

Unit 1: Foundations of Toxicology, Regulatory Guidelines and Good Laboratory Practice

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Pharmacological and Toxicological Screening Methods II, subject code MPL202T, is a core Semester 2 subject of M.Pharm Pharmacology. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. Screening Methods I asked whether a new substance works. This subject asks the harder question that decides whether it may ever be given to a human being: whether it is safe enough, at what exposure its harm begins, and how that harm can be detected, measured and judged before the first clinical trial. Unit 1 builds the foundations: the definition and branches of toxicology, the regulatory guideline systems of the OECD, ICH, EPA and Schedule Y, and the OECD principles of good laboratory practice that make a toxicity study legally believable. Unit 2 covers the general toxicity studies themselves: acute, sub-acute and chronic studies by the oral, dermal and inhalational routes as per OECD guidelines, the local tolerance studies of the eye and skin, and the characterization of the test item without which no result can be interpreted. Unit 3 covers the special toxicity studies: reproductive toxicology in its three segments, the genotoxicity battery built around the Ames test and the micronucleus and chromosomal aberration assays, and the in vivo carcinogenicity bioassay. Unit 4 brings the package together into the IND enabling studies that open the door to clinical trials, and teaches safety pharmacology with its Tier 1 core battery and Tier 2 follow up studies. Unit 5 completes the subject with toxicokinetics, the measurement of exposure inside toxicity studies, and the alternative methods that are steadily replacing animal toxicity testing. A student who completes this subject should be able to name the study, the guideline and the endpoint for every element of a preclinical safety package, and explain why regulators across the world accept each other's data.

1.1 Toxicology: the science of harm

Toxicology is the study of the adverse effects of chemical, physical and biological agents on living organisms, and of the conditions under which those effects appear. Its founding idea is usually credited to Paracelsus, the sixteenth century physician who wrote that all things are poison and nothing is without poison; the dose alone makes a thing not poison. That single sentence still organizes the whole subject: a drug is not safe or unsafe in itself, it is safe or unsafe at a dose, in a species, by a route, for a duration. Toxicology exists to find those boundaries before patients do.

The scope of the science is wide. It covers the detection of adverse effects (what happens), their mechanism (how it happens), their dose and time relationships (how much and how fast), and their prediction for humans (what it means for the patient). In drug development, toxicology is the discipline that stands between a promising pharmacological result and the first human dose: the efficacy screening of Screening Methods I shows that a substance can work, and the toxicity studies of this subject show the price at which it works and the margin between the price and the poison.

1.2 The four branches named by the syllabus

The PCI syllabus names four types or branches of toxicology, and the distinction between them is a distinction of purpose.

- **General toxicology** studies the overall adverse effect profile of a substance: which organs it injures, at what doses, after what duration, and whether the injury reverses when dosing stops. The acute and repeated dose studies of Unit 2 are its main tools.
- **Mechanistic toxicology** asks how the injury happens at the molecular and cellular level: which enzyme is inhibited, which reactive metabolite is formed, which receptor is overstimulated. Mechanistic knowledge turns an observed lesion into an understood risk, and often explains why one species is injured and another is not.
- **Regulatory toxicology** is the applied branch: it designs, conducts and judges studies so that they satisfy the requirements of the authorities who license medicines. It works to named guidelines (OECD, ICH, EPA, Schedule Y) under good laboratory practice, and its product is not a paper but a decision: a licence application accepted, a clinical trial permitted, a warning written.
- **Descriptive toxicology** describes the toxicity of substances in practical terms: toxicity data for existing chemicals, antidotes and treatment of poisoning, and the hazard information carried on labels and safety data sheets. It is the branch closest to clinical and occupational practice.

Around these four sit recognised special areas that grew out of them: reproductive and developmental toxicology (Unit 3), genetic toxicology (Unit 3), carcinogenicity assessment (Unit 3), and the safety pharmacology of Unit 4.

1.3 Dose and response: the grammar of every toxicity study

Every study in this subject is a variation on one experiment: give graded doses, observe graded responses, and find where benefit ends and harm begins. The key terms are used identically by every guideline system in the world.

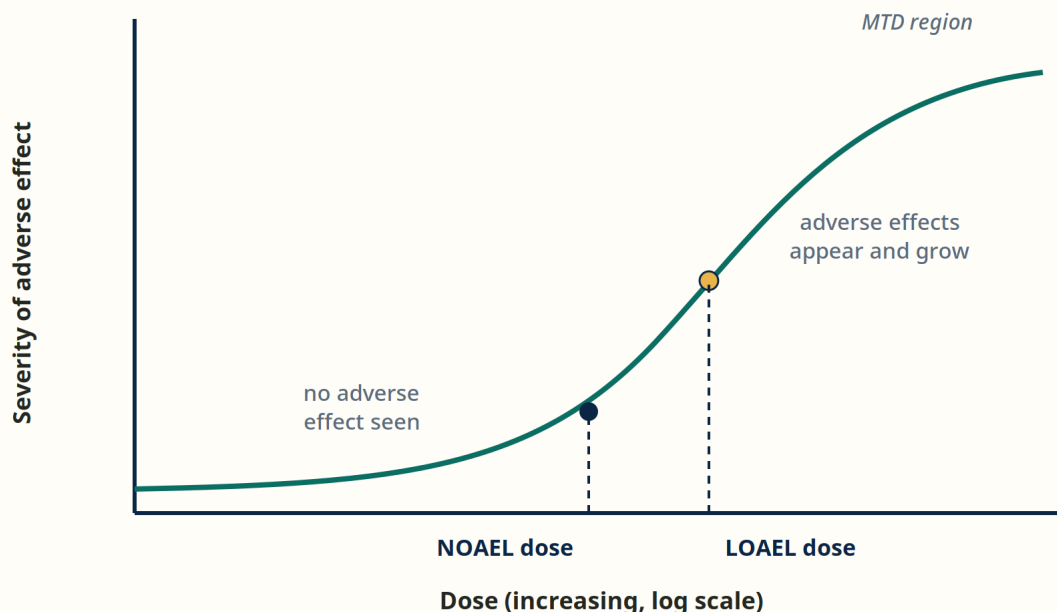
- The **dose response relationship** links the size of the dose to the incidence and severity of an effect. For toxicity work the response of interest is an adverse effect, and the curve is usually steep near the dose where injury starts.
- The **NOAEL** (no observed adverse effect level) is the highest dose at which no adverse effect is seen. It is the single most important number in a toxicity study, because safety margins for human dosing are built from it.
- The **LOAEL** (lowest observed adverse effect level) is the lowest dose at which an adverse effect does appear. Together, NOAEL and LOAEL bracket the threshold of harm.
- The **LD50**, the dose lethal to 50 percent of animals, was the historical centre of acute toxicity testing. Modern guidelines have largely replaced the precise LD50 with classification methods that use far fewer animals (Unit 2), but the concept still explains the older literature.
- **Target organ toxicity** names the pattern regulators look for: most toxicants injure one or two organs first (liver and kidney lead the list because they metabolise and excrete), and the histopathology of those organs is where the NOAEL is usually decided.

A toxicity study is **regulatory** when three conditions hold together: it follows a named guideline, it is conducted under good laboratory practice, and it is performed on a characterized test item (Unit 2). Only then will an authority in another country accept it without asking for the work to be repeated.

The NOAEL also has a practical partner that students should be able to define: the **maximum tolerated dose (MTD)**, the highest dose that produces toxicity without death, severe suffering or a body weight loss so large that the study becomes uninterpretable. Regulatory designs deliberately aim the top dose at or near the MTD, because a study whose highest dose produces no effect at all leaves the regulator asking whether the substance was ever truly challenged. Between the NOAEL below and the MTD above, the

dose response curve of a toxicity study tells its whole story.

Dose, response, NOAEL and LOAEL



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Figure: The dose response grammar of every toxicity study: severity stays at zero through the NOAEL dose, adverse effects appear from the LOAEL dose, and the top doses approach the maximum tolerated dose.

1.4 Why toxicity studies are regulated at all

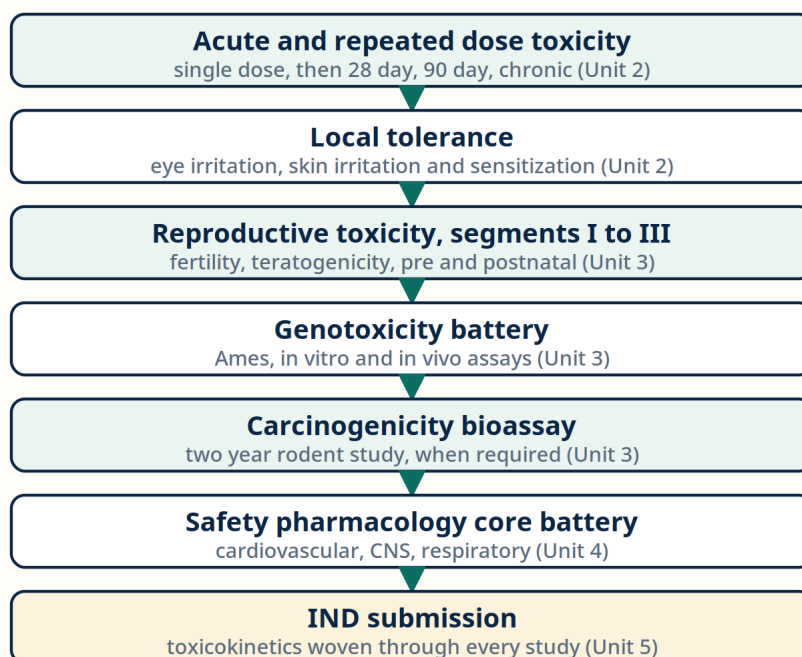
Toxicity data decide whether human beings may be exposed to a new substance, so society does not leave their quality to chance. Regulation serves four purposes. It protects trial volunteers and patients by demanding proof of a safety margin before exposure. It protects animals by standardising studies so that no study is wasted or repeated needlessly. It makes results comparable between laboratories and countries, so a study done once, properly, is accepted everywhere. And it creates trust: a regulator can rely on data it did not watch being generated only if the study followed a guideline, under GLP, with auditable raw data.

The practical shape of the whole subject follows from this: a standard battery of studies, run in a standard order, each one answering a question the regulator will ask.

The standard preclinical safety battery, in the order it is usually built

- Acute and repeated dose toxicity (Unit 2)
 - |
 - Local tolerance: eye, skin (Unit 2)
 - |
 - Reproductive toxicity, segments I to III (Unit 3)
 - |
 - Genotoxicity battery (Unit 3)
 - |
 - Carcinogenicity bioassay, when required (Unit 3)
 - |
 - Safety pharmacology core battery (Unit 4)
 - |
 - Toxicokinetic exposure data throughout (Unit 5)
 - |
 - IND submission and first human dose (Unit 4)

The preclinical safety battery



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Figure: The standard preclinical safety battery in the order it is usually built, from acute toxicity to the IND submission, with toxicokinetics measured throughout.

1.5 The OECD and its test guidelines

The **OECD** (Organisation for Economic Co-operation and Development) is the body whose test guidelines dominate regulatory toxicology worldwide. Its Guidelines for the Testing of Chemicals are numbered methods, each describing one study in operational detail: the species, group sizes, dose levels, observations, and the data to be reported. A study run to an OECD test guideline in an OECD member or adherent country, under GLP, benefits from the OECD system of **Mutual Acceptance of Data (MAD)**: other member countries must accept the data for assessment, which abolishes duplicate testing across borders.

For the student, the OECD guidelines are best learned as a numbered map of this subject: 400 series numbers cover health effects testing, and Unit 2 and Unit 3 of these notes cite the guideline number beside each study design. The OECD also maintains the Principles of Good Laboratory Practice (section 1.10), which are the quality rules under which guideline studies must be run to count as regulatory.

1.6 ICH: harmonising the drug specific requirements

The **ICH** (International Council for Harmonisation) harmonises the technical requirements for registering medicines in its member regions, so that one development programme can serve the world. Its safety (S) series is the drug specific layer that sits above the OECD chemical guidelines:

- **ICH M3(R2)** is the umbrella guidance: it states which nonclinical studies are needed to support each stage of clinical development, and when. It is the document a development team opens first.
- **ICH S3A** covers toxicokinetics (Unit 5).
- **ICH S2(R1)** defines the genotoxicity battery (Unit 3).
- **ICH S5** covers reproductive and developmental toxicity (Unit 3).

- **ICH S1** covers carcinogenicity studies (Unit 3).
- **ICH S7A and S7B** cover safety pharmacology and the QT interval risk (Unit 4).

The division of labour is simple to state: OECD writes the detailed study methods, ICH states which studies a medicine needs and how they fit together.

1.7 EPA and the United States framework

In the United States, drug safety for human medicines is regulated by the Food and Drug Administration (FDA), which receives the IND of Unit 4 and applies ICH and OECD standards. The **EPA** (Environmental Protection Agency) is named in the syllabus because it is the other great American toxicology regulator: it governs pesticides and industrial chemicals under its own test guidelines and its own GLP standard, and much of the classical toxicology literature, terminology and study design in textbooks was shaped by EPA requirements. A student of regulatory toxicology should know that the same study may be judged under FDA rules for a medicine and EPA rules for a pesticide, with closely similar designs and different legal homes.

1.8 Schedule Y and the Indian framework

Schedule Y of the Drugs and Cosmetics Rules is the Indian appendix that historically prescribed the requirements for clinical trials and for the preclinical toxicity data needed to support them, including the animal toxicity studies expected before a new drug could be tried or marketed in India. It is the framework under which generations of Indian toxicology studies were planned, and the syllabus names it for that reason. The clinical trial provisions have since been carried into the New Drugs and Clinical Trials Rules, 2019, which now govern trial permission and conduct in India, while the underlying expectation is unchanged: local regulators, like all others, ask for guideline toxicity studies under GLP, and India participates in the OECD MAD system through its National GLP Compliance Monitoring Authority (NGCMA), which inspects and certifies Indian GLP test facilities.

1.9 The guideline systems compared

System	Who issues it	What it governs	Key instruments for this subject
OECD	Organisation for Economic Co-operation and Development, member countries	Detailed study methods and GLP quality rules for chemicals and medicines	Test Guidelines (400 series), Principles of GLP, Mutual Acceptance of Data
ICH	International Council for Harmonisation	Which nonclinical studies a medicine needs, and their timing	M3(R2), S1, S2(R1), S3A, S5, S7A, S7B
EPA	United States Environmental Protection Agency	Pesticides and industrial chemicals, US	Harmonised test guidelines, EPA GLP standard
FDA	United States Food and Drug Administration	Human medicines, US	IND system, ICH adoption, 21 CFR Part 58 (GLP)
Schedule Y	Government of India, Drugs and Cosmetics Rules	New drug trials and approvals in India (now largely carried into the NDCT Rules 2019)	Toxicity study requirements, Indian GLP monitoring through NGCMA

1.10 Good laboratory practice: history and concept

Good laboratory practice (GLP) is a quality system concerned with the organisational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. It is not about whether the science is clever; it is about whether the data can be trusted and reconstructed years later by someone who was not there.

The history explains the severity of the rules. In the 1970s, inspections of some contract testing laboratories in the United States, most famously Industrial Bio-Test Laboratories, revealed studies that had been fabricated, backdated or so badly recorded that the results could not be believed. The response was regulatory: the US FDA issued GLP regulations in 1978 (21 CFR Part 58), and the OECD adopted its Principles of GLP in 1981 so that the standard, and the data produced under it, could cross borders under MAD. The concept has three pillars: everything is planned in advance in a written study plan, everything done is recorded contemporaneously as raw data, and an independent quality assurance unit audits the work against both.

1.11 The OECD principles of GLP

The OECD principles organise a test facility around responsibility and traceability.

- **Test facility management** appoints the study director, provides resources, and owns the system as a whole.
- The **study director** is the single point of control for one study: they approve the study plan, ensure the work follows it, and sign the final report accepting responsibility for the data.
- A **quality assurance (QA) programme**, independent of the study staff, inspects the study at critical phases, audits the report against the raw data, and issues a QA statement.
- **Standard operating procedures (SOPs)** fix in writing how every routine operation is done, from animal receipt to balance calibration, so that the method does not depend on who is on duty.
- The **study plan (protocol)** is written and approved before work begins; amendments and deviations are documented, never silent.
- **Raw data** are recorded promptly, legibly and indelibly, with every change made so that the original entry remains readable, initialled and dated.
- **Test item and reference item** are characterized and their handling documented (Unit 2), and specimens, raw data and the final report are **archived** for a defined period under controlled access.

1.12 GLP in drug development: why it matters

GLP matters in drug development for one practical reason: nonclinical safety studies are almost never repeated. A two year carcinogenicity study or a 90 day toxicity study is too expensive and too slow to redo, and the ethics of animal use forbid casual repetition. The regulator's decision to let humans be exposed rests, once and permanently, on these studies. GLP is the mechanism that lets a reviewer in any country trust them. Studies that are not run under GLP may still be scientifically interesting, but they generally cannot support an IND or a marketing application, which is why sponsors treat GLP compliance as a gate, not a preference.

1.13 GLP and its neighbours: GCP and GMP

System	Full name	Protects	Where it applies
GLP	Good laboratory practice	Integrity of nonclinical safety data	Animal toxicity and safety studies before and during development
GCP	Good clinical practice	Rights of trial participants and integrity of clinical data	Human clinical trials
GMP	Good manufacturing practice	Quality of the manufactured product	Production and quality control of medicines

The three systems share one philosophy: if it is not written down and checked, it did not happen. GLP is the member of the family that this subject applies.

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