PLANNING YOUR PRECLINICAL ASSESSMENT

for a Successful Regulatory Submission

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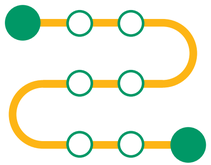
INTRODUCTION

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 **six 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 applying for marketing authorization **are imperative** to ensure that your specific drug development needs are addressed and that a customized strategy is developed to maximize success and approval.

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SUBMISSION CHECKLIST

Your **new drug application** must contain information in three areas, as outlined by the regulatory bodies.

1. Animal Pharmacology and Toxicology Studies

Preclinical data that speaks to the reasonable safety of the product for initial testing in humans. Also include any previous experiences with the drug in humans (often foreign use).

2. Manufacturing Information

Information pertaining to the composition, manufacturer, stability, and controls used for producing the drug substance and the drug product to ensure that the company can adequately supply consistent drug batches.

3. Clinical Protocols and Investigator Information

Include:

- Detailed protocols of proposed studies
- Clinical investigator qualifications
- Informed consent forms
- Institutional Review Board (IRB) requirement

Involve regulatory agencies from the start to help ensure a successful IND submission. The pre-IND meeting is the first crucial interaction with a regulatory agency. It provides an excellent opportunity to enlist support as well as validate and optimize a strategy.

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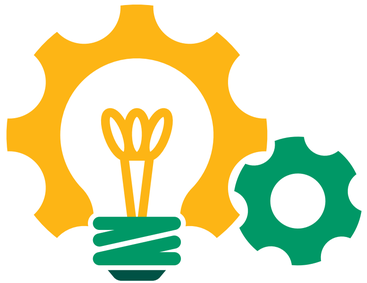
PLAN YOUR PIVOTAL TOXICOLOGY STUDIES

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, 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.

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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:

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

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

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SPECIES SELECTION

For small molecules, ICH guidelines 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.

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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.

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Bioanalysis

According to the Bioanalytical Method Validation guidance[2] 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.

Pivotal Toxicology Studies

Study Type	Species	Duration
Non-GLP dose range finding (DRF) 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.	~ 12 weeks to audited draft report Includes recovery time.
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.

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Safety Pharmacology

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

CORE BATTERY

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.

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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*		~ 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.

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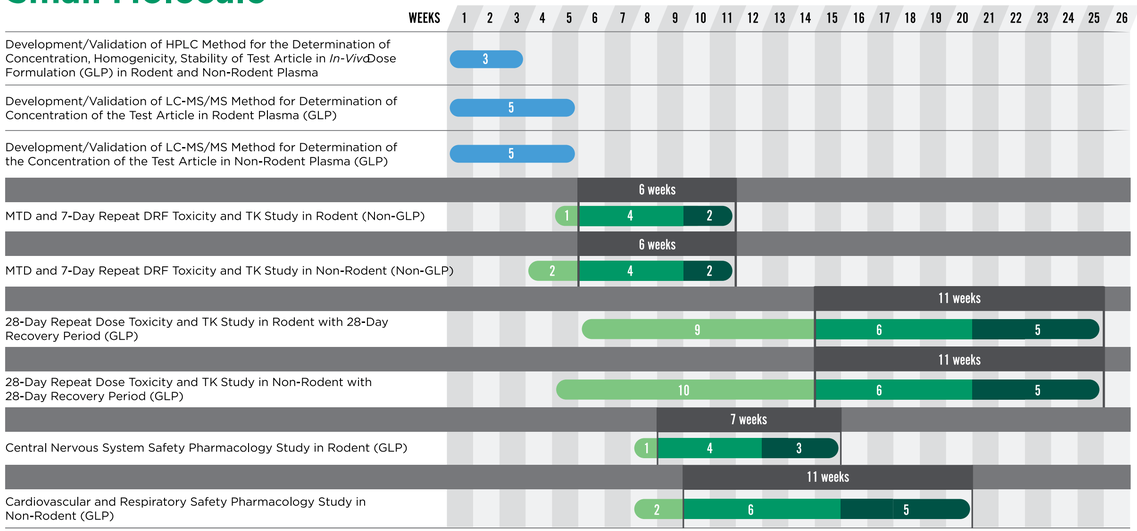
TIMING

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

Small Molecule



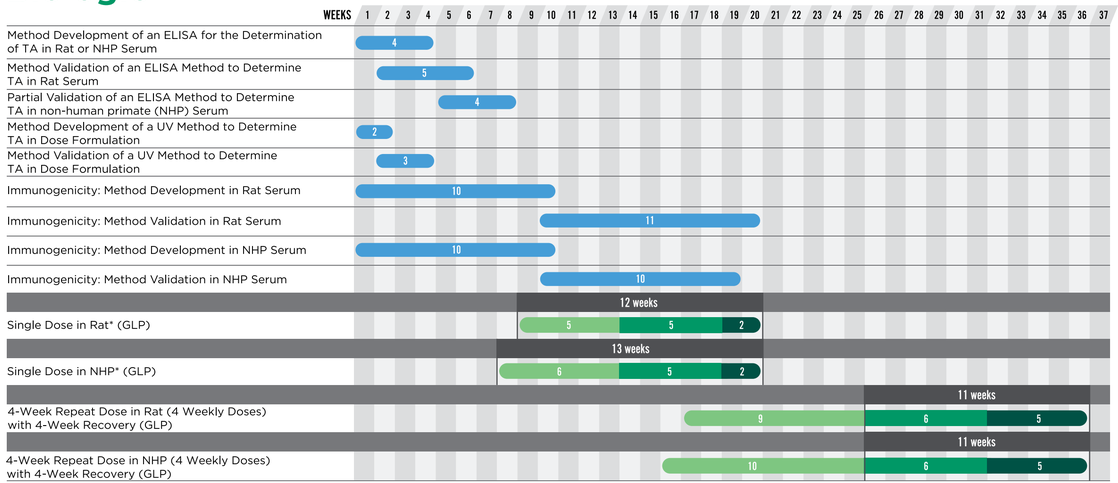
GLP = Good Laboratory Practice; DRF = Dose Range Finding; MTD = Maximum Tolerated Dose; TK = Toxicokinetic

Study In-Life Conduct

Pathology Evaluation and Reporting (Clinical Pathology and Histopathology) for the Toxicity Studies; or Data Evaluation and Reporting for the Safety Pharmacology Studies

Reporting

Biologic



*Study length varies based on PK

Study in-life conduct

Pathology evaluation and reporting (clinical pathology and histology)

Reporting

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SEND DATA

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

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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 don't 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?
- Can your CRO provide integrated project management for your preclinical and clinical programs?

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ABOUT ALTASCIENCES

Altasciences is a forward-thinking, mid-size contract research organization 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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