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The European Association for Bioindustries

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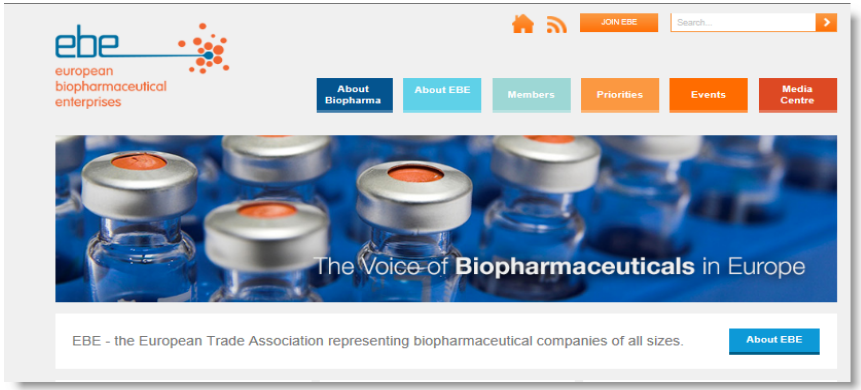
Guideline on Similar Biological Medicinal Products *("Overarching" guideline)*

EMA Workshop on Biosimilars
31 October, 2013

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



http://www.ebe-biopharma.eu/

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Topics

1. Choice of the reference product and three way comparability exercise

2. Other aspects in relation to the Overarching guideline

Choice of reference product – Basic Principles

- The “reference” medicinal product must be authorised in the EEA under Article 6, in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.

- This legal requirement addresses potential differences between the “reference” product and non-EEA authorised comparators available in other territories, e.g.:
  - Dosage form, Administration device, etc.
  - Formulation, Primary packaging
  - Impurity profile

- Legal & Scientific considerations: There is only ONE “reference” product.

Choice of reference product – non-EEA authorised comparator

- We agree that in the context of global development it may be possible for an Applicant to compare the biosimilar in certain in vivo non-clinical studies and clinical studies with a non-EEA authorised comparator provided that this is justified through an appropriate three way comparability exercise.

  a) Criteria for a priori selection a non-EEA authorised comparator

  b) Three way comparability exercise / Bridging program

Criteria for *a priori* selection of a non-EEA authorised comparator

- Authorised in ICH countries (registration standards, GMP control, post-marketing surveillance standards)
- Relationship between the MAH of the EEA reference product and the MAH of the non-EEA authorised comparator ?
- To what extent is the pharmacovigilance profile for the non-EEA authorised comparator characterised and relevant to the EEA reference product ?

Three way comparability exercise / Bridging Program

- We support that it is the Applicant's responsibility to establish that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA.
  - Ensure that decisions regarding relevance of non-EEA authorised comparator are made based on publicly available information and the data generated by the Applicant
  - Compliance with EU legislation (i.e. The marketing authorisation for a biosimilar product should not rely on data from registration dossiers in non-EEA countries)
  - Avoid Intelectual Property and Data Exclusivity issues in other territories.

Content of the three way comparability exercise / Bridging Program

- Same physicochemical, structural and functional comparisons (drug substance, drug product)

- 3-way human PK/PD study
  - Should preserve the sensitivity of the comparison between the biosimilar and the EEA reference product
  - Clinically relevant PD markers needed

Three way comparability exercise / Bridging Program

- The draft guideline states that *"If certain studies of the development programme are performed with only the non-EEA authorised comparator, the Applicant should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable bridge to the EEA-authorised reference product."*

- Clarification needed:

  – Bridging data are needed whether studies are conducted partially or in totality with the non-EEA authorised comparator.

  – EMA position on possibility to use both the EEA-reference product and the non-EEA authorised comparator in the same pivotal study?

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Biosimilars are not generics

- We support EMA's intention to maintain Article 10(4) of Directive 2001/83/EC as the legal basis for the approval of all biosimilars

- The draft guideline suggests that in specific circumstances, similar efficacy and safety may be deduced from "similarity of physicochemical characteristics and biological activity/potency of the biosimilar" and comparative PK data.

- Might not be aligned with the framework outlined in the Annex to Directive 2001/83/EC, as amended, which states that:
  - *" - Information to be supplied **shall not be limited to Modules 1, 2 and 3** (pharmaceutical, chemical and biological data), **supplemented with bio-equivalence and bio-availability data**. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.*
    *- … the need for identified **studies** foreseen in **Modules 4 and 5 shall** be required…."*

Intra-Product vs Inter-Products Comparisons

- Some but not all the principles described in ICH Q5E can apply to the demonstration of biosimilarity between a biosimilar and its reference product.

- Intra-product and inter-products comparisons differ in the nature and the extent of the tests to be performed.
  - Comparison of drug substance and drug product at various steps of the manufacturing process is an important part of the comparability exercise for manufacturing changes by a single manufacturer.
  - This is not possible as part of a biosimilarity assessment since the manufacturer:
    - does not have the extensive manufacturing data and experience of the originator, and
    - can only compare their version of the product with the final product of the originator.

➔ This distinction should be further developed in the final guideline, including a definition of each situation

Conclusions

- We agree that in the context of global development:
  - non-EEA authorised comparators may be used in certain non-clinical and clinical studies
  - provided that this is justified by the Applicant through an appropriate three way comparability exercise.

- We welcome the guideline revision as an opportunity for promoting a better understanding of the biosimilarity concept relative to innovator biologics and generic drugs.