BP707T · B.Pharm Semester VII · Theory Notes

Regulatory Affairs

Unit II — Regulatory Requirements in Drug Development (6 hours)

Unit II (6 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit II (6 hours).

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CHAPTER 3: Drug Discovery and Development Process and Teams

Learning Objectives

After studying this chapter, you should be able to:

1 Describe the complete journey of a medicine from a new idea to the pharmacy shelf — the drug discovery and development process.

2 Distinguish between the discovery phase and the development phase of a new drug.

3 List the main stages of drug discovery (target identification, hit finding, lead optimisation, candidate selection).

4 List the main stages of drug development (non-clinical studies, clinical trials Phase I–IV, marketing approval).

5 Name the key teams involved in drug development and explain the function of each team: chemistry, pharmacology, toxicology, drug metabolism, clinical, regulatory affairs, quality assurance, and project management.

6 Explain how regulatory affairs connects the science teams with the regulatory authorities.

7 Answer exam, viva, and application-based questions on this topic.

Definitions

- **Drug discovery:** The scientific process of finding a new chemical or biological substance that may become a medicine. It starts with an idea (for example, "this protein causes disease") and ends when one promising substance, called a **drug candidate**, is selected for detailed testing.
- **Drug development:** The process of testing the selected drug candidate — first in laboratories and animals, then in humans — to prove it is safe and effective, and finally getting permission from the regulatory authority to sell it. Development includes all clinical trials and the approval application.
- **Biological target:** The specific part of the body involved in a disease that a drug acts upon — usually a protein such as an enzyme or a receptor. The target is the "lock" the drug "key" must fit.
- **Hit:** A chemical substance found in early screening that shows some desired activity against the target (for example, it blocks the harmful enzyme). A hit is only a starting point — it is usually not good enough to become a medicine.
- **Lead compound (lead):** A hit that has been improved by chemists so that it is more potent, more selective, and safer. The lead is the best starting chemical for making a medicine.
- **Drug candidate:** The single best compound, chosen after lead optimisation, that will enter formal safety testing (non-clinical studies) and then human trials.
- **Non-clinical (preclinical) studies:** Laboratory and animal studies done before the drug is tested in humans, to check pharmacology, safety (toxicology), and drug metabolism.

- **Clinical trials:** Studies in human volunteers and patients, done in four phases (Phase I, II, III, IV), to check safety and effectiveness in people.
- **IND (Investigational New Drug) application:** The formal application submitted to the regulatory authority (for example, the US FDA) asking for permission to start testing a new drug in humans.
- **NDA (New Drug Application):** The large application submitted to the regulatory authority asking for permission to market (sell) a new drug, after all testing is complete.
- **Regulatory affairs:** The profession and function that manages all communication between the company and the regulatory authorities, and ensures every step of development follows the applicable rules and guidelines.
- **Regulatory authority:** The government body that approves medicines (for example, CDSCO in India, US FDA in the United States, EMA in Europe).
- **GLP (Good Laboratory Practice):** The set of rules that ensures non-clinical laboratory studies are planned, performed, and recorded properly so the data can be trusted.
- **GCP (Good Clinical Practice):** The set of international ethical and scientific rules for conducting clinical trials in humans.
- **GMP (Good Manufacturing Practice):** The set of rules for manufacturing medicines with consistent quality.

Terminology Table

Term	Simple Meaning
Drug discovery	Finding a new promising substance that may become a medicine
Drug development	Testing that substance in animals and humans and getting approval to sell it
Target	The body protein (enzyme/receptor) involved in the disease — the "lock"
Hit	A chemical that shows early activity against the target — a rough starting point
Lead	An improved hit — the best chemical to build the medicine from
Candidate	The final chosen compound that enters formal testing
SAR (Structure–Activity Relationship)	The study of how changes in a chemical's structure change its activity
ADME	Absorption, Distribution, Metabolism, Excretion — what the body does to the drug
Pharmacology	The study of what the drug does to the body (its effects)
Toxicology	The study of harmful (toxic) effects of the drug
Pharmacokinetics (PK)	How the drug moves through the body over time (absorption, distribution, elimination)
Pharmacodynamics (PD)	What the drug does to the body — its effects and mechanism
CMC (Chemistry, Manufacturing and Controls)	All chemistry and manufacturing work to make the drug reliably and with quality

Term	Simple Meaning
Clinical trial phases	Phase I (safety), Phase II (efficacy), Phase III (large confirmation), Phase IV (post-marketing)
Regulatory submission	A formal set of documents sent to the authority asking for a permission or approval

Simple Explanations

What is drug discovery, in the simplest words?

Imagine thousands of keys, and one lock hidden inside the body that is causing a disease. Drug discovery is the work of (1) finding the lock (the biological target), (2) trying thousands of keys (chemical substances) to see which ones turn the lock, and (3) shaping the best key until it fits perfectly and does not jam other locks. At the end of discovery, you have one well-shaped key — the **drug candidate**.

What is drug development, in the simplest words?

Development is proving that the key is safe to use and really opens the right door. First it is tested in test tubes and animals (non-clinical studies). Then it is tested step by step in people: a few healthy volunteers (Phase I), then some patients (Phase II), then thousands of patients (Phase III). If all tests pass, a huge application (the NDA) is sent to the regulatory authority. If the authority is satisfied, the medicine can be sold. Even after selling begins, the medicine keeps being watched (Phase IV).

Why does this take so many teams?

One scientist cannot do everything. The chemist makes and improves molecules; the pharmacologist checks what the drug does; the toxicologist checks for harm; the drug-metabolism scientist checks how the body handles the drug; the clinician designs human trials; the statistician plans the numbers; the regulatory affairs professional talks to the authority and files the applications; quality assurance checks that every study followed the rules; and the project manager keeps everyone moving together. A new medicine is a team product.

Key takeaway: Discovery = finding the right molecule. Development = proving it is safe and effective in animals and humans and getting approval. Both need many specialist teams working together under regulatory rules.

Classifications

1. Classification of the drug discovery and development process

A. By stage type:

1. **Discovery phase** — target identification → target validation → hit identification → hit-to-lead → lead optimisation → candidate selection.
2. **Development phase** — non-clinical (preclinical) studies → IND filing → clinical trials (Phase I, II, III) → NDA/marketing authorisation application → approval and launch → Phase IV (post-marketing surveillance).

B. By type of drug being developed:

1. **New Chemical Entity (NCE):** A completely new chemical substance never used as a medicine before.
2. **Biologic / biotechnology product:** A medicine made from living cells, such as an antibody or vaccine.
3. **Repurposed drug:** An existing approved drug tested for a new disease (a shorter path, because much safety data already exists).
4. **Generic drug:** A copy of an already approved medicine, developed mainly through bioequivalence studies rather than full discovery.

2. Classification of drug development teams (functional teams)

1. **Medicinal chemistry team** — designs and makes new molecules; improves hits into leads.
2. **Pharmacology team** — tests what the drug does (efficacy, mechanism of action).
3. **Toxicology team** — tests for harmful effects in animals.
4. **Drug metabolism (DMPK/ADME) team** — studies absorption, distribution, metabolism, excretion.
5. **Pharmaceutics / CMC team** — develops the formulation (tablet, injection) and manufacturing process.
6. **Clinical development team** — designs and runs human trials (doctors, nurses, clinical scientists).
7. **Biostatistics team** — plans trial design and analyses the data.
8. **Regulatory affairs team** — prepares submissions and communicates with authorities.
9. **Quality assurance (QA) team** — audits studies and checks GLP/GCP/GMP compliance.
10. **Project management team** — coordinates timelines, budgets, and team communication.

Mechanisms / Processes

Process 1: The drug discovery process (step by step)

1. **Target identification:** Scientists study the disease and find the protein (enzyme, receptor) that drives it. This protein becomes the target.
2. **Target validation:** Experiments confirm that acting on this target will actually treat the disease — not just in theory.
3. **Hit identification (screening):** Thousands to lakhs of chemicals are tested against the target (high-throughput screening) to find a few that show activity — these are **hits**.
4. **Hit-to-lead:** The most promising hits are selected and slightly modified to find a **lead** series — a chemical family worth improving.
5. **Lead optimisation:** Chemists make many small changes to the lead's structure, studying the structure–activity relationship (SAR), to improve potency, selectivity, safety, and drug-like properties (solubility, stability).
6. **Candidate selection:** One best compound — with the right balance of activity, safety, and manufacturability — is declared the **drug candidate** and moves into development.

Process 2: The drug development process (step by step)

1. **Non-clinical development:** The candidate is tested in laboratories and animals — pharmacology, safety pharmacology, drug metabolism, and toxicology studies (detailed in Chapter 4). All done under GLP.
2. **IND filing:** Results are compiled into the IND application; once the authority clears it, human trials may begin.
3. **Phase I clinical trials:** Small number of healthy volunteers (or sometimes patients) — checks **safety** and how the body handles the drug (PK).
4. **Phase II clinical trials:** A few hundred patients — checks whether the drug **works** (efficacy) and finds the right dose.
5. **Phase III clinical trials:** Thousands of patients — large, controlled trials that **confirm** efficacy and monitor side effects; data form the main basis of approval.
6. **NDA / marketing authorisation application:** All data are compiled into a huge submission; the authority reviews and, if satisfied, grants approval.
7. **Phase IV (post-marketing):** After launch, the drug's safety in the large population is monitored (pharmacovigilance); new uses may also be studied.

Process 3: How the teams work together (the workflow)

1. Project management sets the plan and milestones for the programme.
2. Chemistry, pharmacology, toxicology, and DMPK teams generate the scientific data.
3. The clinical team designs trials using that data; biostatistics defines the trial design and sample size.
4. QA audits the studies to confirm GLP/GCP compliance.
5. Regulatory affairs compiles everything into submissions (IND, then NDA) and handles all communication with the authority — including meetings, questions, and deficiency responses.
6. Any question from the authority goes back to the science teams for answers, and regulatory affairs delivers the response.

Textual Diagrams / Flowcharts

Diagram 1: The drug discovery and development pipeline

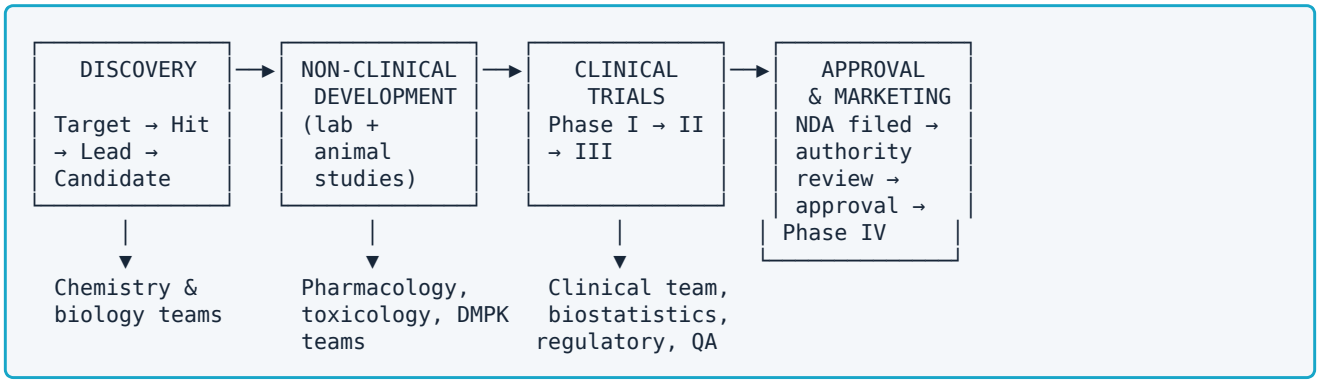


Diagram 2: The discovery funnel (many in, one out)

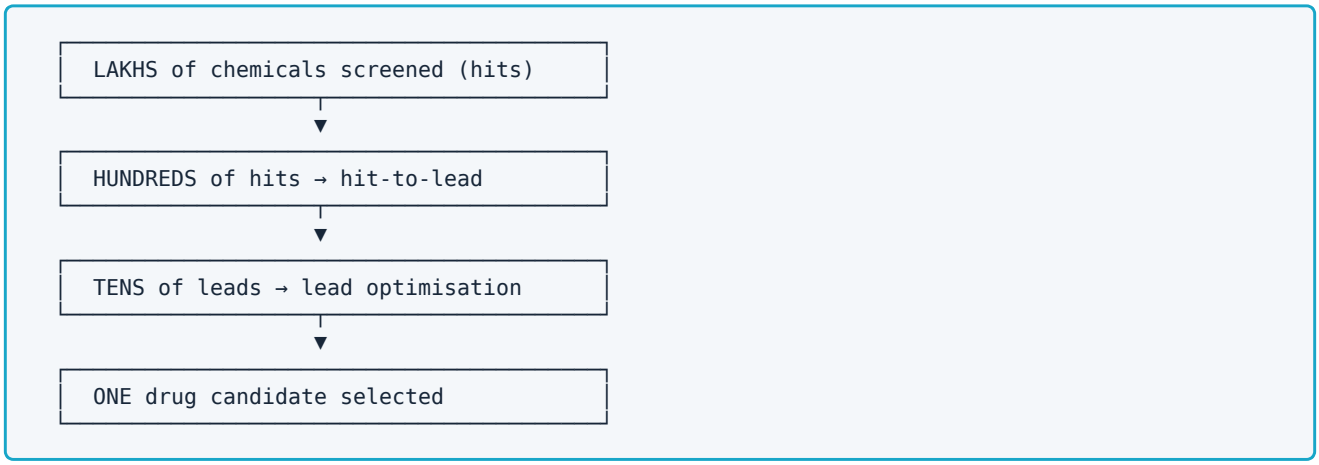


Diagram 3: Which team acts at which stage

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DISCOVERY        : Medicinal chemistry + Biology/Pharmacology (target work)
NON-CLINICAL     : Pharmacology, Toxicology, DMPK, CMC, QA (GLP)
IND FILING       : Regulatory affairs compiles; all teams contribute data
PHASE I–III      : Clinical team, Biostatistics, Regulatory, QA (GCP)
NDA FILING       : Regulatory affairs leads; every team provides its module
POST-APPROVAL    : Pharmacovigilance, Regulatory (variations), Manufacturing
THROUGHOUT       : Project management coordinates; QA audits everything
```

Infographic Concept

INFOGRAPHIC CONCEPT: A horizontal "medicine journey" conveyor-belt infographic. Five stations on the belt: (1) a magnifying glass over a protein lock (Discovery), (2) a flask and a mouse icon (Non-clinical), (3) three human silhouettes of increasing group size labelled I, II, III (Clinical trials), (4) a document folder with an approval stamp (Regulatory approval), (5) a pharmacy cross with a watchful eye (Post-marketing). Below each station, small team badges show which teams work there (chemistry, toxicology, clinical, regulatory, QA). A funnel shape above station 1 shows thousands of chemicals narrowing to one candidate. Colour code: blue for science, green for clinical, orange for regulatory.

Tables

Table 1: Drug discovery vs drug development (comparison)

Feature	Drug Discovery	Drug Development
Main question	"Can we find a molecule that works?"	"Is it safe and effective, and can we sell it?"
Starting point	Disease understanding, biological target	One selected drug candidate
End point	A drug candidate	Marketing approval (+ post-marketing monitoring)
Main activities	Screening, chemistry, lead optimisation	Animal studies, human trials, regulatory filings

Feature	Drug Discovery	Drug Development
Key teams	Chemistry, biology, pharmacology	Toxicology, clinical, regulatory, QA, biostatistics
Regulation intensity	Mostly scientific (GLP for some studies)	Heavily regulated (GLP, GCP, GMP, submissions)

Table 2: Drug development teams and their functions

Team	Core Function	Typical Output
Medicinal chemistry	Designs, synthesises, and improves molecules (SAR)	Lead compounds, drug candidate
Pharmacology	Tests drug effects and mechanism (PD)	Efficacy data, dose rationale
Toxicology	Tests harmful effects in animals	Safety data, safe starting dose for humans
DMPK / Drug metabolism	Studies ADME — what the body does to the drug	PK data, metabolite profiles
Pharmaceutics / CMC	Develops formulation and manufacturing process	Stable tablet/injection, manufacturing controls
Clinical development	Designs and conducts human trials	Trial protocols, clinical study reports
Biostatistics	Trial design, sample size, data analysis	Statistical analysis plans and results
Regulatory affairs	Submissions, authority communication, compliance strategy	IND, NDA, responses to authority queries
Quality assurance (QA)	Audits studies for GLP/GCP/GMP compliance	Audit reports, compliance certification
Project management	Planning, timelines, budgets, coordination	Development plan, milestone tracking

Table 3: Clinical trial phases at a glance

Phase	Who is studied	Main purpose	Typical size
Phase I	Healthy volunteers (sometimes patients)	Safety, tolerability, PK	Small (tens)
Phase II	Patients with the disease	Efficacy, dose finding	Hundreds
Phase III	Large patient groups	Confirm efficacy and safety	Thousands
Phase IV	General population after marketing	Long-term safety, new uses	Very large, ongoing

Examples

1. **Target → drug (concept example):** In pain and inflammation, an enzyme in the body produces pain-causing chemicals. Scientists identified this enzyme as the **target**. Chemicals that block it were found by screening (**hits**), chemists improved them (**leads**), and one optimised compound became the **candidate** that entered testing.
2. **Hit-to-lead:** A screening hit blocks the target but dissolves poorly in water and also blocks a related harmless enzyme. Chemists change parts of its structure (SAR study) until it dissolves well and blocks only the disease target — it is now a **lead**.

3 **Teamwork in action:** During non-clinical development, the toxicology team finds liver changes in animals at high doses. The chemistry team modifies the molecule to reduce this effect, the DMPK team confirms the change worked, and regulatory affairs includes the full story in the IND — showing the authority that the risk was understood and managed.

4 **Phase progression:** A new diabetes drug candidate first goes to 30 healthy volunteers (Phase I, safety), then 200 diabetic patients to find the effective dose (Phase II), then 3,000 patients to confirm it lowers blood sugar safely (Phase III).

Analogies

1 **Building a house:** Discovery is drawing the blueprint and choosing the design. Development is constructing the house floor by floor with inspections at each stage. The regulatory authority is the municipal inspector who checks the plan and the finished building before giving the occupancy certificate. The teams are the architect (chemistry), engineers (pharmacology/toxicology), site supervisor (clinical), and the liaison officer who handles all municipal paperwork (regulatory affairs).

2 **Cricket team:** No single player wins a match. The chemist is the batsman scoring runs (making molecules), the pharmacologist and toxicologist are the bowlers testing the opposition (testing effects and safety), the clinical team fields, the statistician keeps the scorebook, QA is the umpire ensuring fair play, regulatory affairs is the team manager dealing with the board, and project management is the coach.

3 **The funnel:** Discovery is like panning for gold — you wash tonnes of sand (screen lakhs of chemicals) to find a few gold specks (hits), and refine them into one gold coin (the candidate).

Pharmacy Relevance

- Pharmacists work in **regulatory affairs departments** of pharmaceutical companies — preparing dossiers, tracking guideline changes, and responding to authority queries. This chapter is the foundation of that career path.
- Pharmacists in **clinical research** (as clinical research associates or trial pharmacists) run Phase I–IV trials designed by the clinical development team.
- Understanding the development process helps a pharmacist explain to patients **why a new medicine took years to arrive** and why its safety profile is trusted — the drug passed animal testing, three phases of human trials, and regulatory review.
- Pharmacists in **pharmacovigilance** continue the Phase IV work — monitoring and reporting adverse effects after marketing.

India Context

- India's pharmaceutical industry is a major global supplier of medicines, and Indian companies run full drug development programmes — from discovery laboratories to clinical trials to regulatory filings with CDSCO (Central Drugs Standard Control Organization), India's national regulatory authority.
- Clinical trials in India are regulated by CDSCO under the applicable clinical trial rules and GCP guidelines — as per the latest rules/notifications, confirm the current edition before citing specifics.

- Many Indian companies specialise in developing **generic drugs**, where the "development" path is shorter: instead of full discovery and Phase I–III trials, they mainly conduct **bioequivalence studies** (covered in Chapter 5) to show their product matches the already-approved innovator product.
- Indian regulatory affairs professionals prepare submissions both for CDSCO (Indian market) and for foreign authorities such as the US FDA and EMA (export markets), so knowledge of the development process and team functions is essential for both.

Key Points

1. Drug **discovery** finds the molecule; drug **development** proves it safe and effective and gets it approved.
2. Discovery funnel: target identification → validation → hit screening → hit-to-lead → lead optimisation → **one candidate**.
3. Development path: non-clinical studies → IND → Phase I → Phase II → Phase III → NDA → approval → Phase IV.
4. Each specialist team owns one piece: chemistry (molecules), pharmacology (effects), toxicology (safety), DMPK (ADME), CMC (formulation), clinical (human trials), biostatistics (numbers), regulatory affairs (submissions and authority contact), QA (compliance), project management (coordination).
5. Regulatory affairs is the bridge between the science teams and the regulatory authority.
6. GLP applies to non-clinical studies, GCP to clinical trials, GMP to manufacturing.

Common Confusions

1. **Discovery vs development:** Discovery ends with a candidate; development starts with that candidate. Students often mix the order — remember "find first, prove later."
2. **IND vs NDA:** IND = permission to **start human trials**; NDA = permission to **sell** the drug. IND comes before trials; NDA comes after Phase III.
3. **Pharmacology vs toxicology:** Pharmacology studies the **desired** effects (what the drug does to treat disease); toxicology studies the **harmful** effects. Both are done in non-clinical development.
4. **Lead vs candidate:** A lead is the best chemical family under improvement; the candidate is the single final compound chosen for formal testing.
5. **Regulatory affairs vs quality assurance:** Regulatory affairs communicates **outward** (to the authority) and files submissions; QA audits **inward** (checks the company's own studies and systems for compliance).

Common Mistakes

1. Writing that Phase I tests efficacy in patients — Phase I mainly tests **safety** in healthy volunteers.
2. Placing the NDA before clinical trials — the NDA is filed **after** Phase III is complete.
3. Saying toxicology is done in humans — toxicology studies are **animal** studies; human safety is checked in clinical trials.

4 Forgetting QA and project management as teams — examiners expect the full team list, not just scientists.

5 Using "preclinical" and "non-clinical" as different stages — they mean the same phase (studies before human trials); "non-clinical" is the currently preferred regulatory term.

Mnemonics

- **Discovery stages — "To Try, Hit High, Lead On, Choose":** **T**arget identification → **T**arget validation → **H**it identification → **H**it-to-lead → **L**ead optimisation → **C**hoose candidate. (Two T's, two H's, L, C.)
- **Development path — "No Indians Play Cricket matches Without Practice, Please Watch":** **N**on-clinical → **I**ND → **P**hase I → **P**hase II → **P**hase III → **N**DA → a**P**proval → **P**hase IV (**W**atch = pharmacovigilance).
- **Clinical phases purpose — "Safe, Effective, Confirmed, Continued":** Phase I = **Safe**, Phase II = **Effective**, Phase III = **Confirmed**, Phase IV = **Continued** monitoring.
- **Teams — "Chemists Play Toxic Drugs, Clinicians Count, Regulators Question, Managers Plan":** **Chem**istry, **P**harmacology, **T**oxicology, **D**MPK, **C**linical, biostatistics (**Count**), **R**egulatory affairs, **QA**, project **M**anagement (**Plan**).

Exam Summary

Drug discovery finds a new molecule (target → hit → lead → candidate); drug development proves it safe and effective through non-clinical studies, IND filing, clinical trial Phases I–III, NDA filing, approval, and Phase IV monitoring. Ten functional teams contribute: chemistry, pharmacology, toxicology, DMPK, CMC/pharmaceutics, clinical, biostatistics, regulatory affairs, QA, and project management. Regulatory affairs bridges science and the authority; QA ensures GLP/GCP/GMP compliance throughout.

One-Minute Revision

- Discovery = find the molecule (target → hit → lead → candidate).
- Development = prove safe + effective → get approval (non-clinical → IND → Phase I, II, III → NDA → approval → Phase IV).
- IND = start human trials; NDA = sell the drug.
- Teams: chemistry, pharmacology, toxicology, DMPK, CMC, clinical, biostatistics, regulatory affairs, QA, project management.
- GLP = lab/animal studies; GCP = human trials; GMP = manufacturing.

Questions

Short Questions

1 Define drug discovery and drug development.

2 What is a biological target? Give the lock-and-key idea in one line.

3 Differentiate between a hit, a lead, and a drug candidate.

4 What is the purpose of an IND application?

5 List the four phases of clinical trials with one purpose each.

6 Name any four drug development teams and state one function of each.

7 What does QA do in drug development?

8 Expand GLP, GCP, GMP and state where each applies.

Long Questions

1 Describe the stages of the drug discovery process from target identification to candidate selection, with a flowchart.

2 Explain the complete drug development process from non-clinical studies to post-marketing surveillance.

3 Describe the functions of the chemistry, pharmacology, toxicology, and clinical teams in drug development. How do they interact?

4 Discuss the role of the regulatory affairs team as a bridge between the scientific teams and the regulatory authority, with examples of its activities at the IND and NDA stages.

5 Compare the discovery phase and development phase of a new drug under suitable headings.

MCQs (with Answer Key)

1 The stage that ends with the selection of a drug candidate is:

a) Phase III trials b) Drug discovery c) NDA review d) Phase IV **Answer: b**

1 A "hit" in drug discovery is:

a) The final marketed drug b) A chemical showing early activity against the target c) A toxic compound d) A placebo **Answer: b**

1 The IND application is filed to obtain permission for:

a) Marketing the drug b) Starting human trials c) Animal studies d) Export **Answer: b**

1 Phase II clinical trials mainly evaluate:

a) Safety in healthy volunteers b) Efficacy and dose in patients c) Long-term post-marketing safety d) Bioequivalence **Answer: b**

1 Toxicology studies in drug development are conducted in:

a) Humans b) Animals c) Computers only d) Hospitals **Answer: b**

1 Which team prepares and files the NDA?

a) Medicinal chemistry b) Regulatory affairs c) Pharmaceutics d) Project management **Answer: b**

1 GLP applies to:

a) Clinical trials b) Non-clinical laboratory studies c) Manufacturing d) Advertising **Answer: b**

1 Lead optimisation mainly involves:

a) Screening lakhs of chemicals b) Chemical modification guided by SAR c) Filing the IND d) Phase IV monitoring **Answer: b**

Viva Questions

1 What is the difference between drug discovery and drug development?

2 Define target, hit, lead, and candidate in one line each.

3 Why are animal studies done before human trials?

4 What is the role of biostatistics in drug development?

5 IND vs NDA — which comes first and why?

6 Name the teams involved in drug development.

7 What does the QA team audit?

Application-Based Questions

1 A company has identified a protein that causes a disease and found 5 chemicals that weakly block it in test tubes. Which stage of discovery is this, and what should the next two steps be?

2 A toxicology study shows liver damage in rats at high doses of a candidate drug. As a project manager, which teams would you call for a meeting and what would you ask each team to do?

3 A regulatory authority asks for additional safety data before allowing Phase II. Which team generates this data, and who communicates the response to the authority?

4 An Indian company wants to develop a generic version of an approved drug. Which parts of the full discovery-to-NDA path can it skip, and which studies will it still need?

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CHAPTER 4: Non-Clinical Drug Development

Learning Objectives

After studying this chapter, you should be able to:

1 Define non-clinical (preclinical) drug development and state its position in the overall development process.

2 Explain the regulatory purpose of non-clinical studies — why authorities require animal and laboratory data before human trials.

3 Describe the three pillars of non-clinical development: pharmacology, drug metabolism, and toxicology.

4 Classify pharmacology studies (primary, secondary, safety pharmacology) and explain each.

5 Explain ADME (absorption, distribution, metabolism, excretion) and its role in non-clinical development.

6 Classify toxicology studies by duration and by special type (acute, repeated-dose, genotoxicity, carcinogenicity, reproductive toxicity, safety pharmacology).

7 Explain GLP and why non-clinical safety studies must be GLP-compliant.

8 Describe how non-clinical data support the IND application and the safe starting dose in humans.

9 Answer exam, viva, and application-based questions on this topic.

Definitions

- **Non-clinical drug development (preclinical development):** All laboratory (in vitro) and animal (in vivo) studies conducted on a drug candidate **before** it is tested in humans. "Non-clinical" is the term preferred in current regulatory language; "preclinical" means the same thing.
- **In vitro:** Studies done outside a living body, for example in test tubes, cell cultures, or tissue preparations. (Latin: "in glass.")
- **In vivo:** Studies done in a living animal. (Latin: "in the living.")
- **Pharmacology (non-clinical):** Studies that show what the drug does — its desired effects, mechanism of action, and effective doses in laboratory models.
- **Drug metabolism studies (DMPK/ADME studies):** Studies of what the body does to the drug — how it is absorbed, distributed, broken down (metabolised), and excreted.
- **Toxicology:** Studies that identify the harmful effects of the drug, the doses at which harm appears, and whether the harm is reversible.
- **NOAEL (No Observed Adverse Effect Level):** The highest dose tested in animals at which **no** harmful effect is seen. This is the key number used to calculate a safe starting dose for the first human trial.
- **Safety pharmacology:** Studies that check the drug's effects on the body's vital functions — mainly the heart and blood vessels (cardiovascular), lungs (respiratory), and brain and nerves (central nervous system).
- **GLP (Good Laboratory Practice):** The quality system of rules for planning, performing, recording, and reporting non-clinical laboratory studies, so that the data are reliable and acceptable to regulators.

- **IND-enabling studies:** The set of non-clinical studies that must be completed before an IND application can be filed — the studies that "enable" the start of human trials.

Terminology Table

Term	Simple Meaning
Non-clinical / preclinical	Lab and animal studies before human trials (same phase, two names)
In vitro	Tested in test tubes / cell cultures
In vivo	Tested in living animals
Primary pharmacology	Studies proving the drug works against its target (efficacy)
Secondary pharmacology	Studies checking effects on other targets (off-target effects)
Safety pharmacology	Studies on vital functions: heart, lungs, brain
ADME	Absorption, Distribution, Metabolism, Excretion
Toxicokinetics	Measuring drug levels in animals during toxicology studies
Genotoxicity	Ability to damage genes/DNA (mutation risk)
Carcinogenicity	Ability to cause cancer
Reproductive toxicity	Harmful effects on fertility, pregnancy, or the unborn child
NOAEL	Highest animal dose with no harmful effect — basis of safe human starting dose
GLP	Good Laboratory Practice — quality rules for non-clinical studies

Simple Explanations

Why do we test drugs in animals before humans?

You would never give an unknown chemical to a person without first checking whether it harms a living body. Animals are used because their bodies work in broadly similar ways to ours — heart, liver, kidneys, brain. Non-clinical studies answer three questions for the regulator: (1) **Does it work?** (pharmacology), (2) **What does the body do to it?** (drug metabolism/ADME), and (3) **Does it cause harm, and at what dose?** (toxicology). Only when these answers look acceptable does the authority allow the first cautious dose in humans.

What is pharmacology in non-clinical development?

It is the proof that the drug does its job. Primary pharmacology shows the drug acts on its target and produces the desired effect in lab models (for example, lowers blood sugar in diabetic animals). Secondary pharmacology checks whether it accidentally acts on other targets (which could cause side effects). Safety pharmacology checks the vital organs — heart rhythm, breathing, brain function — to catch dangerous effects early.

What is drug metabolism (ADME) in simple words?

ADME tracks the drug's journey through the body: **A**bsorption (does it enter the blood from the gut?), **D**istribution (where does it travel — brain? liver? does it stay in blood?), **M**etabolism (does the liver break it into other chemicals called metabolites, and are those safe?), **E**xcretion (how does it leave — urine?

faeces? how fast?). If a drug is not absorbed, or is destroyed instantly by the liver, or accumulates dangerously, developers must know before human trials.

What is toxicology in simple words?

Toxicology deliberately gives animals increasing doses — including very high doses — to find where harm begins. It identifies which organs are damaged, whether the damage reverses after stopping the drug, and the NOAEL (the highest dose with no harm). The NOAEL, with a large safety margin applied, decides the **starting dose of the first human trial** — so toxicology directly protects the first volunteers.

Why must these studies follow GLP?

Because regulators make life-and-death decisions on this data. GLP ensures every study was planned in a written protocol, performed by trained staff, with calibrated instruments, complete records, and independent QA audit — so the data can be trusted and inspected years later.

Key takeaway: Non-clinical development = prove it works (pharmacology) + track its journey (ADME) + prove it is acceptably safe (toxicology), all under GLP — so the regulator can confidently permit the first human dose.

Classifications

1. Classification of non-clinical studies (three pillars)

1 **Pharmacology studies** — what the drug does to the body.

- *Primary pharmacodynamics:* effect on the intended target / disease model (efficacy proof).
- *Secondary pharmacodynamics:* effects on other targets (off-target profiling).
- *Safety pharmacology:* effects on vital functions (cardiovascular, respiratory, central nervous system).

1 **Drug metabolism / pharmacokinetic (DMPK, ADME) studies** — what the body does to the drug.

- Absorption, distribution, metabolism, excretion studies; metabolite identification; protein binding; toxicokinetics.

1 **Toxicology studies** — harmful effects and safe doses.

- By duration: single-dose (acute), repeated-dose (sub-acute ~2–4 weeks, sub-chronic ~3 months, chronic ~6–12 months).
- By special purpose: genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, immunotoxicity.

2. Classification of toxicology studies

Category	What it checks	When it is needed
Single-dose (acute) toxicity	Effects of one large dose	Early, before first human dose
Repeated-dose toxicity (sub-acute, sub-chronic, chronic)	Effects of daily dosing over weeks–months; target organs; reversibility	Before and during clinical trials; longer trials need longer animal studies

Category	What it checks	When it is needed
Genotoxicity	Damage to DNA/genes (mutation)	Before Phase II (as per latest guidelines — confirm current edition)
Carcinogenicity	Cancer-causing potential (long, ~2-year studies)	Before long-term marketing for chronic-use drugs
Reproductive toxicity	Effects on fertility, embryo, foetus, postnatal development	Before including women of childbearing potential / before marketing
Safety pharmacology	Vital function effects (heart, lungs, CNS)	Before first human dose
Local tolerance	Irritation at the site of administration	For injections, skin, eye products

3. Classification of pharmacology studies

1 **Primary pharmacodynamics** — does the drug produce the intended effect? (e.g., blood-pressure lowering in hypertensive animals).

2 **Secondary pharmacodynamics** — does it hit unintended targets? (screens against panels of receptors/enzymes).

3 **Safety pharmacology core battery** — cardiovascular (blood pressure, heart rhythm/ECG), respiratory (breathing rate), central nervous system (behaviour, movement, convulsions).

Mechanisms / Processes

Process 1: The non-clinical development workflow

1 **Candidate declared** (from discovery) → non-clinical programme begins.

2 **Pharmacology:** primary PD confirms efficacy in disease models; secondary PD profiles off-targets; safety pharmacology core battery checks vital functions.

3 **DMPK/ADME:** absorption and bioavailability, tissue distribution, metabolic pathways and metabolite identification, excretion routes; toxicokinetics run alongside toxicology.

4 **Toxicology:** single-dose → repeated-dose studies of increasing duration; genotoxicity battery; safety margins calculated from NOAEL.

5 **GLP compliance throughout:** written protocols, trained staff, calibrated equipment, raw-data records, QA audit, final study reports.

6 **Compilation:** all reports form the non-clinical part of the IND dossier; the NOAEL-based calculation sets the safe starting dose for Phase I.

7 **Regulatory review:** the authority examines the non-clinical package; only if satisfied does it permit human trials.

Process 2: From NOAEL to the first human dose (concept)

1 Find the NOAEL in the most sensitive animal species (highest dose with no harm).

2 Convert the animal dose to a human-equivalent dose (based on body surface area/species differences, as per the latest guidelines — confirm current method).

3 Apply a large **safety factor** (a divisor that makes the starting dose much lower than the human-equivalent NOAEL).

4 Result: the **safe starting dose** for Phase I — deliberately cautious, then increased step by step in the trial.

Process 3: ADME — the drug's journey (mechanism view)

1 **Absorption:** drug crosses the gut wall into blood (oral) or enters blood directly (injection).

2 **Distribution:** blood carries it around; some binds to plasma proteins; some enters tissues and organs.

3 **Metabolism:** mainly the liver chemically changes the drug into metabolites (often inactive, sometimes active or toxic) — studied via liver preparations and in animals.

4 **Excretion:** kidneys filter drug/metabolites into urine; liver may send them into bile and faeces.

5 Throughout, scientists measure **how much, where, for how long** — this predicts dosing frequency and warns of accumulation.

Textual Diagrams / Flowcharts

Diagram 1: The three pillars of non-clinical development

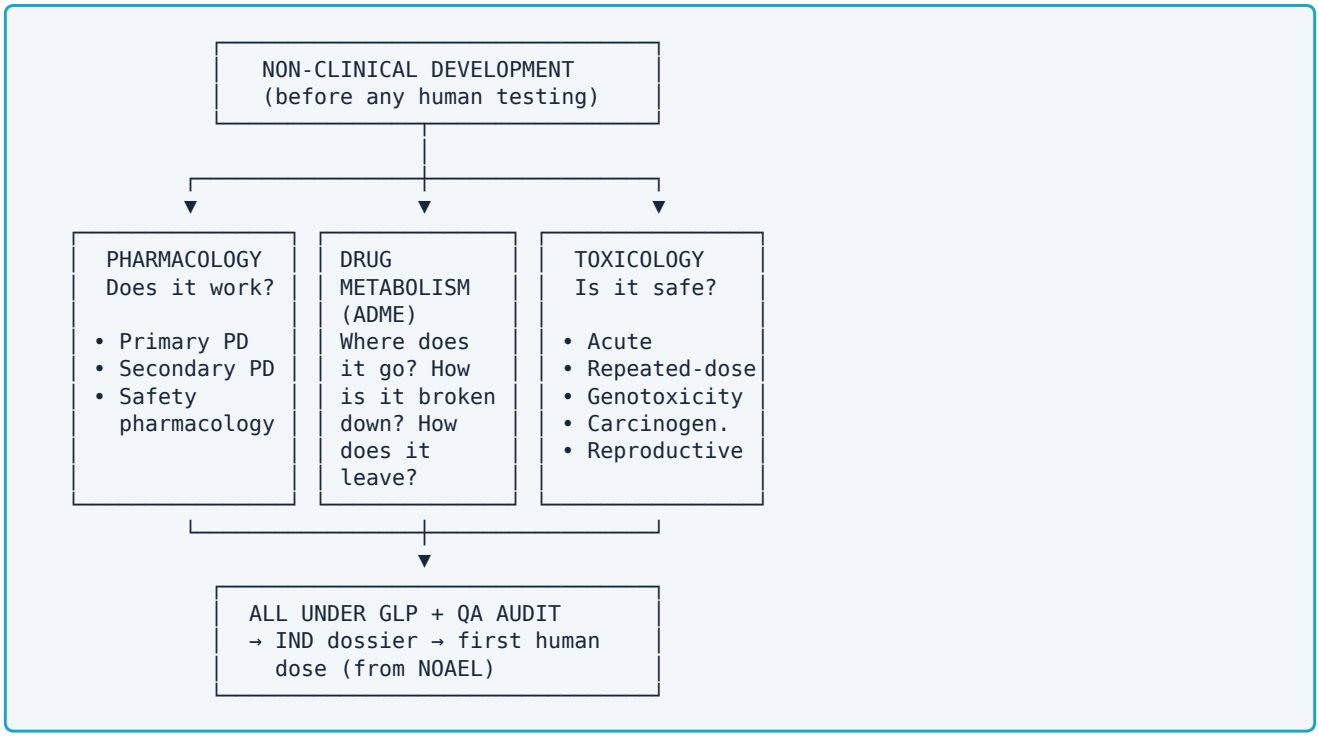


Diagram 2: Toxicology study timeline

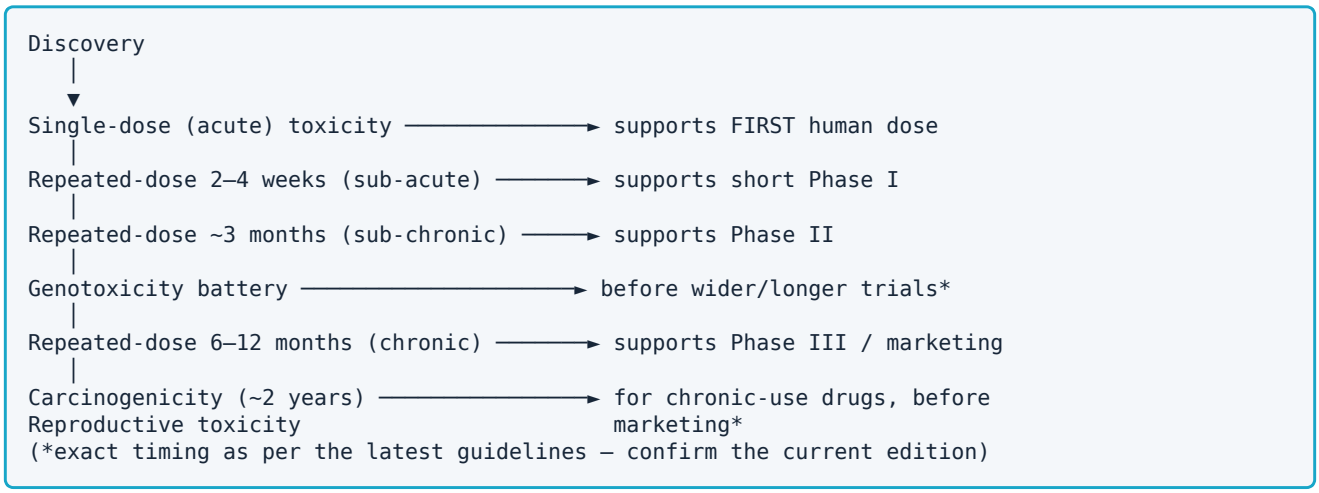
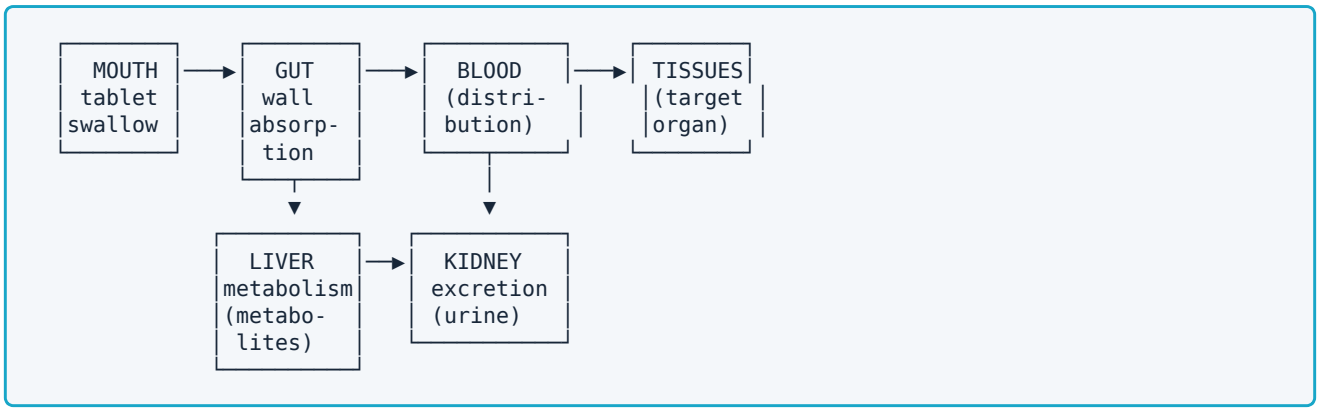


Diagram 3: ADME journey of an oral drug



Infographic Concept

INFOGRAPHIC CONCEPT: A three-pillar temple infographic titled "Non-Clinical Development". Three columns labelled Pharmacology (green, icon: target with arrow), Drug Metabolism/ADME (blue, icon: a capsule travelling through a body silhouette with A-D-M-E checkpoints), and Toxicology (amber, icon: a shield with a checkmark). Each column lists its key studies as stacked blocks. A foundation slab beneath reads "GLP + QA audit", and a roof beam reads "IND application → safe first human dose". A small NOAEL gauge on the toxicology pillar shows a needle pointing at the safe zone, with an arrow to a tiny human figure labelled "Phase I starting dose".

Tables

Table 1: Pharmacology vs drug metabolism vs toxicology (comparison)

Feature	Pharmacology	Drug Metabolism (ADME)	Toxicology
Core question	Does it work?	What does the body do to it?	Does it cause harm?
Focus	Desired effects, mechanism	Absorption, distribution, metabolism, excretion	Harmful effects, target organs
Typical models	Disease models, isolated tissues	Lab preparations, animals	Animals at multiple doses
Key output	Efficacy proof, dose rationale	PK profile, metabolites	NOAEL, safety margins

Feature	Pharmacology	Drug Metabolism (ADME)	Toxicology
Regulatory use	Supports therapeutic claim and dose	Supports dosing schedule, warns of accumulation	Decides safe starting dose in humans

Table 2: Duration-based toxicology studies

Study type	Duration	Purpose in the programme
Single-dose (acute)	One dose, ~2 weeks observation	Identify immediate toxic effects; support first human dose
Sub-acute	Daily dosing ~2–4 weeks	Early repeated-dose safety; target organs
Sub-chronic	Daily dosing ~3 months	Support longer clinical trials (e.g., Phase II)
Chronic	Daily dosing ~6–12 months	Support Phase III and marketing

Table 3: Special toxicology studies

Study	What it detects	Why the regulator wants it
Genotoxicity battery	DNA/gene damage (mutations)	Mutations can lead to cancer or birth defects
Carcinogenicity	Tumour formation over ~2 years	Needed for drugs taken long-term
Reproductive toxicity	Effects on fertility, embryo/foetus, development	Protects pregnant patients and future children
Safety pharmacology	Effects on heart, lungs, CNS	Prevents sudden life-threatening effects in first human dose
Local tolerance	Irritation at injection/skin/eye site	Ensures the formulation itself is not harmful

Examples

1. **Primary pharmacology:** A new blood-pressure drug lowers blood pressure in hypertensive rats in a dose-dependent way — this is the efficacy proof the regulator expects before human trials.
2. **Safety pharmacology catch:** A candidate for arthritis is found to slow the heart rate and disturb heart rhythm in dogs. Development is paused — this is exactly the kind of danger safety pharmacology exists to find before humans are exposed.
3. **ADME insight:** A promising molecule works in test tubes but is almost completely destroyed by the liver before reaching the blood (poor oral bioavailability). The DMPK data tells chemists to redesign the molecule or choose a different route (e.g., injection).
4. **NOAEL in action:** In rats, the NOAEL is 100 mg/kg/day and in dogs 30 mg/kg/day. The more sensitive species (dog) drives the calculation; after conversion and a large safety factor, the Phase I starting dose becomes a tiny fraction of these — protecting the first volunteers.
5. **Reversibility:** A repeated-dose study shows liver enzyme changes that fully disappear after a recovery period without the drug. The regulator notes the effect is reversible — an important detail in the risk assessment.

Analogies

1 **Test-driving a new car model:** Pharmacology = does the car run and reach speed (efficacy). ADME = how fuel flows, where it goes, how exhaust leaves (the drug's journey). Toxicology = crash tests at increasing speeds to find where the car breaks (harm at high doses). GLP = the certified test track with calibrated instruments and recorded results. The IND = the road-worthiness certificate application.

2 **Trying a new recipe for a hostel mess:** First you taste a spoonful yourself and ask friends (lab tests), then you serve a small group and watch for complaints (animal studies), and only then do you put it on the full menu (human trials). You would never serve an untested dish to 500 students.

3 **NOAEL as a bridge weight limit:** Engineers test a bridge with increasing loads until it cracks — the highest load with no crack, divided by a big safety factor, becomes the posted weight limit. Similarly, NOAEL divided by a safety factor becomes the safe starting human dose.

Pharmacy Relevance

- Pharmacists must understand non-clinical data because the **approved product information** (package insert) — which pharmacists counsel from — summarises the pharmacology, metabolism, and key safety findings from these studies.
- Pharmacists working in **regulatory affairs** compile and review non-clinical study reports for IND and marketing applications; those in **drug safety/pharmacovigilance** compare human adverse events with the toxicology findings predicted in animals.
- Understanding ADME helps pharmacists explain **why a drug is taken once daily vs three times daily**, why it must not be taken with certain foods, and why liver or kidney disease changes the dose — all rooted in non-clinical metabolism and excretion data.

India Context

- Non-clinical safety studies intended to support clinical trials and marketing applications in India must follow **GLP**, and India has GLP-certified test facilities whose data are accepted by Indian and many foreign regulators.
- The **CDSCO** reviews the non-clinical data package as part of clinical trial and new-drug applications in India — the same three pillars (pharmacology, ADME, toxicology) apply.
- Indian pharmaceutical companies conducting **generic drug development** rely less on full non-clinical programmes (since the innovator's safety is established) and more on bioequivalence studies — but any **new drug** developed in India needs the complete non-clinical package described in this chapter.
- Exact study requirements and timing should always be checked against the latest CDSCO guidance and applicable rules/notifications — confirm the current edition before citing specifics.

Key Points

1 Non-clinical development = lab + animal studies **before** human trials; "preclinical" means the same.

2 Three pillars: **pharmacology** (does it work?), **drug metabolism/ADME** (what does the body do to it?), **toxicology** (does it harm?).

3 Pharmacology has three parts: primary (efficacy), secondary (off-targets), safety pharmacology (vital functions: heart, lungs, CNS).

4 ADME = Absorption, Distribution, Metabolism, Excretion — predicts dosing and warns of accumulation.

5 Toxicology finds target organs, reversibility, and the **NOAEL** — the highest animal dose with no harm.

6 NOAEL → (conversion + safety factor) → safe **starting dose** for Phase I.

7 All pivotal safety studies must be **GLP-compliant** with QA audit; the data package supports the IND.

Common Confusions

1 **Preclinical vs non-clinical:** Same phase, two names — "non-clinical" is the term currently preferred in regulatory documents.

2 **Pharmacology vs toxicology:** Pharmacology = desired effects; toxicology = harmful effects. Safety pharmacology belongs to the pharmacology pillar but serves a safety purpose — students often file it under toxicology.

3 **NOAEL vs safe human dose:** NOAEL is an **animal** dose; the human starting dose is derived from it after conversion and a large safety factor — never use the NOAEL directly as a human dose.

4 **In vitro vs in vivo:** In vitro = test tube/cells; in vivo = living animal. Both are "non-clinical."

5 **Acute vs chronic toxicity:** Acute = single dose effects; chronic = effects of months of daily dosing. Longer clinical trials require longer animal studies.

Common Mistakes

1 Writing that non-clinical studies are done in humans — they are strictly **before** human trials.

2 Stating the IND is filed before non-clinical studies — the IND is filed **after** the IND-enabling non-clinical package is complete.

3 Confusing ADME letters — memorise as **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion, in that order of the drug's journey.

4 Forgetting GLP — examiners expect "GLP-compliant" whenever non-clinical safety studies are described.

5 Saying toxicology proves efficacy — toxicology proves **safety margins**; efficacy is pharmacology's job.

Mnemonics

- **Three pillars — "PET": P**harmacology, drug m**E**tabolism, **T**oxicology — every non-clinical programme is a PET.
- **ADME — "A Drug Moves Everywhere": A**bsorption, **D**istribution, **M**etabolism, **E**xcretion.
- **Pharmacology types — "Please See Safety": P**rimary, **S**econdary, **S**afety pharmacology.
- **Toxicology duration ladder — "A Sub Sub Chronic Car": A**cute → **Sub**-acute → **Sub**-chronic → **Chronic** → **Car**cinogenicity (plus genotoxicity and reproductive studies alongside).

- **Safety pharmacology core battery — "Heart, Breath, Brain":** **C**ardiovascular, **R**espiratory, **C**NS — the three vital functions.

Exam Summary

Non-clinical (preclinical) development comprises laboratory and animal studies done before human trials, built on three pillars: pharmacology (primary, secondary, and safety pharmacology), drug metabolism (ADME), and toxicology (acute, repeated-dose, genotoxicity, carcinogenicity, reproductive toxicity). Studies must be GLP-compliant with QA audit. Toxicology establishes the NOAEL, from which — after conversion and a safety factor — the safe Phase I starting dose is derived. The complete non-clinical data package supports the IND application.

One-Minute Revision

- Non-clinical = before humans; three pillars: **PET** — Pharmacology, drug mEtabolism, Toxicology.
- Pharmacology: primary (works?), secondary (off-targets), safety (heart, lungs, brain).
- ADME: **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion.
- Toxicology → **NOAEL** → safe starting human dose (with safety factor).
- All under **GLP** → data go into the **IND**.

Questions

Short Questions

1 Define non-clinical drug development. How is it different from clinical development?

2 Name the three pillars of non-clinical development with one question each answers.

3 What are primary, secondary, and safety pharmacology?

4 Expand ADME and explain each term in one line.

5 Define NOAEL and state its regulatory use.

6 Why must non-clinical safety studies be GLP-compliant?

7 List four special toxicology studies and what each detects.

8 What are IND-enabling studies?

Long Questions

1 Describe the three pillars of non-clinical drug development — pharmacology, drug metabolism, and toxicology — with suitable classifications and a flowchart.

2 Classify toxicology studies by duration and by special purpose. Explain how their results support the IND application.

3 Explain the concept of NOAEL and describe how the safe starting dose for the first-in-human trial is derived from non-clinical data.

4 Discuss the role of GLP in non-clinical development. Why do regulators insist on it?

5 A new drug candidate is ready for non-clinical development. Design the sequence of studies (pharmacology, ADME, toxicology) it should undergo before an IND can be filed.

MCQs (with Answer Key)

1 Non-clinical studies are conducted:

a) In humans b) In laboratories and animals before human trials c) After marketing d) Only on computers **Answer: b**

1 Primary pharmacology studies demonstrate:

a) Toxic effects b) Efficacy against the intended target c) Metabolism d) Excretion **Answer: b**

1 ADME stands for:

a) Action, Dose, Metabolism, Effect b) Absorption, Distribution, Metabolism, Excretion c) Activity, Duration, Measurement, Elimination d) Agonist, Dose, Metabolite, Excretion **Answer: b**

1 NOAEL is:

a) The lowest toxic dose b) The highest animal dose with no observed adverse effect c) The human therapeutic dose d) The lethal dose **Answer: b**

1 Safety pharmacology core battery covers:

a) Liver, kidney, skin b) Cardiovascular, respiratory, CNS c) Blood, bone, muscle d) Eye, ear, nose **Answer: b**

1 Genotoxicity studies detect:

a) Liver damage b) DNA/gene damage c) Heart rhythm changes d) Skin irritation **Answer: b**

1 GLP ensures:

a) Faster trials b) Reliable, traceable, auditable non-clinical data c) Cheaper drugs d) Marketing approval **Answer: b**

1 Carcinogenicity studies are required mainly for:

a) Single-dose drugs b) Drugs intended for long-term/chronic use c) Topical creams only d) Vaccines only **Answer: b**

Viva Questions

1 What are the three pillars of non-clinical development?

2 Define NOAEL. How is it used?

3 Why are animals used before humans?

4 What is the difference between primary and safety pharmacology?

5 What does GLP stand for and why does it matter?

6 Name two special toxicology studies and their purpose.

7 What is toxicokinetics?

Application-Based Questions

1 A candidate shows excellent efficacy in rats but causes convulsions in dogs at moderate doses. Which pillar and study type caught this, and what should the development team do next?

2 A company wants to start Phase I but has only completed efficacy studies in mice, with no toxicology data. Can it file the IND? Justify with the regulatory purpose of non-clinical studies.

3 An oral drug candidate has 5% oral bioavailability in rats due to heavy liver metabolism. Explain, using ADME concepts, what formulation or chemistry options the team has.

4 During a 3-month toxicology study, kidney changes are seen at high doses but fully reverse after a 1-month recovery period. How would you present this finding in the IND, and why does reversibility matter to the regulator?

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