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Nonclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

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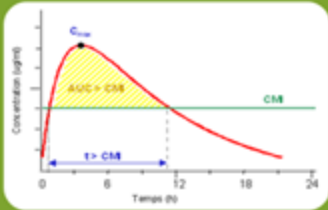


Biotechnology-derived Pharmaceuticals (Biologics) Development Programs



Nonclinical Studies

- Animal PK/PD
- Animal Toxicity



Human Pharmacology

- Pharmacokinetic Studies
- Pharmacodynamic Studies



Clinical Trials

- Phase I
- Phase II
- Phase III



Nonclinical Studies Prior to Human Trials

Appropriate nonclinical studies should be conducted prior to the initiation of human studies and throughout clinical development, as stated in the ICH M3 (R2) and S6 (R1) documents

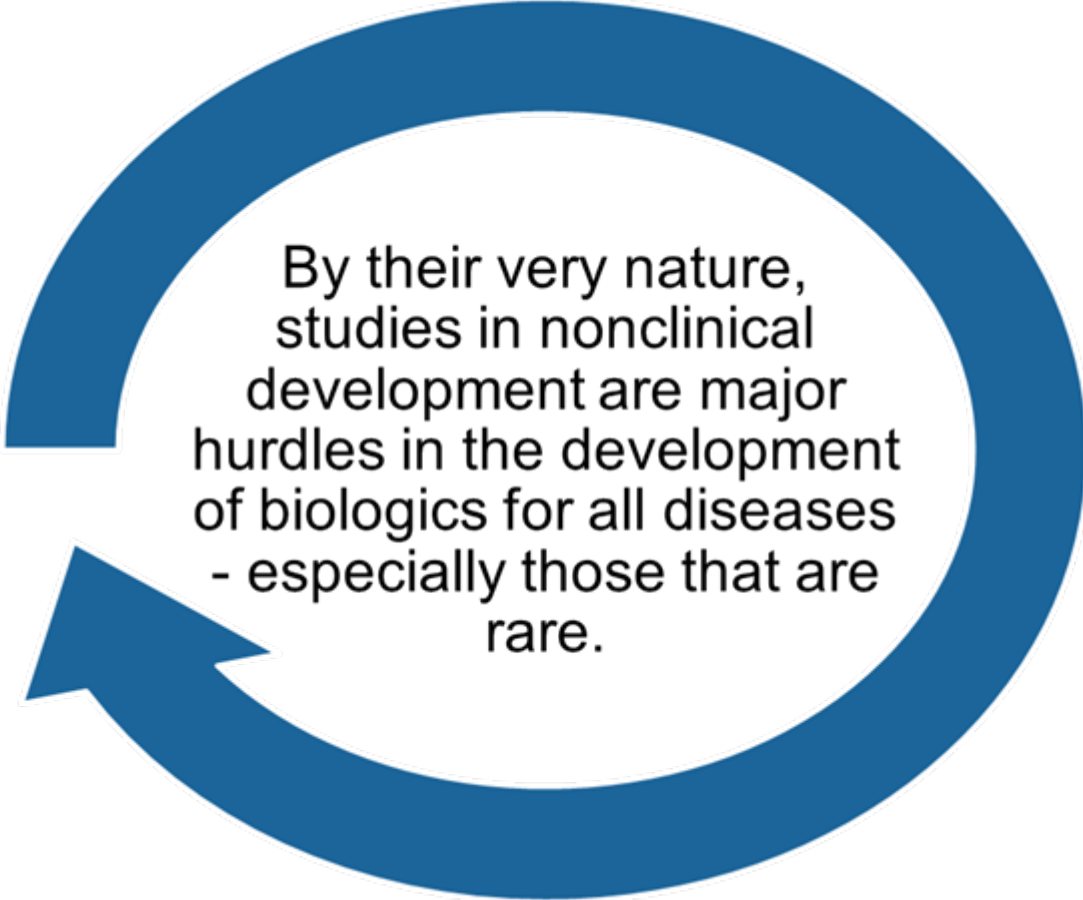


The primary goal of nonclinical studies for biologics is essentially the same as for pharmaceuticals and entails several objectives:

- to identify an initial safe dose and subsequent dose escalations in humans
- to identify potential target organs or physiological systems for toxicity, and reversibility of such toxicity
- to identify safety parameters for clinical monitoring and
- to identify potential “at risk” patient populations



Nonclinical Studies Prior to Human Trials



By their very nature,
studies in nonclinical
development are major
hurdles in the development
of biologics for all diseases
- especially those that are
rare.



Differences between Pharmaceuticals and Biologics

Pharmaceuticals

- Species independent
- Non-immunogenic
- Metabolized
- Short half-life
- Target-mediated drug disposition (rare)
- Linear PK profile
- Toxicity

Biologics

- Species specific
- Immunogenic
- Degraded
- Long half-life
- Target-mediated drug disposition (often)
- Non-linear PK profile
- Exaggerated pharmacology



Fundamental Issues and Concerns for Biologics

Conventional approaches to toxicity testing of pharmaceuticals may not be appropriate for biologics

The biological activity together with species and/or tissue specificity of many biologics often preclude standard toxicity testing designs in commonly used species (e.g., rats and dogs)

Biologics may present special issues to be addressed in nonclinical studies, such as immunogenicity (i.e., induction of an antibody response) and immunotoxicity (agents intended to stimulate or suppress the immune system may cause cell-mediated changes)



Guidance for Safety Testing of Biologics

S6(R1) Preclinical Safety Evaluation of Biologics

The harmonized ICH S6 was finalised in 1997. This document covers the non-clinical safety testing requirements for biologics

An addendum was made in 2011 and the Guideline was then renamed S6(R1) to provide clarification on S6 and an update of the following topics in the original Guideline: species selection, study design, immunogenicity, reproductive and developmental toxicity and assessment of carcinogenic potential



Guidance for Safety Testing of Biologics

S6(R1) has provided the following guidance

- **Chronic study duration:**
 - 6 months sufficient;
 - Longer duration are not anticipated to provide useful information
- **Species for safety evaluation: (default two species)**
 - Two species (if relevant) for 1 month; one species for longer term (e.g. 6 months)
 - One species with 'clinical candidate' sufficient; studies in a second species with a homologous product are not recommended
- **Selection of high dose level:**
 - A dose which gives the maximum intended pharmacological effect or
 - A dose which gives up to 10-fold exposure multiple over the maximum exposure observed in the clinic
- **Reproductive/developmental toxicity:**
 - Evaluation of toxicity to reproduction in pharmacologically relevant species (rodents/rabbits)
 - A single enhanced Pre/Postnatal Development study in NHP for aspects of developmental toxicity if NHP is the only relevant species
 - Use of transgenic mice expressing the human target or homologous protein in a species expressing an ortholog of the human target



Guidance for Safety Testing of Biologics

The ICH S6(R1) Document

Genotoxicity studies

- The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.

➤ *Carcinogenicity studies*

- Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed for
 - Immunomodulators
 - Growth factors



Guidance for Safety Testing of Biologics

ICH S6(R1) has made cross-references to other ICH guidelines

- ICH S1A Guideline: Guideline on the Need for Carcinogenicity Studies for Pharmaceuticals; November 1995
- ICH S5(R2) Guideline: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility; June 1993
- ICH S9 Guideline: Nonclinical Evaluation for Anticancer Pharmaceuticals; November 2008
- ICH M3(R2) Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals; June 2009
- **S7B: The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals; May 2005**



ICH Safety Guidelines Applicable to Biologics

Nonclinical Development

For both the efficacy and toxicity testing, the nonclinical study design should parallel the proposed clinical trial in terms of dose (adjusted for interspecies differences in body size, PK and PD), concentration, schedule, route and duration of administration

Clinical Development



Problems Encountered with Nonclinical Studies

Problems related to nonclinical studies at the time of phase 1 studies, these most often are due to:

- Testing in a pharmacologically insensitive species
- Toxicologic evaluation in too few animals (e.g. n=2/sex/group)
- Evaluation of too few numbers of doses or too low a dose
- Use of a different product formulation in the animal studies than that proposed in the phase 1 human studies
- Little to no histopathologic evaluation of animal tissues taken at necropsy (e.g. evaluation of 'select tissues')
- Submission of only toxicology study summaries
- No provision for a recovery period in the toxicology study design for products where an immunopathologic response may be anticipated and positive toxicology findings are seen



Problems Encountered with Nonclinical Studies

Even with the best nonclinical design and evaluation, unanticipated problems during different phases of studies may delay the product development. The most common reasons are:

- Untoward safety problems in humans that could not have been predicted from the animal toxicology studies (often these are due to 'human-specific' toxicities)
- Poor dose response characterization
- Lack of long term toxicity and reproductive studies prior to phase 3 or prior to marketing authorization



Solutions for Encountered Problems

Nonclinical studies for biologics should

- follow guidance set forth by ICH S6 (R1), and other applicable ICH safety guidelines
- be scientifically justified and designed

Toxicology programs for biological therapeutics may require novel approaches to obtain data

- no “one size fits all” model for biologics
- traditional animal toxicology models may not be appropriate or feasible; NHP or transgenic animals may have to be used
- studies may have to be “individualized” to address specific safety concerns

Seeking regulatory and scientific guidance from Health Canada



Summary

- Biologics are protein therapeutics with unique structural and functional characteristics that are different from pharmaceuticals
- ICH S6 (R1) and other relevant ICH guidelines should be followed
- Relevant species should be used for toxicity testing
- No animal model can predict all responses in human for biologics
- It is highly recommended that sponsors seek advice from regulatory authorities at early stages of biological drug development





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**Thank you
Merci**

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