

NONCLINICAL SAFETY TESTING GUIDE

for a Successful Regulatory Submission



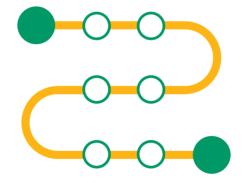
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INTRODUCTION

There are many challenges associated with early drug discovery and development. Advancing your best candidate for regulatory submissions requires a careful assessment of efficacy and toxicity prior to entering human trials. This document is intended to provide a high level overview for the preclinical component of your drug development program.



Initiate discussions
with a CRO at least
nine to twelve months
in advance.



Build capacity, resource availability, and animal supply into your timelines.

Discussions with both Altasciences and the regulatory agency in the country where you are submitting your IND/CTA are imperative to ensure that your specific drug development needs are addressed and that a customized strategy is developed to maximize success and approval.



EXECUTIVE SUMMARY

Use this guide to help you plan your nonclinical assessment.

PLAN YOUR PIVOTAL TOXICOLOGY STUDIES

 How a clinical strategy is key to a successful IND/CTA submission

SMALL MOLECULES VS. BIOLOGICS

 Program requirements for your specific type of therapy

SPECIES SELECTION

• Guidelines for your program

PROGRAM STUDY OUTLINES

Details on study requirements

TIMING

 How timelines may differ between small molecules and biologics

SEND COMPLIANCE

Standards for compliant data

SELECTING THE RIGHT CRO FOR YOU

• Important factors to consider



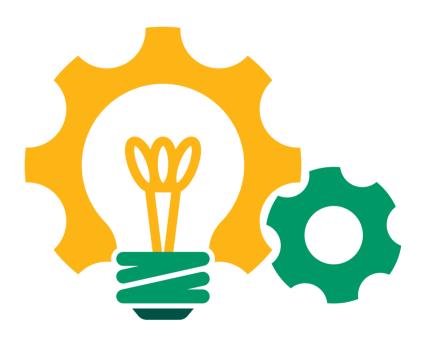
PLAN YOUR PIVOTAL TOXICOLOGY STUDIES

A Proactive Approach

Have a clinical strategy before engaging a CRO. This helps ensure that the data provided by the program of work is sufficient to support your IND/CTA, and reduces the risk of delays.

Considerations for planning your program

- Safe starting dose for clinical trials as well as multiple-dose levels (multiples of expected clinical dose)*
- Species selection and justification
- Route of administration to mimic clinical use
- Identification of potential target organs for toxicity
- Plan for assessing reversibility of toxicities
- Endpoints standard (clinical signs, body weight, clinical and anatomical pathology) and drug specific (biomarkers, immune response, flow cytometry, etc.)
- Analytical and bioanalytical methods



*To determine a safe starting dose for clinical trials, the appropriate drug levels should be selected during your preclinical studies. Dose levels should be determined based on the acceptable margin of safety and generally include a control and three (low, mid, and high) dose levels.



SMALL MOLECULES VS. BIOLOGICS

Small molecules and biologics have different program requirements.

	Small Molecule*	Biologic**
Species Selection	Metabolism as a primary factor (rodent and non-rodent)	Pharmacology as a primary factor; may be only one species
Dose Selection	Based on toxicity (maximum tolerated dose)	Based on pharmacology or maximum feasible dose
Pivotal Toxicology	Required - two species ranging from two weeks to three months	One species — up to six months in duration
Safety Pharmacology	Usually stand-alone studies	Part/all may be in toxicology studies
Genetic Toxicology	Required	May not be required

Guidelines:

^{**}Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1).



^{*}Guideline as per FDA Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

SPECIES SELECTION

For small molecules, <u>ICH guidelines</u> state that two mammalian species are required—a rodent and a non-rodent. Metabolic processes are generally similar across mammalian species; the rat and the dog are typically the rodent/non-rodent species of choice. In some cases, other species may need to be considered.

For biologics, pharmacological relevance is the driver for species selection, determined by the presence of the therapeutic target. Usually, the non-human primate (NHP) is the relevant species. Single-species toxicology packages are commonly accepted.





Formulation, Test Article, and Bioanalysis

When determining dose formulation, generally one method for each vehicle should be used. Dose formulation analyses should include concentration, homogeneity, and stability testing.

Test Article

- Vehicle/Solubility Solubility, stability, dose volume, and tolerability of the vehicle in the preclinical species should be analyzed. For GLP studies, concentration verification of the test article in the vehicle is required. Each analytical method for the test article concentration analysis is specific to the vehicle. Documentation of composition and stability is required.
- Consistency The route of administration for the preclinical studies should be consistent with the intended clinical route.

- Characterization A well-characterized test article must be in accordance with GLP and accompanied by a Certificate of Analysis confirming identity, purity, composition, and stability/retest date.
- Storage Conditions Test materials must be stored according to the Certificate of Analysis and under the same conditions where stability has been established. Recommended temperatures for storage, and hygroscopic and/ or light sensitive character of the test material should be respected.
- Material Safety Data Sheet Should be provided to your CRO study team and laboratory personnel before the test article is shipped.



Bioanalysis

According to the <u>Bioanalytical</u>
<u>Method Validation guidance²</u>
from the FDA:

Validated analytical methods for the quantitative evaluation of analytes (i.e., drugs, including biologic products, and their metabolites) and biomarkers in a given biological matrix (e.g., blood, plasma, serum, or urine) are critical for the successful conduct of preclinical and clinical pharmacology studies. These validated methods provide critical data to support the safety and effectiveness of drugs and biologic products. Validating the analytical method ensures that the data is reliable by addressing certain key questions.





PROGRAM STUDY OUTLINES

Several key studies may be required by regulatory authorities as part of your nonclinical assessment package.

Pivotal Toxicology Studies

Study Type	Species	Duration	
Non-GLP dose range finding (DRF)		includes recovery time	
Maximum tolerated dose (MTD) Escalate dose level in both single and repeat dose stages	Rodent and non-rodent species should be used for small molecules.		
GLP Repeat-Dose Toxicology	One species may be sufficient for biologics.	 2 weeks to 3 months to audited draft report Includes recovery time Reflects proposed clinical trial duration 	



Safety Pharmacology

The core battery is designed to determine pharmacological effect on critical organ systems.

Study Type	Species	Duration	
Cardiovascular	Same as non-rodent in toxicology studies.	~ 12 weeks	
Central nervous system			
Evalutation of various parameters to include locomotion, grip, strength, hind-limb splay, pain perception, reaction to stimuli, etc.	Generally the same rodent species used in toxicology studies.	~ 7 weeks	
Respiratory Measured parameters include respiratory rate, tidal volume, minute volume, etc.	Generally the same rodent species used in toxicology studies.	~ 12 weeks	

Supplemental safety pharmacology studies may be required based on clinical indication or findings in the core battery.



Genetic Toxicology

Depending on your drug candidate and therapeutic indication, genetic toxicology studies may be required. Standard battery tests include:

Study/Test	Study Type	Duration	Timing
AMES Assay Determines if point mutations will be caused, using a panel of bacterial strains	In Vitro	~ 7 weeks	Prior to Phase I clinical trials
Chromosomal Aberration Evaluates the potential for damaged chromosomes in vitro	III VICIO	~ 9 weeks	
Micronucleus Test Evaluates the potential for damaged chromosomes in vivo (rodent)	In Vivo	~ 9 weeks	Prior to Phase II clinical trials

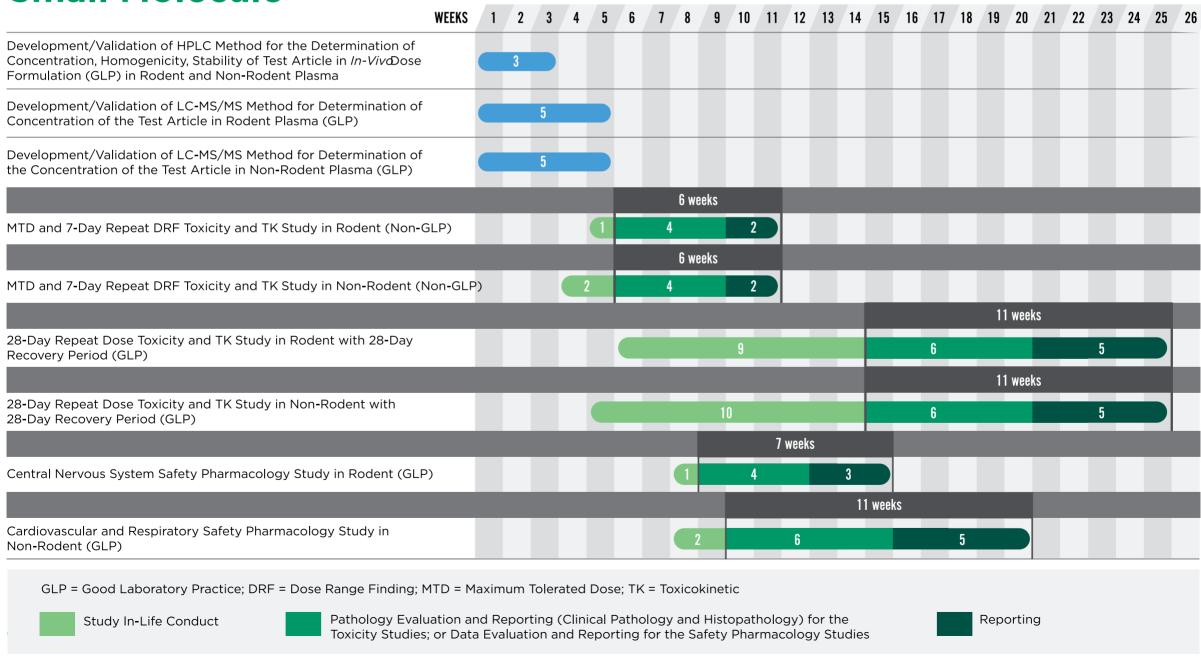
The complete standard test battery is often conducted prior to IND submission. In vivo rodent tests can be incorporated into the main toxicology study. Biopharmaceuticals, such as endogenous peptides, oligonucleotides, and proteins, may be considered exceptions, and a reduced genetic toxicology testing package may be justifiable in certain cases.



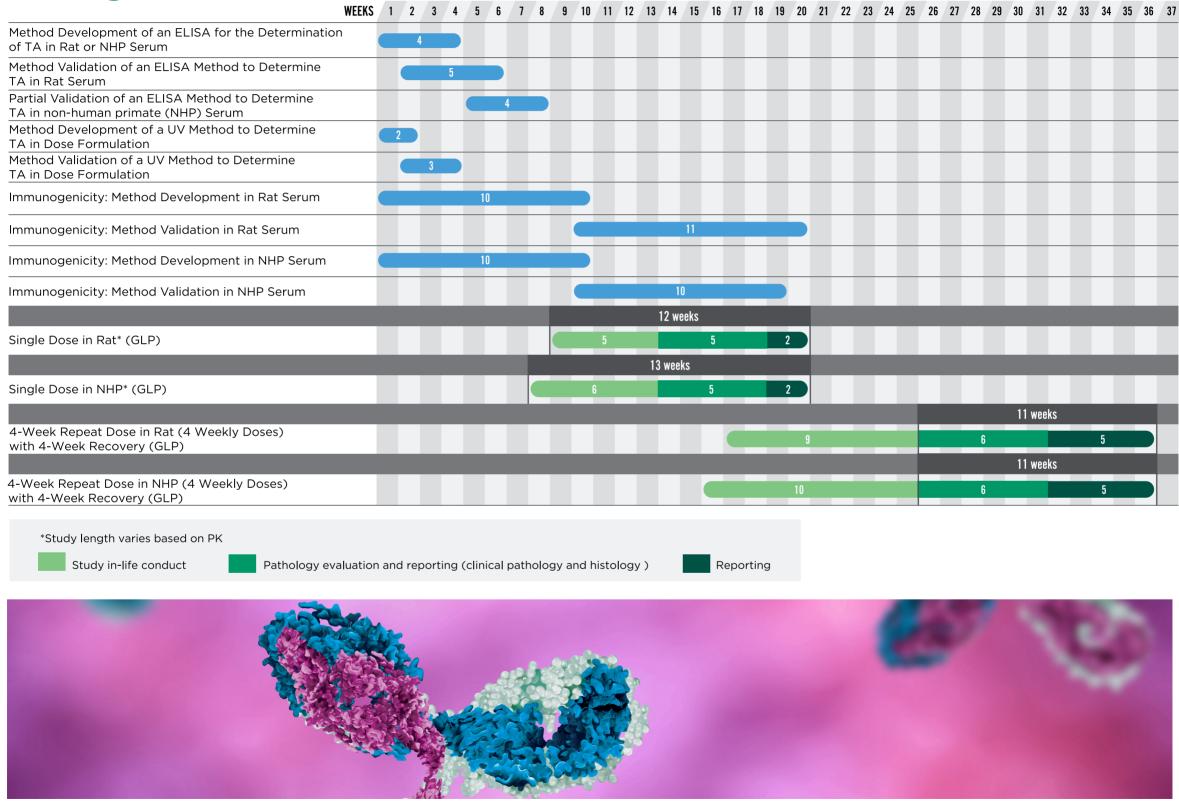
TIMING

Below are illustrative examples of timelines for preclinical activities. Timelines vary and should be customized depending on drug class and molecule type.

Small Molecule



Biologic





SEND COMPLIANCE

The Standard for Exchange of Nonclinical Data (SEND) is an implementation of the CDISC Standard Data Tabulation Model (SDTM) for preclinical studies.

Compliant data follows SEND standards and, depending on the start date of your study, SEND 3.0 or 3.1 is required for your IND submissions.

SEND 3.0

Required for single- and repeat-dose general toxicology and carcinogenicity studies starting on or after:

- December 17, 2016 NDA, ANDA, and certain BLA submissions
- December 17, 2017 IND submissions

SEND 3.1

Required for single- and repeat-dose general toxicology, carcinogenicity studies, and safety pharmacology studies starting on or after:

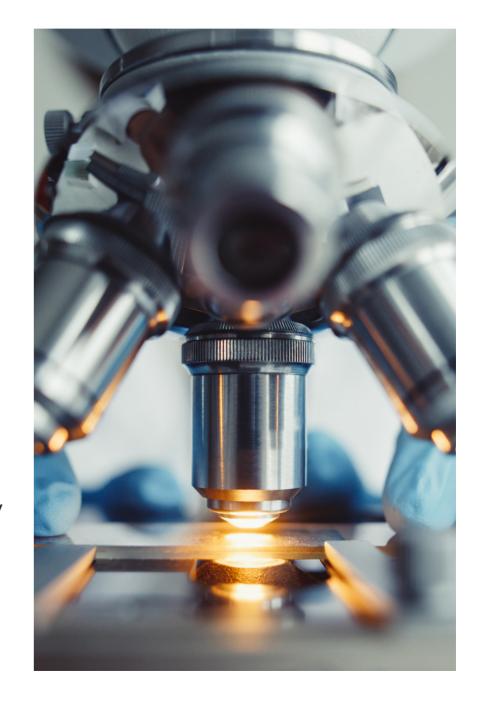
- March 15, 2019 NDA, ANDA, and certain BLA submissions
- March 15, 2020 IND submissions



SELECTING THE RIGHT CRO FOR YOU

When choosing a CRO for your program, consider the following:

- Is the CRO GLP-compliant?
- Do they have a successful history of regulatory inspections and experience with different regulatory agencies?
- Is the facility AAALAC-accredited? Do staff demonstrate a commitment to animal welfare?
- Does the CRO have experience with your molecule type and the species required to develop your therapeutic?
- Does the CRO have the resources and ability to source the capabilities they do not have in-house?
- How responsive is the CRO? Will you communicate directly with the scientific team responsible for your project?
- Does the CRO have a solid on-time reporting history?





ABOUT ALTASCIENCES



Altasciences is a forward-thinking, drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements.

Altasciences helps sponsors get better drugs to the people who need them, faster.

REFERENCES

- **1.** FDA. Investigational New Drug (IND) Application (2017). Available online: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
- **2.** FDA. Bioanalytical Method Development Guidance (2018). Available online: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

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