Unit-3

Industrial Pharmacy 2

B.Pharma 7 Sem Notes

Unit: 3

Regulatory affairs:

- Introduction, Historical overview of Regulatory Affairs, Regulatory authorities, Role of Regulatory affairs department, Responsibility of Regulatory Affairs Professionals

Regulatory requirements for drug approval:

- Drug Development Teams, Non-Clinical Drug Development, Pharmacology, Drug Metabolism and Toxicology, General considerations of Investigational New Drug (IND) Application, Investigator's Brochure (IB) and New Drug Application (NDA), Clinical research / BE studies, Clinical Research Protocols, Biostatistics in Pharmaceutical Product Development, Data Presentation for FDA Submissions, Management of Clinical Studies.

REGULATORY AFFAIRS

Introduction to Regulatory Affairs

- Regulatory Affairs (RA), also called Government Affairs, is a profession developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, foods, cosmetics, and complementary medicines.
- As a discipline, regulatory affairs covers a broad range of specific skills and occupations. It is composed of a group of people who act as a liaison between the government, industry, and consumers to make sure that marketed products are safe and effective when used as advertised.
- Pharmaceutical Drug Regulatory Affairs (DRA) is a dynamic field that includes scientific, legal and commercial aspects of drug development. Every drug before getting market approval must undergo rigorous scrutiny and clinical trials to ensure its safety, efficacy and quality.

Areas Covered Under Drug Regulation

Non-Clinical & Clinical	Drug development guidelines for pre-clinical and clinical studies
Licensing (Patent)	Intellectual property protection for new drug entities
Drug Registration	Formal registration with regulatory authorities
Manufacturing	GMP compliance and quality standards for production
Quality & Safety	Guidance on quality systems and product safety
Pricing & Trademark	Market pricing policies and brand protection
Marketing & Distribution	Import, export and distribution regulations
Pharmacovigilance	Adverse Drug Reaction (ADR) monitoring post-market

📌 **NOTE:** *DRA bridges GOVERNMENT (regulators), INDUSTRY (regulated), and CONSUMERS (market) — ensuring safe and effective products reach patients while keeping unsafe products off the market.*

Historical Overview of Regulatory Affairs

The regulatory framework has evolved over a century, primarily driven by public health disasters that revealed the urgent need for stronger oversight. Key milestones include:

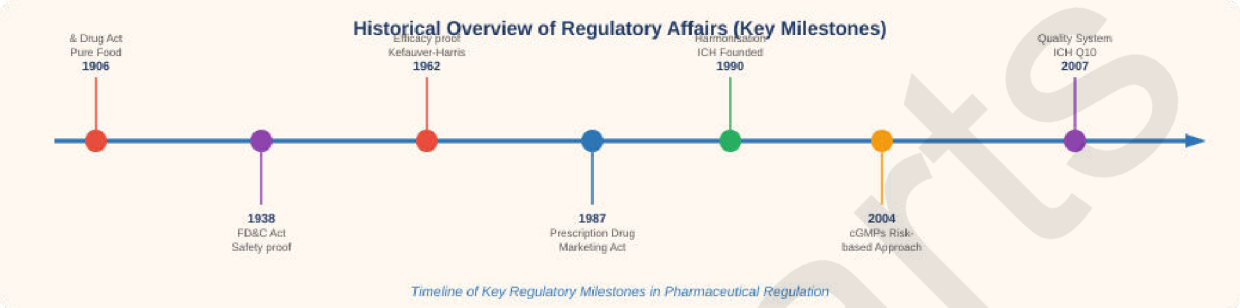

Figure 1: Historical Timeline of Key Regulatory Milestones

1906	Pure Food and Drug Act — First federal law; prevented false claims about drugs
1930	FDA takes its current name; becomes purely regulatory (no research functions)
1938	Federal Food, Drug, and Cosmetic (FD&C) Act — Required proof of safety before marketing (after Sulfanilamide disaster killing 107)
1949	First publication of FDA 'Guidance to Industry' — addressing toxic chemicals in foods
1962	Kefauver-Harris Drug Amendments — Required proof of BOTH safety AND efficacy before marketing (following Thalidomide disaster)
1987	Prescription Drug Marketing Act — Ensured products are safe, effective, and free from counterfeit or adulterated drugs
1990	ICH (International Council for Harmonisation) founded — US, Europe, Japan unite to harmonise pharmaceutical regulations
2004	Pharmaceutical cGMPs for the 21st Century — Risk-based approaches to development and manufacturing
2004	PAT (Process Analytical Technology) Framework — Data acquisition and multivariate analysis as important tools

2005	ICH Q8 (Pharmaceutical Development) — Quality by Design (QbD); design space concept
2005	ICH Q9 (Quality Risk Management) — Quality risk management tools in all phases of product lifecycle
2007	ICH Q10 (Pharmaceutical Quality System) — Science- and risk-based regulatory approaches

Regulatory Authorities

Public health being the prime concern, drugs available for human/veterinary use and medical devices must be both effective and safe for the intended use. Various territorial regulatory bodies were established to ensure this.

Major Global Regulatory Authorities

WHO	World Health Organization — Sets international standards; prequalifies medicines for global procurement
USFDA (USA)	United States Food and Drug Administration — CDER, CBER divisions for drugs and biologics
EMA (EU)	European Medicines Agency — Centralized procedure covering all EU member states
MHRA (UK)	Medicines and Healthcare Products Regulatory Agency — Post-Brexit independent authority
TGA (Australia)	Therapeutic Goods Administration — Manages the Australian Register of Therapeutic Goods (ARTG)
Health Canada	Regulates therapeutic products under the Food and Drugs Act
PMDA (Japan)	Pharmaceuticals and Medical Devices Agency — Rigorous post-market safety surveillance
CDSCO (India)	Central Drugs Standard Control Organisation — Under Ministry of Health; controls import/manufacture

ICH — International Council for Harmonisation

The ICH was founded in 1990 by united efforts of the United States, Europe and Japan to bring together different regulatory bodies globally and set ICH

Guidelines for pharmaceutical drug product development. ICH Guidelines are broadly categorised as:

Q Guidelines	Quality — CMC, stability, analytical procedures (Q1–Q14)
S Guidelines	Safety — Non-clinical safety studies, genotoxicity, carcinogenicity (S1–S12)
E Guidelines	Efficacy — Clinical trials, GCP, statistics, special populations (E1–E20)
M Guidelines	Multidisciplinary — CTD format, non-clinical/clinical timing (M1–M14)

📌 **NOTE:** *Although ICH has harmonised drug regulatory aspects worldwide, the regional regulatory bodies continue to play a pivotal role in drug approvals across their respective territories.*

Role of the Drug Regulatory Affairs Department

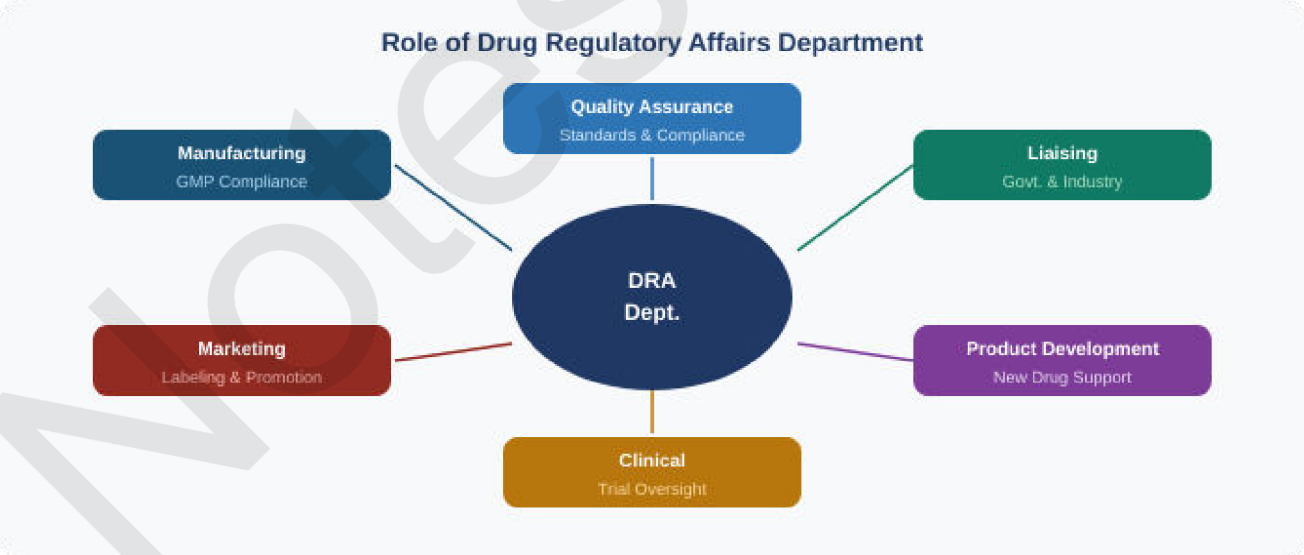

Figure 2: Various Roles of the Drug Regulatory Affairs Department

A) In Development Phase

- Ensuring that all legislative requirements are met

- Recruiting scientific advice from regulatory authorities on development studies to demonstrate safety, quality and efficacy
- Setting up regulatory strategy for the drug candidate
- Participating in cross-functional project teams
- Ensuring application of guidelines for clinical trials
- Submission of application to conduct clinical trials (IND/CTA filing)
- Managing the regulatory submission — minimize time to market; advise on global development plan
- Optimizing submission strategies — dossier preparation, format, document re-use, electronic submissions
- Reviewing high-level documents and reports
- Interacting with the commercial side of business such as pricing and reimbursement

B) In Approval Phase

- Checking progress of evaluation and anticipating questions from regulators
- Clarifying raised questions, planning response and strategies with other departments
- Planning and managing agency meetings and hearings
- Negotiating approval and Product Information (labeling) with regulatory agencies

C) In Post-Approval Phase

- Compliance monitoring and ensuring ongoing GMP/GCP adherence
- Submission of variations/amendments to approved applications
- License renewals and annual reports
- Pharmacovigilance — monitoring adverse drug reactions (ADRs)
- Product information review and labeling updates
- Support for new indications and new formulations

- Regulatory intelligence — monitoring global regulatory changes

Figure 3: Overview of the Drug Approval Process (Compliance with Regulatory Requirements is Necessary at Every Stage)

Responsibility of Regulatory Affairs Professionals

Responsibilities of RA Professionals
▶ Ensuring company compliance with all applicable regulations and laws
▶ Working with federal, state and local regulatory agencies on specific business issues
▶ Advising companies on regulatory aspects that would affect proposed activities
▶ Keeping up with international legislation, guidelines and customer practices
▶ Collecting, collating, and evaluating scientific data from R&D colleagues
▶ Formulating regulatory strategies for domestic, international and contract projects
▶ Coordinating, preparing and reviewing regulatory dossiers for submission within specified timeframes
▶ Preparing and reviewing SOPs, BMR (Batch Manufacturing Records), MFR, and change control documents
▶ Monitoring the progress of all registration submissions
▶ Maintaining records of approved applications and registration fees for DMFs
▶ Responding to regulatory queries and ensuring approvals are granted without delay
▶ Participating in R&D training, Pilot Plant Scale-Up, and Post-Marketing Surveillance (ADR)

- ▶ Managing and reviewing audit reports and compliance, regulatory and customer inspections
- ▶ Providing accurate and complete safety and efficacy information to healthcare professionals

REGULATORY REQUIREMENTS FOR DRUG APPROVAL

Drug Development Teams

Most pharmaceutical and biotechnology firms employ Drug Development Project Teams to guide the processes involved in early drug discovery, through various drug development stages, and finally making the drug candidate into a therapeutic product. These cross-functional teams include individuals with diverse philosophies and approaches.

Responsibilities of Drug Development Project Teams

- Reviewing research results from experiments conducted by various scientific disciplines
- Integrating new research results with previously generated data
- Planning research studies to further characterize the drug candidate
- Preparing a detailed drug development plan including milestones, timelines and critical path
- Monitoring the status of research studies against the timeline and critical path
- Comparing research results and development timelines with competitor drug candidates
- Conducting market surveys to ensure development remains economically justified
- Reporting drug development program status to management with recommendations

Composition of Drug Development Teams

Discovery/Development Team	Basic scientists and chemists who synthesize new molecules; prepare clinical supplies; conduct drug screening studies

Nonclinical Pharmacology & Toxicology	Studies drug in animal models for efficacy and safety; identifies potential safety issues in humans; designs relevant animal studies
Clinical Research Team	Ultimate responsibility for testing in humans; monitors drug safety; generates study reports with biostatisticians and RA; interacts with FDA
Regulatory Affairs Team	Interface with FDA; ensures compliance with FD&C Act and amendments; prepares IND/NDA submissions
Marketing Team	Responsible for marketing and selling the drug; develops labeling and promotional materials; ensures budget goals are met
Legal Team	Manages patent protection; avoids lawsuits from competitors; ensures advertising and promotional materials are compliant
Management Team	Coordinates all teams; ensures successful project completion within time and budget

Non-Clinical Drug Development

Pre-clinical Drug Development involves pharmacological and toxicological assessment of the potential new drug in animal models to establish safety and efficacy before administration to human volunteers. Studies are carried out by both in-vitro and in-vivo methods in accordance with Good Laboratory Practice (GLP) guidelines (21 CFR Part 58).

Models Used in Pre-clinical Studies

In-vitro Models	Cell lines, isolated tissues, enzyme systems (CYP450), hepatocytes, microsomes, liver slices
In-vivo Models	Rodent: Mice, Rats, Guinea Pig, Hamster | Non-Rodent: Dog, Monkey (Non-human primates), Mini-pigs
Duration	Pre-clinical studies can take up to 2 years to complete
Regulatory Basis	GLP Regulations — 21 CFR Part 58; ICH M3(R2) for timing relative to clinical development

Pharmacology

Pharmacokinetic (PK) Profile Study — ADME

Pharmacokinetic studies investigate ADME properties of the drug. Generally conducted in two species (usually rats and dogs) at different dose levels in males and females. The main task is to find an optimal dose level and provide information about dose-effect relationships.

Absorption	Rate and extent of drug absorption from route of administration
Distribution	Volume of distribution (Vd), plasma protein binding, tissue distribution
Metabolism	CYP450 identification, metabolic stability, metabolite profiling (Phase I & Phase II)
Excretion	Routes of elimination — renal, biliary, fecal; half-life; mass balance studies

In-vitro ADME experiments are conducted in: CYP450 isozymes, microsomes, hepatocytes (preferred — contains both Phase 1 and Phase 2 metabolism systems), or liver slices.

For in-vivo metabolism studies, radiolabeled compounds (usually Carbon-14) are used. The radiolabeled compound must be: radiochemically pure, stable, high specific activity, and in a position that does not affect physical/chemical/pharmacological properties. A metabolite is significant when > 5% of parent compound.

Pharmacodynamic (PD) Profile Study

Primary PD Study	Study physiological effects of the drug — desired therapeutic effects at the target
Secondary PD Study	Study mechanism of drug action; effects not related to the desired therapeutic target
Safety Pharmacology	Identify undesirable pharmacodynamic effects on vital physiological functions affecting human safety

Safety Pharmacology Studies

Three types of safety pharmacology studies are performed according to ICH S7A/S7B guidelines:

- Core Battery Studies (mandatory, per GLP) — Before first administration in humans:
  - Cardiovascular system: hERG channel, blood pressure, heart rate, ECG (QT prolongation)
  - Respiratory system: respiratory rate, tidal volume, hemoglobin oxygen saturation
  - Central Nervous System: motor activity, behavioral changes, coordination, reflexes, body temperature
- Follow-up Studies — Deeper insight into kinetics; potential repeat dose administrations on suitable animal species
- Supplemental Studies — Other organ systems not in the core battery: gastrointestinal, renal, immune system

📌 **NOTE:** *Safety pharmacology studies use single dose administration; exposure should be ≥ the potential therapeutic concentration in humans. Animals should ideally not be under anaesthesia for in vivo studies.*

Drug Metabolism and Toxicology

i) Acute and Chronic Toxicity Studies

- Acute Toxicity: Single high dose in rodents (rat and mice, male & female); minimum 2 routes including proposed human route; animals observed for 2 weeks; LD50 determined at 95% confidence level
- Repeated-Dose Toxicity: Minimum 2 species (one non-rodent); small doses 7 days/week for 6–9 months
- Three dose levels required: Highest (produces observable toxicity), Intermediate (some symptoms only), Lowest (no observable toxicity but comparable to human therapeutic dose)

- Observations: Body weight, clinical signs, clinical chemistries, hematology, histopathological changes

ii) Reproductive Toxicity Studies

Evaluates male/female fertility, embryo/fetal death, parturition, neonatal development, lactation, and teratogenicity. Conducted in three segments:

Segment I	Fertility and general reproductive performance in RATS — premating dosing ≥4 weeks (male) and ≥14 days (female); sperm analysis and histopathology
Segment II (Teratology)	Embryotoxicity/teratogenic effects in RATS and RABBITS — drug given during organogenesis (GD 6–15 for rats; GD 6–18 for rabbits); Cesarean delivery; examine for skeletal/visceral abnormalities
Segment III (Perinatal/Postnatal)	Conducted only in RATS — effects on late fetal development, labor, delivery, lactation, neonatal viability, growth; drug given from implantation to end of lactation

iii) Genotoxicity / Mutagenicity Studies

Determines if the drug is capable of inducing DNA damage — by chromosomal structural alterations or changes in nucleotide base sequence. Standard ICH battery of tests:

Ames Bacterial Mutation Assay	Gene mutation test in bacteria (in vitro)
Mouse Lymphoma Assay (MLA) / CHO / Chromosomal Aberration	In vitro evaluation of chromosomal damage
Micronucleus Test (MNT)	Evaluation of in vivo chromosomal damage in bone marrow polychromatic erythrocytes

iv) Carcinogenicity Studies

- Conducted if drug is intended for use over a prolonged period (≥ 6 months)

- Two rodent species — mostly rats and mice — over 2 years
- Two dose types: 1) Maximum Tolerated Dose (MTD) and 2) 25-fold AUC ratio (25:1 exposure ratio of rodent to human plasma AUC)
- Animals observed for development of tumors throughout the 2-year period

v) Immunotoxicity Studies

- Studies the ability of the drug to induce immune response or sensitivity
- Identifies: Immunosuppression (leading to infections/malignancies), hypersensitivity, or autoimmune reactions
- Parameters quantified: antibodies (IgM, IgE, IgG), lymph node weight, lymphoid cell morphology
- May be incorporated into repeated-dose toxicity studies

vi) Toxicokinetic (TK) Studies

- Define systemic exposure in animals alongside dose level and time course of toxicity
- Relate exposure to toxicological findings; assess relevance to clinical safety
- Matrix sampled: blood, plasma, excreta, tissues — frequently enough to estimate exposure without stress
- Doses and duration based on those used in single- and multiple-dose toxicology studies
- Must be conducted according to GLP regulations; performed in conjunction with drug safety studies

Investigational New Drug (IND) Application

After successful completion of pre-clinical research, the drug developer (Sponsor) must submit an IND application to the respective regulatory authority (e.g., FDA in USA, CDSCO in India) in order to start clinical research. The IND is the formal process by which a sponsor requests approval for testing a drug in human subjects.

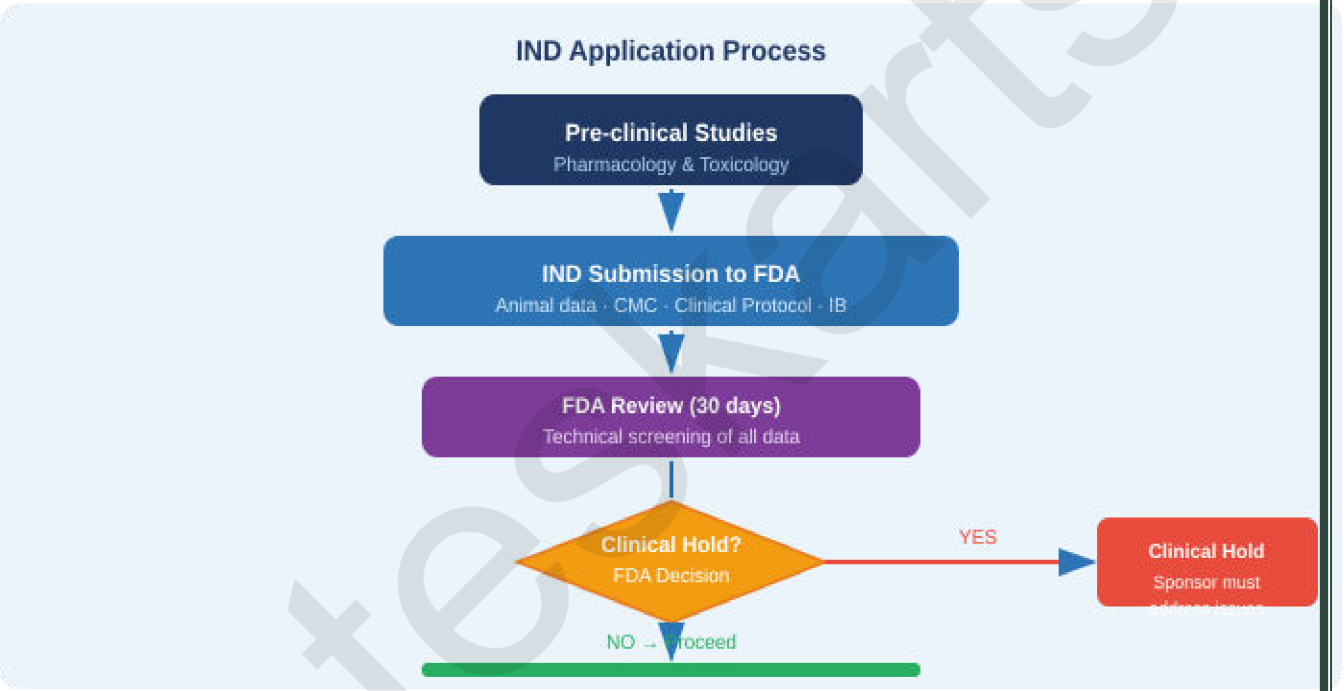

Figure 4: IND Application Process and FDA Review Pathway

Content of the IND Application

Animal Study Data	All pharmacology and toxicology data from pre-clinical studies
Manufacturing Information (CMC)	Chemistry, Manufacturing and Controls — drug substance and drug product
Clinical Protocols	Detailed study plans for proposed clinical trials
Investigator's Brochure (IB)	Comprehensive compilation of clinical and non-clinical data
Prior Human Experience	Any available data from prior human studies or published literature

Investigator Information	Qualifications and details of the clinical investigator(s)
Additional Data	Any other relevant information about the drug candidate

IND Review Timeline

- After IND submission, FDA reviews all data and if satisfied, grants the sponsor approval to begin clinical trials
- It takes 30–60 days after IND submission to receive approval for clinical trial from the FDA
- If FDA issues a Clinical Hold — sponsor must address identified safety issues before proceeding

📌 **NOTE:** *The IND filing is the formal bridge between pre-clinical research and first-in-human clinical trials. Without an active IND, it is illegal to transport an investigational new drug across state lines in the USA.*

Investigator's Brochure (IB) and New Drug Application (NDA)

A) Investigator's Brochure (IB)

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product that is relevant to the study of the product in human subjects. It is required as part of the IND and prepared for presentation to clinical investigators and Institutional Review Boards (IRBs).

- Purpose: Provides investigators with information to facilitate their understanding of the protocol rationale, dose, frequency, administration methods, and safety monitoring procedures
- Review: Must be reviewed at least annually and revised whenever new significant safety information emerges

- Responsibility: Sponsor ensures an up-to-date IB is available to investigators; investigators provide IB to the responsible IRBs

Contents of the Investigator's Brochure (ICH E6)

1. Title Page	Sponsor name, product identity (research number, chemical name, trade name), edition number, release date
2. Confidentiality Statement	Instructions for investigators to treat IB as confidential document
3. Table of Contents	Complete index of all IB sections
4. Summary	Brief overview of all relevant data
5. Introduction	Background on the drug and rationale for development
6. Physical, Chemical & Pharmaceutical Properties	Physicochemical characteristics and formulation details
7. Nonclinical Studies	Pharmacology, PK/Metabolism in animals, Toxicology
8. Effects in Humans	PK/Metabolism in humans, Safety and Efficacy, Marketing experience
9. Summary & Guidance for Investigator	Consolidated guidance on dosing, monitoring, risk-benefit
10. Publications & Reports	References and supporting study reports

B) New Drug Application (NDA)

After successful completion of clinical research, if the drug candidate is proven safe and effective, the drug sponsor can submit an NDA to the respective regulatory authority to obtain a marketing license and begin commercial production.

Documents Required for NDA Filing

- All research data from pre-clinical studies through Phase III clinical trials
- Proposed labeling (prescribing information)
- Safety updates and any additional safety data
- Drug abuse information

- Patent information
- Locations where clinical trial studies were conducted
- Compliance report of pre-clinical studies (GLP certification)
- Directions for use (patient information leaflets)

NDA Review Outcomes

Not Approvable	List of deficiencies provided; cause of rejection explained — major issues with safety, efficacy, or CMC
Approvable	Minor changes are suggested before marketing approval is granted
Approved for Marketing	Full approval granted; company may begin commercial sales

Timeline: It takes 6–12 months after NDA submission to receive an approval letter for marketing from the FDA (Standard Review: 12 months; Priority Review: 6 months).

📌 **NOTE:** *Phase IV trials are post-approval trials in which adverse drug reactions (ADRs) are monitored to ensure drug safety after being marketed. Also called post-marketing surveillance studies — conducted by drug sponsor, government agency, or individual research organizations.*

Clinical Research / BE Studies

Pre-clinical research provides basic ideas about drug safety in animal models, but it is not a substitute for human subjects. Clinical research refers to studies (trials) involving human subjects to establish safety and efficacy.

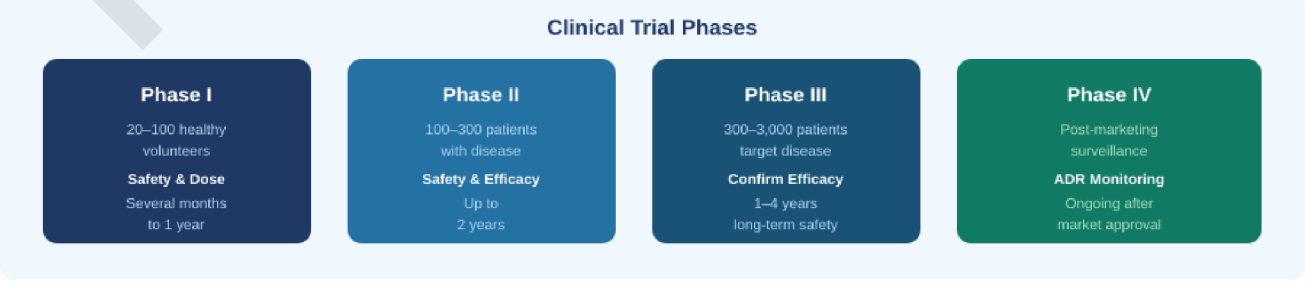

Figure 5: Four Phases of Clinical Drug Development

Phases of Clinical Trials

Phase I	20–100 healthy volunteers | Several months to 1 year | Purpose: Safety and dose range finding (SAD, MAD studies; PK profiling; MTD determination)
Phase II	100–300 patients with the target disease | Up to 2 years | Purpose: Safety and Efficacy signals; dose-response; optimal dose selection
Phase III	300–3,000 volunteers with target disease | 1–4 years | Purpose: Confirm Efficacy and long-term Safety; monitor adverse reactions; pivotal studies for NDA
Phase IV	Post-approval | Ongoing | Purpose: Post-marketing surveillance; detect rare ADRs; new populations/indications; comparative effectiveness

Bioequivalence (BE) Studies

BE studies demonstrate that different formulations or regimens of a drug product are similar in terms of therapeutic benefit (efficacy) and non-therapeutic side effects (safety). They are pivotal for generic drug approval under ANDA (Abbreviated New Drug Application).

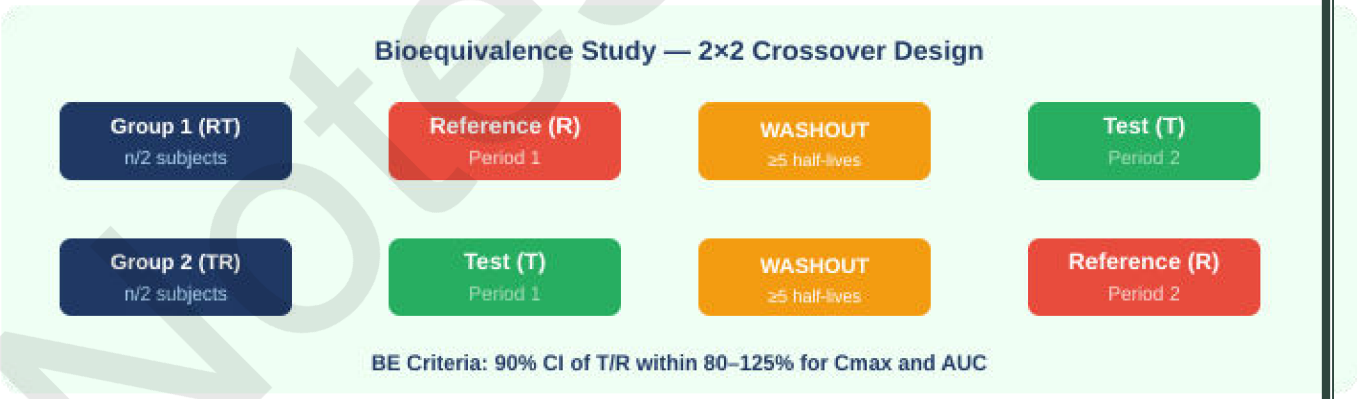

Figure 6: 2×2 Crossover Design used in Standard Bioequivalence Studies

BE Study Design — Standard 2×2 Crossover

- Subjects: Male and female healthy volunteers
- Formulations: T = Test (new/generic) and R = Reference (innovator/standard) formulation

- Two sequences: Group 1 receives R then T (RT); Group 2 receives T then R (TR)
- Washout period: ≥5 half-lives between each administration period — ensures complete elimination of previous dose
- Blood samples: Collected at pre-specified timepoints to generate complete PK concentration-time curve

BE Criteria and PK Parameters

Cmax (Rate)	Maximum plasma concentration — reflects rate of absorption
AUC (Extent)	Area Under the Curve — reflects total drug exposure; extent of absorption
90% Confidence Interval	Must fall within 80–125% of the Reference for both Cmax and AUC
NTI Drugs	Narrow Therapeutic Index — tighter criteria of 90–111.11%; replicate designs required
Highly Variable Drugs	Scaled Average Bioequivalence (SABE) approach with wider acceptance criteria

Applications of BE Studies

- Primary use: Demonstrate formulation used in Phase III clinical trials is similar to final commercial formulation
- Generic drug approval: Generic pharmaceutical industry uses BE to gain market access when the innovator patent expires
- Post-marketing: Required following substantial post-marketing formulation alterations or manufacturing site changes

Clinical Research Protocols

A clinical trial protocol is a document that describes how a clinical trial will be conducted (objectives, design, methodology, statistical considerations, and organization) and ensures the safety of trial subjects and integrity of data.

Trials are conducted in accordance with Good Clinical Practice (GCP) and ICH guidelines (E6 R2).

Contents of a Clinical Trial Protocol (ICH E6)

1. General Information	Protocol title, number, date; sponsor details; investigator name, title, address; laboratory details
2. Background Information	Drug description; nonclinical findings with clinical significance; known risks and benefits; population to be studied
3. Trial Objectives & Purpose	Detailed description of primary and secondary objectives; hypothesis
4. Trial Design	Primary/secondary endpoints; type of trial (double-blind, placebo-controlled, parallel, crossover); randomization; blinding; stopping rules; CRF identification
5. Selection & Withdrawal	Inclusion criteria; exclusion criteria; withdrawal criteria and procedures; subject replacement procedures
6. Treatment of Subjects	Drug name, dose, schedule, route; permitted/not permitted medications; compliance monitoring
7. Assessment of Efficacy	Efficacy parameters; methods and timing for assessing and recording efficacy
8. Assessment of Safety	Safety parameters; AE/SAE reporting procedures; follow-up procedures
9. Statistics	Statistical methods; sample size calculation and justification; significance level; interim analysis; missing data handling; analysis populations
10. Direct Access to Source Data	Monitoring, audit, IRB/IEC review and regulatory inspection rights
11. Quality Control & QA	Monitoring plan; data management and quality assurance procedures
12. Ethics	Ethical considerations; informed consent procedures; IRB/IEC approval
13. Data Handling & Record Keeping	CRF design; data lock procedures; archiving requirements
14. Financing & Insurance	Subject compensation; indemnification arrangements
15. Publication Policy	Authorship; publication rights; data sharing
16. Supplements	Appendices, supporting documents

Biostatistics in Pharmaceutical Product Development

Statistics plays a crucial role in drug product development. Correct use of biostatistics is critical for the success of drug development programs at every stage from discovery through commercialization.

Applications of Biostatistics in Drug Development

- Provides scientific methodology for target identification and go/no-go decisions (significance testing — p value)
- Quantification of effect on target of interest — assessing if animal models translate to human outcomes
- Provides critical input into risk quantification (Risk Assessment)
- Establishes criteria for stopping dose escalation in Phase I studies
- Assists in appropriate study design selection and selection of primary endpoints
- Design and implementation of randomization systems to minimise bias
- Helps in sample collection, data analysis and refinement, error and bias detection
- Design and optimization of formulations; optimization of process parameters in pilot plant scale up
- Analytical methods validation tool

Statistical Concepts

Type I Error (α)	False positive — concluding efficacy when drug has no effect; set at $\alpha = 0.05$ (5%)
Type II Error (β)	False negative — missing a true treatment effect; typically set at $\beta = 0.10–0.20$
Statistical Power (1-β)	Probability of detecting a true treatment effect; minimum 80% required
p-value	Probability of observed result if null hypothesis is true; $p < 0.05$ considered statistically significant

Confidence Interval	Range of plausible values for the true treatment effect; 95% CI is standard
Randomization	Random allocation to treatment groups to prevent selection bias
Blinding	Prevents knowledge of treatment allocation from biasing assessments (single, double, triple blind)

Statistical Support at Different Development Phases

Nominate API for Clinical Development	Multiple comparison techniques; combinatorial chemistry analysis; genomic data analysis; animal safety studies
Phase I Clinical Studies	Analysis of historical data; design and analyze experiments; accelerated stability regression analysis
Phase IIA (Dose Ranging) & IIB (Proof of Concept)	Factorial and mixture experiments; response surface experiments; excipient compatibility studies
Phase III Clinical Studies	Factorial/mechanistic/response surface experiments; multivariate analysis; PAT applications
NDA Submission	Product and process understanding experiments; ICH stability campaign analysis (set expiry)
Commercial Production	SPC (Statistical Process Control), PAT; annual stability lot analysis; DoE, Six Sigma, Lean techniques

Data Presentation for FDA Submissions

The quality of data presentation in regulatory submissions directly impacts the FDA's ability to efficiently review and evaluate the drug. NDA submissions contain enormous amounts of data; critical judgment must be exercised in selecting key data for presentation.

A) Text Exposition Guidelines

Content	Present only data necessary for the thesis within the document body; less important data summarized briefly in appendices; avoid extraneous data that slows review
Tone	Formal without being stilted; avoid legal language or colloquial/informal language

Conciseness	Simple, straightforward language; use recognised acronyms (spelled out at first mention); eliminate redundancies
Correctness	Text must agree with tabular data; tabular data must agree with data source — inconsistencies make entire submission suspect
Consistency	Consistent punctuation, capitalisation, abbreviations and styling conventions throughout
Clarity	Reviewer should read without stopping; careful attention to punctuation, sentence structure, parallelism
Global to Specific	Begin sections with global statements/data then discuss specifics (e.g., overall AEs before breakdown by severity/relationship)

B) Tabular Presentation Guidelines

- Use in-text tables whenever they simplify presentation and reduce text substantially
- Avoid comprehensive multipage tables that interrupt text — place in appendices if necessary
- All tables, figures, and graphs in appendices must have in-text references
- Commentary on tables should PRECEDE the table, beginning with an introduction to the table by number
- Title: All tables require concise but descriptive titles
- Data Source: Every table should identify source data (usually in a footnote)
- Footnotes: Assigned letters (superscripted), not symbols or numbers to avoid confusion with data
- Orientation: Portrait tables preferred to landscape; if data doesn't fit, revise axes
- Order of Presentation: Maintain consistent order in multiple tables (e.g., active drug always in column 1)
- Present meaningful data together: Data to be compared should be placed as close together as possible

Management of Clinical Studies

The key elements in managing clinical programs involve systematic processes from investigator selection through study close-out, all governed by FDA CFR (Code of Federal Regulations) and ICH GCP Guidelines.

Elements of Clinical Trial Management

1. Investigator Selection

- ▶ US GCP Regulations (21 CFR 312.53) and ICH GCP Guidelines mandate sponsor selects only investigators qualified by training and experience
- ▶ Investigator must be an appropriate expert to evaluate the investigational product
- ▶ Pre-screening of qualifications, facilities and patient population access is conducted

2. Pre-Investigational Site Visits (PISV)

- ▶ Conducted after prescreening of potential investigators is established
- ▶ Performed by monitor or authorized individual appointed by sponsor
- ▶ Assesses investigator's ability and commitment to conduct the trial
- ▶ Reviews site facilities, staff qualifications, and patient recruitment potential

3. Study Initiation Visits (SIV)

- ▶ Last training on the protocol before beginning subject recruitment
- ▶ Covers: Study Protocol, AE/SAE reporting, Product dispensation/accountability, CRF completion, Regulatory documents review, Source documentation
- ▶ Ensures site staff are competent to conduct the trial per protocol and GCP

4. Periodic Monitoring Visits

▶ Required by both CFR and ICH GCP guidelines

▶ Purpose: Assure investigators follow GCP; protect rights of subjects; verify data completeness, accuracy, and verifiability

▶ Includes Source Data Verification (SDV) — comparing CRF data against original source documents

5. Subject Recruitment

▶ One of the surest ways to decrease overall trial time is to recruit subjects in the shortest time

▶ Planning requires understanding the target subject population meeting protocol criteria

▶ Must understand subject motivations, current treatment, and medical condition status

6. Product Accountability

▶ Mandatory strict control on any investigational product — not yet received marketing authorisation

▶ Investigator responsible for accountability; drug prescribed only by investigator or authorized sub-investigators

▶ Detailed records: Date dispensed, quantity, subject ID, batch number

▶ Sponsor retrieves/verifies disposition of all used and unused product

7. AE and ADR Reporting

▶ Drug safety and adverse reactions are closely monitored under strict FDA legislative control

▶ Federal regulations require sponsors to report adverse experiences for investigational products

▶ Reporting required at both investigational and post-marketing stages

▶ Serious Adverse Events (SAEs): Reported to FDA within 7 days (fatal/life-threatening) or 15 days (others)

8. Financial Disclosure

▶ Required on all current/ongoing clinical trials filed in an IND (effective USA February 2, 1999)

▶ Defined as: compensation related to study outcome, proprietary interest in product, significant equity interest in sponsor, significant payments to investigator

▶ Ensures FDA that steps were taken to minimise bias in design, conduct, reporting and analysis

9. Study Close-Out Visits (SCV)

▶ Conducted after all subjects completed the trial or were withdrawn and all data queries resolved

▶ Checklist: All subjects accounted for; All CRF pages completed and retrieved; All data queries resolved; All AEs/ADRs reported and followed up; All investigational product accounted for

▶ Regulatory records organized in Trial Binder; All remaining supplies returned or disposed of properly

10. Records Retention and Inspections

▶ Record retention is critical to the ongoing viability of the study data

▶ FDA may conduct on-site inspection to verify data at some time after NDA submission

▶ Both CFR and ICH require records be retained for 2 years after marketing application approval

▶ Records must be readily available at the site at all times

Abbreviations / Glossary

ADME	Absorption, Distribution, Metabolism, Excretion
ADR	Adverse Drug Reaction
ANDA	Abbreviated New Drug Application (generic drug)
AUC	Area Under the Curve
CFR	Code of Federal Regulations
Cmax	Maximum (peak) plasma concentration
CDSCO	Central Drugs Standard Control Organisation (India)
CTD	Common Technical Document
DMF	Drug Master File
EMA	European Medicines Agency
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
LD50	Lethal Dose for 50% of test population
MTD	Maximum Tolerated Dose
NCE / NME	New Chemical Entity / New Molecular Entity
NDA	New Drug Application
PAT	Process Analytical Technology
PK/PD	Pharmacokinetics / Pharmacodynamics
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Statistical Process Control
TK	Toxicokinetics
USFDA	United States Food and Drug Administration

Thank You for Reading!

We hope this book helped you in your studies.

If you want to access complete notes, PDFs, and study material for your course, scan the QR code below.

Scan & Download All Notes

What You'll Get:

- B.Pharm & D.Pharm Notes
- Exam-Oriented PDF Materials
- Regular Updates & New Content

Stay Connected for More Updates

Visit: https://noteskarts.com/

Contact: noteskartsconnect@gmail.com

One Scan = All Notes at Your Fingertips!