#1_S6+M3

Title	**A Comparison of ICH S6 and ICH M3** **S6과 M3 비교**
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Bio	Dr. Jian Wang is the Division Manager for Clinical Evaluation Division - Radiopharmaceuticals and Haematology in Centre for Evaluation of Radiopharmaceuticals & Biotherapeutics (CERB), Biologic and Radiopharmaceutical Drugs Directorate (BRDD), Health Canada. The division has regulatory responsibility for assessing non-clinical, pharmacology and clinical data for biological drugs, including advanced therapies, gene therapies and biosimilars, for the treatment of malignant and non-malignant haematologic diseases, and COVID 19. The Division also regulates diagnostic and therapeutic radiopharmaceuticals for all clinical indications. Dr. Wang has broad regulatory experience in pre-market drug regulations for generics, biologics, biosimilars and radiopharmaceuticals. He joined the Health Canada Pesticide Management Regulatory Agency in 1996. He started working for the Therapeutic Products Directorate (TPD) in early 1999. Then in 2001, Dr. Wang moved to BRDD. He actively participates in various Health Canada, ICH, WHO and DIA working groups and expert committees. Dr. Jian Wang received his MD from Harbin Medical University, Harbin, China in 1982, and his PhD from the University of British Columbia, Vancouver, Canada.
Summary	The presentation will provide an overview of types and timing of Non-clinical studies required at different stages for drug development and a comparison of regulatory requirements for non-clinical studies between small molecules and large molecules.

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Nonclinical Safety Evaluation: A Comparison of ICH S6 and ICH M3

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

Overview

- Purpose of conducting –non-clinical studies
- ICH M3 (R2) guidance on non-clinical safety studies
- ICH S6 (R1) guidance on non-clinical safety evaluation of biotechnology derived pharmaceuticals
- Issues for Non-clinical studies conducted for biological drugs

Non-Clinical Perspectives

Non-clinical studies are conducted

- to support clinical trials and,
- to support approval for new drugs' marketing authorization.

The FDA offers a more substantive definition of nonclinical laboratory studies in Section 58.3 of Good Laboratory Practice for Nonclinical Laboratory Studies:

Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety.

- *The term does not include studies utilizing human subjects or clinical studies or field trials in animals.*
- *The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.*

Relevance of Non-clinical Studies in Drug Development

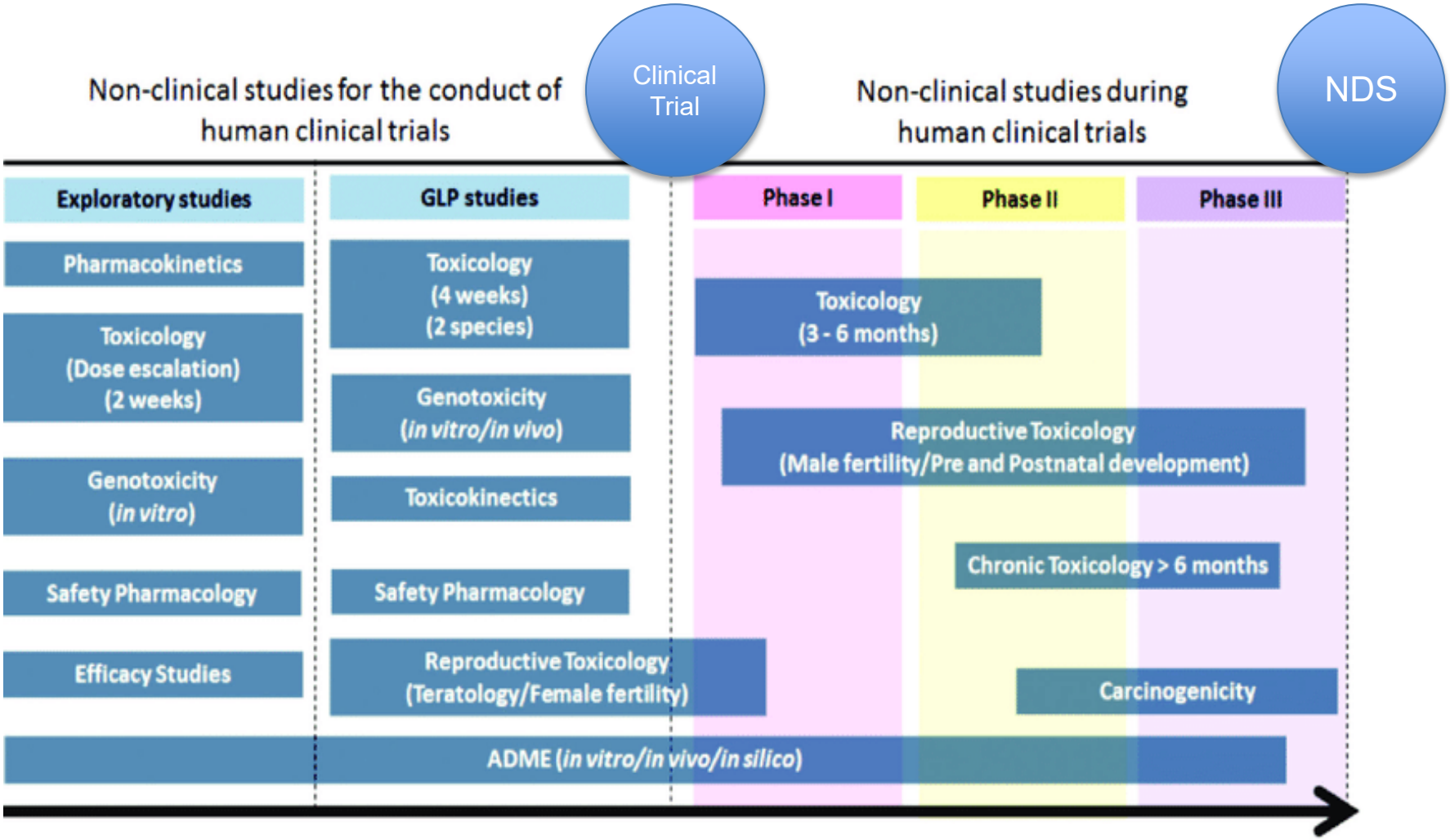
Basic Goals:

- Identify the pharmacological properties
  - *PK (metabolism)*
  - *PD (mode of action)*
  - *Comparative physiology (extrapolation of animal data to humans)*
- Understand the toxicological profile
  - *Establish a safe initial dose level of the first human exposure*
  - *Identify parameters for clinical monitoring of potential adverse effects Special toxicity (e.g. genotoxicity, carcinogenicity, reproduction toxicity)*

ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

- The purpose of this document is to recommend international standards for harmonization of the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals
- This guideline applies to the situations usually encountered during the conventional development of pharmaceuticals and should be viewed as providing general guidance for drug development
- Appropriate nonclinical studies should be conducted prior to the initiation of human studies and throughout clinical development

Overall Non-clinical Study Strategy



Non-Clinical Studies M3(R2)

- Safety pharmacology
- Repeated dose toxicity studies
- toxicokinetic and nonclinical pharmacokinetic studies
- Genotoxicity
- Carcinogenicity
- Reproductive toxicology
- Special studies (case by case)
  - phototoxicity studies, immunotoxicity studies, juvenile animal toxicity studies, and abuse potential studies

Guideline ICH M3(R2):Types and Timing of Non-Clinical Studies

- Safety pharmacology
- Repeated dose toxicity (2W)
- Toxicokinetic and Pharmacokinetic Studies
- Local tolerance
- Genotoxicity *in vitro*
- Male reproductive organs

Phase I

- Repeated dose toxicity (2W-6M)
- Genotoxicity *in vivo*

Phase II

-Repeated dose toxicity (1M – chronic)
-Reprotoxicity
Male and female fertility
Embryofetal
Peri-post natal
- ADME

Phase III

Types and Timing of Non-Clinical Studies

Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials		
Maximum Duration of Clinical Trial	**Rodent**	**Non-rodent**
Up to 2 weeks	2 weeks	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
> 6 months	6 months	9 months

Types and Timing of Non-Clinical Studies

Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing		
Duration of Indicated Treatment	**Rodent**	**Non-rodent**
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months	9 months

Nonclinical Programs for Small Molecules

Study Type	Oral	Dermal	Ocular
General toxicology	Rat and dog	Mini-pig (dermal) Rat (systemic)	Rabbit, pig, dog, monkey (ocular) Rat/non-rodent (systemic)
Genotoxicity	Yes	Yes	Yes
Safety Pharmacology	Yes	Generally yes, but consider systemic exposure and body surface area	Not routinely expected
Melanin Binding	Not routinely	Not routinely	Generally yes
Photosafety	As needed	As needed	As needed
Hypersensitivity	Not routinely	Yes	Not routinely
Reproductive toxicology	Yes	Yes	Might be able to waive some studies
Carcinogenicity	Yes	Yes	Might be able to waive

Exceptions

- ICH M3's recommendations for types and timing of studies most directly applicable to systemically- administered small molecules intended to treat non-life-threatening conditions

- Exceptions
  - Life-threatening conditions
  - Topically-applied products (skin and eyes)
  - Certain medical imaging agents
  - Biologics (ICH S6)

Nonclinical Studies Prior to Human Trials for Biologics

- The ICH guideline (M3) provides general insight for biologics only with regard to timing of nonclinical studies relative to clinical development stage.
- 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 irreversibility/reversibility of such toxicity
  - provide guidance for safety monitoring/risk management
  - to identify potential “at risk”

Differences between Pharmaceuticals and Biologics

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

Pharmaceuticals

- Species independent
- Non-immunogenic
- Metabolized
- Short half-life
- Target-mediated drug disposition (rare)
- Linear PK profile
- Toxicity
- Synthesized, well-characterized, and easily purified

Biologics

- Species specific
- Immunogenic
- Degraded/catabolized
- Long half-life
- Target-mediated drug disposition (often)
- Non-linear PK profile
- Exaggerated pharmacology
- rDNA technology, complex manufacturing and control but simple formulations for parenteral use

Fundamental Issues and Concerns for Biologics

- Conventional approaches to toxicity studies 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 studies in commonly used species (e.g., rats and dogs). NHP may be the only relevant species
- 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)

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.

- The immunological response of animals to a human protein limits the value of longer term, multiple dose studies

- Since immunogenicity data from animal studies are poorly predictive of the behaviour in humans, it is more informative to obtain data from subjects under treatment

Use Pharmacologically Relevant Species

- **Identify pharmacologically relevant species**
- **Characterize potential differences in potency**

Target expression
Sequence homology

Binding characteristics

Functional assays
Human vs animal cell assays

***In vivo* pharmacology**

S6(R1) Guidance for Safety Testing of Biologics

- **Species for safety evaluation: (default two species)**
  - Short term general toxicity studies in two species.
  - Two species (if relevant) for 1 month; one species for longer term (e.g. 6 months)
  - One species with ‘clinical candicate’ sufficient; studies in a second species with a homologous product are not recommended
- **Selection of high dose level:** the higher of the two,
  - A dose which gives the maximum intended pharmacological effect or
  - A dose which gives up to a 10-fold exposure multiples to be achieved in clinic
- **Frequency and route of administration:** mimic intended dosing (but adjust taking PK into account)
- **Chronic study duration:**
  - 6 months sufficient;
  - Longer duration are not anticipated to provide useful information

S6(R1) Guidance for Safety Testing of Biologics

Reproductive/developmental toxicity:

- A single Enhanced Pre- and Post-natal Development (ePPND) study in NHP will assess all aspects of developmental toxicity in an NHP
- Separate Embryo-fetal developmental (EFD) study in NHP is of little or no value for large molecular proteins

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

Considerations When Evaluating Biologics

Understand Differences between Small and Large Molecules

	Small Molecules	Large Molecules
The high dose in the toxicity studies	50-fold exposure margin over the anticipated clinical exposure at the highest dose.	The multiples of the human dose that are needed to determine adequate safety margins may vary.
Metabolism	Classical biotransformation studies	Understanding the behaviour of the biologics in the biologic matrix and the possible influence of binding proteins is important

Types and Timing of Non-clinical Studies

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Pharmacodynamics	Prior to Phase 1	Yes	Yes
In vitro metabolic profile and plasma protein binding	Prior to Phase 1	Yes	No
Systemic exposure	Prior to Phase 1	Yes	Yes
Comparative in vivo animal and human metabolism data	Generally prior to phase 3	Yes	No

Types and Timing of Non-clinical Studies

Study Type	(Relative to Clinical Trials)	Small Molecule	Biologic
Safety pharmacology • Cardiovascular • Respiratory • CNS	Prior to Phase 1	Yes	Product specific
General toxicology	Prior to Phase 1, 2 and 3	Yes (2 species)	Yes (1 species acceptable)

Types and Timing of Non-clinical Studies

Study Type	Timing Relative to Clinical	Small Molecules	Biologics
Genotoxicity • Bacterial mutation • *In vitro* chromosomal aberrations • *In vivo* chromosomal aberrations • *In vivo* micro nucleus	• Prior to Phase 1 • Prior to Phase 1 • Prior to Phase 2	Yes	Generally no

Types and Timing of Non-clinical Studies

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Reproductive Toxicology • Embryo-fetal development • Male fertility • Female fertility • Pre-/post-natal development	• Prior to Phase 3 • Prior to Phase 3 • Prior to Phase 3 • Marketing approval	Generally Yes	Product specific
Carcinogenicity	Marketing approval	Yes (chronic drugs)	Product specific

Non-clinical Studies: Special situations for Biologics

- **Target expressed at no/low levels in healthy animals:**

  Incorporating safety endpoints in proof-of-concept (disease model) study may be of value.

- **No relevant species available**

  Homologous molecule, transgenic animals, human cell assays (each have pros and cons, justify if used)

- **Gaps in knowledge**

  Possible to manage in the protocol and acceptable for the indication?

Evaluating Safety of Biologics, Special Considerations

- **Toxicity often due to exaggerated pharmacology (on-target)**
  - e.g. anti-CD20 antibody->B cell depletion->increased risk for infections.

  Characterization of Pharmacology and PK/PD relationships is important

- **Off-targets toxicity/class related effects**

  Antibodies -> Fc-part related effects (e.g. cytokine release) or immunogenicity.

Guidance for Safety Testing of Biologics

Antibody-Drug Conjugate: small molecule, biologic and conjugate

- No specific guidance available: guidelines for both pharmaceuticals and biologics could be applicable
- Consideration: a full battery of toxicity study is required for the new drug substance plus testing on the conjugate
- Available data/information: justifiable for not doing toxicity study for each component of the conjugate

Guidance for Safety Testing of Biologics

Therapeutic Monoclonal Antibodies

- Non-target specific binding to human tissue may have serious consequences
- Cross-reactivity studies of therapeutic Abs in human tissues should be conducted prior to Phase I clinical trials to search for cross-reactivity or non-target tissue binding
- human tissue panels
- animal tissue panels (not for species selection but may be of value for assessment of toxicity)
- Tissue binding per se does not indicate biological activity in vivo.
- In addition, binding to areas not typically accessible to the antibody in vivo (i.e., cytoplasm) is generally not relevant

Immunogenicity

Human proteins often immunogenic in animals. Development of anti-drug antibodies (ADA) may impact exposure, pharmacodynamics, and toxicity.

Measurement of anti-drug antibodies (ADA) in nonclinical studies should be evaluated when there is:

(1) evidence of altered PD activity;

(2) unexpected changes in exposure in the absence of a PD marker;

(3) evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.)

Not predictive of immunogenic potential in humans

ICH Safety Guidelines Applicable to Biologics

Nonclinical Development

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

Required nonclinical studies are also driven by indications: e.g. repro study is unlikely required for a late stage cancer indication, but it would be required when a new indication for a chronic disease is added

Clinical Development Phase I, II, III

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) or single sex
- Evaluation of too few numbers of doses or too low a dose or too short a duration
- 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')
- 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
- Submission of only toxicology study summaries

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

ICH Safety Guidelines Applicable to 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

Summary

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

Seeking regulatory and scientific guidance from regulatory agencies

- Proceed phase I study with caution: stepwise approach, low dose, small number of patients