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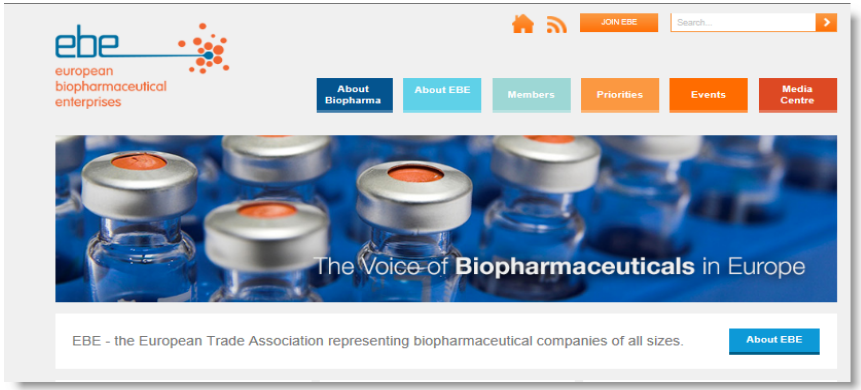
Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues

EMA Workshop on Biosimilars
31 October, 2013

- EBE & EuropaBio represent the views of companies developing both novel biologics and biosimilars.



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Topics

1. Quality Target Product Profile
2. Significant Quality Differences
3. Use of Different/Novel Expression Systems

Quality Target Product Profile (QTPP)

QTPP (per ICH Q8): "A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."

- QTPP is a valuable tool that can be used for development of novel products as well as biosimilars
  - While QbD principles are equally applicable to biosimilar development, the biosimilar design space can not be identical to that of the reference product
- QTPP generation is dynamic in nature, developed as reference product knowledge is gained and incorporated into the proposed biosimilar
  - Any variability detected in the reference product will be reflected in the QTPP
  - QTPP could comprise several reference product presentations, with justification
- Identification of the QTPP, together with QA criticality assessment ensures a meaningful analytical assessment
  - Identifies attributes most relevant to biosimilarity, facilitates development of meaningful target acceptance criteria for biosimilarity

Quality Target Product Profile (QTPP)

EBE recommends reinforcing the role of the QTPP in a stepwise approach to biosimilar development

- The biosimilar QTPP should be quantitative (where relevant), derived from analysis of a sufficient number of reference product lots and other relevant information.
- The QTPP should be established at the outset of development in order to inform cell line and process development.
- Ultimately, the QTPP should link to "**target acceptance criteria**" for the stepwise biosimilarity exercise
  - Clarity on the relationship between the "target acceptance criteria" and the QTPP is required
  - Setting quantitative, meaningful criteria is a technically complex topic that merits further discussion in the proposed reflection paper on statistical methodology
  - Such a paper should answer the available questions, while maintaining sufficient operational flexibility to encourage innovation

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Significant Quality Differences

'Significant Quality Difference "should be further defined and related to the stepwise development

- A **quality difference** exists where a quality attribute is observed to be outside the target acceptance criteria.
  - Any difference should be considered the context the degree of difference(s), the relative importance of the quality attribute and potential impact of difference(s)
- In the event that quality differences cannot reasonably be avoided, sponsors should be recommended to promptly seek scientific advice to confirm:
  - That the difference is not considered a **significant quality difference** that may effectively preclude development as a biosimilar.
  - That for less significant differences, the proposed analytical, nonclinical and clinical program is sufficient to demonstrate safety and efficacy in all indications sought.
- Given the stepwise approach, there is a challenge to ensuring continuity of oversight from review of CT applications through to license application.

Significant Quality Differences

The role of functional assays should be clarified and related to quality differences

- Functional characterization is an essential element of biosimilar development, in that it
  - Confirms quality and potency (e.g. Fab and Fc) of the product
  - Acts as a tool for evaluating integrity of the higher order structure
  - Confirms similarity in terms of mechanism(s) of action
    - presence of expected function, absence of new function
    - specificity of target binding
- Sponsors should ensure appropriate assay design, statistical methods, sample preparation, and coverage of known MOA(s) to optimize sensitivity and comprehensiveness of similarity assessment.
- Differences in quality attributes that result in functional differences relevant to the MOA(s) of a given product may constitute **significant quality differences**.
- Functional assays should not be assumed to predict clinical outcomes, evidence of such a correlation should be required.

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Difference/Novel Expression Systems

EBE supports the draft Quality guidance recommendation on different/novel expression systems

- Use of a different expression system should be considered in the context of (additional) potential risk
  - Requiring assessment of the degree of difference(s), and impact of difference(s)
  - Differences include the absence of species and creation of new species
  - Potential risks require assessment and justification, with non-clinical / clinical studies as appropriate
- Definiton of the term “novel” is required
  - Assumed to refer to an expression system new to the biotech industry, not previously used in any clinical setting, which may introduce additional risk
  - Not considered to be the same situation as a different but well established and understood expression system