

Unit 4: Non Clinical Drug Development and Global Submissions

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4.1 Purpose of non clinical development

Non clinical development is the laboratory and animal work done before, and alongside, the first studies in humans. ("Non clinical" is the modern regulatory term; "preclinical" is the older synonym.) Its job is to answer three questions before a human receives the drug: what does the drug do (pharmacology), what harm can it do (toxicology), and what happens to it in the body (pharmacokinetics and metabolism). The results decide whether human testing may start, the safe starting dose and escalation plan for the first trial, and the monitoring the protocol must build in.

The work is done under **Good Laboratory Practice (GLP)** for the safety studies: a quality system covering organisation, facilities, written procedures, raw data and archiving, with an independent quality assurance unit, because regulators must be able to reconstruct and trust studies they did not witness. Pivotal toxicology studies that do not follow GLP are generally not accepted in support of human dosing.

4.2 The non clinical study programme

- **Pharmacology:** primary pharmacodynamics (the intended action and potency), secondary pharmacodynamics (other actions of the drug), and **safety pharmacology**, the core battery of studies on the cardiovascular, respiratory and central nervous systems (ICH S7), which looks for dangerous functional effects (for example effects on cardiac conduction, studied through the hERG channel and QT interval work) before human exposure.
- **Pharmacokinetics and toxicokinetics:** absorption, distribution, metabolism and excretion in animals, plasma protein binding, metabolite identification, and the measurement of drug exposure inside the toxicity studies (toxicokinetics), so that animal doses can be compared with human doses by exposure, not by dose alone.
- **Toxicology:** single dose (acute) studies, repeated dose studies of increasing duration matched to the intended length of human use (ICH M3 sets the matching), genotoxicity testing (ICH S2, the standard battery for mutation and chromosome damage), carcinogenicity studies for long term use products (ICH S1), reproductive and developmental toxicology (ICH S5) before populations that include women of childbearing potential are exposed, and local tolerance and immunotoxicity work where the product needs it.

The governing logic is proportionality and sequence: short animal studies open short human trials, and longer animal coverage is added as human exposure lengthens, so the non clinical programme and the clinical programme grow together.

4.3 The Investigational New Drug application (IND)

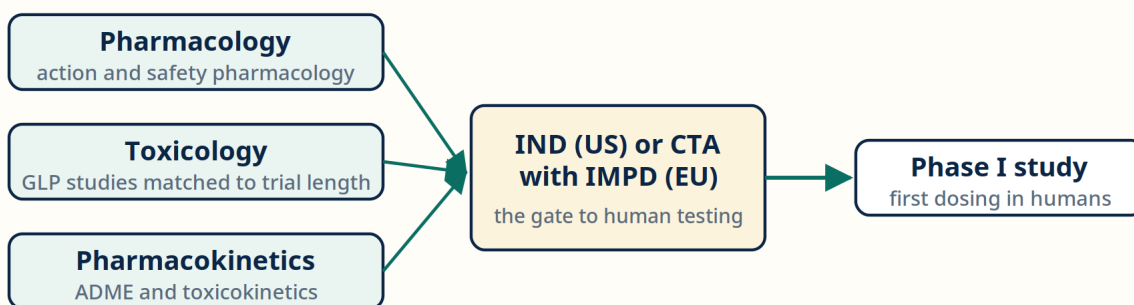
In the US, a drug that is not approved may not be shipped across state lines for human testing unless an exemption applies; the **IND** is that exemption. A sponsor files an IND with FDA containing:

- The general investigational plan and the protocol for the first clinical study (Unit 5).
- The investigator brochure (Section 4.6).

- The completed non clinical pharmacology and toxicology evidence, and any earlier human experience with the drug.
- The CMC information for the investigational product, enough to show it can be made consistently and safely for trial use.
- The commitment to conduct the trial under GCP, with IRB review and informed consent.

The IND goes into effect 30 days after FDA receipt unless the agency places a **clinical hold** (for example because the non clinical data show an unreasonable risk, or the protocol is too unsafe to proceed). The sponsor then maintains the IND with protocol amendments, safety reports and annual reports for the life of the development programme. Other regions run the same gate under other names: the clinical trial application (CTA) in the EU, built around the IMPD (next section), and the clinical trial permission route through CDSCO in India under the New Drugs and Clinical Trials Rules, 2019.

Non Clinical Evidence Opens the Clinical Gate



Longer animal studies are added as human exposure lengthens (ICH M3).
Investigator brochure carries this evidence to every investigator.

Figure: Non clinical evidence opens the clinical gate: the IND in the US, or the CTA supported by the IMPD in the EU.

4.4 Global submission of IND, NDA and ANDA

Unit 1 and Unit 2 described the US applications one at a time; this section puts the three together as a global filing pattern.

Application	What it authorises	Evidence core	Typical filer
IND (US) / CTA with IMPD (EU)	Testing the drug in humans	Non clinical package, protocol, investigational product CMC	Innovator sponsor, occasionally academic or generic sponsors for BE work under local rules
NDA (US) / MAA (EU)	Marketing a new drug	Full quality, non clinical and clinical evidence owned by the applicant	Innovator company
ANDA (US) / generic MAA (EU)	Marketing a generic copy	Quality package, bioequivalence, reliance on the reference product's established safety and efficacy	Generic company

The practical meaning of "global submission" is that the applicant writes the evidence core once, in CTD modules, and then runs the gates of each region in sequence: trial authorisation before trials, marketing application after pivotal trials, and generic applications only when the reference product's protections allow. The regional wrappers differ (Module 1, fees, local representatives), the evidence logic does not.

4.5 The Investigational Medicinal Product Dossier (IMPD)

The **IMPD** is the dossier that supports a clinical trial application in the EU; it is the trial-stage counterpart of the marketing dossier. Its contents mirror the CTD in miniature:

- **Quality data** on the investigational medicinal product and any comparator or placebo: manufacture, characterisation, specifications, stability for the trial period.
- **Non clinical data:** the pharmacology and toxicology summary and reports relevant to the proposed trial, drawn from the programme of Section 4.2.
- **Clinical data:** previous human experience with the product, if any.
- **Risk and benefit assessment:** an overall evaluation tying the non clinical and clinical evidence to the specific protocol, population and doses proposed.

A simplified IMPD can be used where the product is already authorised or has been assessed in an earlier application, because the authority can cross refer to what it already holds. The IMPD plus the protocol and the investigator brochure form the core of the CTA package.

4.6 The investigator brochure (IB)

The **investigator brochure** is the compiled briefing document given to every clinical investigator: the single place where the sponsor sets out everything known about the investigational product that matters for running the trial safely. Its contents, per GCP (ICH E6):

- Description of the product and its formulation.
- Summary of non clinical pharmacology, toxicology and pharmacokinetics, with the sponsor's interpretation of what they mean for humans.
- Effects in humans so far, including safety and efficacy findings and marketed experience if the product is sold elsewhere.
- Guidance for the investigator: expected risks and adverse reactions, precautions, dose modification and stopping guidance, and the management of overdose or special populations.

The IB is a living document: it is updated as new data arrive, at least annually in an active programme, and material new safety information in it is one of the triggers for protocol amendments and fresh consent information (Unit 5). Both the IND and the CTA rely on it, which is why the syllabus places the IMPD and the IB together: they are the two documents through which the non clinical work is presented for human testing.