Your Guide to General Toxicology

Questions to consider.

What do you do if you have toxicity findings?

How does your general toxicology studies fit into your larger drug development plan?

How will your general toxicology studies impact your other preclinical milestones?

Drugs and Products May Include

- Small molecule
- Chemical
- Large molecule
- Agrochemicals and biocides
- Medical devices
- Gene and cell therapies

Why It Matters

The health of patients, safety of the environment, and success of your program all depend on a thorough investigation of safety and toxicology properties of products you want to develop.

Program Challenges

1

Regulatory Guidance

Maintaining a state of compliance is arguably one of the more important elements of your toxicology program. Not meeting these requirements could result in a delayed submission to the FDA or rejected data. Your CRO should be able to understand the extensive regulatory guidelines for preclinical work to give your study the best chance for success. Our Scientific Advisory Services (SAS) team will strategize, guide, and support your compliance requirements while meeting your business objectives.

2

Experience and Technologies

Your *in vivo* study designs must identify signs of toxicity, organs that may be affected, the reversibility of any observed toxicities, and identify potential biomarkers. Therefore, specialized procedures for measuring drug exposure, biomarkers, and recording specific endpoints may be required. Furthermore, human dosing regimen of your compound will need to be replicated in toxicology animal studies. You can overcome this hurdle by ensuring your partner has well-trained and experienced scientific staff to conduct these studies, coupled with the specific, calibrated equipment needed to accomplish this.

3

Model Selection

Selecting the most appropriate animal model, coupled with proper study design, goes a long way to understand the safety and efficacy of your product. It's also a critical component to help protect animal welfare and remain committed to the 3Rs of research (reduce, replace, refine). To overcome this challenge, you need experts that can help you find the right models in the appropriate quantities and to set appropriate dosage levels.

4

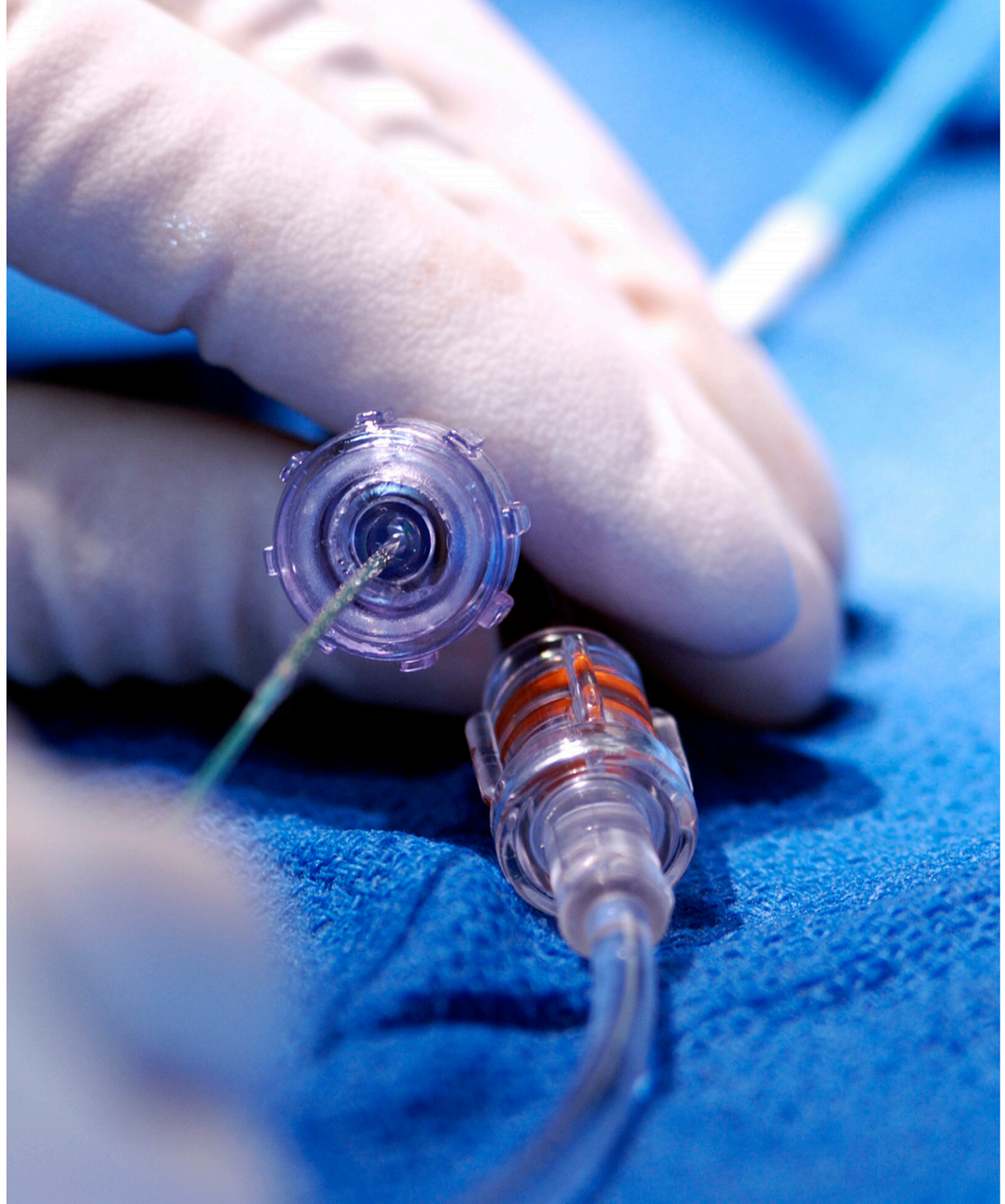
Route of Administration

The most common routes of administration are oral (by gavage, capsule, or incorporation into formulated laboratory diets), dermal, and subcutaneous, intravenous, and intramuscular bolus injections. It is critical that the intended way the drug will be administered to a patient is used in animal toxicology studies, so that information collected on these studies are directly translatable to humans. Specialty dose routes are also available to enables you to deliver drugs in any method you require, including:

- Inhalation
- Intranasal
- Intrathecal
- Intra-ocular
- Intraventricular cerebral injections
- Continuous infusion

Acute and Dose Range Finding Studies

Acute single dose toxicity testing and short, repeat dose range-finding studies are used to help define and characterize the intrinsic toxicities of potential drug substances and provide data for establishing acute exposure to the substance being tested. Information generated in acute studies, along with dose range-finding assessments, is used to guide the design and selection of dose levels for subsequent subchronic and chronic toxicity studies. The selection of appropriate dose levels for toxicity studies is crucial to accurately assess any risk to humans. At a minimum, your chosen partner should understand your compound, have the scientific capabilities you require, and be able to perform the work within your timelines.



Readout

Design of dose-range studies should include dose escalation/maximum tolerated dose studies to provide sufficient information that can be used to advance to longer-term studies.

Advantages

We offer *in vitro* and *in vivo* regulatory-compliant studies in a host of accepted laboratory species to evaluate general systemic toxicity.

Study Types

- Maximum tolerated dose
- Dose escalation
- Dose range-finding

Subchronic and Chronic Studies

Using rodent and nonrodent models, there are a wide array of subchronic and chronic toxicity studies, which are conducted to support longer-term human clinical trials with an expanded number of patients.

Readout

Detection of physiological and pathological effects of a test article using a battery of assessments and specialty endpoints, as required.

Advantages

Experienced toxicologists with experience in different modalities are able to oversee the longer-term studies to completion and analyze the data that has been collected.

Study Types

- 28-day/4-week study
- 91-day/13-week/3-month study
- 26-week/6-month study
- 39-week/9-month study

What's Next?

A toxicology program is just one part of the overall required study program required to submit to the FDA, with the intention of being accepted and proceeding to a first-in-human clinical trial. As a developer, you should consider all the necessary studies to fully develop your product and how to efficiently proceed forward.

Choosing a CRO to work with is another challenging decision to make. It's imperative to consider quality, data and report delivery, SEND services, and support services. Why ship your test articles and methods to different laboratories when one CRO can understand every aspect of your product and make your goals the priority? We offer the following support services to help you effectively plan the next step in your development journey so that you know what comes next after toxicology studies.

Support Services

- *In vitro* characterization/ADME
- Formulation development
- Analytical chemistry
- Bioanalysis
- Biomarkers
- Immunology (flow cytometry, cytokine, complement, immunogenicity)
- Clinical and anatomical pathology
- Digital pathology
- Biodistribution
- Drug metabolism/pharmacokinetic/ toxicokinetic
- Regulatory support
- SEND and data support

Experience Matters

With over 35 years of conducting general toxicology studies and over 400 general toxicology study directors and scientists around the globe, we're capable of giving you the support to advance your compounds further down the drug development pipeline.

In 2020 alone:

282
dose range-finding studies conducted

350
28-day studies conducted

1325
IND programs supported per year

8500+
GLP studies conducted per year

100%
of SEND datasets accepted by the FDA

237
of those IND programs submitted to agency

Next Step in Preclinical Planning

IND Toolbox

Planning for your IND-enabling studies requires the right partner to support your program, preparing the proper test articles, and planning your submissions. Make sure you choose a partner that can quickly mitigate any risks, deliver reports quickly, and offer actionable insights to submit your investigational new drug application on time.

IND eGuide

Our IND eGuide will help you understand how and when to plan your preclinical IND-enabling program as an integral part of meeting specific milestones necessary to timely and efficient IND submission.

IND Gantt Chart Builder

Your lead candidate selection should flow seamlessly into the development phase. Simply provide a few details in our form, and we'll generate a sample Gantt chart with an estimated timeline for your IND or CTA milestones to help you plan accordingly.

askcharlesriver@crl.com | www.criver.com