EMA Workshop on Biosimilar Monoclonal Antibodies, 24 October 2011

Session 2.1: Clinical Issues

«Could we accept non-inferiority instead of equivalence trials in specific situations?»

Innovator Industry Presentation

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Equivalence versus Non-inferiority Clinical Trial Design for Similarity

- **EBE agrees with the current position of the BMWP that equivalence trials are clearly preferred for the clinical comparison of a biosimilar and its reference product with regard to efficacy / safety**
- **Non-inferiority studies can be done if appropriately justified**
  - The objective of an equivalence trial is to show that there are no clinically important differences between control and study treatments
  - The objective of a non-inferiority trial is to show that the study treatment is not substantially worse than the control treatment
    - It does not rule out superiority over the reference product
    - Superiority in efficacy, for example, infers a different clinical effect that could also be associated with a different safety profile

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Reasons Why Non-Inferiority is not the Preferred Study Design for Establishing Biosimilarity

- Superior efficacy of the study treatment of the biosimilar infers a different clinical or physiological effect of the product - such a product may have a different safety profile
- In some instances, superior efficacy could bring increased rates or severity of adverse events

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Equivalence versus Non-inferiority Clinical Trial Design for Similarity

A situation that may allow for a non-inferiority design:

- Non-inferiority could be used if the target receptor is continuously saturated at the clinical dose and well known to be the MOA for the clinical effect
- A hierarchical test should be considered to first test for non-inferiority and then superiority
- If superiority is determined clinically, then the product should no longer be considered a biosimilar
- Such a product must be evaluated as a new product and undergo the usual regulatory review for innovator products

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Determination of Equivalence Trial Margins

- By ICH E10 guidelines, this must be based on both clinical and statistical factors
- The biosimilar company must justify the margins based on clinical setting and may vary depending on therapeutic area
- Different statistical margins may be appropriate or required based on effect size and clinical setting (ex. in oncology: adjuvant breast cancer versus metastatic breast cancer)

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