Biosimilar Industry Perspective on Draft Guideline on Immunogenicity Assessment of Monoclonal Antibodies

4.2

London, 24 Oct 2011

Thomas B. May, Ph.D.

Research R&D Fellow

Immunogenicity of mAbs

- EGA welcomes the opportunity to participate in development of the guideline on immunogenicity assessment of monoclonal antibodies
- The two questions posed for this forum are important considerations for immunogenicity testing of mAbs
  - *How should antibodies against mAb therapeutics be assessed?*
  - *What are the risk factors? Is there anything special for mAbs as compared to other biologicals?*

Q1 - mAb Antibody Assessments

- The issues in conducting immunogenicity assessments for biosimilar mAbs are no different than for the originator molecule
- From an immunogenicity perspective, biosimilars should be treated like a process change for originator molecule
- Biosimilar companies have prior knowledge of the product specific issues, and these can be considered both in assay design and risk assessment

Q1 – mAb Antibody Assessments (Positive Controls)

- **Measurement of assay sensitivity is a reflection of the positive control antibody**
  - The primary purpose of the positive control is to inform assay performance
  - No positive control antibody represents the range of possible anti-drug antibody responses to a therapeutic mAb in humans
- **Some assay formats inherently provide greater sensitivity and should be considered**
  - Assays should as sensitive as possible to give the best chance of detecting antibody in patient samples
  - Assay sensitivity is likely sufficient if anti-drug antibody is detected in nonclinical or clinical settings

Q1 – mAb Antibody Assessments (Drug Tolerance)

- Long serum half-life is a unique attribute of mAb and this has implications on assay tolerance to drug product present in samples
- Generally a combination of considerations are required to address drug tolerance
  - Assay format
  - Delayed sample testing
  - Acid dissociation
  - Sample dilution
- Changes in PK/PD in the absence of an antibody response may suggest inadequate assay drug tolerance and/or assay sensitivity

Q2 - Risk Assessment (1)

- Risk assessment considerations for mAbs should be similar to process for other biotherapeutic proteins
- mAbs as a class are generally low risk for causing clinically important immune responses (i.e., no higher risk than most other biologics)
- Additional anti-drug antibody characterization (e.g., isotyping, quantification, NAb) is warranted if PK/PD changes or in presence of an adverse clinical response

Q2 - Risk Assessment (2)

- **The risk of unwanted immune responses for process changes and biosimilars should be viewed in context of the original molecule**
  - Molecule specific immunogenicity risks are known in contrast to first in human studies for the originator mAb
  - A low historical immunogenicity rate for the originator mAb may support assigning a lower risk than might otherwise be justified
- **Assignment of the specific risk category for process changes and biosimilars should consider the totality of the data**
  - A focus on impurities, aggregates and immunogenic product variants during comparative quality assessment may support assigning a lower risk category
  - Comparative non-clinical studies, if performed, may support assigning a lower risk category

Summary

- The risk assessment process for mAbs should be similar to those used for all biotherapeutics
- mAbs as a class are inherently low risk for causing clinically meaningful anti-drug antibody responses
- Immunogenicity assays should be developed to detect clinically meaningful responses
- Assays should be as sensitive as possible, balancing sensitivity and drug tolerance considerations