Listen to a recording of this issue

The Altascientist

SCIENTIFIC JOURNAL

ISSUE NO. 11

IN THIS ISSUE:

PLANNING YOUR PRECLINICAL ASSESSMENT
for a Successful Regulatory Submission

There are many challenges associated with early drug discovery and development. With timelines, budget and market competition being critical factors, advancing your best candidate for regulatory submissions requires a careful assessment of efficacy and toxicity prior to entering human trials. Partnering with the right Contract Research Organization (CRO) early on can increase your chances of success and ensure you meet your milestones. It is recommended that you initiate discussions with a CRO at least six months in advance. Capacity, resource availability, and animal supply must be built into your timelines.

This document is intended to provide a high level overview for the preclinical component of your drug development program. It is important to note that discussions with both your CRO and the Food and Drug Administration (FDA) are imperative to ensure that your specific drug development needs are addressed and that a customized strategy is developed to maximize success and approval.

PREPARE A SUBMISSION CHECKLIST

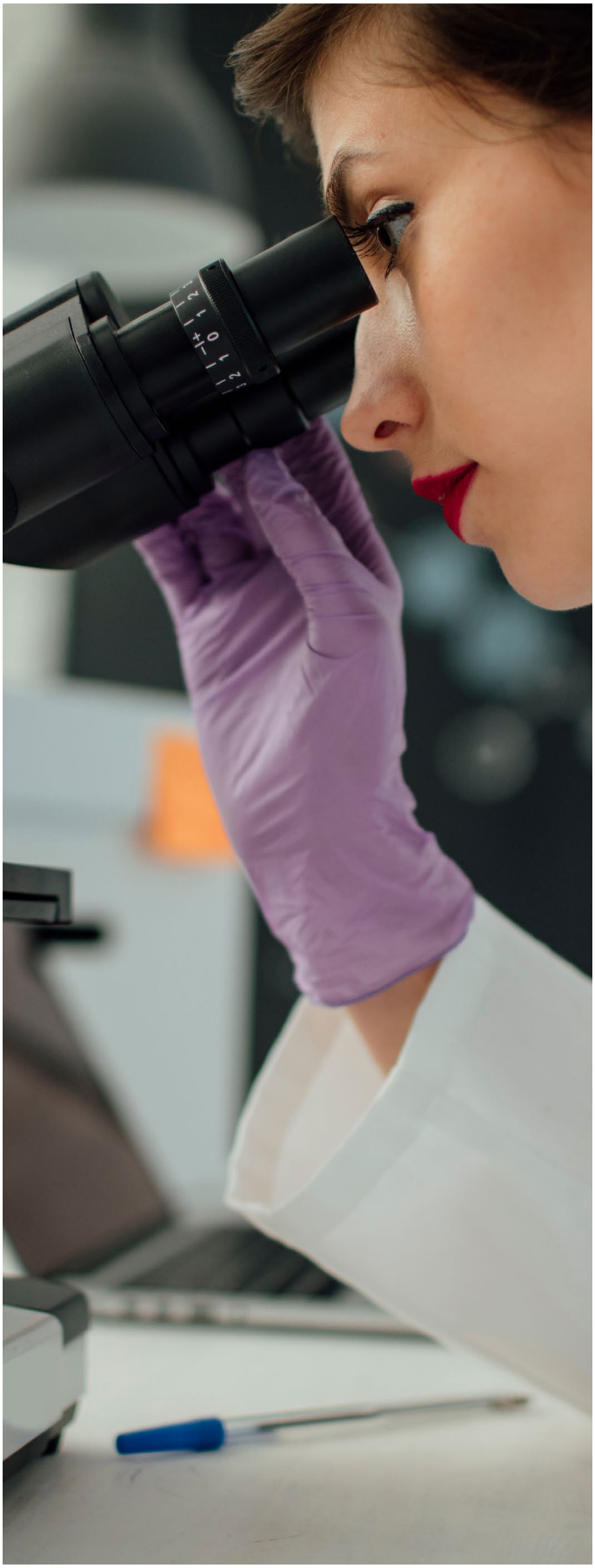
Your IND application must contain information in three areas, as outlined by the U.S. FDA.

1. **Animal Pharmacology and Toxicology Studies**
   Preclinical data to permit an assessment as to the reasonable safety of the product for initial testing in humans is required. Also to be included are 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 is required. This information is assessed to ensure that the company can adequately supply consistent batches of the drug.

3. **Clinical Protocols and Investigator Information**
   Detailed protocols for proposed early clinical studies to assess tolerance and risk should be submitted. Information on the qualifications of clinical investigators to assess their ability to fulfill their clinical trial duties is also required. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.[1]

   Moving a drug from preclinical testing into the clinic requires that all conditions outlined by the FDA be met. Therefore, it is important that you and your CRO have a thorough understanding of the requirements. Involving regulatory agencies from the start can help lead you in the right direction and ensure a successful IND submission. It is essential to communicate with the FDA as early as possible to make certain that the test plan is acceptable. The pre-IND meeting is the first crucial interaction with the FDA. This meeting provides an excellent opportunity for you to enlist the FDA's support as well as validate and optimize a strategy.



PLAN YOUR PIVOTAL TOXICOLOGY STUDIES
A Proactive Approach

Being proactive in your approach and having a clinical strategy before engaging a CRO will ensure that the data provided by the program of work is sufficient to support your IND, and will reduce the risk of study start-up 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

*Dose selection is one of the most critical factors in preclinical toxicology study designs. 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.

Frequently Asked Questions in Preparing your preclinical studies

How much test article will be required for my preclinical toxicology studies? And when will appropriate formulation of the test article be available?

Accounting for the time required to manufacture the test article in required formulations avoids potential delays. The amount of test article required can generally be estimated using the maximum preclinical dose levels established from early exploratory studies or from preliminary range finding studies at the CRO.

Should I use research grade or clinical grade material for my pivotal toxicology studies?

The use of research grade material for early discovery phase studies may be acceptable. Using clinical grade materials for preclinical studies can help you to avoid confounding effects of impurities contained in research grade material and avoid the need for approval of a new batch of material for the clinical studies.

Has previous preclinical work been carried out?

Using and sharing data from studies conducted prior to initiating safety assessment can help save time in the design of pivotal toxicology studies and help with the test article requirement calculations.

SMALL MOLECULES VS. BIOLOGICS

When planning your preclinical safety assessment program, the type of drug candidate under development must be considered.

	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. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization

**Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals

BEFORE YOU BEGIN

Species Selection

Typical small molecule regulatory studies use two species (rodent and non-rodent) for safety assessment. Use of an appropriate animal model is crucial to help predict human effects. *In vitro* metabolic profiling is used to determine the rodent and non-rodent species that best correspond to the metabolic profile in humans. While rats and dogs are appropriate models for most small molecules, their profile can differ from that of a human, and other species may need to be considered.

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

Formulation, Test Article, and Bioanalysis

Proper formulation of drugs and vehicles helps ensure appropriate exposure to the test article. 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 considered. 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. Vehicles intended for use in parenteral administration routes should be sterile and have appropriate documentation of endotoxin levels. For all vehicles (regardless of administration), documentation of composition and stability is required.
- **Consistency.** The route of administration for the IND portion of preclinical studies should mimic the route you intend to use in the clinic.
- **Characterization.** A well-characterized test article must be in accordance with GLP and accompanied by a Certificate of Analysis. This certificate confirms identity, purity, composition, and stability/retest date, and is required to start preclinical GLP studies. Although not required, Good Manufacturing Practices (GMP) grade material is often used for GLP studies and requires a compliance exception because it is not manufactured under GLP conditions.
- **Storage Conditions.** Test materials should be stored according to the Certificate of Analysis and within the same conditions under which stability has been established. Besides the recommended temperatures for storage, the hygroscopic and/or light sensitive character of the test material should be considered.
- **Material Safety Data Sheet.** To ensure safe and proper handling of the material, the safety data sheet should be provided to your CRO study team and laboratory personnel before the test article is shipped.

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

Global regulations require that potential new medicines be tested for safety and tolerability in animals before initiating first-in-human (FIH) trials. This requirement supports the FIH dose setting and benefit/risk assessment, and also supports longer term dosing in humans, whether for healthy people, patients, or special populations (e.g., children, elderly, women of childbearing age).

Study Type	Species	Duration
Non-GLP Dose Range Finding (DRF) Maximum Tolerated Dose (MTD)	Rodent and non-rodent species should be used for small molecules. One species may be sufficient for biologics.	Timeline should account for recovery time. Dose level should be escalated to define the MTD in both the single- and repeat-dose stage.
GLP Repeat-Dose Toxicology		Duration of repeat-dose studies is based on study design and should include a recovery period.

MTD/Dose Range Finding (i.e. single dose)
Determines the acute or single dose toxicity of the drug in at least two species (rodent and non-rodent). A typical acute/dose range finding study might take approximately 12 weeks from animal arrival to an audited draft report. This data can be used to set dose levels for the studies which are used to assess toxicity after repeated dosing.

Repeat-Dose Toxicology
Short-term toxicity studies ranging from two weeks to three months, depending on the proposed clinical trial duration. For example, a 28-day toxicology study usually takes 18 weeks from animal arrival to an audited draft report.

Safety Pharmacology

A core battery of safety pharmacology studies determines any pharmacological effect on critical organ systems. These studies generally include:

Study Type	Species	Duration
Cardiovascular	Same as non-rodent in toxicology studies.	~ 12 weeks
Central Nervous system Evaluation 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 same rodent species used in toxicology studies.	~ 12 weeks

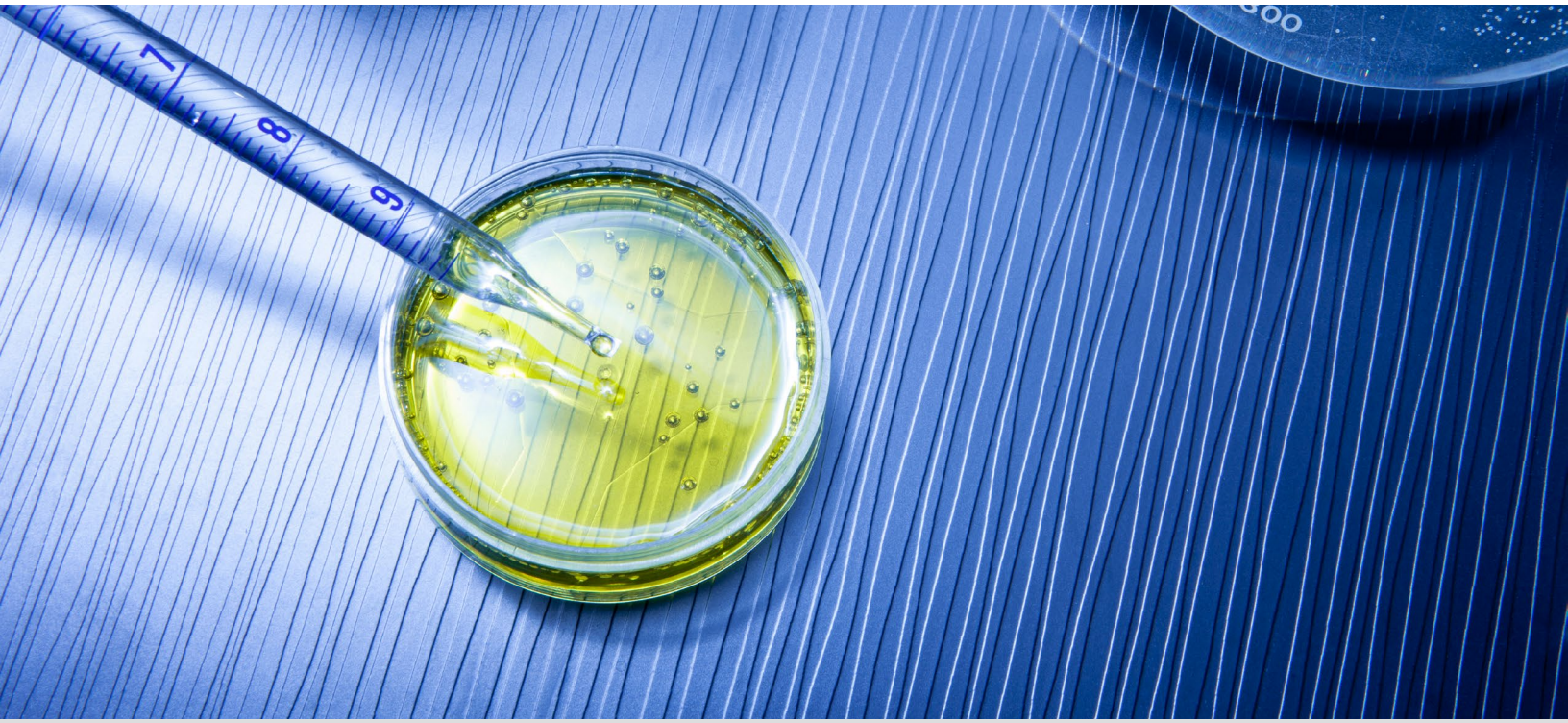
Running a core battery of safety pharmacology studies, which usually include CNS, respiratory, and cardiovascular assessment, as well as *in vitro* hERG assays, are normally included as part of an IND program. Tier 2 safety pharmacology studies may need to be conducted depending on the clinical indication or findings in the core battery.

Genetic Toxicology

Depending on your drug candidate and therapeutic indication, genetic toxicology studies can be required prior to the start of FIH studies. Data produced in genetic toxicology studies is used to determine if the drug has the potential to damage DNA or pose potential carcinogenic risks. When required, standard battery tests include:

Study/Test	Duration
AMES Assay Determines if point mutations will be caused, using a panel of bacterial strains	~ 7 weeks
Chromosomal Aberration Evaluates the potential for damaged chromosomes *in vitro*	~ 9 weeks
Micronucleus Test Evaluates the potential for damaged chromosomes *in vivo* (rodent)	~ 9 weeks

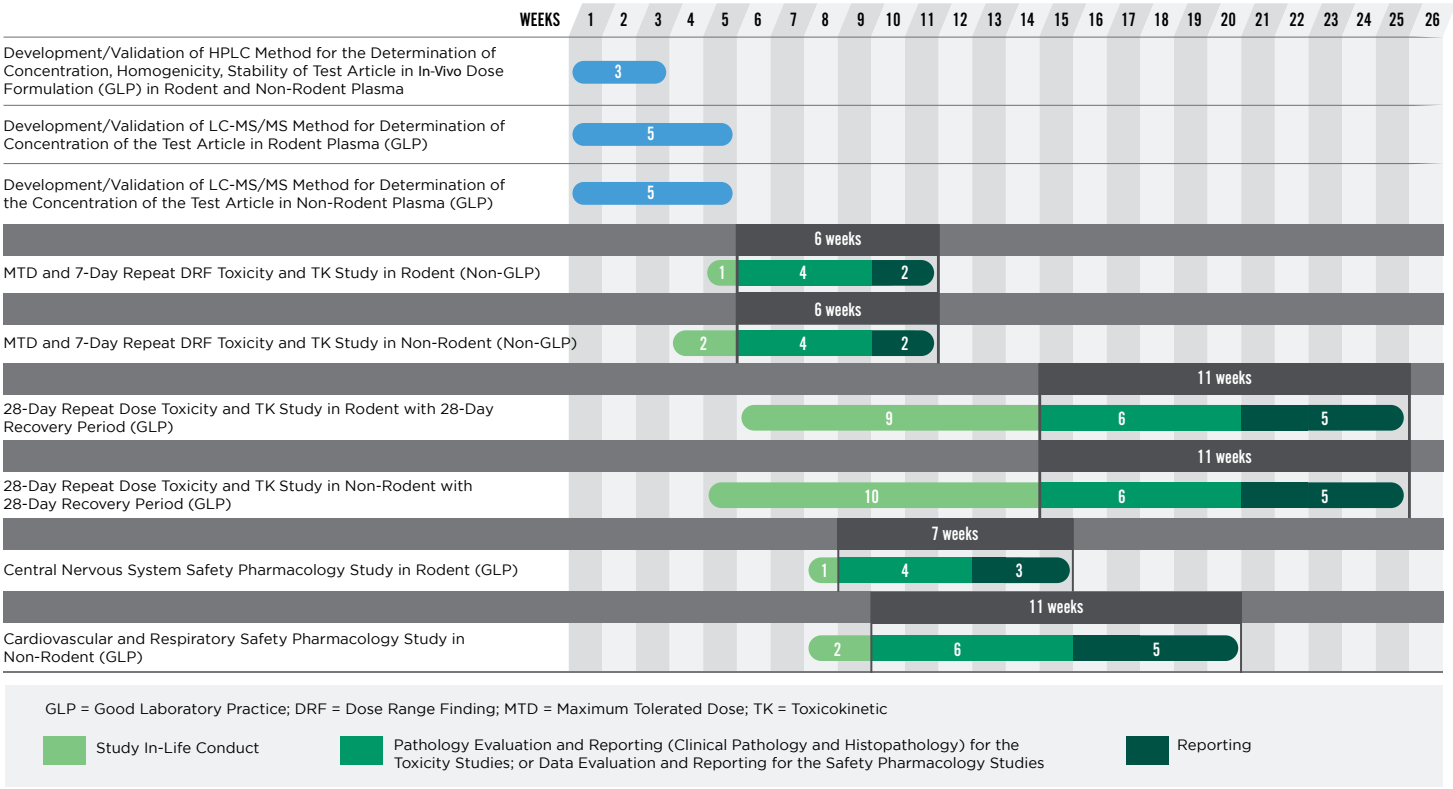
A standard test battery of genetic toxicology studies consists of two *in vitro* tests performed prior to initiation of Phase I clinical trials (Ames Test and the Chromosome Aberration Assay) and an *in vivo* rodent test for chromosome damage performed prior to Phase II clinical trials (Rat Micronucleus Test). In most cases, companies opt to conduct the complete standard test battery 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.



START EARLY

Understanding the preclinical activities and timelines required to move your molecule towards regulatory submission will help you create a roadmap and minimize risks, uncertainty and delays. Below are illustrative examples of timelines for preclinical activities. **Timelines vary and should be customized depending on drug class and molecule type.**

Small Molecule



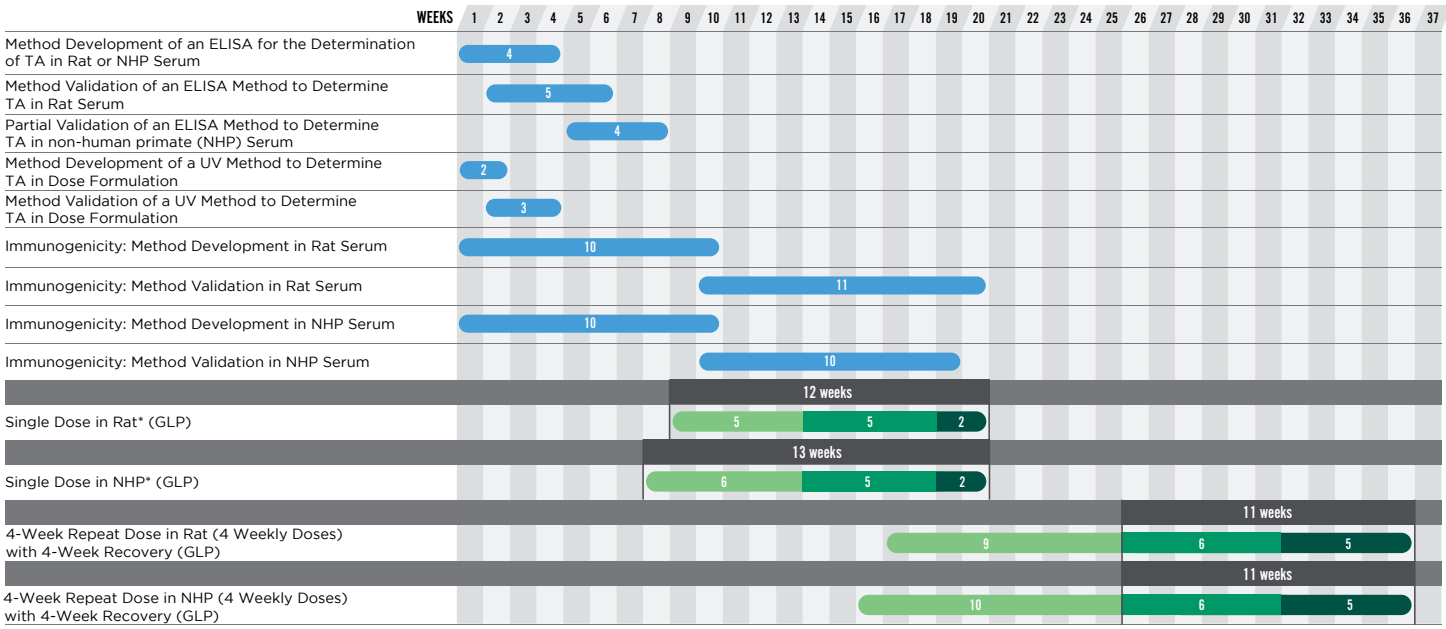
GLP = Good Laboratory Practice; DRF = Dose Range Finding; MTD = Maximum Tolerated Dose; TK = Toxicokinetic

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


WEEKS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Method Development of an ELISA for the Determination of TA in Rat or NHP Serum
4
Method Validation of an ELISA Method to Determine TA in Rat Serum
5
Partial Validation of an ELISA Method to Determine TA in non-human primate (NHP) Serum
4
Method Development of a UV Method to Determine TA in Dose Formulation
2
Method Validation of a UV Method to Determine TA in Dose Formulation
3
Immunogenicity: Method Development in Rat Serum
10
Immunogenicity: Method Validation in Rat Serum
11
Immunogenicity: Method Development in NHP Serum
10
Immunogenicity: Method Validation in NHP Serum
10
12 weeks
Single Dose in Rat* (GLP)
5
5
2
13 weeks
Single Dose in NHP* (GLP)
6
5
2
11 weeks
4-Week Repeat Dose in Rat (4 Weekly Doses) with 4-Week Recovery (GLP)
9
6
5
11 weeks
4-Week Repeat Dose in NHP (4 Weekly Doses) with 4-Week Recovery (GLP)
10
6
5
*Study length varies based on PK
Study in-life conduct
Pathology evaluation and reporting (clinical pathology and histology)
Reporting

SEND DATA

The Standard for Exchange of Nonclinical Data (SEND) is an implementation of the CDISC Standard Data Tabulation Model (SDTM) for preclinical studies which specifies a way to present preclinical data in a consistent format. The format enables more efficient review of preclinical data, offering improved data quality, accessibility, and predictability.

Preparing and accounting for eCTD (electronic submissions) for your preclinical datasets supports timely completion. 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 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?

SUMMARY

Ensuring your IND program stays on track requires proactive planning and preparation. Since there are many key dependencies between preclinical and clinical studies, developing an integrated plan with an experienced CRO team helps streamline and accelerate your drug development pathway to advance your molecule towards regulatory approval and to deal more efficiently with unexpected findings during your early drug development.

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

ABOUT ALTASCIENCES

Altasciences is an integrated 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.