



Creating Global Value in Product Development: from Proof of Principle to Regulatory Strategy

Toxicology Considerations for Effective Nonclinical Product Development

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Introduction

The best way to add value to your product development is to be informed.

This talk will provide background information and tips for individuals developing biologics or expanding existing SCE operations to include biologics in the pipeline.



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Overview of Preclinical Development for Small Chemical Entities (SCEs)

Follow classical design of preclinical safety assessment

- MTD, dose ranging study in rodent, non-rodent species
- Pharmacokinetic study in rodent, non-rodent species
- Acute repeat dose toxicology study in rodent, non-rodent species
- ADME studies in rodent, non-rodent species (preclinical?)
- Subchronic/chronic repeat dose study in rodent, non-rodent species
- Genotox (in vitro)
- Safety pharmacology, CNS, and Respiratory (multiple species)

Regulatory guidelines are generally well-established

Carcinogenicity and reprotox are standard, usually rodent.



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Overview of Preclinical Development for Biologics

Non-classical design for preclinical safety assessment

- Dose ranging study in non-rodent, frequently not in rodent
- Pharmacokinetic study in non-rodent, rodent optional
- Acute repeat dose toxicology study in non-rodent, rodent optional
- Receptor-binding and/or tissue cross-reactivity assays
- Subchronic /chronic repeat dose study in non-rodent, second species optional
- Immunogenicity
- Safety pharmacology, CNS, Respiratory Safety are case-by-case
- Genotox only in special cases

Regulatory guidelines are often less-defined

Is carcinogenicity study relevant? What species for reprotox?



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Considerations for Preclinical Study Designs of Biologics

Biologics are often highly species-specific, immunogenic, and generally exert their effects without penetrating cells

Biologics require an expression vector and cell factory for manufacture

Testing can be platform specific (ie, monoclonal antibodies, gene therapy vectors, and vaccines each require different developmental considerations)

Biologics often have complex pharmacokinetic behavior, which strongly influences their pre-clinical testing strategy

Determine which studies need to be GLP-compliant and how much test item is needed...do you need help with design or test item estimates?



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Manufacturing/CMC of Biologics

Can you manufacture in-house? If not, find a GMP facility that has expertise with your class of molecules

Expression vector banks and/or cell banks, as well as the end product, require molecular and/or biological characterization

CMC issues are important not only for the ultimate product but also for the expression vector and cell factory used in manufacture

Sterility, stability, purity, absence of endogenous agents, as well as concentration, shelf-life, long-term stability of stocks, and other characterizations must be performed for a biologic... the expression vector... and its cell bank master seed and working stocks

Characterization of the final product may be platform-specific...each class of molecule requires its own types of analyses



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Manufacturing/CMC of Biologics

Chemical characterization is a major challenge for biologics due to their physicochemical properties (size, protein structure content, etc)

Biologics are sensitive to alteration or degradation in many media that are commonly used to characterize SCEs, procedures need to be performed in aqueous environments that are free of proteases and/or nucleases

Complete characterization of product is impossible...subunits of the product must be analyzed

Product-specific molecular techniques are required for pharmacokinetics, pharmacodynamics, analytical and bioanalytical assessments (eg., PCR, ELISA, FLOW cytometry)

No two biologics are identical and subtle differences may result in loss of efficacy, different biodistribution in animals/humans, or greater toxicity-know which structural characteristic(s) is(are) important for your molecule



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Choosing and Working with a CRO

Determine whether you need manufacturing or preclinical testing CRO

Visit the facilities and audit their processes; compare facilities on equal footing...make sure their bids are representing equivalent studies

Talk with the project manager and/or study director. Make sure there is a good communication, you will need to spend a lot of time discussing results and problems

Get references for the site from colleagues in your field...look for experts within the CRO for your molecular class or study design

If you are seeking regulatory advice or help with program/study design, find a CRO with experienced individuals in drug development, not a list of outside consultants...outside consultants are an expense added.



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Regulatory Planning for Biologics

Assess your in-house ability to evaluate the regulatory requirements of the product

Therapeutic biologics range from traditional biologics (like blood and blood components, fractionated blood products, and antitoxins) to monoclonal antibodies, cytokines (e.g. interferon, interleukine), tissue growth factors, vaccines, and gene transfer products

Regulatory guidance may be available for your specific class of compound...check with your CRO, your regulatory agency, or with consultants

New guidances are evolving to cover the rapid development of new technologies and safety concerns for biologics

Biosimilar requirements, as well as some specific biologics requirements, vary with regulatory jurisdiction



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Translational Assessment of Data

Consider how predictable parameters of your animal studies have been in previous clinical studies

Weigh your outcomes based on prior clinical correlations

If responses are expected to be species-specific, the translational efficiency may be low or graded

Don't spend money and time pursuing parameters that are not clinically relevant

Don't make your preclinical safety studies investigative research projects

Most importantly,

Many problems and concerns with biologics are not predicted in preclinical studies and only become apparent once the therapies are in humans (eg., induction of TLR activity, cytokine storm, reactivation of rare infections).

These events exemplify the difficulty in determining what is translational to a clinical program and what isn't.



Summary

Species-specificity is more prevalent with biologics than with SCEs and will influence the preclinical path

Biologics are difficult to define chemically and this may influence the duration of the preclinical development...complexity may increase manufacturing time and delay animal studies

Immunogenicity is central to the activity of many biologics but may also impact the efficacy or safety of the product

Due to diversity of expression vector, cell factory, and protein bioactivity of a biologic, CMC and development of each biologic will likely present unique challenges...get help, balance the advantages and/or costs of in-house or extramural help

Determine your jurisdictional target and understand the appropriate regulatory needs for your molecule

Don't get delayed by trying to understand every biological pathway that may be influenced by your therapy. Get out of preclinical analysis and into humans.



Thank You !