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PHARMACEUTICAL REGULATORY SCIENCE

B.Pharm 8th Semester

UNIT - V

REGULATORY CONCEPTS

09 Hours

SYLLABUS COVERAGE — UNIT V

Topics: Basic Terminology (Guidance, Guidelines, Regulations, Laws & Acts) | Orange Book (FDA Approved Drug Products with Therapeutic Equivalence Evaluations) | Federal Register | Code of Federal Regulations (CFR) | Purple Book (FDA Biological Products Reference Database)

Introduction to Regulatory Concepts

Pharmaceutical regulation is a specialized field that governs the development, manufacture, quality, safety, efficacy, and marketing of drugs and biological products. Understanding the hierarchy of regulatory instruments — from aspirational guidance documents to enforceable laws — is essential for every pharmaceutical professional. This unit covers the foundational regulatory vocabulary and critical reference documents used in the US (and globally) for drug regulation.

> *The regulatory framework for pharmaceuticals operates as a hierarchy: Laws (Acts) are the highest authority → Regulations (CFR) implement the laws → Guidance Documents provide interpretation and recommendations → Guidelines offer scientific/technical standards. Understanding this hierarchy is essential for regulatory compliance.*

Regulatory Instrument	Legal Binding?	Issued by	Examples
Laws / Acts	Binding (mandatory)	Legislature (Congress, Parliament)	FD&C Act (USA), D&C Act (India), PHSA
Regulations / Rules	Binding (mandatory)	Regulatory Agency (FDA, CDSCO)	21 CFR, NDCT Rules 2019, Schedule M
Guidance Documents	Non-binding (recommended)	FDA, EMA, ICH, WHO	FDA Guidances, EMA Guidelines, ICH Q1-Q14
Guidelines	Non-binding (best practice)	ICH, WHO, IUPAC, USP	ICH E6 GCP, WHO GMP guidelines
Pharmacopoeias / Standards	Binding if referenced in law	USP, BP, IP, Ph. Eur.	USP, BP, IP standards for drug quality
Orange Book	Reference (non-binding)	FDA/CDER	Therapeutic Equivalence ratings (A/B)
Purple Book	Reference (non-binding)	FDA/CDER	Biological product exclusivity and reference data
Federal Register	Legal record (binding when final)	US Federal Government (GPO)	Final rules, proposed rules, FDA notices

Basic Regulatory Terminology

Regulatory science uses a precise vocabulary. The following key terms form the foundation of pharmaceutical regulatory practice. Understanding the difference between terms such as 'guidance' vs. 'regulation' vs. 'law' is critical for interpreting regulatory requirements correctly.

Core Regulatory Terms — Definitions

GUIDANCE	A guidance document is a written communication from the regulatory authority (e.g., FDA) that explains the agency's current thinking on a topic and describes approaches or policies that satisfy regulatory requirements. Guidances are non-

	binding — they do not establish legally enforceable responsibilities. The word 'should' in guidance means recommended but not required; 'must' means legally required.
GUIDELINE	A guideline is a systematic statement of policy or procedure that recommends practices for achieving a specific outcome. In pharmaceutical contexts, guidelines are often issued by international scientific bodies (ICH, WHO, IUPAC) and represent consensus-based best practices. Like guidances, guidelines are generally non-binding unless incorporated by reference into law or regulation.
REGULATION	A regulation (also called a rule) is a legally binding requirement enacted by a regulatory agency under authority granted by a law (statute). Regulations carry the force of law — failure to comply can result in enforcement actions, fines, product seizure, or criminal prosecution. In the US, regulations are codified in the Code of Federal Regulations (CFR). In India, regulations are issued under the Drugs and Cosmetics Act.
LAW / ACT / STATUTE	A law (Act or Statute) is legislation enacted by the legislative branch of government (Congress, Parliament). It is the highest-level regulatory instrument — all regulations, rules, and guidance must be consistent with the enabling statute. In the US: Federal Food, Drug, and Cosmetic Act (FD&C Act). In India: Drugs and Cosmetics Act, 1940.
STANDARD	A standard is a documented, established set of criteria, specifications, methods, or characteristics for a product, process, or service. Standards may be voluntary (e.g., ASTM, ISO) or compulsory when referenced in law (e.g., pharmacopoeial standards). In pharma: USP, BP, IP standards for drug quality.
DIRECTIVE	A directive is a regulatory instrument used in the EU that requires member states to achieve a particular result but allows national authorities flexibility in how to implement it. Directives must be transposed into national law. Example: EU Directive 2001/83/EC on medicinal products.
MONOGRAPH	A monograph is an official, detailed description of a drug substance or drug product, including its identity, strength, quality, purity, and testing methods. Pharmacopoeial monographs (USP, BP, IP, Ph. Eur.) are legally enforceable standards for quality. ICH Q3A/Q3B set thresholds referenced in monographs.

Extended Terminology — Regulatory Science

Term	Definition / Significance
New Drug	Any drug not previously approved for marketing in a given country; requires full regulatory review (NDA/BLA/Form 44). In India: defined under D&C Act Section 2(x) — includes new chemical entity,

	new combination, new indication, new dosage form, new route of administration
Innovator Drug	The original brand-name drug product first approved by the regulatory authority based on complete pre-clinical and clinical data; also called Reference Listed Drug (RLD) in the US
Generic Drug	A drug product that is pharmaceutically equivalent and bioequivalent to the innovator drug; approved via abbreviated pathway (ANDA/505(j)); contains the same API in same dosage form, strength, route
Biological Product	A therapeutic product derived from living organisms (proteins, antibodies, vaccines, blood products, gene therapies, cell therapies); regulated under PHSA Section 351 in the US; more complex structure than small molecules
Biosimilar	A biological product highly similar to an already-licensed reference biological product; no clinically meaningful differences in safety, purity, and potency; requires demonstration of biosimilarity
Reference Listed Drug (RLD)	The specific drug product identified by FDA as the basis for generic drug approval (ANDA); the innovator product listed in the Orange Book; ANDA applicants must demonstrate BE to the RLD
Reference Standard (RS)	The drug substance or reference material established by a pharmacopoeia or regulatory authority against which test samples are compared; primary RS and working RS
Labeling	All written, printed, or graphic matter on or accompanying a drug product; includes package insert (PI/SmPC), container labels, carton labels, patient information leaflet (PIL); regulated under 21 CFR Part 201 (US)
Prescribing Information (PI)	The official labeling for prescription drugs (Package Insert in US, SmPC in EU); contains indication, dosage, administration, contraindications, warnings, adverse reactions, pharmacology, clinical studies; must be approved by FDA
Compendium	A collection of official pharmaceutical standards (pharmacopoeia); includes USP (United States Pharmacopeia), BP (British Pharmacopoeia), IP (Indian Pharmacopoeia), Ph. Eur. (European Pharmacopoeia), JP (Japanese Pharmacopoeia)
GRAS (Generally Recognized As Safe)	US regulatory concept for food substances/excipients that are generally recognized as safe by qualified experts; exempts them from formal FDA approval; relevant for excipients in drug formulations
Breakthrough Therapy	FDA designation for drugs showing substantial improvement over existing therapies for serious conditions; expedited development and review; more frequent FDA interactions
Orphan Drug	Drug for diseases affecting fewer than 200,000 patients in the US (or fewer than 5 per 10,000 in EU); benefits: market exclusivity, tax credits, fee waivers, grants; regulated under Orphan Drug Act 1983
Over-the-Counter (OTC)	Drugs approved for direct consumer use without a prescription; marketed under FDA OTC monograph system (21 CFR Part 330) or via NDA/ANDA; defined by safe and effective use without professional supervision

Schedule H Drug (India)	Prescription-only medicines in India; require prescription from a registered medical practitioner; cannot be sold OTC; listed in Schedule H of D&C Rules 1945
Schedule X Drug (India)	Highest restriction in India for narcotic and psychotropic drugs; require special prescription and record-keeping; Schedule under D&C Rules 1945
USAN (United States Adopted Name)	Non-proprietary (generic) name assigned to a drug substance by the USAN Council; basis for INN (International Nonproprietary Name); standardized for prescribing and labeling in the US
INN (International Nonproprietary Name)	Generic name established by the WHO for drug substances; used globally; forms basis for national non-proprietary names (USAN, BAN, etc.); appears on all regulatory submissions and labeling
Drug Master File (DMF)	Confidential reference document submitted to FDA containing detailed information about facilities, processes, or materials used in drug manufacturing; reviewed only when referenced in an application (IND/NDA/ANDA)
Therapeutic Equivalence (TE)	Two drug products are therapeutically equivalent if they are pharmaceutically equivalent, bioequivalent, labeled appropriately, and manufactured per GMP; classified in FDA's Orange Book as 'A' (TE) or 'B' (not TE)

Guidance vs. Guideline vs. Regulation vs. Law — Comparison

Parameter	Guidance (FDA)	Guideline (ICH/WHO)	Regulation (CFR)	Law / Act
Issued by	FDA/CDER/CBER	ICH, WHO, EMA, IUPAC	FDA (regulatory agency)	US Congress / Parliament
Legal status	Non-binding; recommended	Non-binding; best practice	Legally binding	Legally binding; highest authority
Language used	Should, recommend, consider	Should, recommend	Shall, must, required	Shall, prohibited, required
Enforcement	Not directly enforceable	Not directly enforceable	Enforceable; violations penalized	Enforceable; criminal penalties possible
Examples	FDA Guidance for Industry	ICH Q1A, ICH E6(R2)	21 CFR Part 211 (cGMP)	FD&C Act, PHSA, Hatch-Waxman Act
How developed	Internal FDA process; public comment	Expert working group; consensus	Rulemaking (notice-and-comment)	Legislative process (Congress)
Revision process	Updated by FDA; no formal rulemaking	ICH consensus revision	Formal rulemaking (notice, comment, final)	Congressional amendment

Indian equivalent	CDSCO guidance documents	ICH guidelines (adopted)	NDCT Rules, Schedule M	Drugs & Cosmetics Act, 1940

Regulatory Language

Term in Regulation	Meaning	Context
Shall / Must	Mandatory requirement; no discretion; legally required	Regulations (21 CFR); Acts
Should	Recommended but not mandatory; deviation allowed with justification	FDA Guidance documents; ICH Guidelines
May	Permissive; an option available but not required	FDA Guidance; General explanatory text
Will	FDA's statement of what the agency intends to do	FDA Guidance; Regulatory commitments
Is encouraged to	Voluntary; strong recommendation without obligation	FDA Guidance for voluntary best practices
Current Good Manufacturing Practice (cGMP)	The 'c' stands for current — standards evolve with science; minimum required for drug manufacturing	21 CFR Parts 210/211
Premarket Approval	Regulatory review and approval required before a product can be marketed	NDA, BLA, PMA (devices)
Post-market Requirements	Obligations that continue after approval: PV reporting, PSUR, label updates, inspections	FDA post-marketing commitments
Adverse Effect / Adverse Event	Any undesirable outcome; AE = clinical trial; ADR = post-marketing; SAE = serious adverse event	ICH E2A; 21 CFR 312.32/314.81
Corrective Action Preventive Action (CAPA)	Response to identified quality/compliance deficiency; root cause analysis + actions to fix + prevent recurrence	GMP (21 CFR 211); ICH Q10

Laws and Acts — Key Pharmaceutical Legislation

Pharmaceutical laws (Acts, Statutes) are the highest-level regulatory instruments, enacted by legislatures. They define the scope of regulatory authority, establish the legal framework for drug approval and marketing, and set penalties for violations. Below are the key pharmaceutical laws in the US and India.

US Pharmaceutical Laws

FEDERAL FOOD, DRUG, AND COSMETIC ACT (FD&C ACT) — 1938

The FD&C Act is the primary US federal law governing the regulation of food, drugs, cosmetics, and medical devices. It grants the FDA the authority to regulate these products to ensure they are safe, effective, and properly labeled.

- **Enacted:** 1938 — triggered by the Elixir Sulfanilamide disaster (1937) that killed 107 people; replaced the Pure Food and Drug Act (1906)
- **Scope:** Regulates all drugs (prescription and OTC), biological products (along with PHSA), medical devices, food, cosmetics, tobacco
- **Key Provisions — Section 501:** Adulteration: defines conditions under which a drug is considered adulterated (manufactured in unsanitary conditions, not meeting pharmacopoeial standards, strength/purity differs from label claim)
- **Key Provisions — Section 502:** Misbranding: defines conditions under which a drug is considered misbranded (false/misleading labeling, inadequate directions for use, missing required information)
- **Section 505:** Requires FDA approval (NDA) for new drugs before marketing; defines 505(b)(1) full NDA, 505(b)(2) hybrid NDA, 505(j) ANDA; establishes data exclusivity
- **Section 503:** Prescription drug exemption; defines Rx vs. OTC classification
- **Section 512:** New Animal Drug Application (NADA) for veterinary drugs
- **Major Amendments:** Durham-Humphrey Amendment (1951): established Rx/OTC distinction | Kefauver-Harris Amendment (1962): added efficacy requirement for drug approval | Hatch-Waxman Act (1984): generic drugs | PDUFA (1992): user fees | FDAMA (1997) | FDASIA (2012) | DSCSA (2013): drug supply chain security

Exam Note: The FD&C Act (1938) added two revolutionary requirements: (1) Safety must be proven BEFORE marketing (pre-market approval), and (2) FDA must approve the labeling. The 1962 Kefauver-Harris Amendment added the requirement to prove EFFICACY in addition to safety.

PUBLIC HEALTH SERVICE ACT (PHSA) — 1944

- **Purpose:** Governs biological products (vaccines, blood products, gene therapies, cell therapies); requires licensure via BLA (Biologics License Application)
- **Section 351:** Primary provision for biological products: requires BLA for approval; defines biologics; grants FDA authority to inspect and license manufacturers
- **Section 352:** Misbranding of biological products

- **Biosimilars:** Biologics Price Competition and Innovation Act (BPCI Act, 2010) amended PHSA Section 351(k) to create the biosimilar approval pathway
- **Key Difference:** Biologics (PHSA) vs. Drugs (FD&C Act): biologics require BLA; small molecule drugs require NDA/ANDA; some products regulated under both

DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT — HATCH-WAXMAN ACT (1984)

The Hatch-Waxman Act is arguably the most important amendment to the FD&C Act in terms of pharma industry impact. It created the modern generic drug approval system in the US.

- **Generic Drug Pathway:** Created ANDA (Abbreviated New Drug Application) under Section 505(j); generic manufacturers can rely on innovator's safety/efficacy data; only need to demonstrate bioequivalence
- **Patent Certification System:** Paragraph I (no patent), II (expired), III (will wait), IV (invalid/not infringed) — see Unit II notes
- **180-Day Exclusivity:** First ANDA filer with Para IV certification gets 180-day generic market exclusivity
- **Patent Term Restoration:** Allows restoration of patent term lost during FDA review (up to 5 years; max 14 years remaining after approval)
- **Data Exclusivity:** 5 years for NCE; 3 years for new clinical studies (new indication/formulation); prevents ANDA submission during exclusivity period
- **Orange Book:** Required FDA to publish list of approved drugs with patent and exclusivity information — this is the Orange Book

PRESCRIPTION DRUG USER FEE ACT (PDUFA) — 1992

- **Purpose:** Authorized FDA to collect user fees from pharmaceutical industry to fund NDA/BLA review activities
- **Impact:** Significantly reduced NDA review times from average 27 months to 10-12 months; enabled FDA to hire more reviewers
- **Reauthorization:** Reauthorized every 5 years: PDUFA I (1992) → II (1997) → III (2002) → IV (2007) → V (2012) → VI (2017) → VII (2022)
- **GDUFA:** Generic Drug User Fee Amendments (GDUFA, 2012): user fees for ANDA review; reduced generic drug review times
- **BsUFA:** Biosimilar User Fee Act (BsUFA, 2012): user fees for biosimilar (351(k)) applications

BIOLOGICS PRICE COMPETITION AND INNOVATION ACT (BPCI ACT) — 2010

- **Purpose:** Created the biosimilar approval pathway under PHSA Section 351(k); analogous to Hatch-Waxman for biologics
- **Biosimilar:** Highly similar to reference biologic with no clinically meaningful differences in safety, purity, potency

- **Interchangeable Biosimilar:** May be substituted for reference product without prescriber intervention; highest standard of biosimilarity
- **Exclusivity:** 12-year market exclusivity for the reference biologic; 4-year data exclusivity; 1-year exclusivity for first interchangeable biosimilar
- **Purple Book:** Requires FDA to maintain the Purple Book listing all licensed biological products and their biosimilar status

OTHER IMPORTANT US PHARMACEUTICAL LAWS

Act / Law	Year	Key Provision
Food and Drug Administration Safety and Innovation Act (FDASIA)	2012	Breakthrough therapy designation; generic drug user fees (GDUFA); biosimilar fees (BsUFA); pediatric drug safety; accelerated approval pathways
Orphan Drug Act	1983	Incentives for rare disease drugs: 7-year market exclusivity, tax credits (50% on clinical trial costs), waiver of NDA user fees, FDA grants for orphan drug development
Drug Quality and Security Act (DQSA) / DSCSA	2013	Drug Supply Chain Security Act: track-and-trace for prescription drugs; electronic drug pedigrees; serialization requirements; compounding pharmacy regulations
21st Century Cures Act	2016	Accelerates medical product development: expanded use of real-world evidence; pediatric drug development; regenerative medicine designation; NIH funding
Food and Drug Administration Amendments Act (FDAAA)	2007	REMS (Risk Evaluation and Mitigation Strategy) authority; required post-market safety studies; clinical trial registration (ClinicalTrials.gov); sentinel system
Durham-Humphrey Amendment	1951	Established the distinction between prescription (Rx) and over-the-counter (OTC) drugs; defined drugs that must be dispensed only by prescription
Kefauver-Harris Drug Amendments	1962	Required drug manufacturers to prove EFFICACY (in addition to safety) before marketing; triggered by thalidomide tragedy in Europe; required adequate and well-controlled studies
Pure Food and Drug Act	1906	First major US food and drug legislation; prohibited adulteration and misbranding of food and drugs; predecessor to FD&C Act; lacked pre-market approval requirement

Indian Pharmaceutical Laws

Act / Rule	Year	Key Provision
Drugs and Cosmetics Act (D&C Act)	1940	Primary legislation governing import, manufacture, distribution, and sale of drugs and cosmetics in India; Schedule M (GMP), Schedule H (Rx drugs), Schedule X (narcotic drugs); enforced by CDSCO (central) and SLAs (state)

New Drugs and Clinical Trials Rules (NDCT Rules)	2019	Replaced Schedule Y; governs clinical trials, bioequivalence studies, new drug approvals, ethics committees; introduced compensation for trial-related injury; strengthened EC oversight
Drugs and Magic Remedies (Objectionable Advertisements) Act	1954	Prohibits advertisements making claims of curing certain serious diseases; defines prohibited drugs for advertising
Narcotic Drugs and Psychotropic Substances Act (NDPS Act)	1985	Controls manufacture, sale, import, export of narcotic drugs and psychotropic substances; harsh penalties for trafficking
Pharmacy Act	1948	Regulates the pharmacy profession; requires registration to practice pharmacy; establishes State Pharmacy Councils and Pharmacy Council of India (PCI)
Medical Devices Rules	2017	Separate regulatory framework for medical devices in India; classifies devices (Class A-D); registration with CDSCO; replaces previous D&C Rules provisions for devices
Drugs (Prices Control) Order (DPCO)	2013	Price control for essential medicines listed in NLEM (National List of Essential Medicines); administered by NPPA (National Pharmaceutical Pricing Authority)
Indian Patent Act	1970 (amended 2005)	Patent protection for drugs; Section 3(d) prevents evergreening of patents; product patents for pharmaceuticals reinstated in 2005 per TRIPS compliance; 20-year patent term from filing

Orange Book

The Orange Book is the common name for the FDA publication titled 'Approved Drug Products with Therapeutic Equivalence Evaluations'. It is one of the most important reference publications in pharmaceutical regulation, serving as the authoritative source for information about FDA-approved drug products and their therapeutic equivalence ratings.

ORANGE BOOK — FDA Approved Drug Products with Therapeutic Equivalence Evaluations
Official Title: Approved Drug Products with Therapeutic Equivalence Evaluations (commonly called the Orange Book due to the color of its original printed cover)
Published by: FDA / CDER (Center for Drug Evaluation and Research)
First Published: 1980 (originally as a printed book; now available electronically at FDA website: orangebook.fda.gov and via FDA's Electronic Orange Book downloadable database)
Legal Basis: Hatch-Waxman Act (1984) mandated FDA to publish the list of approved drugs with patent and exclusivity information to facilitate generic drug development
Primary Purpose: Provides a listing of approved drug products with therapeutic equivalence evaluations to assist states, prescribers, and pharmacists in identifying interchangeable drug products
Updated: Daily (electronic version at orangebook.fda.gov); printed edition published annually

Users: Generic drug manufacturers (ANDA applicants), state boards of pharmacy, prescribers, pharmacists, patent attorneys, health insurers, PBMs (pharmacy benefit managers)

Contents of the Orange Book

Section / Content	Description
Part I — Approved Prescription Drug Products	Listed drug products approved by FDA under Section 505 of FD&C Act; organized by active ingredient; includes: proprietary name, applicant name, strength, dosage form, route of administration, approval date, application number (NDA/ANDA number)
Part II — Approved OTC Drug Products	OTC drug products approved via NDA (not OTC monograph products); same information as prescription drug products
Part III — Drug Products with Approval under Section 505 of the Act Administered by Center for Biologics Evaluation and Research (CBER)	Biological products that were originally approved as drugs but transferred to CBER; includes certain insulin products, interferon products
Patent Listings	Every active patent for the approved drug product; patent number, expiration date, patent type (drug substance, drug product, method of use); listed in the Orange Book by the NDA holder
Exclusivity Listings	All periods of market exclusivity granted (NCE exclusivity 5 years, new clinical study exclusivity 3 years, pediatric exclusivity 6 months, orphan drug exclusivity 7 years, competitive generic therapy exclusivity 180 days)
Therapeutic Equivalence (TE) Codes	Alpha-numeric codes indicating whether drug products are therapeutically equivalent to each other; the most important and widely used feature of the Orange Book
Discontinued Drug Products	Products that were approved but have since been withdrawn from the US market for reasons other than safety or efficacy (not a 'market withdrawal')

Therapeutic Equivalence (TE) Evaluation System

The central feature of the Orange Book is the Therapeutic Equivalence rating system. FDA assigns a two-letter code to each drug product to indicate its therapeutic equivalence status.

> *Drug products are considered therapeutically equivalent if they are: (1) pharmaceutically equivalent, (2) bioequivalent, (3) labeled appropriately, and (4) manufactured per cGMP. ONLY A-rated products can be freely substituted for each other.*

'A' Rating — Therapeutically Equivalent

Products rated 'A' are considered therapeutically equivalent to other pharmaceutically equivalent products and can be freely substituted. Sub-codes indicate the dosage form or additional characteristics:

A-Code	Dosage Form / Situation	Meaning
AA	Conventional dosage forms (no known equivalence problems)	Oral tablets, capsules, solutions — no documented or potential BE problems; no prior history of problems
AB	Products meeting necessary bioequivalence requirements	Most common 'A' code; generic products that demonstrated in vivo or in vitro bioequivalence per FDA standards; freely substitutable
AN	Solutions and powders for aerosolization	Inhalation solutions; may not require in vivo BE if chemical and physical properties match
AO	Injectable oil solutions	Therapeutically equivalent if same composition, container, labeling
AP	Injectable aqueous solutions	Aqueous injections meeting BE standards
AT	Topical products	Creams, ointments, gels meeting BE standards (in vitro release testing or clinical endpoint studies)
AB1, AB2, AB3	Multiple source drugs requiring separate in vivo BE studies	Multiple ANDA filers for same reference product where each group demonstrates BE separately

'B' Rating — NOT Therapeutically Equivalent

Products rated 'B' are NOT considered therapeutically equivalent to other similarly rated products. They should not be freely substituted. Pharmacists and prescribers must be aware that B-rated products may not produce the same clinical effect.

B-Code	Situation	Examples
BC	Extended-release (ER) oral dosage forms	Extended-release tablets/capsules where different ER mechanisms may produce different release profiles; full BE studies required
BD	Active ingredients with documented BE problems	Drug substances with known history of bioavailability problems (e.g., digoxin, phenytoin, warfarin, carbamazepine)
BE	Delayed-release oral dosage forms	Enteric-coated products; pH-dependent release; complex BE evaluation required
BN	Aerosols and nebulizers; spacers	Inhalation products requiring clinical endpoint study or in vitro equivalence data
BP	Active ingredients with potential BE problems	Drugs with narrow therapeutic index where variations in BE could have clinical consequences
BR	Suppositories and enemas	Complex local and systemic absorption; BE standards not clearly established
BS	Drug products with standard of identity concerns	Products where differences in formulation or processing may affect safety/efficacy

BT	Topical products with known or potential BE problems	Topicals where systemic absorption or local site concentration may vary significantly
BX	Insufficient data to determine TE	Products where FDA cannot make a TE determination due to insufficient data

Key Exam Tip: TE code starting with 'A' = can be substituted (therapeutically equivalent). TE code starting with 'B' = cannot be substituted (not therapeutically equivalent). The second letter specifies the dosage form or situation. 'AB' is the most common generic drug code.

Patent Listings in the Orange Book

NDA holders are required to list all applicable patents in the Orange Book within 30 days of NDA approval (or within 30 days of patent issuance after approval). The patent listing rules are specified in 21 CFR 314.53.

- Types of listable patents: Drug substance patents (composition of matter), Drug product patents (formulation, delivery system), Method of use patents (specific approved indication)
- Non-listable patents: Process patents, Packaging patents, Metabolite patents, Intermediate patents
- Consequences: Listed patents trigger the Paragraph certification requirement for ANDA filers; Para IV certification triggers the 30-month stay of ANDA approval
- 30-Month Stay: When NDA holder sues ANDA filer within 45 days of receiving Para IV notice, FDA cannot approve ANDA for 30 months (or until court decision, whichever comes first)
- Patent delisting: If a patent is found invalid by a court, it may be removed from Orange Book; FDA may delist patents that are listed incorrectly

Exclusivity Listings in the Orange Book

Exclusivity Type	Duration	Criteria
New Chemical Entity (NCE) Exclusivity	5 years from approval of NDA	NDA contains no previously approved active moiety; prevents ANDA/505(b)(2) submission (except Para IV at 4 years)
New Clinical Study (NCS) Exclusivity	3 years from approval	New clinical investigations essential to approval; for new indications, formulations, combinations, dosing regimens
Pediatric Exclusivity	Additional 6 months added to existing exclusivity	Sponsor conducts pediatric studies per FDA Written Request; added to existing patent/exclusivity period
Orphan Drug Exclusivity	7 years from approval	Drug approved for orphan indication; FDA cannot approve same drug for same disease during exclusivity period

Competitive Generic Therapy (CGT) Exclusivity	180 days	First ANDA applicant for CGT-designated drug with no more than one ANDA on file; incentivizes generic entry for drugs with limited competition
Innovator's 12-Year Biologics Exclusivity	12 years from approval of reference biologic	Reference biological product exclusivity under BPCI Act; prevents biosimilar approval during this period (4-year data exclusivity period within the 12 years)
First Interchangeable Biosimilar Exclusivity	1 year (from first commercial marketing)	First interchangeable biosimilar approved; others cannot be approved as interchangeable during this period

Using the Orange Book — Practical Application

1. Go to orangebook.fda.gov or FDA's searchable database
2. Search by: Active ingredient, Proprietary name, Applicant name, or Application number
3. Identify the Reference Listed Drug (RLD) — basis for ANDA submissions
4. Check TE codes — 'A' products are interchangeable; 'B' products are not
5. Review patent listings — determine Paragraph certification needed for ANDA
6. Check exclusivity expiry dates — determine earliest ANDA submission date
7. In retail pharmacy: used by pharmacists for generic substitution per state laws; 'A' rated generics can be substituted for brand-name drugs

State Pharmacy Laws: Most US states have drug product substitution laws that allow (or require) pharmacists to substitute a generically equivalent (A-rated) product for a brand-name prescription. Some states require patient notification; a few states allow prescribers to block substitution by writing 'Brand Medically Necessary' or equivalent.

Federal Register

The Federal Register (FR) is the official daily journal of the United States Federal Government. It is published by the Office of the Federal Register, National Archives and Records Administration (NARA). The Federal Register serves as the primary legal vehicle through which the US government communicates its regulatory actions, proposed rules, final rules, notices, and presidential documents to the public.

THE FEDERAL REGISTER (FR)
Official Definition: The official daily publication for rules, proposed rules, and notices of federal agencies and organizations, as well as executive orders and other presidential documents
Published by: Office of the Federal Register (OFR), National Archives and Records Administration (NARA)
Publication Frequency: Every federal business day (Monday through Friday, excluding federal holidays); published since March 14, 1936
Online Access: Available free at federalregister.gov and govinfo.gov; full text searchable from 1994 onwards; older editions scanned
Legal Significance: Final rules published in the Federal Register have the force of law when they become effective; the FR serves as constructive notice to the public of regulatory requirements
Format: Each daily issue contains: Table of Contents, Full text of documents, Preambles explaining rule rationale, CFR parts affected, Effective dates, Comment periods
Volume / Citation: Cited as: Volume Number FR Page Number (Date) — e.g., 88 FR 12345 (March 1, 2023)
FDA Relevance: FDA uses the FR to publish: proposed rules, final rules, guidance documents, drug approval notices, safety alerts, public meeting announcements, grant/contract notices, import alerts, warning letters (via notice)

Types of Documents Published in the Federal Register

Document Type	Published in FR?	Description / Examples
Proposed Rules (NPRM)	Yes	Notice of Proposed Rulemaking; FDA's proposed changes to regulations (21 CFR); public comment period (usually 60-90 days); includes preamble explaining rationale
Final Rules	Yes	Regulations that have gone through notice-and-comment rulemaking; legally binding upon effective date; codified in CFR; example: 'Requirements for Foreign Supplier Verification Programs' final rule
Interim Final Rules	Yes	Final rules that take immediate effect due to urgency but still seek public comment post-publication; used for emergency situations
Notices	Yes	Non-rulemaking announcements: FDA public meetings, availability of guidance documents, data call-ins, user fee

		rates, import alerts, product approvals, drug shortage notices
Advance Notices (ANPRM)	Yes	Advance Notice of Proposed Rulemaking; FDA exploring a topic before formal rulemaking; seeks early public input; no binding obligations
Presidential Documents	Yes	Executive orders, presidential proclamations, presidential memoranda; may direct FDA to take specific regulatory actions
Agency Guidance Notices	Yes	Notice of availability of FDA guidance documents; the actual guidance is not published in FR but available on FDA website; FR notice initiates comment period
Corrections	Yes	Corrections to previously published rules or notices; may affect regulatory requirements if the original was incorrect

Federal Register Rulemaking Process

The Administrative Procedure Act (APA, 1946) requires federal agencies, including FDA, to follow a formal notice-and-comment rulemaking process for most regulations:

- ANPRM (Advance Notice of Proposed Rulemaking): Optional early public input on regulatory concepts — published in FR
- NPRM (Notice of Proposed Rulemaking): Proposed rule published in FR with: preamble, proposed regulatory text, economic impact analysis, request for public comments, comment period (usually 60-90 days)
- Public Comment Period: Any person (individual, company, organization) can submit comments; FDA must consider all significant comments
- FDA Review of Comments: FDA reviews, categorizes, and responds to all comments; may modify the proposed rule based on comments
- Final Rule: Published in FR with: preamble responding to comments, final regulatory text, effective date (usually 30-60 days after publication); codified in CFR
- Effective Date: The rule becomes law on the effective date; companies must comply by the compliance date (may differ from effective date)
- Challenges: Final rules can be challenged in federal court on procedural or substantive grounds

Important: FDA can bypass formal rulemaking for 'guidance documents' — these do not need to go through the Federal Register notice-and-comment process (though FDA often publishes them in the FR for public comment as a matter of good practice). Only regulations (rules) require formal FR rulemaking.

Federal Register vs. Code of Federal Regulations (CFR)

Feature	Federal Register (FR)	Code of Federal Regulations (CFR)
Nature	Daily journal; records all regulatory actions as they occur	Codified, organized compilation of regulations currently in force

Format	Chronological; includes preambles, history, context, and full text of new/proposed/final rules	Organized by Title, Chapter, Part, Section; only contains current regulatory text
Legal Status	Final rules published in FR are legally binding; proposed rules are not binding	Contains only binding, in-force regulations; authoritative legal text
Frequency	Published every business day	Updated annually; Title 21 (FDA) updated April 1 each year
How to use	Search FR to understand WHY a regulation was written; find recent changes; find proposed rules	Search CFR to find WHAT the current regulatory requirement is; cite CFR for compliance purposes
Example	88 FR 12345 (March 1, 2023) — cites a specific Federal Register publication	21 CFR 314.50 — cites a specific regulation in Code of Federal Regulations
Online access	federalregister.gov; govinfo.gov	ecfr.gov (Electronic Code of Federal Regulations); govinfo.gov

Code of Federal Regulations (CFR)

The Code of Federal Regulations (CFR) is the official codification of all general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the US Federal Government. It represents the current, in-force body of federal regulatory law. For pharmaceutical professionals, Title 21 of the CFR (21 CFR) is the most important section, as it contains all FDA regulations.

CODE OF FEDERAL REGULATIONS (CFR)
Definition: The codification of the general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the US Federal Government
Published by: Office of the Federal Register (OFR), National Archives and Records Administration (NARA)
Updated: Annually; divided into quarters: Titles 1-16 (January 1), Titles 17-27 (April 1), Titles 28-41 (July 1), Titles 42-50 (October 1). Title 21 (FDA) updated April 1
Organization: 50 Titles → Chapters (agency) → Parts (subjects) → Sections (specific requirements); cited as 'X CFR Y.Z' where X=Title, Y=Part, Z=Section
Online Access: Electronic Code of Federal Regulations (eCFR) at ecfr.gov — real-time, unofficial, always current; Official CFR at govinfo.gov — annual edition, official legal text
Legal Authority: Binding law; failure to comply = legal violation; subject to enforcement actions (Warning Letters, 483s, import alerts, seizure, injunction, prosecution)
Title 21: Food and Drugs — FDA's entire regulatory framework; most relevant Title for pharmaceutical professionals; contains GMP, NDA/ANDA, labeling, clinical trial regulations, biologics, medical devices
Citation Format: 21 CFR Part 211 Section 110 = 21 CFR 211.110 = Section 110 of Part 211 of Title 21

Structure of the CFR

Level	Name	Example
Title	Broad subject area (50 titles in CFR)	Title 21 = Food and Drugs (FDA); Title 42 = Public Health; Title 45 = Public Welfare (human research subjects)
Chapter	Issuing agency within the Title	Chapter I = FDA; Chapter II = DEA (Drug Enforcement Administration); Chapter III = ONDCP
Part	Specific regulatory subject area	Part 210 = cGMP for finished pharmaceuticals (general); Part 211 = cGMP for finished pharmaceuticals (specific); Part 314 = NDA/ANDA
Section	Specific regulatory requirement within a Part	Section 211.22 = responsibilities of QC unit; 211.68 = automatic, mechanical, electronic equipment; 314.50 = NDA content and format
Paragraph	Specific provision within a section	211.22(a), (b), (c), (d) — specific GMP requirements for QC

Parts of Title 21 CFR — Pharmaceutical Relevance

TITLE 21 CFR — KEY PARTS FOR PHARMACY STUDENTS

21 CFR Part	Subject	Key Requirements
Part 11	Electronic Records and Electronic Signatures	Requirements for electronic records/signatures to be equivalent to paper; audit trails; system validation; user authentication; applicable to all FDA-regulated computer systems
Part 50	Protection of Human Subjects	Informed consent requirements for clinical trials; elements of informed consent (21 CFR 50.25); documentation; exceptions for emergency research
Part 54	Financial Disclosure by Clinical Investigators	Financial disclosure and certification requirements for clinical investigators; conflicts of interest disclosure in NDAs/ANDAs
Part 56	Institutional Review Boards (IRBs)	IRB composition, functions, operations, record-keeping, reporting requirements; membership requirements; quorum; types of review; FDA audit authority over IRBs
Part 58	Good Laboratory Practice (GLP)	GLP regulations for non-clinical laboratory studies supporting NDA/IND submissions; facilities, equipment, personnel, SOPs, records
Part 101	Food Labeling	Food labeling requirements; nutrition facts; allergen labeling; health claims; structure/function claims
Part 201	Drug Labeling	General drug labeling regulations; physician labeling (package insert/PI) requirements; OTC labeling; container/closure labeling; pregnancy/lactation labeling
Part 202	Prescription Drug Advertising	Regulations for direct-to-consumer (DTC) advertising and professional advertising; brief summary requirements; fair balance
Part 210	Current GMP — General	General cGMP regulations for all finished pharmaceuticals; establishes minimum standards; definitions
Part 211	Current GMP — Finished Pharmaceuticals	Detailed cGMP requirements: organization and personnel, buildings and facilities, equipment, control of components/containers, production and process controls, laboratory controls, records and reports, returned and salvaged drug products
Part 312	Investigational New Drug Application (IND)	IND requirements: content, format, submission; sponsor/investigator responsibilities; safety reporting (SAE/SUSAR); IND exemptions; clinical holds
Part 314	Applications for FDA Approval to Market a New Drug	NDA/ANDA/505(b)(2) content, format, submission; bioequivalence; patent certifications;

		supplements; post-approval changes; labeling; user fees
Part 320	Bioavailability and Bioequivalence Requirements	BA/BE requirements for oral dosage forms; study design; statistical criteria (90% CI, 80-125%); waivers; in vivo BE studies
Part 330	OTC Human Drug Products	OTC drug monograph system; safety and efficacy conditions for OTC marketing; labeling requirements; new OTC drug applications
Part 600-680	Biological Products	BLA requirements; GMP for biologics; labeling; post-approval changes; testing and release requirements for vaccines, blood products, cell/gene therapies
Part 803	Medical Device Reporting	MDR (Medical Device Report) requirements; reporting of device-related deaths, serious injuries, and malfunctions
Part 820	Quality System Regulation (QSR) / Quality Management System	cGMP for medical devices; design controls, CAPA, document controls, records; applicable to device manufacturers

Important 21 CFR Sections — cGMP (Part 211)

21 CFR Part 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals) is one of the most frequently cited and inspected CFR parts. Key sections:

21 CFR Section	Requirement
211.22	Responsibilities of quality control unit (QC); QC independent authority to approve/reject; final release authority
211.42	Design and construction features of buildings; adequate space, lighting, ventilation, sanitation; prevention of mix-ups
211.68	Automatic, mechanical, and electronic equipment; validation; qualification; audit trails; backup of computer-controlled systems
211.84	Testing and approval or rejection of components, drug product containers, and closures; specifications; sampling; identity testing of each container
211.100	Written procedures (SOPs) required for production and process controls; deviations from procedures must be recorded and justified
211.110	Sampling and testing of in-process materials and drug products; in-process specifications; process validation
211.165	Testing and release for distribution; final product testing; specifications must include tests for identity, strength, quality, purity
211.180	General requirements for records and reports; retention period (1 year after expiry or 3 years after distribution, whichever is longer)
211.192	Production record review; full review before batch release; investigations of discrepancies
211.198	Complaint files; written procedures for handling complaints; investigation of drug product defects

eCFR — Electronic Code of Federal Regulations

- The eCFR (ecfr.gov) is an unofficial, but currently updated, online version of the CFR maintained by the Office of the Federal Register
- eCFR is updated on a rolling basis as final rules are published in the Federal Register — more current than the annual print CFR
- Provides full text search, cross-references, and link to Federal Register history of each section
- eCFR is NOT the official legal text — for official citations, use govinfo.gov (official CFR edition)
- For practical compliance purposes, eCFR is preferred as it reflects the most current requirements

Purple Book

The Purple Book is the common name for the FDA database titled 'Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations'. It is the biological product equivalent of the Orange Book, serving as the authoritative reference for licensed biological products and their biosimilar/interchangeable status.

PURPLE BOOK — Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations
Official Title: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations
Published by: FDA / CDER (Center for Drug Evaluation and Research) — also covers some CBER-regulated biologics
Legal Basis: Biologics Price Competition and Innovation Act (BPCI Act, 2010) amended PHSA Section 351(k); required FDA to publish lists of biological products and their biosimilar/interchangeable status
First Published: 2014 (as a searchable list on FDA website); significantly expanded and improved over subsequent years
Online Access: Purple Book online database at fda.gov/drugs/biosimilars/purple-book-lists-licensed-biological-products; searchable by brand name, active ingredient, manufacturer
Updated: Regularly updated as new biological products are approved, biosimilarity/interchangeability designations are granted, and exclusivity periods change
Primary Users: Biosimilar developers (351(k) applicants), prescribers, pharmacists, payers (insurance companies), biosimilar policy analysts, investors

Why the Purple Book? — Background

Before the BPCI Act (2010), there was no abbreviated approval pathway for biological products. Each biosimilar had to be approved via a full BLA (with complete clinical data), as the Hatch-Waxman ANDA pathway applied only to small molecule drugs. The BPCI Act created the 351(k) biosimilar pathway under PHSA, and mandated FDA to maintain the Purple Book as a companion reference to the Orange Book for biologics.

- **Key Need:** Biological products are complex; unlike small molecules where bioequivalence is relatively straightforward, biosimilarity requires extensive structural, functional, and clinical data to demonstrate no clinically meaningful differences
- **Interchangeability Standard:** Higher than biosimilarity; requires proof that the product can be substituted for the reference product without increasing safety risks; can be substituted by pharmacist without prescriber intervention
- **Purple Book vs. Orange Book:** Orange Book covers small molecule drugs (FD&C Act Section 505); Purple Book covers biological products (PHSA Section 351); both serve analogous functions for their respective product categories

Contents of the Purple Book

Section / Content	Description
Reference Biological Products	All reference biological products (originator biologics) licensed under PHSA Section 351(a); includes: proprietary name, active ingredient (proper name), dosage form, route of administration, manufacturer, application number (BLA number), license date
Biosimilar Products	Biological products approved as biosimilar under 351(k); each biosimilar is linked to its reference product; includes: proprietary name, proper name, manufacturer, BLA number, approval date, reference product identified
Interchangeable Products	Biosimilars that have been additionally designated as interchangeable with their reference product; can be substituted by pharmacist without prescriber intervention; first interchangeable biosimilar also gets 1-year exclusivity
Reference Product Exclusivity Dates	12-year market exclusivity for reference biological products (BPCI Act); 4-year data exclusivity (no 351(k) application can be submitted during first 4 years); dates listed for each reference product
Biosimilarity Status	Whether FDA has determined the product is biosimilar (no clinically meaningful differences in safety, purity, potency) — the basic 351(k) approval standard
Interchangeability Status	Whether FDA has determined additional standard of interchangeability (can be substituted without increased risks); state laws govern pharmacist substitution of interchangeable biologics
Application Numbers	BLA numbers for reference products (original BLA under 351(a)) and biosimilars (abbreviated BLA under 351(k)); useful for cross-referencing FDA approval letters and product labeling
Transition Products	Small molecule drugs that were previously approved under FD&C Act Section 505 but were reclassified as biological products under PHSA Section 351 (e.g., insulin, glucagon, certain other products transitioned March 23, 2020)

Orange Book vs. Purple Book — Comparison

Parameter	Orange Book	Purple Book
Covers	Small molecule drugs (FD&C Act Section 505 NDAs/ANDAs)	Biological products (PHSA Section 351(a)/(k) BLAs)
Legal Basis	Hatch-Waxman Act (1984); 21 CFR 314.53	BPCI Act (2010); PHSA Section 351

Approval pathway	NDA (innovator), ANDA (generic)	BLA (reference biologic), 351(k) (biosimilar)
Equivalence concept	Therapeutic Equivalence (TE) — A and B codes	Biosimilarity and Interchangeability — higher standards
Substitution standard	A-rated generics can be freely substituted	Only 'Interchangeable' biosimilars can be substituted by pharmacist
Exclusivity for reference product	5 years (NCE) or 3 years (NCS)	12 years market exclusivity; 4 years data exclusivity
Exclusivity for first generic/biosimilar	180 days (first Para IV ANDA filer)	1 year for first interchangeable biosimilar
Patent listing	NDA holder lists patents; triggers para IV process	No direct patent listing in Purple Book (no Orange Book equivalent for biologics)
TE Rating system	A/B codes with sub-codes (AA, AB, BC, etc.)	Biosimilar or Interchangeable designation (no A/B codes)
Practical use	Pharmacist substitution decisions; ANDA planning	Prescriber/pharmacist biosimilar substitution decisions; 351(k) planning

Interchangeable Biological Products —Concept

Interchangeability is a higher regulatory standard that goes beyond biosimilarity. The FDA must determine that an interchangeable biosimilar:

- Is biosimilar to the reference product, AND
- Can be expected to produce the same clinical result as the reference product in any given patient, AND
- For a biologic that is administered more than once to an individual: the risk of alternating between the biosimilar and the reference product is not greater than the risk of using the reference product without such alternation

State Laws on Biosimilar Substitution: Most US states have enacted laws allowing pharmacists to substitute interchangeable biosimilars for reference biologics (similar to generic substitution for small molecules). These laws typically require: use of the Purple Book to verify interchangeability, patient notification within specified time frame, prescriber may prohibit substitution.

Biological Product Proper Naming Convention

FDA requires a unique nonproprietary naming convention for biological products to facilitate pharmacovigilance and accurate prescribing:

- Reference biologics: Core name + 4-letter suffix (e.g., adalimumab-atto; where 'adalimumab' is the INN/core name and '-atto' is the FDA-assigned 4-letter suffix)
- Biosimilars: Same core name + different 4-letter suffix (e.g., adalimumab-adbm for Cyltezo, a biosimilar of adalimumab/Humira)
- Interchangeable biosimilars: Same naming convention as other biosimilars; interchangeability is denoted in the Purple Book database, NOT in the name itself

- Purpose: Distinguishes between different versions of the same biologic; enables accurate tracking of adverse events to specific products; facilitates pharmacovigilance signal detection
- Example: Humira (adalimumab, ref.) has biosimilars including Hyrimoz (adalimumab-adaz), Hadlima (adalimumab-bwwd), Cyltezo (adalimumab-adbm — interchangeable)

— Best Of Luck For Your Exam —

—PHARMACEUTICAL REGULATORY SCIENCE —

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