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

Session 1.4: Non-Clinical Issues

«Risk-based approach – rationale and decision points»

Innovator Industry Presentation

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Risk-based approach

EBE welcomes opportunity to comment on this guideline. A 'risk-based approach' is generally supported, but should be clarified for two major aspects:

- **The current 'risk-based approach' allows to fully rely on in-vitro similarity prior to first human safety/efficacy trials**
  - However, innovator industry considers one **animal study** with the biosimilar candidate prior to FIM to verify that no unexpected findings (PK/PD/Safety) are observed (slide 3)
  - The extent of in-vivo testing should be based on level of concern (slide 4 & 5)

- **Clarification is needed on...**
  - Selection and qualification criteria for analytical and in-vitro assays
  - Additional factors important for the in-vivo nonclinical strategy

  (slide 5)

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Risk-based approach – Animal Testing

- **Innovator industry recommends an animal PK/PD/safety study should be considered prior to clinical trials of a biosimilar mAb until sufficient data on biosimilars is accumulated**
  - To **safeguard human subjects** prior to FIM safety/efficacy trials (mirrors existing EMA biosimilar framework) for potential in-vivo findings
  - Endpoints could be combined in **one animal study** (eg, PK/PD with safety evaluation) depending on level of concern
  - In certain cases the sponsor may consider progressing into **FIM without an in-vivo study** based on **sound scientific justification** and **careful risk assessment**
  - Once more thorough experience with classes of mAb biosimilars has been obtained, requirements for in-vivo animal testing may be revisited and adjusted

Risk-based approach – Minimum *vs* Extended FIM-enabling Animal Study

- Proposed **minimum *vs* extended animal testing:** The extent of in-vivo testing should be based on **level of concern (Risk-based approach)**

Minimum Design*	Extended FIM-enabling Design
1-2 dose level(s)/cpd	≥ 2 dose levels/cpd
One gender	Both genders
No recovery groups	Recovery groups
Possible shorter treatment duration	Treatment between 4 and 13 wks
Reference product – case-by-case	Reference product
PK/PD/toxicity evaluation	

*) e.g. if no analytical/in vitro flags, no concern in healthy animals with originator mAb

  - Even if not pharmacologically relevant, the **rodent** may be considered an **alternative test species** in some cases (eg, for PK)

- In-vivo testing should evaluate if important **PK/PD/safety findings** occur. Testing for **differences** between biosimilar and reference product can be case-by-case
- A **scientific rationale** for the Risk-based approach on animal testing should be provided (eg, justification for gender, dose levels, duration, recovery)

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Risk-based approach – Clarification on in-vitro criteria and factors for in-vivo strategy

- **Clarification is needed on...**
  - **Selection and qualification criteria for analytical and in-vitro assays**
    - How to determine the (minimal) acceptable level of difference, range of variability etc.
      - Choice of assay defines/limits quality of data (assay variability may depend on cellular system used, e.g. ADCC assay with PBMCs vs cell lines)
      - Qualification of reagents used to characterize potency, identity, etc.

      ⇒*topics for revision of EMA biosimilar quality guideline?*

  - **Additional «factors important for the in-vivo nonclinical strategy = step 2»**
    - Nature and range of critical differences in quality attributes (eg, any *vs* some glycosylation differences and/or changes leading to differences in charge)
    - Where data from analytical and in-vitro assays or the assays themselves are considered limited or inadequate (ie, selection and quality of tests need to be defined – see above)
    - Where an originator mAb mediates effects in-vivo that are not yet fully elucidated
    - Where there is a narrow safety margin with originator
    - Key safety attributes that can only be characterized/compared in nonclinical models (eg, evaluable only by histology), or rationale for why they are deferred to clinical testing.

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Risk-based approach - Summary

- **The current 'risk-based approach' allows to fully rely on in-vitro comparability prior to a first human safety/efficacy trial**
  - However, innovator industry recommends one **animal study** with the biosimilar candidate prior to FIM to verify that no unexpected findings (PK/PD/Safety) are observed
  - The extent of in-vivo testing should be based on level of concern

- **Clarification is needed on...**
  - Selection and qualification criteria for analytical and in-vitro assays
  - Additional factors important for the in-vivo nonclinical strategy