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PHARMACEUTICAL REGULATORY SCIENCE

B.Pharm 8th Semester

UNIT - II

REGULATORY APPROVAL PROCESS

SYLLABUS COVERAGE — UNIT II

Part A — Regulatory Approval Process: IND (Investigational New Drug) approval process & timelines | NDA (New Drug Application) process & timelines | ANDA (Abbreviated New Drug Application) process & timelines | Changes to an approved NDA/ANDA

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PART A: REGULATORY APPROVAL PROCESS

Overview of Regulatory Approval

Regulatory approval is the formal authorization granted by a drug regulatory authority that allows a pharmaceutical company to conduct clinical trials on humans or to market a drug product in a given country. The approval process is designed to ensure that drugs are safe, effective, and of acceptable quality before reaching patients.

> *The three primary regulatory submissions in the US are: IND (for clinical trials), NDA (for new drugs), and ANDA (for generic drugs). Each has its own data requirements, review timelines, and regulatory pathways.*

Submission Type	Purpose	Submitted By	US Regulation
IND	Permission to initiate clinical trials in humans	Sponsor (Pharma/Biotech)	21 CFR Part 312
NDA	Permission to market a new drug product	Innovator/Sponsor	21 CFR Part 314
ANDA	Permission to market a generic drug product	Generic Manufacturer	21 CFR Part 314
BLA	Permission to market a biologic drug product	Sponsor	21 CFR Part 601
sNDA/sANDA	Supplemental changes to approved NDA/ANDA	Approved NDA/ANDA holder	21 CFR Part 314

Investigational New Drug (IND) Application

Definition and Purpose

An Investigational New Drug (IND) application is a request for authorization from the US Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR Part 312, no clinical trial may be initiated in the US without an active IND.

- **Legal Basis:** 21 CFR Part 312 (US); New Drugs and Clinical Trials Rules, 2019 (India); Directive 2001/20/EC (EU)
- **Exemptions:** Studies using lawfully marketed drugs that do not alter risk, where blinding does not change labeling, and are not for commercial purposes may qualify for IND exemption

Types of IND

Type of IND	Description
Investigator IND	Submitted by a physician who initiates and conducts the investigation and uses the drug solely under their supervision
Emergency Use IND	Allows FDA to authorize use of an experimental drug in life-threatening emergency situations without prior formal IND submission; reviewed within 24 hours
Treatment IND	Allows use of investigational drugs in patients with serious or immediately life-threatening conditions outside of clinical trials while the drug is being studied
Expanded Access IND	Provides access to investigational drugs for individual patients or groups outside clinical trials, for compassionate use
Commercial IND	Submitted by a company (sponsor) intending to commercialize the drug; most common type

Contents of IND Application (21 CFR 312.23)

An IND application consists of the following components:

Section 1 — Cover Sheet (Form FDA 1571)

- Sponsor name, address, telephone number
- Name of investigational drug (chemical name, trade name if any)
- Phase of clinical investigation
- Commitment to conduct trials per GCP; not to begin before 30-day safety review

Section 2 — Table of Contents

Section 3 — Introductory Statement and General Investigational Plan

- Brief description of drug substance and drug product
- Broad objectives and planned phases of investigation
- Estimated number of subjects and studies planned

Section 4 — Investigator's Brochure (IB)

- Compilation of all clinical and non-clinical data relevant to the study of the drug in human subjects
- Summary of physicochemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information
- Must be updated as new significant information becomes available

Section 5 — Clinical Protocol(s)

- Objectives and purpose of each planned study

- Design and methodology: randomization, blinding, controls
- Inclusion/exclusion criteria for subject selection
- Dose, route, regimen, and duration of administration
- Observations and measurements to be made
- Stopping rules for individual subjects and entire study
- Statistical analysis plan

Section 6 — Chemistry, Manufacturing, and Controls (CMC)

- Drug Substance: description, synthesis, characterization, purity, stability, reference standard
- Drug Product: formulation, manufacture, controls, container/closure, stability
- For Phase I: more flexibility acceptable; CMC data expands with each subsequent phase

Section 7 — Pharmacology and Toxicology Information

- Pharmacological studies in animals: mechanism of action, pharmacokinetics
- Toxicological studies: acute, subacute, chronic (as appropriate for phase)
- Assessment of risk to humans: therapeutic dose vs. toxic dose
- GLP compliance statement for pivotal toxicology studies

Section 8 — Previous Human Experience

- Summary of known prior human experience with the drug (foreign and domestic)
- Published or unpublished reports; post-marketing data if available

Section 9 — Additional Information

- Relevant information such as drug abuse potential, radioactive drug information, pediatric studies plan

IND Review Process and Timelines

After submission, the FDA has a 30-day review period before clinical trials may begin. The review is conducted by a multidisciplinary team including pharmacologists, toxicologists, CMC reviewers, and clinical reviewers.

Day	Activity
Day 0	IND received by FDA; assigned IND number; triaged to review division
Day 1-5	Administrative review; document completeness check
Day 5-25	Scientific review by multidisciplinary team (CMC, pharmacology/toxicology, clinical)
Day 25-30	Integration of review; decision made
Day 30	If no 'Clinical Hold' issued, sponsor may proceed with clinical trials

After Day 30	FDA may issue an Information Request (IR) or Study Risk Information Amendment (SRIA)

Clinical Hold: A clinical hold is an order by FDA to delay a proposed clinical investigation or to suspend an ongoing investigation. Reasons include: unreasonable risk to subjects, poorly designed protocol, inadequate investigator qualifications, misleading IB.

IND Amendments and Annual Reports

- **Protocol Amendments:** Required for new protocols, changes in existing protocols, new investigators (Form FDA 1572 for each investigator)
- **Information Amendments:** Report new non-clinical findings, changes in CMC, or other relevant data
- **Safety Reports:** IND Safety Reports required within 7 days (fatal/life-threatening SUSAR) or 15 days (serious unexpected ADRs)
- **Annual Progress Report:** Submitted within 60 days of anniversary of IND going into effect; includes progress summary, subject enrollment, safety summary

IND in India (CDSCO)

In India, a clinical trial application equivalent to IND is submitted to CDSCO under the New Drugs and Clinical Trials Rules, 2019.

- Form CT-04: Application for permission to conduct clinical trial with a new drug
- Review by New Drug Advisory Committee (NDAC) - disease-specific expert committees
- Target review timeline: 30 working days (Phase I) to 90 working days (Phase II/III)
- Academic/investigator-initiated trials have a separate streamlined pathway
- Mandatory Ethics Committee (EC) registration and approval before CDSCO submission

New Drug Application (NDA)

Definition and Purpose

A New Drug Application (NDA) is a formal submission to the US FDA requesting approval to market a new drug product in the United States. The NDA is the vehicle through which a drug sponsor formally proposes that the FDA approve a new drug for sale and marketing. It contains all available evidence on the safety and effectiveness of the drug.

- **Legal Basis:** Section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR Part 314
- **Indian Equivalent:** New Drug Permission (Form 44) under the New Drugs and Clinical Trials (NDCT) Rules, 2019, submitted to CDSCO
- **EU Equivalent:** Marketing Authorization Application (MAA) submitted to EMA or national competent authority

Types of NDA Submissions (USFDA)

Section 505 Type	Description
505(b)(1) NDA — Full NDA	Contains complete reports of all pre-clinical (safety) and clinical (efficacy) investigations conducted by or for the applicant; standard pathway for innovator drugs
505(b)(2) NDA — Paper NDA / Hybrid NDA	Relies in part on published literature or FDA's finding of safety/effectiveness of a previously approved drug; used for new formulations, new indications, new dosage forms, OTC switches; most common for modified/improved products
505(j) NDA — ANDA	Abbreviated application for generic drugs; relies on the safety and efficacy established by the innovator's NDA; requires only bioequivalence demonstration

Content of an NDA — CTD Format

Since 2003, the FDA requires NDA submissions in the Common Technical Document (CTD) format, harmonized with ICH M4 guidelines. CTD is organized into 5 modules:

Module	Content	Scope
Module 1	Administrative Information	Cover letter, application forms, prescribing information (labeling), patent certification, debarment certification — region-specific, not harmonized
Module 2	CTD Summaries	Overall CTD ToC, Introduction, Quality Overall Summary (QOS), Non-clinical Overview, Non-clinical Written/Tabulated Summaries, Clinical Overview, Clinical Summary
Module 3	Quality (CMC)	Drug Substance: manufacture, characterization, control, stability; Drug Product: description, formulation, manufacture, specification, stability; Container closure; Appendices
Module 4	Non-clinical Study Reports	Full study reports for pharmacology, PK/TK, toxicology (all types); GLP compliance statements
Module 5	Clinical Study Reports	Tabulation of clinical study reports; all Phase I, II, III study reports; case report forms; patient data

		listings; integrated summaries of safety and efficacy

NDA Review Process (USFDA)

The NDA review process is structured and follows defined timelines under the Prescription Drug User Fee Act (PDUFA).

Step	Activity	Timeline
1. Submission	NDA submitted electronically (eCTD format) to CDER or CBER	Day 0
2. Filing Review	60-day preliminary review for completeness and acceptability for filing	Day 1-60
3. Refuse to File (RTF)	FDA may refuse to file if application is incomplete or unacceptable; sponsor has 30 days to respond	Day 60 (if applicable)
4. Substantive Review	Multidisciplinary review: Medical, Statistical, Pharmacology, CMC, Microbiology, Clinical Pharmacology reviewers	Day 60-300
5. Advisory Committee	Optional but recommended for novel drugs/mechanisms; public meeting of expert advisors	During review
6. Labeling Negotiation	FDA and applicant negotiate prescribing information (package insert)	Late in review
7. Facility Inspection	Pre-approval inspection (PAI) of manufacturing site(s)	During/late review
8. Complete Response Letter (CRL)	If not approved: FDA issues CRL listing deficiencies requiring resolution	PDUFA date
9. Approval	FDA issues approval letter; product may be marketed	PDUFA date

PDUFA Review Timelines

The Prescription Drug User Fee Act (PDUFA) sets target review timelines based on the designation of the application:

Review Designation	Criteria	Target Review Time
Standard Review	Drugs offering little or no therapeutic advantage over existing treatments	12 months from filing (10 months from receipt)

Priority Review	Drugs that offer major advances in treatment or provide therapy where no adequate therapy exists	6 months from filing (8 months from receipt)
Accelerated Approval	Serious conditions; based on surrogate endpoint reasonably likely to predict clinical benefit	Varies; confirmatory trials required post-approval
Breakthrough Therapy	Preliminary clinical evidence shows substantial improvement over available therapy on a clinically significant endpoint	Expedited development and review; rolling review allowed
Fast Track	Serious conditions; potential to address unmet medical need	More frequent FDA meetings; rolling NDA review allowed
REMS (Risk Evaluation)	Required for drugs with serious safety concerns; includes medication guides, ETASU, communication plans	Part of approval conditions

PDUFA Goal: FDA must complete review of 90% of NDAs within the PDUFA goal date. User fees collected under PDUFA fund FDA's review activities.

Special Designations and Incentives

Designation	Eligibility and Benefit
Orphan Drug Designation	Drugs for diseases affecting <200,000 patients in the US; benefits: 7-year market exclusivity, 50% tax credit on clinical trial costs, waiver of NDA user fee, grants
Pediatric Exclusivity	Additional 6 months of market exclusivity if sponsor conducts pediatric studies per FDA's Written Request
New Chemical Entity (NCE) Exclusivity	5-year exclusivity from approval date; ANDA applicants cannot submit during this period (or 4 years + Paragraph IV challenge)
New Clinical Investigation Exclusivity	3-year exclusivity for new clinical studies for supplements (new indication, new dosage form, etc.)
Rare Pediatric Disease Priority Review Voucher	Voucher for priority review of a future application, awarded for approval of a rare pediatric disease drug

NDA in India — New Drug Application (CDSCO)

In India, permission to market a new drug is obtained from CDSCO under the Drugs and Cosmetics Act, 1940 (as amended) and the New Drugs and Clinical Trials Rules, 2019.

Application Forms

- Form 44: Application for grant of permission to manufacture for sale/distribution of a new drug
- Form CT-21: Application for conduct of clinical trials (new drugs developed in India)
- Form CT-20: Application for manufacture and conduct of clinical trial (NDCT Rules 2019)

Data Requirements for New Drug Marketing Approval in India

- Full CTD/eCTD format preferred
- Phase I, II, III clinical trial data conducted in India OR waiver with justification
- For drugs already approved in ICH countries: bridging studies may be acceptable
- CMC data for drug substance and drug product per Indian Pharmacopoeia/IP/BP/USP standards
- Safety data: as per ICH S1-S9 and Schedule Y guidelines

Review Timeline (CDSCO)

- Target: 12 months for new drug applications from India; 6 months for drugs approved in ICH countries (with Indian clinical data)
- Expert committee review: New Drug Advisory Committee (NDAC)
- Drug Controller General of India (DCGI) grants final approval

Abbreviated New Drug Application (ANDA)

Definition and Legal Basis

An Abbreviated New Drug Application (ANDA) is a submission to the FDA for approval of a generic drug product. It is 'abbreviated' because it does not require the same clinical trial data as a full NDA; instead, it demonstrates that the generic product is bioequivalent to an already-approved brand-name drug (the Reference Listed Drug - RLD).

- **Legal Basis:** Drug Price Competition and Patent Term Restoration Act, 1984 (Hatch-Waxman Act); 21 CFR Part 314 Subpart C
- **Central Act (India):** New Drugs and Clinical Trials Rules, 2019; Drugs and Cosmetics Act, 1940; Rule 122B (Form 44 for manufacturing approval)
- **Principle:** Generic drug manufacturers rely on the FDA's finding that the RLD is safe and effective, rather than repeating the expensive clinical trials

Content of an ANDA (21 CFR 314.94)

Component	Details
Cover Sheet (Form FDA 356h)	Applicant details, drug name, RLD name, paragraph certification, debarment certification
Bioequivalence (BE) Data	In vivo BE study reports (fasting and/or fed); may include in vitro dissolution data for biowaiver
Pharmaceutical Equivalence	Same active ingredient, dosage form, strength, route of administration as RLD
Labeling	Must be same as RLD labeling except for carve-outs (Section VIII carve-out), differences in inactive ingredients, and permissible differences (company name, expiry, etc.)
Chemistry, Manufacturing, Controls (CMC)	Drug substance source and specs; drug product formulation, manufacturing process, controls, stability per ICH Q1
Patent Certification	One of: Para I (no listed patent), Para II (patent expired), Para III (patent to expire - wait), Para IV (patent invalid/not infringed)
Inactive Ingredient Statement	List of all inactive ingredients with safety justification per FDA's Inactive Ingredient Database (IIG)
Environmental Impact	Categorical exclusion or Environmental Assessment
Field Alert Reports	Commitment to report product quality problems within 3 days

Patent Certification — Paragraph IV

The Hatch-Waxman Act requires ANDA applicants to certify the status of each patent listed in the FDA's Orange Book for the RLD:

Certification	Meaning and Timeline
Paragraph I	No patent listed for the RLD in the Orange Book; ANDA can be approved immediately
Paragraph II	Listed patent(s) have expired; ANDA can be approved immediately after demonstrating BE
Paragraph III	Applicant agrees to wait until the listed patent expires before marketing the generic drug; tentative approval until patent expiry
Paragraph IV	Applicant certifies that the listed patent is invalid, unenforceable, or will not be infringed; most commercially attractive; may trigger patent litigation (30-month stay); first Para IV filer gets 180-day generic exclusivity

180-Day Exclusivity: The first ANDA applicant to file a Paragraph IV certification is eligible for 180 days of marketing exclusivity, during which FDA cannot approve another ANDA for the same drug from a different applicant.

ANDA Review Process and Timelines

Step	Activity	Timeline
1. Submission	ANDA submitted electronically (eCTD format) to FDA's Office of Generic Drugs (OGD)	Day 0
2. Completeness Assessment	Refuse-to-Receive (RTR) check; OGD assesses if application is complete and reviewable	Day 1-60
3. Primary Review	CMC reviewer, bioequivalence reviewer, labeling reviewer, microbiology (if applicable)	Month 2-10
4. Mid-Cycle Meeting	If necessary, applicant-OGD communication to resolve major issues	Month 6 (approx.)
5. Complete Response Letter (CRL)	If deficiencies found, OGD issues CRL; applicant has 1 year to respond (3-year limit total)	
6. Pre-Approval Inspection (PAI)	FDA inspection of manufacturing facility and any registered sites	Before approval
7. Tentative Approval	Issued when ANDA meets all requirements but patent/exclusivity block prevents final approval	When ANDA is otherwise approvable

8. Final Approval	Full approval; ANDA holder may market the generic drug	After patent/exclusivity expiry

GDUFA Timeline Goals (Generic Drug User Fee Amendments)

- GDUFA II (2017-2022) standard review goal: 10 months for complete, amendable applications
- GDUFA III goal: Complete review of 90% of original ANDAs within 10 months
- Completeness Assessment: within 60 days of receipt
- Prior Approval Supplement (PAS): 10-month standard; 6-month expedited

ANDA in India (CDSCO)

India does not use the term 'ANDA'; instead, manufacturers apply for marketing approval of a generic drug through a simplified process:

- Form 44 under the Drugs and Cosmetics Act for permission to manufacture and market a generic drug
- Bioequivalence data required for systemic generic drugs with narrow therapeutic index or complex formulations
- CDSCO Bioequivalence Guidelines (2005; updated 2020 draft) mandate in vivo BE studies for certain drug classes
- For drugs not requiring in vivo BE: dissolution profile comparison (f2 similarity) or formulation comparison acceptable
- Application reviewed by Drug Consultative Committee (DCC) and State Licensing Authorities (SLAs) for state-level manufacturing licenses

Changes to an Approved NDA / ANDA

5.1 Overview

After a drug product is approved, the holder of the NDA or ANDA may need to make changes to the product, process, labeling, or manufacturing site. All such changes must be reported to the FDA. The type of reporting required depends on the potential impact of the change on product quality, safety, or efficacy.

> *FDA regulations (21 CFR 314.70 for NDA; 21 CFR 314.97 for ANDA) classify post-approval changes into three categories based on their risk and impact: Prior Approval Supplement (PAS), Changes Being Effected (CBE-30 or CBE-0), and Annual Report.*

Categories of Post-Approval Changes

Change Category	Requirements and Examples
Prior Approval Supplement (PAS / Major Change)	Requires FDA approval BEFORE implementing the change. Examples: New indication or labeling changes affecting safety; New manufacturing site; New synthetic route for API; Changes in release mechanism (IR to MR); New container closure system; Significant formulation changes; Addition of new strength. Timeline: Standard 12 months; Priority 6 months.
CBE-30 (Changes Being Effected in 30 Days / Moderate Change)	Notify FDA at least 30 days before implementing. May implement after 30 days if no FDA objection. Examples: Relaxation of in-process test limits; New analytical procedure; Moderate formulation change within design space; Addition of manufacturing site for packaging; Change in batch size (within 10x scale-up per SUPAC).
CBE-0 (Changes Being Effected / Minor Change)	Notify FDA at the same time the change is implemented (Day 0). Examples: Minor editorial changes to labeling; Change of expiry date format; Addition of alternative analytical equipment; Tightening of specification limits; Change in container size/shape (not closure system).
Annual Report (AR / Least Significant Change)	Report in the Annual Product Review (APR) submitted within 60 days of anniversary of approval date. Examples: Changes to manufacturing instructions within approved ranges; Deletion of a strength no longer marketed; Minor rewriting of batch records; Changes in in-house reference standards.

SUPAC (Scale-Up and Post-Approval Changes)

SUPAC guidelines provide specific guidance on allowable post-approval changes for different dosage forms and the required regulatory reporting for those changes.

SUPAC Guideline	Dosage Form and Provisions
SUPAC-IR (1995)	Immediate Release solid oral dosage forms. Level 1 (minor, AR), Level 2 (moderate, CBE-30 with dissolution), Level 3 (major, PAS with BE study).
SUPAC-MR (1997)	Modified Release solid oral dosage forms. More stringent than SUPAC-IR due to complex release mechanisms; Level 3 changes always require in vivo BE.
SUPAC-SS (1997)	Semisolid dosage forms (creams, ointments, gels). Uses in vitro release testing (IVRT) as surrogate for in vivo performance; Level 3 always requires clinical or BE study.
SUPAC-DP (1998)	Drug Products containing drug substance changes. Addresses changes in particle size, polymorphic form, and synthesis of drug substance.

SUPAC Equipment (1999)	Guidance on changes in manufacturing equipment (non-sterile solids); equipment class changes can be Level 1-3.

Changes to Labeling (Prescribing Information)

- New safety information discovered post-approval must be added promptly — FDA may require label update via Post-Marketing Requirement (PMR)
- 'Dear Healthcare Provider' letters required for important safety communications
- Risk Evaluation and Mitigation Strategy (REMS) may be added or modified if post-marketing safety signals emerge
- Boxed warning addition: PAS required; often triggered by pharmacovigilance data
- Label revisions under 21 CFR 314.70(c) for safety reasons: CBE-0 allowed for sponsor-initiated safety updates

Complete Response Letter (CRL) and Resubmission

- FDA issues a CRL when an NDA/ANDA review is complete but the drug is not approvable in current state
- CRL lists all deficiencies (clinical, CMC, labeling, facility) that must be addressed
- Class 1 Resubmission (minor deficiencies): target 2-month review after resubmission
- Class 2 Resubmission (major deficiencies, new clinical data): target 6-month review after resubmission

PART B: REGULATORY AUTHORITIES AND AGENCIES

Overview of International Regulatory Authorities

Regulatory authorities are government bodies responsible for evaluating, approving, and monitoring drugs, biological products, and medical devices to ensure public health safety. They operate under national legislation and may participate in international harmonization initiatives such as ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use).

Country/Region	Regulatory Authority	Legislation
India	CDSCO (Central Drugs Standard Control Organisation)	Drugs and Cosmetics Act, 1940; NDCT Rules, 2019
United States	USFDA — CDER / CBER / CDRH	FD&C Act (1938); PHSA; 21 CFR Parts 300-900
European Union	EMA (European Medicines Agency) + NCAs	Regulation (EC) 726/2004; Directive 2001/83/EC
Australia	TGA (Therapeutic Goods Administration)	Therapeutic Goods Act, 1989
Japan	PMDA (Pharmaceuticals and Medical Devices Agency)	Pharmaceuticals and Medical Devices Act (PMD Act), 2014
Canada	Health Canada — HPFB (Health Products and Food Branch)	Food and Drugs Act (F&DA), 1985

IN INDIA — Central Drugs Standard Control Organisation (CDSCO)

Central Drugs Standard Control Organisation (CDSCO)

CDSCO is the national regulatory authority of India functioning under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. It is the equivalent of the US FDA for India.

Organizational Structure of CDSCO

CDSCO operates through a central office and six zonal offices across India:

Level/Office	Location and Jurisdiction
Central Office (CO)	New Delhi — National policy, drug regulation, import approvals, clinical trial oversight
Zonal Office — North	New Delhi — Punjab, Haryana, HP, J&K, Delhi, Uttarakhand, UP

Zonal Office — East	Kolkata — West Bengal, Odisha, Bihar, Jharkhand, Sikkim, NE States
Zonal Office — West	Mumbai — Maharashtra, Goa, Gujarat, MP, Rajasthan, Chhattisgarh, Daman & Diu, Dadra & NH
Zonal Office — South	Chennai — Tamil Nadu, Kerala, Karnataka, Andhra Pradesh, Telangana, Puducherry, A&N Islands
Sub-Zonal Office	Ahmedabad, Hyderabad, Bengaluru — Regional activities
Port Offices	Mumbai, Kolkata, Chennai, Delhi — Import clearance of drugs
State Licensing Authorities (SLAs)	State-level — Manufacturing licenses for drugs sold within the state (Form 25/28 under D&C Rules)

Functions of CDSCO

- Regulatory approval of new drugs, vaccines, biologicals, cosmetics, and medical devices
- Licensing of blood banks, large-scale manufacturing units (Schedule M compliance — GMP)
- Import licensing for drugs and medical devices
- Permission for clinical trials in India
- Post-marketing surveillance and pharmacovigilance (PvPI — Pharmacovigilance Programme of India)
- Ban or restriction of drugs found harmful
- Setting standards in coordination with Indian Pharmacopoeia Commission (IPC)
- International harmonization — participation in WHO, ICH, BRICS regulatory forums

Officials

- Drug Controller General of India (DCGI): Head of CDSCO; exercises powers under D&C Act for Central licence
- Deputy Drug Controllers: Support DCGI in technical reviews
- New Drug Advisory Committees (NDACs): Disease-specific expert committees for new drug/CT review (12 NDACs covering Oncology, Cardiology, Anti-infectives, Vaccines, etc.)
- Technical Expert Committee (TEC): Reviews challenging safety issues

Types of Applications to CDSCO

Application Type	Form / Description
New Drug Clinical Trial	Form CT-04: Permission to conduct Phase I/II/III/IV clinical trials for new drugs
New Drug Marketing Approval	Form 44: Permission to manufacture new drug for sale; submitted with CTD data

Import of New Drug	Form 45: Permission to import new drug for clinical trials or marketing
Subsequent New Drug	New drug already approved in ICH country; Form 44 with bridging data; expedited review
Waivers / Exemptions	Application for waiver of local clinical trial data under NDCT Rule 101
Bioequivalence Studies	Form CT-07: Permission to conduct BE study for generic products
Orphan Drug Designation	Form CT-09: Application for Orphan Drug Designation under NDCT Rules 2019
Medical Device Registration	Form MD-14 (new device), MD-15 (import) — under MDR 2017
Blood Bank License	Form 27C under D&C Rules 1945 for blood bank licensing
Pharmacovigilance	ADR reporting through PvPI portal (National Coordination Centre at IPC, Ghaziabad)

US UNITED STATES OF AMERICA — Food and Drug Administration (FDA)

United States Food and Drug Administration (USFDA)

The US FDA is one of the world's most influential regulatory agencies, responsible for protecting and promoting public health through the regulation and supervision of food safety, pharmaceutical drugs, biological products, medical devices, cosmetics, and tobacco products. It operates under the Department of Health and Human Services (DHHS).

Organizational Structure of FDA

Center / Office	Responsible for
CDER — Center for Drug Evaluation and Research	Evaluation and approval of prescription and OTC drugs (small molecules); NDAs, ANDAs, BLAs for therapeutic biologics
CBER — Center for Biologics Evaluation and Research	Vaccines, blood and blood products, cellular/gene therapy products, tissues, allergenics
CDRH — Center for Devices and Radiological Health	Medical devices, in vitro diagnostics (IVDs), radiation-emitting products
CVM — Center for Veterinary Medicine	Animal drugs, feeds, and veterinary devices

CFSAN — Center for Food Safety and Applied Nutrition	Food safety, cosmetics, dietary supplements
CTP — Center for Tobacco Products	Regulation of tobacco products under Tobacco Control Act
ORA — Office of Regulatory Affairs	Field operations: facility inspections, import/export, sample collection, enforcement
NCTR — National Center for Toxicological Research	Scientific research to support FDA regulatory decisions
Office of the Commissioner	Overall agency leadership, policy, interagency coordination

Structure of CDER (Most Relevant for Pharma)

- Office of New Drugs (OND): Reviews NDAs and supplements for new chemical entities
- Office of Generic Drugs (OGD): Reviews ANDAs for generic drugs
- Office of Pharmaceutical Quality (OPQ): CMC review of NDAs, ANDAs, BLAs; GMP oversight
- Office of Surveillance and Epidemiology (OSE): Post-marketing safety surveillance
- Office of Translational Sciences (OTS): Biostatistics, clinical pharmacology, pharmacometrics
- Office of Compliance (OC): Enforcement actions, warning letters, import alerts

Types of Applications to USFDA

Application	Description
IND (Investigational New Drug)	21 CFR 312 — Permission to conduct human clinical trials; Commercial IND, Treatment IND, Expanded Access IND
NDA — 505(b)(1)	21 CFR 314 — Full NDA for new chemical/biological entities with complete clinical data package
NDA — 505(b)(2)	21 CFR 314 — Hybrid NDA relying partly on published literature or previously approved drugs
ANDA — 505(j)	21 CFR 314 — Abbreviated NDA for generic drugs; bioequivalence demonstration required
BLA (Biologics License Application)	21 CFR 601 — For vaccines, blood products, cell/gene therapies, therapeutic biological products
sNDA / sANDA (Supplements)	Post-approval changes (PAS, CBE-30, CBE-0, AR) to approved NDA/ANDA
510(k) Premarket Notification	For Class II medical devices; substantial equivalence to predicate device

PMA (Premarket Approval)	For Class III medical devices; safety and effectiveness data required
EUA (Emergency Use Authorization)	Rapid authorization during public health emergencies (e.g., COVID-19 vaccines)
OTC Monograph	21 CFR 330 — Marketing of OTC drugs under established monograph conditions without individual approval

EU EUROPEAN UNION — European Medicines Agency (EMA)

European Medicines Agency (EMA)

The European Medicines Agency (EMA) is a decentralized agency of the European Union responsible for the scientific evaluation, supervision, and safety monitoring of medicines in Europe. It coordinates with National Competent Authorities (NCAs) of 27 EU member states plus Iceland, Liechtenstein, and Norway (EEA).

EMA is headquartered in Amsterdam, Netherlands (relocated from London after Brexit in 2019).

Organizational Structure of EMA

Committee / Body	Responsibilities
CHMP (Committee for Medicinal Products for Human Use)	Scientific evaluation of marketing authorization applications; issues opinions on centralized procedure; most important committee for pharma
CVMP (Committee for Medicinal Products for Veterinary Use)	Evaluates veterinary medicinal products for EU authorization
CAT (Committee for Advanced Therapies)	Gene therapies, somatic cell therapies, tissue-engineered products; provides opinion to CHMP
COMP (Committee for Orphan Medicinal Products)	Criteria for orphan designation; maintains orphan register
HMPC (Committee on Herbal Medicinal Products)	Scientific opinions on herbal substances; EU herbal monographs
PDCO (Paediatric Committee)	Paediatric Investigation Plans (PIP); pediatric drug development
PRAC (Pharmacovigilance Risk Assessment Committee)	Post-marketing safety; risk-benefit assessment; signal detection; PSUR review
SCENIHR / SAG	Scientific advisory groups for specific therapeutic areas
Management Board	Governance; budget; strategic direction; includes EC, EP, member state representatives

Regulatory Pathways in EU

Authorization Procedure	Description and Use
Centralized Procedure (CP)	Mandatory for: biotechnology products, orphan drugs, advanced therapy products, new active substances for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune; Optional for other new innovative products; EMA issues one MA valid throughout EU; 210-day timeline (CHMP review)
Decentralised Procedure (DCP)	For products not eligible for CP; simultaneous applications to reference member state (RMS) and concerned member states (CMS); RMS leads assessment; 210-day timeline
Mutual Recognition Procedure (MRP)	Drug already approved in one EU member state (reference country); approval recognized in additional member states; 90-day timeline
National Procedure	Application submitted to only one EU member state; approval valid only in that country; used for locally marketed generics, traditional herbal products, homeopathic products
Generic Application (Art. 10.1)	ANDA-equivalent in EU; bioequivalence to reference medicinal product; 8-year data exclusivity + 2-year marketing protection for RMP
Hybrid Application (Art. 10.3)	Combination of bibliographic data and new clinical data (similar to 505(b)(2) NDA)
Well-Established Use (Art. 10a)	Minimum 10 years of use in EU with recognized efficacy and safety; purely bibliographic application
Fixed Combination (Art. 10b)	For combinations of active substances with established individual history of use
Exceptional Circumstances	For rare or chronic serious diseases where comprehensive data cannot be obtained; annual re-assessment
Conditional MA	For products with unmet medical need; subject to specific obligations; renewal of authorization

EU Data Exclusivity and Market Protection

- 8+2+1 Rule: 8 years data exclusivity + 2 years market protection + 1 year additional for new indication = 11 years total protection for reference products
- Orphan Drug Designation: 10 years market exclusivity (may reduce to 6 years if conditions no longer met)
- Paediatric extension: Additional 6-month patent extension if PIP complied with

AU AUSTRALIA — Therapeutic Goods Administration (TGA)

Therapeutic Goods Administration (TGA)

The TGA is the regulatory body for therapeutic goods in Australia, functioning within the Australian Government Department of Health. It evaluates and monitors the safety, quality, and effectiveness of therapeutic goods including medicines, medical devices, blood products, and biologicals. All therapeutic goods must be included in the Australian Register of Therapeutic Goods (ARTG) before being supplied in Australia.

Organizational Structure

- TGA is a division of the Department of Health, Australian Government
- Office of Prescription Medicines (OPM): Evaluates prescription medicines — new chemical entities, new combinations, OTC-to-prescription switches
- Office of Generic Medicines and Biosimilars (OGMB): Evaluates generic medicines and biosimilars
- Office of Over-the-Counter Medicines (OOTCM): Evaluates OTC medicines
- Office of Biologicals (OB): Evaluates biological medicines, cell/gene therapies
- Office of Devices Authorization (ODA): Medical devices, IVDs
- Office of Laboratory and Scientific Services (OLSS): Quality testing, laboratory analysis
- Advisory Committee on Medicines (ACM): Expert scientific advisory body for medicines evaluation

Types of Applications to TGA

Application Type	Description
Category 1 Application	New chemical entity or new biological entity; major change to existing product; uses TGA's full evaluation pathway; highest fee; ~255 working days (Category 1 standard)
Category 2 Application	Generic medicines and biosimilars requiring abridged evaluation; new strength, form, or route of existing product; ~255 working days
Category 3 Application	Minor variations to registered products (new labeling, minor formulation changes); faster review
Provisional Approval	For medicines with promising preliminary clinical evidence for serious conditions; equivalent to FDA's Accelerated Approval; 2-year registration renewable
Priority Review	For serious conditions with no alternative treatment; target 150 working days
ARTG Registration	All therapeutic goods must be included in ARTG before supply in Australia

Clinical Trial Notification (CTN)	Self-assessment notification for most clinical trials in Australia; no TGA review required prior to start
Clinical Trial Exemption (CTX)	Full TGA review of the IND-equivalent; required for drugs with no prior human data or novel mechanism
OTC (Listed Medicines)	Low-risk medicines containing only permitted ingredients; submitted via TGA Business Services (TBS) portal; sponsor self-certifies quality
Biosimilar Applications	Abridged evaluation showing comparability to EU/TGA-approved reference biologic

Features of Australian Regulation

- Australia participates in the Access Consortium (formerly MHRC): joint reviews with Canada, Singapore, Switzerland, UK for certain drugs
- TGA recognizes submissions from trusted overseas regulators (FDA, EMA, Health Canada) — Work Sharing Initiative
- Australian Regulatory Guidelines for Prescription Medicines (ARGPM) provide detailed guidance
- AUST R number: Registration number for higher-risk medicines in the ARTG
- AUST L number: Listing number for lower-risk listed medicines

JP JAPAN — Pharmaceuticals and Medical Devices Agency (PMDA)

Pharmaceuticals and Medical Devices Agency (PMDA)

PMDA is Japan's integrated regulatory agency, operating under the Ministry of Health, Labour and Welfare (MHLW). It was established in April 2004 to integrate the functions of previously separate agencies. PMDA reviews applications, conducts GMP/GCP/GLP inspections, and coordinates adverse drug reaction relief programs.

Organizational Structure of PMDA

Division	Responsibilities
New Drug Division I-V	Review of new drug applications organized by therapeutic category (oncology, cardiovascular, CNS, anti-infectives, etc.)
Biological Products and Cellular & Tissue Therapy Division	Vaccines, blood products, cell and gene therapies
Office of Pharmaceutical Safety	Post-marketing safety, pharmacovigilance, safety information management
Office of Conformity Audit	GMP/GCP/GLP inspections and compliance audits; on-site and document inspections
Office of Standards and Guidelines	Development of Japanese guidelines; harmonization with ICH

Office of Medical Devices and In-Vitro Diagnostics	Evaluation of medical devices and IVDs
ADR Relief Division	Administration of Adverse Drug Reaction Relief Fund for drug injury victims
Research and Development	Research on drug evaluation methodologies
MHLW	Issues marketing authorizations based on PMDA scientific opinions

Japanese Drug Approval Process

- Marketing Authorization Holder (MAH) submits application (Shonin-Shinsei) to MHLW/PMDA
- PMDA conducts scientific review; issues Review Report; MHLW grants approval
- Standard review timeline: 12 months (new drugs); 9 months (priority review)
- Japan accepts CTD format (J-CTD) for all applications per ICH M4
- Kakodan-based review: Japan requires additional domestic clinical data in many cases (bridging studies) due to ethnic differences — ICH E5 guideline governs

Types of Applications in Japan

Application Type	Description
New Drug Application (Shonin-Shinsei)	For new chemical/biological entities; full CTD data required; domestic clinical data or bridging studies per ICH E5
Generic Drug Application	Must demonstrate bioequivalence per MHLW guidelines; Japanese BE guideline 2012; accelerated review ~12 months
Partial Change Application	For significant changes to approved drug (new indication, new strength, new route, major CMC change)
Minor Change Notification	For minor changes; notified to PMDA without prior approval
Biologic / Biosimilar Application	Evaluated by Biological Products Division; PMDA biosimilar guideline harmonized with EMA/ICH Q5E
OTC Drug Application	Reclassification from Rx to OTC (switch); or new OTC product; evaluated by PMDA
Foreign Clinical Data Acceptance	Japan accepts foreign clinical data under ICH E5 bridging strategy; full waiver of Japanese trial possible if bridging study acceptable
Sakigake Designation	Priority review for innovative drugs addressing unmet medical needs with Japan as the primary development country; target 6-month review

CA CANADA — Health Canada (HC) — Health Products and Food Branch (HPFB)

Health Canada — Health Products and Food Branch (HPFB)

Health Canada is the federal department responsible for helping Canadians maintain and improve their health. The Health Products and Food Branch (HPFB) of Health Canada regulates pharmaceuticals, biologics, natural health products, radiopharmaceuticals, blood products, and medical devices. It operates under the Food and Drugs Act (F&DA) 1985 and its regulations.

Organizational Structure

Directorate / Branch	Responsibilities
Biologics and Genetic Therapies Directorate (BGTD)	Human biological drugs: vaccines, blood products, fractionated blood products, cell and gene therapy products, tissues and organs
Pharmaceutical Drugs Directorate (PDD)	Synthetic (small molecule) drug products: new drugs, generics, narcotics, controlled substances
Medical Devices Directorate (MDD)	Medical devices classified I-IV; licensing and post-market surveillance
Natural and Non-prescription Health Products Directorate (NNHPD)	Natural health products (NHPs), homeopathic medicines, OTC drugs
Regulatory Operations and Enforcement Branch (ROEB)	Compliance monitoring, inspections, enforcement actions
Marketed Health Products Directorate (MHPD)	Post-market safety surveillance; Canada Vigilance Program (ADR reporting)
Office of Clinical Trials	CTA review; GCP oversight

Drug Approval Process in Canada

- Governed by the Food and Drugs Act (F&DA) and Food and Drug Regulations (FDR)
- Standard Review Target: 300 days for New Active Substance (NAS); 180 days for Priority Review
- Canada uses CTD/eCTD format aligned with ICH M4 guidelines
- Canada Vigilance Program: post-marketing ADR surveillance
- Project Orbis: Health Canada participates with FDA, EMA, TGA, MHRA, Swissmedic for concurrent review of oncology medicines

Types of Applications to Health Canada

Application Type	Description
New Drug Submission (NDS)	For new active substances, new dosage forms, new routes of administration; full CTD data; standard 300-day review
Abbreviated New Drug Submission (ANDS)	For generic drugs; demonstrates bioequivalence to Canadian Reference Product (CRP); equivalent to ANDA; ~300-day review target
Supplemental New Drug Submission (SNDS)	Changes to approved NDS: new indication, new dosage form, labeling change, formulation change; review 180-300 days
Abbreviated Supplemental NDS (SANDS)	Changes to approved ANDS: comparable to ANDA supplements
Clinical Trial Application (CTA)	Required before initiating clinical trials in Canada; Health Canada has 30-day review period; no response = implicit approval
Priority Review	For drugs that provide substantial improvement over existing treatments for serious life-threatening conditions; 180-day review target
Notice of Compliance (NOC)	Final approval document issued by Health Canada for NDS/ANDS; equivalent to US FDA's approval letter
NOC/c (Notice of Compliance with Conditions)	Conditional approval for promising drugs with serious/life-threatening indications; confirmatory data required post-approval
Breakthrough Therapy Designation	Introduced 2019; for serious conditions with promising preliminary evidence; enhanced interaction with Health Canada
Special Access Programme (SAP)	Access to unauthorized drugs for patients with serious/life-threatening conditions; humanitarian or emergency access

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