHFW, Government of India. The goal of the IPC is to establish the country's drug standards. Its primary role is to periodically amend the standard of drugs frequently used in the treatment of epidemics in the region. In the form of the IP, IPC publishes authoritative papers that help to improve the drug quality by introducing new monographs and amending current ones. In addition, it publishes the National Formulary of India, which encourages the judicious utilization of generic medicines. IP Reference Substances are also provided by the IPC as fingerprints to identify the tested item and its purity specified in IP.[12] HYPERLINK "https://en.wikipedia.org/wiki/Indian_Pharmacopoeia_Commission"]

NPPA

It was established by resolution of the Government of India of 29 August 1997 as an office under the Department of Drugs, Ministry of Chemicals and Fertilizers with as an independent regulator that sets drug prices and ensures availability and accessibility of drugs. The following functions have been delegated by NPPA:

1. Strengthen and perform the provisions of the Drug Price Control Order, according to the powers assigned to it
2. Supervise the supply of medicines or drugs, analyze shortages (if any), and take corrective actions
3. Compile/manage data on production, import and export, individual company's market share, company profitability, etc., for bulk drugs and bulk preparations
4. Process all legal matters arising from the authority's decision
5. Advise to the central government on changes/revisions about drug policies
6. Assist in handling congressional affairs related to medicines/drug prices to the central government.[13]

Regulatory Submission in India

A dossier is a file document that is sent to the FDA for novel drug or drugs approval. CTD is a harmonized data presentation format for ICH areas. It is optional in several nations. The procedure of reviewing and evaluating the dossiers in support of a drug from the point of view of the marketing of that product (also called license, registration, approval, etc.), apparently completed to improve by issuing a document also known as marketing authorization. This procedure is carried out by virtue of the legislation that establishes the specifications mandatory for submitting the application to the reference regulatory body (competent), the description of the evaluation process (depending on safety, quality standards, and efficiency), and the reasons for an application's approval or rejection, as well as the situations in which a marketing license has been issued, can be revoked, suspended, or withdrawn.

In India for drug product approval, dossier submission is done in the form of Common Technical Document (CTD). CTD is a unified format used to present data in the areas of ICH of drug product. CTD is a format used for preparation of well-structured presentation for making dossier application that is submitted to regulatory authorities in India. The document is designed in accordance with the international filing requirements of the CTD, which has five modules.[14] Figure 1 describes about the CTD and its modules as per Indian guidelines.

Types of Five Modules in CTD are as Follows

Module 1: Administrative/legal information

The module must include documentation relevant to India, such as Form 44, Treasury challan fees, or labels to be used in India. This module contains various documents specific to each country. The module's content and pattern can be stated by the governing body of that particular region. It is not part of the CTD format. Application forms and other proposed label, etc., are used in this Module.[14]

Module II: Summaries (quality, non-clinical, and clinical)

Module 2 contains a summary of the CTD, which should first be introduced, including its proposed pharmacology category, mechanism of action, and therapeutic application. This module must also give a general overview of the "quality" data, providing clinical summaries and non-clinical summaries, along with non-clinical reported abstracts and tabular abstracts as well as

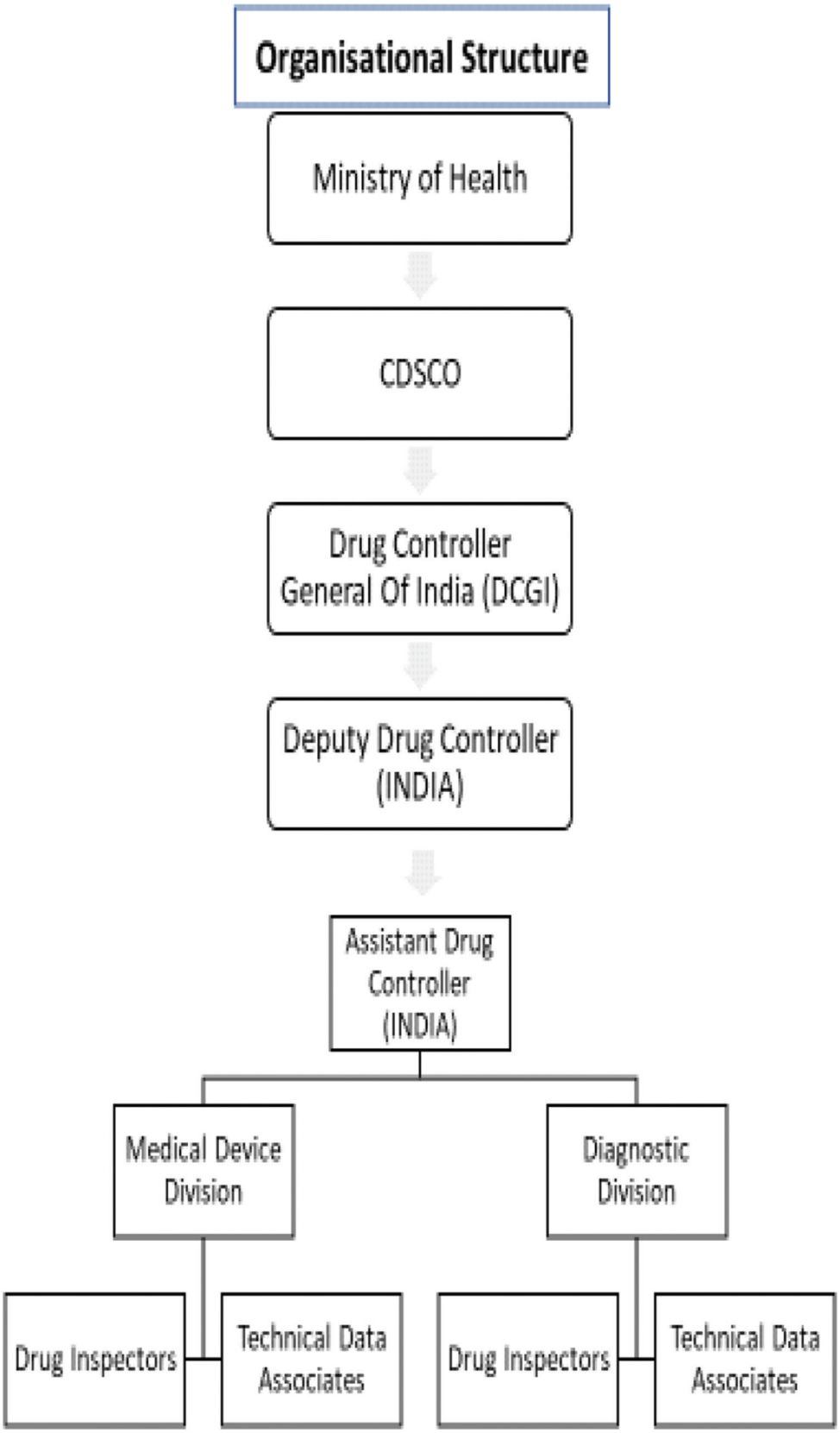

Figure 1: Organizational Structure of Central Drugs Standard Control Organization

clinical summaries. It includes general introductions to drugs, pharmacological action patterns (MOA), and clinical uses. It includes common introduction (quality overall summary, non-clinical overview, and clinical overview) comes in this module.

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

The Quality portion of the General Technical Document (M4Q) offers a uniform format and design for providing CMC information (chemistry, production, and control) in the registering dossier. There are sections on pharmaceutical substances and drugs in the index. Furthermore, there are various appendices, as well as portions for particular area information. The Module III contains the information on quality standards in the standardized format specified in the guidelines of M4Q. It provides the format of an API registration application form and also for their related drugs product.[14,15]

Module IV: Non-clinical study reports

The CTD Safety Guide (M4S) outlines the format and design of the non-clinical summary in Module 2 of the CTD and also offers the planning and reporting of Module 4, non-clinical studies. Comprehensive and detailed analysis of pharmacokinetics, pharmacological and toxicological assessments of non-clinical synthetic drugs should generally not more than 30 pages. Reported non-clinical analysis (100–150 pages) is endorsed for providing more comprehensive summaries and an analysis of preclinical information on pharmacology, pharmacokinetics, and toxicology. Module IV contains information on safety standards in the structured pattern described in the M4S guide. It offers a rigorous investigation of the data obtained from non-clinical trials, necessary for the medicine's safety in the community for which it is intended.[15,16]

Module V: Clinical study reports

The effectiveness of CTD (M4E) outlines the format and structure of clinical information in an application, comprising analysis, and comprehensive study summaries. The module 2 of the CTD includes two high-level clinical reports: The first is clinic summary, a brief document that gives a thorough evaluation of data obtained from clinical trials; and the second is clinical overview, which is a larger document which emphasizes on data integration and summary. Module 5 of the CTD contains the clinical trial results and raw data (where relevant). Module V contains information on efficiency standards in the organized format specified in the M4E guide. This form includes the full summary including pharmaceuticals, pharmacokinetics, and clinical efficacy and clinical safety.[16,17]

Approval of New Drugs in India

In India, any company wants to manufacture/import a novel medicine that should be applied to the licensing agency (Drugs Controller General of India) on completion of form no. 44 as well as acknowledge the information as described in the schedule Y of D and C Act 1940 and Standards 1945.[17]

It proves the safety and effectiveness of product. Clinical studies are conducted in the Indian population in compliance with Schedule Y guidelines and present the results of these studies in a specific pattern. However, Rule 122A of the D and C Act of 1940 and Rules 1945 contain provisions which might grant permission for import of new drugs in other countries also.[18,19]

Stages of Approval Process

The following parameters are evaluated during approval process.[20,21]

- For evaluation safety and efficacy, clinical trial application (CTA) is submitted
- Permission required for NDA

Table 1-5 gives requirements for drug approval process in India.

Table 1: Administrative requirements for new drug approval

Requirements	*India*
Type of authority	Drug Controller General of India
Process of registration	One registration process
Study data on TSE/BSE	Data required
Braille code	Braille code is not required on labeling.
Post-approval changes	Required (major and moderate)
Approval timeline	12–18 months
Amount of fee	50,000 (INR)

Table 2: Requirements on finished product control

Requirements	*India*
Justification	ICH (Q6A)
Assay	90–110% present
Disintegration	Required (necessary)
Identification of color	Required (necessary)
Water content	Required (necessary)

Table 3: Requirements on manufacturing and control products

Requirements	*India*
Batches required	One
Packaging	Not addressed
Process validation	Required (necessary)
Batch size	Pilot scale batch

Table 4: Requirements on stability study

Requirements	*India*
Number of batches	Two pilot scale/production scale (if stable API) Three primary batches (if the API is unstable)
Condition: Long-term stability, accelerated stability	Long term: 30°C/70% RH Accelerated: 40%/75% RH (0, 3, and 6 months)
Minimum time period at submission	6 months accelerate and 6 months long term
Orientation of the container	Vertical and inverted
Clause	ICH guidelines (ICH Q1F)
QP certification	Required necessary

Table 5: Requirements on bioequivalence study

Requirements	*India*
Audits (CRO)	CDSCO
Sample storage	-
Fasted/fed	CDSCO guidance
Sample retention time	Three years from the date of submission of the application
Bioequivalence study for generic drugs	Across the EU/US/Australia in any country, with the exception of Thailand, where it must be performed locally with respect to a local reference product

- Changes in biological products after approval of quality, safety, and efficacy documents
- Information quality information for the new approval of medicines.

Clinical Trials Phases in India

There are four phases of clinical trials in India and are as follows: [22,23]

- Pre-clinical study – this study is performed on small animals such as rabbit and monkeys for collecting data in support of the safety of the new treatment
- Phase I: Human pharmacology and safety – emphasis is on safety and tolerability of the product
- Phase II: Therapeutic exploration – for the establishment of therapeutic efficacy and dose ranging
- Phase III: Therapeutic confirmation – for the establishment of the value of the drug in relation to existing therapy
- Phase IV: Post-marketing surveillance – is study and performs after drug approval.

Evaluation for Submission of CTA

Parameters for efficacy and safety data for the evaluation of CTA are as follows

It contains all data list in detail which needs to be given for CTA submission.[24]

- Phase I and Phase II clinical trial
- General information
- Introduction and brief description about company
- It provides address of company headquarters
- To provide information for manufacturing facilities in pharmaceutical products
- Status in regulatory and intellectual property in other countries in pharmaceutical field
- Details patent information status in India and other countries
- Details chemistry manufacturing control (CMC)
- Information on product development
- Provide strain development.
- Detail on drug substance.
- Drug product information.

Phase III Clinical Trials Study Reports

All the information in Phase III are identical as in the Phase I and Phase II.

- Details on general information.
- Provides CMC
- Non-clinical trial.[25]

Requirements for New Drugs Approval

Under the requirements of the Drugs and Cosmetics Act 1940 and Standards 1945, manufacturers must submit application form 44

Table 6: List of new drugs approved by CDSCO in the year 2021 till date

S. No.	*Drug name*	*Date of approval*	*Indication*
1.	Avanafil (bulk and tablets)	February 26, 2021	For the treatment of • Erectile dysfunction
2.	Omidenepag isopropyl (ophthalmic solution)	March 12, 2021	For the treatment of • Glaucoma and • Ocular hypertension
3.	Ozenoxacin (bulk and cream)	April 15, 2021	For the topical treatment of • Impetigo (in adult and pediatric patients)
4.	2-Deoxy-D-Glucose (bulk)	May 1, 2021	Used as an adjunct therapy for • COVID-19 patients (moderate to severe)
5.	Capmatinib (film-coated tablets)	May 12, 2021	For the treatment of • Metastatic non-small cell lung cancer
6.	Rucaparib camsylate (bulk and tablets)	May 12, 2021	For the treatment of • Ovarian cancer • Deleterious BRCA mutation • Prostate cancer
7.	Trientine tetrahydrochloride (bulk and capsules)	June 8, 2021	For the treatment of • Wilson's disease (hepatolenticular degeneration)
8.	Rucaparib (tablets)	June 18, 2021	For the treatment of • Ovarian cancer • Deleterious BRCA mutation • Prostate cancer
9.	Vigabatrin (bulk and powder for oral solution)	June 18, 2021	Used as an adjunctive therapy in the treatment of • Refractory complex partial seizures • Infantile spasms
10.	Cangrelor tetra sodium (bulk and for injection)	June 21, 2021	Used as an adjunct in PCI (percutaneous coronary intervention)
11.	Rifapentine	June 28, 2021	For the treatment of • latent tuberculosis
12.	Lemborexant (tablets)	July 1, 2021	For the treatment of • Insomnia
13.	Cetilistat (bulk and tablets)	July 9, 2021	For the treatment of • Obesity
14.	Benzonatate (bulk and capsules)	July 15, 2021	For the treatment of • Refractory cough
15.	Cariprazine hydrochloride (bulk and capsules)	July 16, 2021	For the treatment of • Schizophrenia (in adults)
16.	Gadoteridol (for injection)	July 29, 2021	For IV use in magnetic resonance imaging

for New Drugs Approval. Similarly, rule 122A contains another provision which states that clinical studies may be suspended in the context of novel drugs that have been approved and are used in other countries for many years.[22] Table 1 shows the concerned authorities and requirements for the new drug approval. The central drug standard control organization gave approval during month of March in the year 2018 Cadexomer Iodine Bulk and Powder, Dalfampridine Bulk and Film-coated extended release tablet. Ulipristal acetate 5 mg tablets.[26-28]

Table 6 gives the details on list of drugs approved by CDSCO in 2021.

Conclusion

Based on the foregoing analysis, it could be inferred that all clinical research results and information associated to the approval of novel drugs in India must submit NDA to provide the FDA with the necessary requirements. eCTD and CTD undoubtedly minimize the time and money required to prepare the applications of drug registration for human use. It simplifies the preparation of electronic presentations. In general, the approval process of drugs mainly includes two steps, namely, application for clinical trials and application for drug marketing authorization to regulatory authorities, clinical research report, and relevant information on the approval process of new drugs in India. The focus is on clinical trials, which must follow the Schedule Y, D and C rules given by CDSCO. The rules to be enforced are listed in rule numbers 122 A, 122 DA, 122 B, and 122 D.

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