IND-Enabling Studies

An active Investigational New Drug (IND) application is required by the U.S. Food and Drug Administration (FDA) before human studies may be conducted. For new drugs and even most follow-on products (besides generics), the results of certain nonclinical studies, known as IND-enabling studies, must be submitted with the IND to support investigational drug use in humans. IND-enabling studies help:

1. Predict potential safety concerns
2. Allow estimation of safe starting doses and dose ranges for clinical trials
3. Identify key parameters for monitoring

What are IND-Enabling Studies

IND-enabling studies include in vitro and in vivo assessments that help define the pharmacological and toxicological properties of a drug. This includes dose and exposure dependencies and the reversibility of toxic effects.

Relevant regulatory guidances includes International Council for Harmonisation (ICH) M3(R2) "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" and ICH S6 and S6 Addendum "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals," which have been adopted by the FDA.

IND-enabling studies assess:

- Pharmacodynamics and safety pharmacology
- Pharmacokinetics, including absorption, distribution, metabolism, and excretion (ADME) and radiolabeled mass balance studies
- Toxicology, including single-dose, repeated-dose, reproductive and developmental toxicity, and genotoxicity studies

Additional studies, such as immunotoxicity and local tolerance studies, may also be required to enable initial human trials, depending on the drug, route of administration, and indication.

Finally, while IND-enabling studies support initial human studies, this is not the end of nonclinical development. On the contrary, most development programs require additional, often long-term, nonclinical studies to characterize the potential for long-term toxicity (including carcinogenicity). Juvenile animal studies may also be required before the drug can be administered to pediatric patients.

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What IND-Enabling Studies Are Needed?

PHARMACOLOGY

IND-enabling safety pharmacology studies assess effects of a drug on the cardiovascular, central nervous, and respiratory systems in animals. Primary pharmacodynamic studies are generally also included to define the therapeutic effects of the drug, including relationships to dose and/or exposure.

PHARMACOKINETICS (PK)

IND-enabling PK assessments typically include in vitro metabolism and plasma protein binding studies, as well as systemic exposure studies in the same species as repeated-dose toxicity evaluations. While these studies are generally sufficient for supporting initial human trials, additional studies to characterize ADME, drug-drug interactions, and metabolite profiling are often required prior to conducting later phase clinical studies. The amount of information needed depends in part on the phase of development and design of the proposed clinical study.

TOXICOLOGY

The IND-enabling toxicology assessment may include both acute (single-dose) and repeated-dose toxicity studies. Acute toxicity studies are generally conducted in two mammalian species (one non-rodent) using the clinical route of administration and a parenteral route (e.g., intravenous or subcutaneous). Dose levels should be chosen for these studies that will allow the determination of a maximum tolerated dose (MTD) and a no-observed-adverse-effect level (NOAEL). These parameters are important for predicting human safety and for clinical dose selection.

Acute toxicity studies can be the primary IND-enabling toxicology studies, but they are often combined with repeated-dose toxicology studies. Repeated-dose studies are designed with a similar duration and route of administration as the proposed clinical trial.

These studies should match or exceed the duration of treatment of the proposed human clinical trial. Dose levels and dose regimens should be selected so that observed exposures (Cmax and AUC) in nonclinical species will adequately cover expected clinical exposures.
To determine the mutagenic potential of an investigational drug, a gene mutation assay (e.g., Ames assay) is conducted to support single dose clinical trials.

Additional chromosomal damage assessments are conducted to support repeated-dose clinical studies. Complete genotoxicity testing should be completed prior to Phase 2.

Depending on the drug, mechanism of action, indication, and other considerations, other toxicity studies may be conducted and submitted with the initial IND application. These may include reproductive toxicity (e.g., embryo-fetal toxicity), immunotoxicity, phototoxicity, and abuse liability testing. Long-term carcinogenicity studies are typically carried out after the initial IND submission.

Conclusions

IND-enabling studies are conducted to evaluate potential toxicity risks prior to human studies and to estimate starting doses for clinical trials. Key IND-enabling studies include pharmacology, pharmacokinetics, and toxicology assessments.

A complete IND-enabling program is dependent on the class of drug, route of administration, planned indication, and planned duration of treatment.

Contact us today to discuss key aspects of a nonclinical, IND-enabling program with one of our experts.

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