Nonclinical Safety Assessment of Biotherapeutics

BIO-Latin America
Regulatory Session
10 September 2014
Rio de Janeiro

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BioSafe Organization and Annual Meetings

BioSafe Leadership Committee

BioSafe General Membership

Special Biologics Work Group
Pharmacokinetics / Pharmacodynamics (PK/PD) Work Group
Mechanism of Action / Mechanism of Toxicity Work Group

BioSafe General Membership Meeting *(Spring)*
BioSafe Europe *(Fall)*

BioChina, Bio Latin America
BIO International Conference

BioSafe –FDA Liaison Meetings *(Yearly)*
BioSafe –Liaison Meetings with other HA's (EMA, PMDA, CFDA)
We share a common mission

- To serve as a resource for BIO members and BIO staff by identifying and responding to key scientific and regulatory issues related to the preclinical safety evaluation of biopharmaceutical products.

- We are representatives from pharmacology, pharmacokinetic, toxicology and regulatory departments of large and small biopharmaceutical companies.
Nonclinical Safety Assessment of New Therapeutics – View from BIOSafe

Goal: The evaluation and identification of potential human safety issues through evaluations in predictive model systems

- Identification of target organs of toxicity and characterization of those toxicities
  - Nature of effect, reversibility, translatability (animals-to-humans)
  - Inform patient monitoring

- Establish the relationship between safety observations and drug exposure ($C_{\text{max}}$ and/or AUC)

- Goal of nonclinical safety testing is the identification of:
  - Safety margins or therapeutic windows
  - Safe starting doses, dose escalation rationale
Nonclinical Safety Assessment of Biotherapeutics – Regulatory Background

• These principles are outlined in:
  o **ICH S6(R1)** [Preclinical safety evaluation of biotechnology-derived pharmaceuticals]
  o **ICH S9** [Nonclinical evaluation for anticancer pharmaceuticals]
  o **ICH M3(R2)** [Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals]
  o **WHO** Guideline on rDNA Products

Generally, do HA’s in Latin America accept nonclinical submissions conducted in accordance with these guidances? Are there routine areas of concern or additional expectations in Latin America?
General safety concerns for biologics are distinct from small molecules

Goal: The evaluation and identification of potential human safety issues through evaluations in predictive model systems

- Catabolized to ‘building blocks’ (amino acids), not metabolized to other active or reactive molecules.
- Generally, do not cross biological membranes to interact with DNA or other intracellular molecules.
- Highly specific binding properties with few ‘off target’ effects.
- Because of size do not interact with ion channels.
- Only rarely affect metabolizing enzymes.
- Modality (construction) associated with unique biological characteristics.
- The pharmacology of the biologic determines the toxicity profile and the required safety assessment design.

Leads to a ‘case-by-case’ design of the non-clinical program
Non-Clinical Development of Biologics: Defining the Case by Case Approach

Despite diverse modalities and targets, characteristic concerns exist – Are we aligned?

- **Nonclinical species selection**
  - Justification
  - Number of species

- **Dose extrapolation to humans - PKPD**

- Duration of longest general toxicity studies

- Developmental and reproductive toxicity assessment

- **Carcinogenicity assessment**
  - Genotoxicity assessment
  - Cardiovascular safety assessment
  - Dose selection for toxicity studies
  - Tissue cross-reactivity
  - Immunotoxicity testing
  - Immunogenicity
• What data support animal species selection for biotherapeutic toxicity studies?

  o ‘Pharmacological relevance’ used to justify a species
    - Similarity to humans in pharmacologic response (e.g., signaling pathway, target binding, pharmacodynamic activity)

  o Species choice will depend on the relevant pharmacology and the assessment tools available

  What is similar enough?

As with small molecules, one each of rodent and non-rodent species, if possible

- Many biotherapeutics are only pharmacologically active in nonhuman primates
  - A single nonhuman primate species is sufficient, usually cynomolgus macaque
  - Studies in chimpanzee no longer conducted due to ethical and practical issues
- Special case: **No suitable species** (e.g., target is only expressed with disease, no cross-reactive species)
  - Options: Use engineered models, ex vivo tools, ‘paper-based’ argument to create weight-of-evidence argument for patient dosing decisions

PK Support of First in Human Dosing and Beyond

- Predict key PK parameters in man (CL, $V_{ss}$, bioavailability)
  Input parameters for exposure estimates

- Estimate exposure (AUC, $C_{max}$) at the starting dose
  Needed for calculation of safety margins

- Estimate therapeutic exposure (based on PK/PD)
  Need to estimate efficacious dose range

- Hints for non-linearity / higher variability (Target mediated disposition)
  Potential impact on dose steps in SD escalation study

- Give hints for special risks based on biologics modality
  (e.g. Metabolism, Drug-Drug Interactions, Distribution)
  Planning of clinical monitoring
Carcinogenicity assessment

- Does the therapeutic promote tumor formation by non-toxic genetic or epigenetic mechanisms?

Small molecules
- Two year rat carcinogenicity study + six month (transgenic mice) or two year mouse carcinogenicity study

Biotherapeutics
- Carcinogenicity weight-of-evidence ‘assessment’: literature review, in vitro and/or in vivo studies
- Two year rodent studies are generally not appropriate
- Special concerns: Growth factors and immunomodulators


New Challenges in Non-clinical safety testing of Biologics

- Approaches to refine use of non-human primates in non-clinical safety testing of biologics and current experience on the use of minipigs as alternative non-rodent species.

- Tissue distribution studies as a useful tool to support pharmacokinetic/pharmacodynamic (PKPD) assessment of biologics, in that they provide valuable mechanistic insights at drug levels at the site of action.

- Mechanisms of nonspecific toxicity of antibody drug conjugates (ADC) and ways to increase the safety margins.

- Although biologics toxicity typically manifests as exaggerated pharmacology there are some reported case studies on unexpected toxicity.

- Specifics of non-clinical development approaches of noncanonical monoclonal antibodies (mAbs), like bispecifics and nanobodies.