

Nonclinical Toxicity and Immunogenicity Testing: Key Issues for Biogenerics

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Objectives of Presentation

- To highlight some of the biologic products currently in development and the challenges faced by sponsors and regulators
- Review the regulatory expectations for nonclinical development of biologics therapies prior to IND and Phase 1
- Highlight the rapid development of biological and immunological methods and the impact on regulatory expectations
- Discuss recent and ongoing changes at FDA that impact biogeneric development

Emerging Classes of Novel Biologics

- New viral vectors
- Humanized mAbs
- Mucosal Vaccines
- Stem Cell Therapies
- RNAi Therapies
- Bacterial Therapies
- Tissue Therapy
- Tumor vaccines
- Gene Therapy
- Complex Proteins (CDER)
- Immunomodulators

Comparison of Drugs vs. Biologics

Traditional Drugs

Guidelines

Previous examples

Historical data base

Maximal tolerated dose

Species-independent

Metabolized

Specific mechanisms



Biologic Therapies

Guiding principles

Unique

Concurrent controls

Optimal biologic dose

Species-specific

Degraded

Pleiotropic mechanisms

Goals of Preclinical Safety Evaluation

- Recommend initial safe starting dose and safe dose escalation scheme in humans
- Determine an acceptable risk/benefit ratio in man
- Identify potential target organ(s)
- Identify clinical parameters to monitor
- Identify “at risk” patient populations
- Discern the mechanism of action
- Satisfy Liability concerns
- Data to support Labeling

Approaches to Preclinical Safety Evaluation

- **Traditional – CDER**
 - “guideline-driven”
 - traditional, formal toxicology program
- **Product or Indication-Specific – CBER**
 - rational, science-based
 - targeted, less formal toxicology approach
 - product characteristics and/or clinical use dictate the study design
- **Do little/nothing**
 - based on prior experience

Preclinical Safety Assessment of Biologics

Analysis of risk will vary with the stage of product development:

- **Licensed product**
 - new indication and/or new formulation
- **Previously studied investigational drug**
- **Modification of previously studied drug**
- **Analogous/partially identical to previous drug**
- **Novel, untested product**

Preclinical Safety Assessment of Biologics

Analysis of risk will vary for each agent and/or clinical indication:

- Chronic therapies
- Acute therapy in life-threatening diseases
- Blood components for replacement therapies
- Childhood vaccines
- AIDS vaccines/tumor vaccines
- Cell therapies
- Xenotransplantation/therapies

Preclinical Safety Assessment of Biologics

Analysis of risk will vary with each product:

- Autologous/allogeneic tumor vaccines
 - frequency of injection
 - local irritation
 - tissue cross-reactivity with antigen
 - induction of aberrant immune response

Preclinical Safety Assessment of Biologics

Analysis of risk will vary with each product:

- **Monoclonal antibodies (naked, conjugated)**
 - cross-reactivity with normal tissue
 - conjugate and/or linker toxicity
 - immunogenicity/antibody production
 - “bystander” toxicity of radiolabeled species

Preclinical Safety Assessment of Biologics

Analysis of risk will vary with each product:

- Cytokines and/or growth factors
 - frequency/duration of therapy
 - species-specificity
 - interaction of host endogenous cascade
 - immunogenicity/antibody formation
 - tumor-promoting potential

Preclinical Safety Assessment of Biologics

Analysis of risk will vary with each product:

- Cellular and/or Gene therapies
 - phenotype/activation state of target cell
 - type of vector, mode of introduction
 - aberrant localization or trafficking
 - level and/or persistence of gene expression
 - inappropriate expression of gene product
 - inappropriate immune activation

Preclinical Safety Assessment of Biologics

- So, for a variety of different products, there is no one “standard” approach to preclinical safety evaluation
- CBER recommends/reviews preclinical safety and toxicity studies on an “individualized” basis

Biologics Approach to Preclinical Safety and Toxicity Testing

- Creative, problem-solving
- Data-driven
- Should be based on best available science, technology to date
- Careful design and judicious use of animals
 - should allow early initiation of clinical studies
 - should allow uninterrupted clinical development

Questions to Answer

- Do you understand...
 - dose/activity relationship?
 - relationship of route and dose regimen to activity/toxicity?
 - dose/toxicity relationship?
 - risks for toxicity?
 - how does the toxicity/lesion(s) compare to other disease-induced lesions?
 - what is the incidence of toxicity/lesion(s) in normal animals?

Questions to Answer

- Do you understand...
 - do other drugs/chemicals in the same pharmacologic class produce similar toxicities/lesions?
 - what are the potential mechanisms for the toxicity/lesion(s)?
 - relevance to humans
 - relationship to the product
 - can the product be modified to retain efficacy and reduce toxicity?

Implications for Biogenerics

- Highly complex products
- Mechanisms of action multi-faceted
- Proprietary information of innovator
- Availability of suitable analytical methods
- No current CBER mechanism or guidelines for generic submissions
- Full IND/BLA submission for new products

Immunogenicity and Biologic Products




Immunogenicity: Cellular or Humoral (antibody) response to a foreign protein or antigen

- The potential for immunogenicity must be assessed prior to introduction into the clinic.....Preclinically
- Methods for assessing immunogenicity consisting evolving and RAISING THE BAR for follow-on products

Causes of Immunogenicity

- Differences from endogenous human protein
- Structural modifications
 - Conformational changes
 - Oxidation
 - Glycosylation, amidation, others?
- Formulation
- Storage Conditions (container/vials)
- Production/Purification
- Patient related issues (Immune status)

Possible Effects of Immunogenicity

- More rapid clearance of product  PK
- Neutralization of product efficacy  PD
- “Sustaining” Antibody  PK or PD
- Limited exposure and misleading toxicity data
- Immune complex formation
- IgE, allergic or anaphylactic response
- Cross reaction or sensitization to endogenous protein (Epo Example-Pure Red Cell Aplasia)

Assessing Immunogenicity

- ELISA
 - Direct
 - Indirect
 - Bridging
- Radioimmunoassay or precipitation
- Surface Plasmon Resonance (SPR)-BIAcore
- Electrochemiluminescence (ECL)

Characterizing “Anti-Drug” Antibodies

- Determination of Antibody Isotype (IgG, IgM)
- Binding with soluble drug
- Affinity
- Relative Concentration
- Specificity to product or endogenous prot.
- Neutralizing potential in bioassay-Determine link to antibody

FDA Expectations for Immunogenicity

- Monitor for Immunogenicity in both nonclinical and clinical studies
- Normally take blood samples and develop immunogenicity assay for animal studies
- Determine neutralization potential if Abs present
- No requirement to characterize or phenotype response for early stage studies
- Come to agreement with FDA on expectations

Immunogenicity and Biogenerics

- Even very subtle MFR changes can induce elicit changes in immunogenicity
- Biogeneric or “follow-on” biologic product should have suitable available information to eliminate much early work-Pilot tox, target organs, etc.
- Since nonclinical toxicology studies cannot be completely ruled out, include immuno endpoints
- Use final formulation prep
- Include comparator product (maybe)

Changing Regulatory Environment

- New FDA Chief (as of September 23rd)
- Recent Safety Issues (Vioxx) and Congressional hearings
- Flu Vaccine, Plan B, other issues
- Move of CBER divisions to CDER
- FDA relocation to White Oak Facility
- Shifting to potentially more conservative stance

Issues to Consider.....

- Site of Toxicity
- Immunogenicity
- Species Selectivity
- Mucosal Immunity
- Local or Systemic Immunity
- Route-dependent toxicity
- Antigenicity vs. Inflammation
- Proper animal model
- Vector attenuation
- Biodistribution and detection
- Dose Response
- Ultimate Patient Population
- Cellular Differentiation in vivo
- Toxicity in immunocompromised animals
- FDA review division

Questions to Answer

Do you understand...

- The biology and full range of activity of your therapy?
- Whether other drugs/chemicals in the same class produce similar toxicities/lesions?
- The putative target organs for your therapy
- The therapy's potential local and systemic distribution
- The potential mechanisms for the toxicity/lesion(s)?
 - relevance to humans
 - relationship to the product
- Whether the product be modified to retain efficacy and reduce immunogenicity and toxicity?

Achievement of Goals

- Solid understanding of the Product's Biology
- Early dialog with FDA welcome (Pre-Pre-INDs)
- Pre-IND meetings
 - Prior to enabling GLP safety program
 - Obtain FDA “buy in” on plan well before IND
 - assays to measure product
 - preclinical safety (toxicity) issues
 - preclinical pharmacology “proof-of-concept” studies
 - rationale for starting human dose
 - Duration of studies
 - Any additional studies or prior FDA experience with product

Thank You!

Questions or Comments.....

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