

Non-clinical safety requirements for clinical trials

As part of the work of the International Conference on Harmonisation (ICH [www.ich.org]), regulators and industry experts have established a guideline for the minimum amount of animal toxicology data required to progress a therapeutic product from animals to humans. The M3 (R2) guideline (*Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*) governs pharmaceuticals.¹ Biologic toxicology requirements are covered in ICH Guideline S6 (*Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*). Pharmaceuticals for conditions such as cancer, resistant HIV infection and congenital enzyme deficiency diseases warrant a case-by-case approach in order to optimize clinical development.

A variety of animal toxicology studies are conducted as part of the non-clinical portion of a marketing application. These include:

- pharmacology studies
- single- and repeated-dose toxicity
- toxicokinetic and non-clinical pharmacokinetic studies to assess absorption, distribution, metabolism and excretion
- reproduction toxicity
- genotoxicity
- local tolerance
- carcinogenicity

The nature of the drug and its proposed indication will dictate the types of studies conducted and their duration. For instance, reproduction toxicology studies should be conducted as appropriate for the population exposed.

The toxicology studies should be adequate to characterize potential adverse effects that may occur under the conditions of the clinical trial, or the future marketed use. General toxicity studies should be conducted according to Good Laboratory Practice (GLP) regulations.

Toxicology studies usually assess effects that can be potentially clinically relevant up to the maximum tolerated dose. Doses providing a fifty-fold margin of exposure (usually based on the mean group AUC [area under the curve] values) to clinical systemic exposure are generally considered acceptable as the maximum dose for acute and repeated-dose toxicity in any animal species. The information from these studies is used to determine a human equivalent dose and, with the application of a safety factor, supports the selected starting dose for phase I clinical studies.

Before initiating human clinical trials, the *in vitro* metabolic and plasma protein binding data for animals and humans and the systemic exposure data in the species used for repeated-dose toxicity should be evaluated. The information from these studies is used to adjust the safety factor applied to the starting dose selected for the phase I clinical studies.

The core safety pharmacology studies on the effects of the investigational drug on the cardiovascular, central nervous and respiratory systems should be completed before human clinical studies begin.

For phase III clinical trials in the US, dose-limiting toxicity should be identified in at least one species when using the fifty-fold margin of exposure as the limit dose.

¹ International Conference on Harmonisation. (2009, June). *Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* [Efficacy guideline M3 (R2)], Step 4, 11 June 2009. Retrieved February 25, 2010, from <http://www.ich.org/cache/comp/502-272-1.html>

Exhibit 1 outlines the minimum amount of repeated-dose toxicology data required to proceed from non-clinical to human testing. The toxicology studies must be done in one rodent and one non-rodent species.

Exhibit 1: Duration of repeated dose toxicity studies to support the conduct of clinical trials

Maximum duration of clinical trial	Recommended minimum duration of repeated-dose toxicity studies to support clinical trials	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks ^a	2 weeks ^a
Between 2 weeks and 6 months	Same as clinical trial ^b	Same as clinical trial ^b
> 6 months	6 months ^{b,c}	9 months ^{b,c,d}

^a In the US, as an alternative to two-week studies, extended single-dose toxicology studies can support single-dose human trials. Clinical studies of less than 14 days can be supported with toxicology studies of same duration as clinical study.

^b In some circumstances, clinical trials of longer than three months can be initiated provided that data are available from three-month rodent and three-month non-rodent study, and that complete data from chronic rodent and non-rodent study are made available before extending dosing beyond three months in clinical trial.

^c In cases where a pediatric population is the primary population, and existing animal studies have identified potential developmental concerns for target organs, long-term toxicology in juvenile animals can be appropriate.

^d In the EU, six-month studies in non-rodents is acceptable. Where studies with a longer duration have been conducted, it is not acceptable to conduct an additional study of six months.

The following are examples of when non-rodent studies up to six months can also be appropriate for Japan and the US: when immunogenicity or intolerance confounds conduct of longer-term studies; repeated short-term drug exposure even if clinical trial duration exceeds six months, such as intermittent treatment of migraine, erectile dysfunction or herpes simplex; drugs administered on a chronic basis to reduce the risk of cancer recurrence; drugs for indications where life expectancy is short.

Source: International Conference on Harmonisation. *Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, <http://www.ich.org/cache/compo/502-272-1.html>

Exhibit 2 outlines the repeated-dose toxicology requirements needed in order to market a drug.

Exhibit 2: Recommended duration of repeated-dose toxicity studies to support marketing

Duration of indicated treatment	Recommended duration of repeated-dose toxicity studies to support marketing	
	Rodents	Non-rodents
Up to 2 weeks	1 month	1 month
> 2 weeks to 1 month	3 months	3 months
> 1 month to 3 months	6 months	6 months
> 3 months	6 months ^a	9 months ^{a, b}

^a In cases where a pediatric population is the primary population, and existing animal studies have identified potential developmental concerns for target organs, long-term toxicology in juvenile animals can be appropriate.

^b In the EU, six-months studies in non-rodents are acceptable. Where studies with a longer duration have been conducted, it is not acceptable to conduct an additional study of six months.

Source: International Conference on Harmonisation. Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, <http://www.ich.org/cache/compo/502-272-1.html>

In all cases, a toxicology program should be designed in a manner that is scientifically and ethically appropriate. Note that this article provides a very brief overview of some of the repeated-dose toxicology requirements prior to conducting human clinical trials—it is not all-inclusive. The final design of the pre-clinical package of information is expected to be highly dependent on the route and duration of administration of the drug, the proposed indication and the characteristics of the drug itself.

For full information on pre-clinical requirements, visit www.ich.org.