Biologics vs TPD Toxicology Requirements “101”

Jon Daniels, PhD, DABT, ERT
Intrinsik Health Sciences Inc.

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Overview

- Introductory Comments
- Fundamental differences between small molecules and biologics
- Challenges specific to biologics
  - Species specificity
  - Immunogenicity
- Types and timing of nonclinical studies
- Selection of starting doses in clinical trials
- Summary

Introduction

- Objective of presentation:
  - To describe the principles and the underlying science behind the sometimes different approaches to the assessment of small molecules and biotechnology-derived therapeutics (rather than just listing the different requirements)
- Reminder - guidelines are designed only to provide general direction for typical situations; they cannot be applied universally to all products and all circumstances

Pharmaceuticals

- Majority are small molecule (traditional) pharmaceuticals
  - Extensive experience and historical database
    - Industry
    - Regulators
  - Scientific and regulatory expectations for nonclinical toxicology programs to support clinical trials and marketing authorizations are well defined
    - ICH M3(R2)
    - ICH S9

Pharmaceuticals (Continued)

- Biotechnology-derived therapeutics (biologics)
  - Increased production over the last 25 years for use in various clinical indications
    - Relatively new (compared to small molecules)
  - Less experience
    - Industry
    - Regulatory agencies
  - Smaller historical database
    - Clinical and nonclinical

Biologics

- Definition - protein pharmaceuticals derived from living organisms including:
  - Humans
  - Animals
  - Plants
  - Microorganisms
  - Biotechnology methods (recombinant DNA/cell culture technology)

Therapeutic Biologics

- Biologics include:
  - Vaccines
  - Cell and gene therapy products
  - Anti-toxins
  - Blood and blood derived products
  - **Monoclonal antibodies**
  - **Fusion proteins**
  - **Recombinant antibodies**

⇐ Therapeutic Biologics

Therapeutic Biologics (Continued)

- Biologics (using recombinant DNA technology)
  - Initially developed in the early 1980s
  - Revolutionized the treatment of human disease by:
    - Mimicking or supplementing a human endogenous protein (e.g., growth hormone, erythropoietin)
    - Activating (agonistic) or blocking (antagonistic) a signaling pathway through specific receptor or ligand binding (e.g., recombinant human insulin for diabetes, Interferon-α-2b for hairy cell leukemia)

Small Molecules vs Biologics

- Fundamental differences exist between small molecules and biologics
  - Differences influence the types of nonclinical toxicology studies to support safety assessment
  - Regulatory guidance documents support a different approach for the nonclinical toxicology studies (ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals)

Small Molecules vs Biologics (Continued)

- Small Molecules
  - Manufactured by chemical process
  - Low molecular weight
    - < 1000 daltons
    - Potential for extensive distribution within the body
  - Structure
    - Simple and well defined
  - Example: ibuprofen (Advil®), MW ~207 g/mol
- Biologics
  - Derived from genetic manipulation of living cells
  - High molecular weight
    - ≥ 1000 daltons
    - High molecular weight proteins are largely confined initially to the vascular space
    - More limited distribution within the body
  - Structure
    - Complex and defined by manufacturing process
  - Example: Monoclonal antibody (IgG), MW ~150,000 daltons

Small Molecules vs Biologics (Continued)

- Small Molecules
  - Generally administered orally
  - Metabolized
    - Liver
  - Metabolic pathways characterized
    - Biotransformation studies
    - Parent & metabolites identified
    - Potential for active or toxic metabolites
- Biologics
  - Generally administered parenterally (IV, SC, IM)
  - Catabolized by body (proteolytic degradation)
    - Amino acids
    - Small peptides
  - Active or toxic breakdown protein products generally not a concern
  - Biotransformation studies generally not performed

Small Molecules vs Biologics (Continued)

- Small Molecules
  - Food-effect may be a concern
  - Drug-drug interactions potential concern
    - Studies typically required
  - Half-life relatively short
    - Minutes
    - Hours
- Biologics
  - Generally no concern for food-effect
  - Drug-drug interactions are less of a concern
  - Half-life can be very long
    - Up to ~3 weeks (i.e., approaching that of endogenous IgG)

Small Molecules vs Biologics (Continued)

- Small Molecules
  - Impurities generally consist of:
    - Starting materials
    - Related compounds
    - Solvents
    - Toxicity studies for impurities may be necessary
  - Immunogenicity is rarely a concern
- Biologics
  - Impurities generally consist of host cell products:
    - DNA
    - Protein
  - Immunogenicity is often a challenge
    - Animals
    - Humans

Small Molecules vs Biologics (Continued)

- Small Molecules
  - Less target specificity (compared to biologics)
    - Toxicities often nonspecific/not related to the intended target
    - Off-target toxicity
  - Species limitations generally not a concern
    - 2 species usually used for toxicology studies (1 rodent; 1 nonrodent)
- Biologics
  - High target specificity
    - Toxicity often relate to the intended target (pharmacologic activity) of the drug
      - On-target toxicity
      - Exaggerated pharmacology
  - Species limitations may be a challenge
    - Only 1 relevant animal species may be available (or none)

Challenges Specific to Biologics: Species Specificity

- Most therapeutic biologics are:
  - Human proteins that are highly targeted to a human receptor
  - Antibodies specific for a human protein or receptor
- Due to high specificity to the human target, many biologics do not recognize the target in animal species commonly used in nonclinical toxicology studies
  - Mice
  - Rats
  - Dogs
  - Rabbits

Challenges Specific to Biologics: Species Specificity (Continued)

- Toxicology studies for biologics should be conducted in a pharmacologically relevant animal species (ICH S6(R1))
- Relevant species - one in which the biologic is pharmacologically active due to the expression of the intended target (e.g., receptor or epitope)
  - Potentially unable to use animal species commonly used in toxicology studies
    - Rodents, dogs (typical species for small molecule general toxicology studies)
    - Many biologics are highly specific for human targets
      - Nonhuman primate (NHP) may be the only pharmacologically relevant animal species
      - Problematic if the chimpanzee is the only animals where cross reactivity occurs

Challenges Specific to Biologics: Species Specificity (Continued)

- ICH S6(R1) - toxicology studies in non-relevant animal species (one that does not express the target) can be misleading and are discouraged
  - Unreliable safety data
  - Not predictive of potential human toxicity
- There are cases when only one relevant animal species can be identified
  - NHP (i.e., cynomolgus monkey)
  - May be acceptable with sufficient justification
    - Demonstrate other species were evaluated

Challenges Specific to Biologics: Species Specificity (Continued)

- ICH S6(R1) - necessary to demonstrate the animal species used in toxicology studies is/are pharmacologically relevant
- Species selection is an important early activity in the toxicology program
  - Often occurs in a similar timeframe as biological characterization of the lead molecule

Challenges Specific to Biologics: Species Specificity (Continued)

- Demonstrating relevance and species selection:
  - Sequence homology between human and animal target
  - Expression and distribution of the target between human and animal species (e.g., mRNA, protein)
  - Binding affinity to human and animal target
  - Functional bioassay to demonstrate pharmacologic activity of the molecule in human and animal cells
    - In vitro
    - Ex vivo
      - Cell proliferation
    - In vivo biomarkers
      - Serum marker of pharmacologic activity
      - Up-/down-regulation receptor

Challenges Specific to Biologics: Immunogenicity

- Immunogenicity is a unique property of biologics
- Distinguishes this class from small molecules
- Being proteins, biologics can be immunogenic in both humans and in animals
- Biologics are often immunogenic in the animals used in the safety evaluation process

Challenges Specific to Biologics: Immunogenicity (Continued)

- Production of anti-drug antibodies (ADAs) in animals can affect the outcome of a toxicology study ranging from:
  - No effect
  - Alterations in the pharmacokinetic and/or pharmacodynamic profile
  - Life-threatening consequences
- Measuring ADA responses in toxicology studies may provide information to:
  - Aid in the interpretation of study results
  - Assist the design of subsequent studies

Challenges Specific to Biologics: Immunogenicity (Continued)

- ADA responses in animal studies are not relevant in predicting immunogenic response in humans
- Four types of ADAs and responses can occur nonclinically and clinically
  - Binding
    - Minimal to no impact (i.e., no toxicity and does not affect exposure/activity)
  - Clearing
    - Increase clearance and decrease systemic exposure of drug
    - Can alter distribution of drug to tissues (e.g., target organs not exposed)

Challenges Specific to Biologics: Immunogenicity (Continued)

- Sustaining
  - Rare
  - Decreases clearance thus results in prolonged half-life/exposure of the molecule
  - Potentially lead to toxicity (or increased toxicity)
- Neutralizing
  - Interfere with molecule binding to the target
  - Neutralizes the pharmacological activity/efficacy of the molecule

Challenges Specific to Biologics: Immunogenicity (Continued)

- Primary concern for development of clearing and/or neutralizing antibodies in toxicology studies:
  - Lower exposure of the target (if present) and target organs to the drug
  - Results in fewer treatment-related toxicities
- ADA responses in toxicology studies:
  - Affects the interpretation of the toxicology study
  - Generates misleading toxicity data
  - Data not predictive of the potential for human toxicity

Types and Timing of Nonclinical Studies

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Pharmacodynamics	Prior to Phase 1	Yes	Yes (May provide critical safety data in a disease model)
In vitro metabolic profile and plasma protein binding	Prior to Phase 1	Yes	No
Systemic exposure (PK)	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 Nonclinical Studies (Continued)

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Safety Pharmacology -Cardiovascular -Respiratory -CNS	Prior to Phase 1	Yes (Stand-alone studies not required for anticancer products)	Product Specific
General Toxicology	Prior to Phase 1, 2, and 3 (see ICH M3(R2)	Yes 2 Species (1 rodent + 1 nonrodent)	Yes (1 species acceptable if justified; duration may be limited by ADAs)

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Types and Timing of Nonclinical Studies (Continued)

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Genotoxicity -In vitro bacterial mutagenicity -In vitro mammalian chromosomal aberrations -In vivo chromosomal aberrations	 Prior to Phase 1 Prior to Phase 1 Prior to Phase 2 (unless there is a "signal")	Yes (See ICH S2(R1) for new options)	No (Rare exceptions)

Types and Timing of Nonclinical Studies (Continued)

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Reproductive and Developmental Toxicity -Fertility -Embryofetal development (teratology) -Pre-/postnatal development	 Prior to Phase 3 Prior to Phase 3 Marketing authorization	Yes (Typically)	Product Specific
Carcinogenicity	Marketing authorization	Yes (chronic use agents)	Product Specific

Establishing a Safe Starting Clinical Dose

- United States (FDA 2005) guidance:
  - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
    - [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078932.pdf]
- Europe (EMA 2007) guidance:
  - Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products
    - [http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf]
  - MABEL = Minimal Anticipated Biological Effect Level

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FDA 2005

- Applies to small molecules and biologics
- Not limited to FIH trials in healthy volunteers
- Defines 2 basic approaches
  - Toxicology
  - Pharmacology
- Toxicology (NOAEL; No Observed Adverse Effect Level) approach
  - Used most frequently
  - Determine NOAEL from toxicology studies
  - Convert NOAEL to human equivalent dose (HED)
    - Normalizes dose (mg/kg) to body surface area (mg/m^2)

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FDA 2005 (Continued)

- Choose HED from most appropriate species
  - Expresses target (receptor/epitope)
  - Biologic binds to target
  - Binding elicits relevant effect(s)
- Apply a safety factor to obtain the maximum recommended starting dose (MRSD)
  - 10X is the standard default
  - Causes for concern may increase the safety factor applied
    - See next slide

FDA 2005 (Continued)

Causes for Concern

- Steep dose response curve
- Severe toxicities
- Unmonitorable toxicity
- Toxicities without premonitory signs
- Variable bioavailability
- Irreversible toxicity
- Unexplained mortality
- Large variability in doses/plasma levels eliciting effects
- Nonlinear pharmacokinetics
- Inadequate dose-response data
- Novel therapeutic targets
- Animal models with limited utility (differences relative to humans)

FDA 2005 (Continued)

- Pharmacology approach
  - Used less frequently
  - Utilizes pharmacologically active dose (PAD)
  - Convert PAD to pharmacologic HED
  - Compare directly to MRSD
  - Consider decreasing clinical starting dose if pharmacologic HED < MRSD

EMA 2007

- Minimal Anticipated Biological Effect Level
  - Anticipated dose level leading to a minimal biological effect in humans
- Applies to small molecules and biologics
- Factors of risk
  - Mode of action (e.g., novel, amplification)
  - Nature of target (e.g., understanding, function)
  - Relevance of animal model(s) (e.g., extent to which model reflects human)

EMA 2007 (Continued)

- NOAEL
  - Obtained from nonclinical safety studies
  - Adjusted using allometric factors or pharmacokinetics
- MABEL
  - Applied to address increased risk (as identified from risk factors)
  - Utilizes all available in vitro and in vivo information from pharmacokinetic/pharmacodynamic studies
  - Safety factor may be applied to MABEL
  - PK/PD modeling should be used wherever possible
  - Some companies are applying the MABEL concept on their own outside EU

Summary

- There are fundamental differences between small molecules and biologics
- Properties of biologics can influence the overall approach and the specific designs of the nonclinical toxicology studies
- Critical to conduct the most appropriate studies based on the properties of the therapeutic under evaluation
- Conducting inappropriate toxicology studies can set precedence or inappropriate expectations by the regulators