Non-clinical development: Types of non-clinical study

Introduction

The non-clinical (or pre-clinical) development phase primarily aims to identify which candidate therapy has the greatest probability of success, assess its safety, and build solid scientific foundations before transition to the clinical development phase.

Also, during the non-clinical development phase, the candidate compound should meet non-medical objectives, including defining the intellectual property rights and making enough medicinal product available for clinical trials. The non-clinical development of a medicine is complex and regulatory-driven. This article covers the various types of non-clinical study, including their objectives and other specifics.

Types of non-clinical study

Pharmacodynamics (PD)

Primary:

The objective is to determine how the intervention causes the body to react (efficacy). These studies can be done *in vivo* and/or *in vitro*.

Secondary:

The objective is to determine how the intervention acts on other aspects of the body (i.e. not the target). Secondary PD studies may not be needed; published literature may provide enough information.

Safety:

The objective is to identify undesirable effects on key physiological functions within the therapeutic dose range and higher. Usual studies evaluate respiratory, central nervous system (CNS), and cardiovascular functions.

Follow-up studies may be needed if concerns arise. Where possible, evaluation should be conducted *in vitro* in order to reduce animal use.

Pharmacokinetics (PK)

Pharmacokinetic studies aim to address:

- ADME: A (absorption), D (distribution), M (metabolism), E (excretion)
- Toxicokinetics (how much of the intervention is in the body and where/when undesirable effects happen)

Toxicology

Toxicology studies aim to address the toxicity of the compound:

- Single-dose
- Repeated-dose
- Genotoxicity (damage within a cell causing genetic mutations)
- Carcinogenicity (can it cause cancer?)
- Development and reproductive toxicity

Single dose and dose-range finding studies

These studies are initially conducted in rodents (mice or rats), followed by studies in a larger animal species (for example dogs)

The objective is to establish the toxicity profile:

- the maximum tolerated dose, and the non-observed adverse effect level (NOAEL).
- Identify target organ(s) of toxicity
- Establish doses for future toxicology studies or first-in-human dosing

The objective is to:

- Establish the toxicity profile when administered repeatedly for a given period of time
- Identify target organ(s) of toxicity
- Reversibility of adverse effects
- Establish dose(s) for future toxicology studies or clinical trials

The standard duration is:

- Sub-chronic: 7, 14 and 28 days and 3 months
- Chronic: 6, 9 and 12 months

Genotoxicity studies

The objective is to detect potential interactions with DNA or chromosomes that lead to the induction of gene mutations and/or chromosomal damage.

Carcinogenicity

Carcinogenicity studies include:

- 2-year mouse or 26-week transgenic mouse
- and 2-year rat bio-assay

Development and reproductive toxicology studies

Development and reproductive toxicology (DART) studies include:

- Fertility (typically rat)
- Teratology (the relationship between two preparations of the same medicines in the same dosage form that have a

similar bioavailability; typically rat and rabbit)
- Peri- and post-natal (typically rat)

First dose estimation in humans

Estimation of the first dose in humans is an important element to protect subjects participating in first-in-human studies (Phase I).

All relevant non-clinical data should be considered, but NOAEL gives the most important information.

For exploratory clinical studies in humans, the dose estimation can be done on less or different non-clinical data; criteria to determine the starting dose are part of the regulatory guidelines.[2]

Non-clinical outcomes that can stop development of the compound

A primary purpose of non-clinical studies is to discover target organ toxicity, and from this information stop the development of the compound or use this information for monitoring possible toxicities in humans.

The non-clinical outcomes that can stop the development of a new medicine are:

- Discovery of target organ toxicity, e.g. if a compound is hepatotoxic (toxic to the liver) in animal, further development may be reconsidered, although predictive value of animal studies may be questioned.
- Identification of poor PK properties, e.g. if a product is doesn’t get to its target, or if it accumulates, or generates toxicity. This also explains why early ADME studies are performed, in order to optimise selection of successful product candidates.

Specifics of non-clinical development for biological compounds

Biologics are complex in comparison to small molecules (e.g. large molecules, tissues, cells, proteins). Although the principles are the same, the non-clinical development plan for biologics must be adapted, following a case-by-case approach.

However, standard development plans are also emerging for biologics, distinct from those well established for small molecules, driven by lessons learned from experience and new regulatory guidance.

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