2nd EMA Workshop on Biosimilar Monoclonal Antibodies, 24 October 2011

Session 4.3: Immunogenicity of mAbs

«Risk based approach – What are the risk factors»

Innovator Industry Presentation

Mike Moxness, Amgen
Scientific Director
Clinical Immunology

On behalf of EBE and EurpaBio

ebe
european biopharmaceutical enterprises

Immunogenicity Assessment of Monoclonal Antibodies Using a Risk-Based Approach

On behalf of EBE, we consider unwanted immunogenicity of mAbs to be an important clinical concern and appreciate the opportunity to participate in the development of this guideline

Contributors:

Abbott: Ingeborg Dreher

Amgen: Michael Moxness (Presenter)

BMS: Martin Ullmann

LFB: Françoise Rossi

Merck KGaA: Beatrix Metzner

Novartis: Peter Lloyd

Pfizer: Judith MacDonald

Roche: Valerie Quarmby, Anna-Maija Autere, Julia Heinrich

ebe
european biopharmaceutical enterprises

Risk-Based Immunogenicity Assessments

- EBE welcomes a clinical risk-based approach
  - Which should be applied for each novel and biosimilar mAb
  - Each indication may require a separate risk assessment
  - Likelihood of an immune response is related to product, process and patient specific risk factors; unique risk factors for mAbs include:
  - More micro-heterogeneity than other biologics
  - Higher dosing and longer half-life, therefore, significant exposure to low level product variants and process impurities can occur
  - Idiotypes that may appear foreign to the immune system
- Severity of an immune response is often limited to loss of efficacy and/or hypersensitivity; unique risk factors for mAbs include:
  - Immune complex formation in the presence of high drug and anti-drug antibody (ADA) concentrations which leads to enhanced clearance and/or adverse events
  - ADA cross-linked mAbs may induce unexpected agonistic or antagonistic activity

ebe
european biopharmaceutical enterprises

Perceived Risk Drives the Extent of Clinical ADA Testing and Characterization

- Appropriate methods and sampling strategies should be used to detect ADA responses in studies where high drug concentrations are expected
- Impact of ADA on PK, PD and efficacy may be used as a surrogate for neutralizing activity in some circumstances
- Drug-specific IgE assays may be needed if allergic reactions are observed and there is an identified potential for hypersensitivity
- Post-authorization monitoring of ADA (and potential impact) may be necessary if pivotal studies are not adequately powered for rare events

ebe
european biopharmaceutical enterprises

Other Recommendations for Clarification in Final Guidance Document

- Immunogenicity strategy may be different for biosimilar mAbs
  - Primary goal is to establish similarity with sufficient clinical data pre-approval, acknowledging that post-authorization monitoring may also be necessary
  - Data should be generated in a direct comparison of innovator and biosimilar mAbs using state-of-the-art assays and appropriate sampling
  - Extrapolation considerations should include a risk-based assessment, however, more experience is necessary to validate this approach
- Immunogenicity strategy may be different for mAb analogues
  - Fc-fusions, mAb conjugates, mAb fragments and mAbs with multi-functional domains may require ADA epitope characterization and/or multiple assays to define binding and neutralizing activities
- Sponsors should determine whether to conduct *in silico / in vitro* T cell assays to predict immunogenicity potential, since they are not yet clinically validated

ebe
european biopharmaceutical enterprises

Immunogenicity Risk Based Approach Summary

- EBE welcomes a risk-based approach for immunogenicity assessment of mAbs, acknowledging:
  - Likelihood risk factors are predominantly related to product, process and patient, but also include extensive micro-heterogeneity of mAbs and high circulating drug levels
  - Severity risk factors are predominantly loss of efficacy and hypersensitivity, but also include unexpected activity due to cross-linking and enhanced clearance due to immune complex formation
  - Post-authorization monitoring may be necessary in some cases
  - Assessment of neutralizing potential and allergic reactions requires careful consideration of assay capabilities
- Clarification is requested for:
  - Differences in strategy for biosimilars and novel mAb-based analogues
  - Whether it is a choice or a requirement for the sponsor to conduct immunogenicity prediction assays

ebe
european biopharmaceutical enterprises