

Unit 4: IND Enabling Studies and Safety Pharmacology

Free notes at pharmacolearn.fyi

4.1 The IND: the licence to test in humans

IND stands for Investigational New Drug. In the United States system, a new drug may not legally be given to humans, or even shipped across state lines for a trial, until an IND application is in effect with the FDA. The application tells the regulator what the drug is, how it is made, what the animal studies showed, and exactly how the first human trial will be run. The FDA then has 30 days from receipt to raise a clinical hold; if it does not, the trial may begin. Other systems use other names for the same gate (the clinical trial application in Europe and in India's NDCT Rules framework), but the concept the syllabus teaches is universal: human exposure is a permission earned with preclinical data, and the **IND enabling studies** are the preclinical studies performed to earn it.

4.2 Importance of the IND: the industry perspective

From the industry side, the IND is the first great value gate of development. Up to the IND, spending is comparatively small and failure is cheap; after it, clinical trials consume the great majority of the development budget. Companies therefore treat the IND enabling package as a disciplined investment decision: the studies must be the right ones, run under GLP, reported to a standard that survives regulatory review the first time, because a clinical hold costs months and a refused programme costs everything spent so far. The IND also converts science into a negotiable asset: a candidate with an accepted IND and a permitted trial is worth a multiple of the same molecule without one, which is why the studies of Units 2 and 3 are scheduled backwards from the intended IND date in every development plan.

4.3 The list of studies needed for IND submission

The IND enabling sequence

```
Pharmacology proof of concept and dose ranging (Screening Methods I)
|
Safety pharmacology core battery (this unit)
|
Genotoxicity battery: Ames + in vitro + in vivo (Unit 3)
|
Repeated dose toxicity in two species, rodent and non-rodent,
duration at least equal to the planned trial (Unit 2)
|
Toxicokinetic exposure data from those studies (Unit 5)
|
Local tolerance for the intended route (Unit 2)
|
Compilation into the IND (pharmacology and toxicology summaries)
|
Submission: 30 day regulator review, then the first human dose
```

In concrete terms, the standard first in human IND package contains: the primary pharmacology and dose ranging data; the safety pharmacology core battery; the genotoxicity battery; repeated dose toxicity studies in a rodent and a non-rodent species whose duration supports the planned trial length under ICH M3(R2), with toxicokinetics; local tolerance data for the clinical route; and reproductive toxicity and carcinogenicity studies staged later, before the trial phases and populations they protect (embryofoetal studies before trials including women of childbearing potential under the applicable regional rules, carcinogenicity normally

before marketing). The examiner's phrase "list of studies needed for IND submission" refers to exactly this list.

4.4 Safety pharmacology: origin and concept

Safety pharmacology grew out of classical general pharmacology. Through the twentieth century, new drugs were examined for secondary effects beyond their target organ, informally and inconsistently. Two forces formalised the discipline: a series of drug withdrawals for unexpected effects on the heart's electrical rhythm, and the ICH decision to give the field its own guidelines, S7A for safety pharmacology studies for human pharmaceuticals and S7B for the delayed ventricular repolarisation (QT interval) risk. The concept is precise: **safety pharmacology studies investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within and above the therapeutic range.** The emphasis differs from toxicology: toxicology studies structural injury at high doses over time, safety pharmacology studies functional disturbance, often immediate and dose related, in the systems whose failure can kill quickly: the cardiovascular system, the central nervous system and the respiratory system.

4.5 Tier 1: the core battery

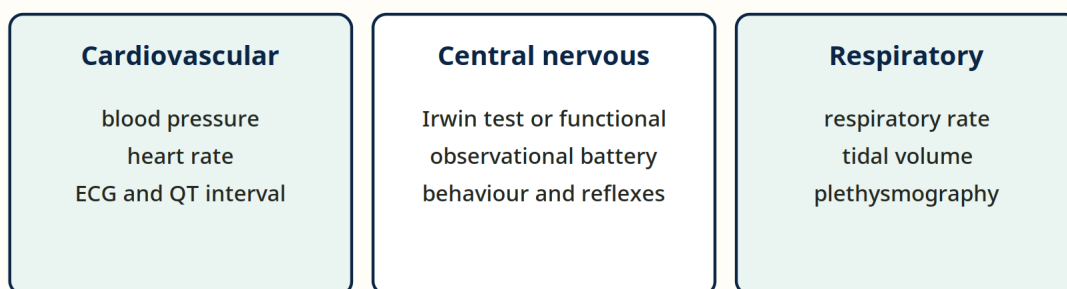
The syllabus calls the core battery **Tier 1**. Before first human exposure, three systems are examined as a rule:

- **Cardiovascular system:** blood pressure, heart rate and the electrocardiogram, usually in a conscious non-rodent by telemetry, with the QT interval under special scrutiny (section 4.6).
- **Central nervous system:** a functional observational battery or modified Irwin test in rodents, scoring motor activity, behaviour, coordination, reflexes and body temperature.
- **Respiratory system:** respiratory rate and measures such as tidal volume, usually by plethysmography in rodents.

These studies are normally run as stand alone single dose studies at exposures bracketing the therapeutic exposure, and their findings feed directly into the monitoring plan of the first clinical trial.

Safety pharmacology: the Tier 1 core battery

Tier 1, before the first human dose (ICH S7A)



Follow up (Tier 2) adds GI, renal and other systems where signals point

© 2026 PharmacoLearn, pharmacolearn.fyi

Figure: The Tier 1 core battery: cardiovascular, central nervous and respiratory function are examined for every new drug before the first human dose.

4.6 The hERG assay and the QT story

The **hERG assay** is the in vitro centrepiece of cardiovascular safety pharmacology. hERG (human ether-a-go-go related gene) potassium channels carry the rapid delayed rectifier current, I_{Kr} , that repolarises the heart's ventricles after each beat. A drug that blocks this channel delays repolarisation, lengthens the QT interval on the ECG, and can trigger torsades de pointes, a potentially fatal arrhythmia. The non antiarrhythmic drugs terfenadine and cisapride were withdrawn from the market for exactly this mechanism, and the lesson was written into ICH S7B: the hERG assay, in which the drug's block of the channel current is measured in cells expressing the channel (commonly by patch clamp electrophysiology), is run alongside an in vivo QT study, and the two together judge the risk before and during clinical development. A hERG margin is usually expressed by comparing the concentration that blocks the channel with the free plasma concentration expected in patients: the wider the margin, the safer the reading.

From hERG block to torsades risk

Why one potassium channel decides cardiac safety (ICH S7B)



Terfenadine and cisapride were withdrawn for this mechanism

© 2026 PharmacoLearn, pharmacolearn.fyi

Figure: One blocked potassium channel, four steps later a lethal arrhythmia risk: the mechanism that made the hERG assay a gate in drug development.

4.7 Tier 2: follow up and supplemental studies

Tier 2 studies are not automatic; they are triggered by what Tier 1 and the toxicity studies suggest, or by the drug's class and target population.

- **Gastrointestinal:** gastric emptying and intestinal transit (charcoal meal), gastric secretion and pH.
- **Renal:** urine volume and composition, electrolytes, glomerular filtration, in conscious animals over collection periods.
- **Other systems as needed:** autonomic function, skeletal muscle and neuromuscular transmission, immune and endocrine functions, blood and haemostasis parameters.

The tiered logic is the concept to carry away: a defined core for every drug, then depth where the signals point, exactly the **follow up** and **supplemental** studies of ICH S7A under the syllabus's tier names.

4.8 Safety pharmacology and toxicology side by side

Feature	Safety pharmacology	General toxicology
Question	Does it disturb vital functions	Does it injure organs
Typical design	Single dose, functional endpoints, exposures near and above therapeutic	Repeated dose, structural and clinical pathology endpoints, up to maximum tolerated dose
Core systems	Cardiovascular, CNS, respiratory	All organs by histopathology
Guideline home	ICH S7A and S7B	OECD test guidelines, ICH M3(R2)

Feature	Safety pharmacology	General toxicology
Timing	Core battery before first human dose	Staged with the clinical programme

*More free M.Pharm notes and unit wise PDFs at pharmacolearn.fyi
Free video lectures on the PharmacoLearn YouTube channel*