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COMPARATIVE OVERVIEW OF DRUG APPROVAL PROCESS: USFDA, EMA, AND CDSCO

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ABSTRACT

A comparison of USFDA, EMA, and CDSCO's drug approval process in India is provided in this article. Differences between preclinical studies, clinical trial regulations, submission guidelines, and marketing permission are all being emphasized in this step-by-step guide. Critical components such as formats for applications, timelines, regulatory review stages, and post-marketing surveillance methods are compared in the report. Approval processes vary greatly in documentation, review duration, and authority, although their goals are identical. The CDSCO employs electronic submission through SUGAM, the EMA employs a broadly structured MAA process, and USFDA employs an explicitly defined IND-NDA pathway. The FDA, EMA, and CDSCO oversee drug approval processes, ensuring safety, efficacy, and quality. The FDA has a structured process, while the EMA in the EU uses scientific review and peer review. The CDSCO in India handles application submission, scrutiny, and site inspection. Understanding these differences is crucial for global pharmaceutical development.

INTRODUCTION

In the pharmaceutical industry, it's not sufficient to just discover or make a new drug, it also has to meet strict safety, quality, and effectiveness standards. This is where rules and regulations come into the picture. Regulatory affairs are the link between drug companies and the government agencies that approve new drugs. They make sure that every product that comes out has the right scientific evidence and follows the law. There are different government agencies in each country that look over and approve drugs. The USFDA, the EMA, and India's CDSCO are three of the most well-known. They all have their own ways of checking to see if new drugs are safe for people to use. Even though everyone wants the same thing in the end, the steps, deadlines, submission formats, and evaluation methods are all different.

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GRAPHICAL ABSTRACT

Characteristic	USFDA	EMA	CDSCO
Preclinical Studies	Varies based on drug type	Follows EU guidelines, adaptable	Less stringent, local data preferred
Clinical Trial Regulations	Strict adherence to GCP guidelines	Similar to USFDA, with EU variations	Less strict, focus on local population
Submission Guidelines	Detailed and structured format required	Harmonized format through Common Technical Document	Varies, less structured than US/EU
Marketing Authorization	Granted after thorough review process	Centralized or decentralized procedures	Granted based on local clinical data
Post-Marketing Surveillance	Robust system for adverse event reporting	Similar to USFDA, EU-wide network	Less comprehensive, focus on local reports
Application Formats	Electronic submissions preferred	Common Technical Document (CTD) format	Varies, often paper-based submissions
Timelines	Relatively predictable, but can be lengthy	Can vary, depending on procedure	Often longer, subject to delays
Review Stages	Multi-stage review process	Centralized or decentralized review	Less transparent, can be bureaucratic

OVERVIEW OF REGULATORY BODIES

A. United States Food and Drug Administration (USFDA)

Key Role: The Centre for Drug Evaluation and Research (CDER) at USFDA evaluates the safety, efficacy, and quality of new drugs before they reach the market.

Major Steps

1. Preclinical Studies

Preclinical development is a key step in drug development that happens before clinical trials and involves gathering information on drug safety, feasibility, and testing in laboratory animals. The main goals of preclinical studies are to find a safe starting dose for first-in-human studies and to test the possible toxicity of medical devices, prescription drugs, and diagnostics.

Drug Development Process



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There are different types of preclinical studies, such as pharmacodynamics (PD), pharmacokinetics (PK), ADME, and toxicology studies. The tests help scientists figure out what a safe dose is for starting clinical trials in people. To make sure that non-drug medical devices will last in models of living systems, they have to pass good laboratory practices (GLP) safety tests and biocompatibility tests.

Safe human testing requires animal testing, typically in two species: canines and murine, though primates and pigs are also used. Concerns about the circulatory system, gut, enzyme activity, and other areas are taken into consideration when choosing one species over another. Larger animals, such as dogs, pigs, and sheep, are used for the majority of testing because they can be used as human size models.

Before approving a human trial, regulatory agencies like the FDA, EMA, and other national and international regulators require safety testing in at least two mammalian species, one of which must be a non-rodent species. The majority of studies will still use animal testing for the required anatomical and physiological similarity, even though it has decreased recently for ethical and financial reasons. [1]

2. IND applications

Investigational New Drug (IND) Application IND application is submitted to FDA requesting for permission to begin human trials. The NDA application must include preclinical data, drug composition, manufacturing details, proposed clinical trials, investigator information, safety and pharmacological data. The FDA takes 30 days to review the IND application. If no clinical hold is issued by FDA within 30 days, the sponsor may proceed for human trials. IND approval is a green light for clinical research not a final marketing approval. It ensures that preclinical data is evaluated and human subjects are not exposed to unreasonable risk.

3. Clinical Trials

Phases I–III After approval of IND from FDA, the investigational drug enters in clinical testing that is conducted in three major phases.

Phase I: Safety and Dosage.

Phase 1 is conducted on 20-100 healthy volunteers or patients and focus is on assess safety, tolerability and pharmacokinetics that takes several months.

Phase II: Efficacy and Side Effects.

Phase 2 is conducted on 100 to 300 patients with the target condition, focusing on determining optimal dose and initial efficacy. This phase takes several months to two years in completion.

Phase III

The drug is typically tested in several hundred to several thousand patients with the targeted disease in double-blind, placebo-controlled trials to demonstrate its specific efficacy. Fewer than 30% of drug candidates successfully pass this phase. This large-scale phase focuses on confirming effectiveness, monitoring side effects, and comparing the drug with existing treatments. The duration of this phase ranges from 1 to 4 years. [2]

4. NDA

The New Drug Application (NDA) is the formal process through which drug sponsors request the U.S. Food and Drug Administration (FDA) to approve a new pharmaceutical for sale and marketing in the United States. Only about 30% or fewer of initial drug candidates successfully

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complete the multi-year drug development process and receive NDA approval.

The primary goal of the NDA is to provide sufficient information for FDA reviewers to evaluate the entire history of the drug candidate. The application must include the following instructions

a) Patent details and manufacturing information.

b) Evidence of the drug's safety and effectiveness for its intended use, when used as directed.

c) Reports on the design, compliance, and outcomes of completed clinical trials reviewed by an Institutional Review Board.

d) Information on the drug's potential for abuse.

e) Proposed labelling (package insert) and usage instructions.

The NDA documentation is expected to present "the drug's whole story"—including clinical trial data, ingredients, animal study results, how the drug behaves in the body, and how it is manufactured, processed, and packaged.

5. FDA review

Once the application is submitted, the FDA has 60 days to perform a preliminary review to determine if the NDA is "sufficiently complete to permit a substantive review." If the FDA finds the application incomplete, it issues a Refuse to File (RTF) letter explaining the deficiencies. If the application is reviewed but cannot be approved for substantive reasons, the FDA sends a Complete Response Letter (CRL) detailing the issues that must be addressed before approval can be granted. [3]

Once the FDA approves an NDA, the drug can be legally marketed in the U.S. starting that very day.

6. Post-Marketing Surveillance (Phase IV)

FDA approval is not the final step in a drug's journey. Phase IV studies, also known as post-marketing surveillance, are conducted after the drug is available in the market. This phase focuses on monitoring long-term safety, detecting rare side effects, evaluating potential drug interactions, and studying the drug's effects in special populations such as pregnant women and the elderly. [2]

B. EMA (EUROPEAN MEDICINES AGENCY)

Key Role: The EMA, via the Committee for Medicinal Products for Human Use (CHMP), reviews marketing authorization applications for centralized approval across all EU member states.

Major Steps

1. Preclinical and Clinical trials

(Phase 1 to Phase 3) Similar to FDA

2. MAA Submission

Submission Format: CTD

Applications are submitted using the Common Technical Document (CTD) structure:

Module 1 – EU-specific administrative and product information.

Modules (2–5) – Common to all regions; covering summaries, quality data, non-clinical and clinical documentation.

3. Evaluation Process

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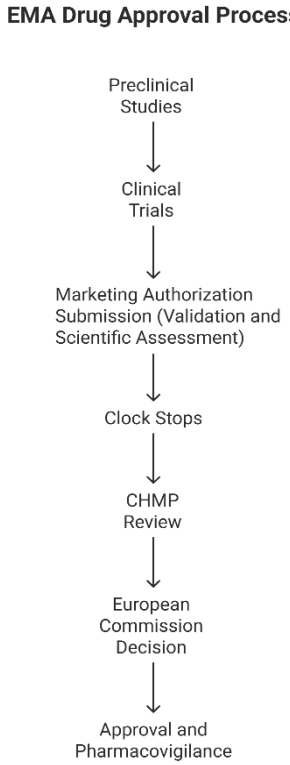

a) Validation Phase

Before starting the scientific review, EMA conducts a validation to ensure the dossier is complete (30 days). If any information is missing, the agency issues a request for Validation Supplementary Information (VSI). Applicants are given two months to address these deficiencies. Failure to meet this deadline may result in the dossier being rejected at the validation stage.

b) Scientific Assessment

Once validated, the application moves into full evaluation. 120 days time period for initial review. The CHMP (Committee for Medicinal Products for Human Use) handles most medicines, while CAT (Committee for Advanced Therapies) reviews ATMPs (Advanced therapy medicinal products). The EMA's scientific evaluation begins, and rapporteurs will draft separate assessment reports with inputs. [4]

4. Clock Stops

This time is interrupted by one or two 'clock-stops' during which the applicant prepares the answers to any questions raised by the CHMP. The maximum duration of a clock-stop depend on how long the applicant thinks it will take to respond, but must be agreed by the CHMP. The first clock-stop usually lasts three months, and the second clock-stop one month.

Overall, the assessment of a new medicine usually lasts around a year.

Clock Stop 1

This first evaluation lasts up to 120 days. The evaluation is then paused (first clock-stop) while the applicant prepares the responses to the CHMP's questions and updates the medicine's risk management plan. The developer generally has up to three months to answer the list of questions.

Clock Stop 2

If a list of outstanding issues is agreed, the evaluation is paused again (second clock-stop) while the applicant prepares responses. The developer generally has up to one month to answer these questions. It may attend an oral explanation.

Further consultations (by day 210)

Oral explanation (if requested)

After the second clock-stop, an oral explanation in which the applicant directly addresses the committee can be requested either by the applicant or by the CHMP. It is usually organised when the CHMP still has major objections with the application. If this occurs, the applicant is asked to provide clarifications on the committee's outstanding issues. [5]

5. EC Decision

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Following CHMP Discussion and Opinion Adoption:

The CHMP adopts its opinion along with the corresponding CHMP Assessment Report, outlining whether a marketing authorisation should be granted for the medicine and, if approved, under what conditions it should be used. At this stage, consensus is also reached on the wording of the product information intended for both healthcare professionals and patients—this includes the Summary of Product Characteristics (SmPC), labelling, and the Package Leaflet (PL). A timetable is also established for submitting translated versions of these documents.

Additionally, any post-authorisation data requirements from the applicant are agreed upon.

By Day 215 (latest): The applicant submits the SmPC, labelling, and PL in all official EU languages to the EMA. The EMA circulates these draft translations to Member States for their review.

By Day 232 (latest): The applicant submits final translations of the product information, incorporating feedback received from Member States by Day 229.

By Day 237: The opinion and annexes, translated into all EU languages, are shared with the applicant, the European Commission, Standing Committee members, and the EEA countries—Liechtenstein, Norway, and Iceland.

By Day 277: Within 67 days from the CHMP opinion, the European Commission either grants or denies the marketing authorisation. The final decision is recorded in the Community Register of Medicinal Products for Human Use.

Once approved, the EMA publishes a European Public Assessment Report (EPAR) for the medicine. In case of rejection, a refusal EPAR is published, including a Q&A document and the full assessment report.

AR – Assessment Report; EPAR – European Public Assessment Report; PAR – Public Assessment Report. These are documents summarising the scientific evaluation of a medicine. [6]

6. Pharmacovigilance under EMA (Post-Approval)

After a drug is approved, the EMA monitors its safety through systems like Eudra Vigilance for adverse event reporting, Risk Management Plans (RMPs), and Periodic Safety Update Reports (PSURs). The Pharmacovigilance Risk Assessment Committee (PRAC) reviews any safety concerns and can recommend changes, additional studies, or even suspension. In some cases, companies must conduct Post-Authorization Safety Studies (PASS) to gather more safety data.

C. CDSCO (Central Drugs Standard Control Organization)

Key role: The CDSCO, led by the DCGI under the Ministry of Health, regulates drugs and medical devices in India, similar to the FDA/ EMA. [8]

Major steps

1. Preclinical Development Overview

Preclinical development (also called nonclinical studies) is the phase of drug research that takes place before human trials. It involves feasibility testing, repeated experiments, and gathering safety data, often using animal models.

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The primary aim is to identify a safe starting dose for human trials and to evaluate potential toxicity. This phase applies to products like prescription drugs, diagnostics, and medical devices.

Statistically, only 1 in 5,000 compounds entering the drug discovery pipeline successfully reaches approval. Preclinical testing varies by product type. Drugs typically undergo pharmacodynamics (PD), pharmacokinetics (PK), ADME, and toxicology assessments to estimate safe human doses. Devices without a drug component may bypass some tests and proceed directly to GLP-based safety evaluations. Some devices also require biocompatibility tests to assess if materials are suitable for use in living organisms. Both in vitro and in vivo tests are performed. Toxicity studies examine which organs are affected and whether the compound causes long-term harm, such as cancer.

Animal Models: Species Selection

Species are selected based on their similarity to human beings for adequate consideration of absorption, metabolism, and toxicity information. Dogs, for example, can never be requested to validate testing of an oral drug due to accelerated gastric emptying and variations in gut structure. Rodents also cannot be utilized for testing antibiotics disrupt gut flora. Drugs are metabolized differently by various species, most often propelling independent toxicity pathways and opposing their true therapeutic effect.

In the case of testing devices, larger animals such as pigs, dogs, and sheep are used because those anatomical or organ-level characteristics are similar to those of humans. Specific models are chosen based on the organ in physiology- e.g., swine for cardiac and dermatology studies, goats for mammary implants, and dogs for gastric/cancer work.

Typically, global regulatory agencies like the FDA or EMA will legally mandate safety assessments of at least two mammalian species (one usually a non-rodent species) conducted before the initiation of human clinical trials. [1]

2. CDSCO and Clinical Trial in India (as per CT Rules, 2019)

a. Prepare a preclinical study report

b. Apply for Permission from CDSCO

Submit Form CT-04 for clinical trial permission through the SUGAM online portal.

The national regulatory body for clinical trials in India as per the New Drugs and Clinical Trials Rules, 2019 (CT Rules, 2019), is the Central Drugs Standard Control Organization (CDSCO), which operates under the Ministry of Health and Family Welfare.

It is led by the Drugs Controller General of India (DCGI)—who in the CT Rules, 2019, has also been mentioned as the Central Licensing Authority (CLA)—who, above all, issues permissions for the conduct of clinical trials, monitors import of drugs for trials, and ensures regulatory steps are followed.

It works under the Directorate General of Health Services (DGHS) and does the approval of new drugs, standard setting, surveillance of drug quality on imports, and coordination with state authorities on drug manufacture and distribution.

The CT Rules, 2019, create two regulatory bodies helping the DCGI:

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i. Drugs Technical Advisory Board (DTAB) – gives technical advice on drug-related matters.
ii. Drugs Consultative Committee (DCC) - maintains coordination of drug control measures in the Centre and States.

Subject Expert Committees (SECs) are established under the CT Rules for the assessment of clinical trial applications, comprising of experts in the concerned therapeutic area. These committees assess study protocols, investigator brochures, and other documents. The 13 Jan 2020 Order allows the DCGI to form SECs from a pool of ~550 specialists from medical colleges and institutions. The SEC Division of CDSCO conducts meetings to review Investigational New Drug (IND) proposals, as referenced in Notice 31 Jan 2024. [7]

3. Clinical Trials Under Schedule Y (India – CDSCO)

In India, clinical trials are carried out as per Schedule Y of the Drugs and Cosmetics Rules. These guidelines explain how a new drug should be tested on humans before it gets approval. The entire process is divided into different phases (Phase I, II, and III), each with a specific goal.

Phase I – First Time in Humans

Typically involving a few healthy volunteers, this phase has 20 to 100 subjects. The goal is primarily to establish that the drug is safe and evaluate its behavior when in the body. This is how it is absorbed, distributed, metabolized, and then ultimately excreted (this is referred to as pharmacokinetics): The information also assists in determining the appropriate dosage range.

Phase II – Testing in Patients

Once it proceeds through Phase I, the drug reaches Phase II and patients (approximately 100-300) suffering from the disease in question are administered the drug. The effectiveness of the drug and side-effects at various levels of dose are assessed by scientists.

Phase III – Confirming Results

At this phase, a far greater number of patients, between 500 and 3,000 or more, are used to verify the drug's efficacy and to identify any long-term adverse characteristics. These types of studies are usually carried out at multiple different hospitals and compared against current treatments. [7]

4. NDA Submission

It is an e-platform for filing applications, viewing their status, and overseeing regulatory procedures regarding drug and medical device approvals in India. Form 44 or Form CT-04 is used for filing requests for clinical trial approvals or new drug approvals under the CDSCO's SUGAM portal. Application Process

The process usually involves the choosing of the right form and category, entering information regarding the drug or the trial, submitting the documents required, and the payment of fees due via the portal.

Submit Form CT-04 for clinical trial permission through the SUGAM online portal Include:

a) Investigational brochure
b) Preclinical data
c) Trial protocol
d) Ethics Committee approvals
e) Details of investigators/sites
f) Informed consent forms
g) Insurance and compensation details

5. SEC Review and DCGI Decision

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6. Post-Marketing Surveillance and Marketing Approval

Approval of a drug is not where it ends. After a drug has been given marketing approval and is made available to the population, it enters into a very important stage referred to as post-marketing surveillance (also Phase IV). In this phase, regulatory agencies and drug manufacturers keep following the safety of the drug, searching for unusual or long-term adverse effects that may not have appeared in clinical trials. This is particularly crucial when the drug is taken by a larger and more heterogeneous population, such as older people, pregnant women, or people with underlying conditions.

Approval for marketing itself occurs only after careful consideration of all preclinical and clinical trial information, demonstrating that the drug is safe as well as effective for its intended application. But approval doesn't equal the medicine being absolutely risk-free. That is why post-marketing surveillance is important; it can identify such problems as drug interactions, abuse, and unforeseen side effects down the road. If there are significant issues, regulators can revise use guidelines, include warnings, or even pull the drug off the market.

COMPARATIVE OVERVIEW OF DRUG APPROVAL PROCESSES – USFDA VS EMA VS CDSCO

Step	USFDA (USA)	EMA (Europe)	CDSCO (India)
Regulatory Body	Centre for Drug Evaluation and Research (CDER), USFDA	European Medicines Agency (EMA)	Central Drugs Standard Control Organization (CDSCO)

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Governing Law/Rules	Federal Food, Drug, and Cosmetic Act	EU Regulation (EC) No 726/2004	Drugs & Cosmetics Act, 1940 & New Drugs & CT Rules, 2019
Initial Submission	Investigational New Drug (IND) Application	Clinical Trial Application (EU Clinical Trials Regulation)	Clinical Trial Application (Form CT-04)
Clinical Trials	Phase I → Phase II → Phase III (safety & efficacy)	Phase I → III under GCP and ICH	Phases I–III under Schedule Y
Final Application Format	New Drug Application (NDA), in CTD/eCTD format	Marketing Authorization Application (MAA), in CTD format	Form 44 submitted via SUGAM Portal (CTD format)
Review Authority	FDA reviewers, advisory committees if needed	Committee for Medicinal Products for Human Use (CHMP)	Subject Expert Committee (SEC) and DCGI
Review Timeframe	10 months (Standard), 6 months (Priority Review)	~210 days + EC decision within 67 days	~6–12 months (faster under new 2025 rules for priority cases)
Approval Decision	USFDA (CDER)	Final decision by European Commission	Final decision by DCGI (Ministry of Health)
Expedited Pathways	Fast Track, Breakthrough, Accelerated, Priority Review	Accelerated Assessment, PRIME	Fast-track approval (as per new CDSCO rules)
Post-Marketing Surveillance	MedWatch, Phase IV studies, REMS	EudraVigilance, RMP (Risk Mgmt. Plan)	PvPI (Pharmacovigilance Programme of India), PSUR
Digital Submission Platforms	eCTD via Electronic Submissions Gateway	CTD/eCTD via EMA systems	eCTD via SUGAM Portal

CONCLUSION

The process of drug approval is lengthy and intricate, and each nation has its own method of ensuring that new drugs are safe, effective, and of good quality. In this article, we looked at how three key regulatory agencies USFDA, EMA, and CDSCO, go about it. Although the general framework of preclinical testing, clinical trials, application filing, and post-marketing surveillance is the same, each agency adopts different procedures, timelines, and documentation formats. USFDA is recognized for its organized NDA system and fast-track facilities. EMA follows a

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centralized process with the participation of CHMP and the European Commission, whereas India's CDSCO has improved with electronic submission and transparent guidelines through Schedule Y and the New Drugs and Clinical Trials Rules, 2019. Knowledge of these variations is vital not just for students but also for anyone engaged in pharmaceutical research, marketing, or regulatory affairs. A clear understanding of global regulatory systems facilitates streamlining international drug development and ensures greater access to safe drugs across borders.

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