BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Equivalence vs. Non-Inferiority
Regulator‘s View

BMWP / EMA Workshop on Biosimilar MAbs
24 October 2011, London

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General Guideline: (Non)Clinical Issues

- Mentions „clinical comparability exercise“ and „demonstration of clinical comparability“
- “Clinical comparability margins should be prespecified and justified, primarily on clinical grounds.”
- “Any differences …will have to be justified …”
- “If a clinical comparability trial design is not feasible, other designs should be explored and their use discussed with the competent authorities.”

$\Rightarrow$ No clear advice, non-inferiority designs not categorically excluded

Product Class-Specific Guidelines

- Some product class-specific guidelines are more specific, requiring equivalence trials
- No mention of non-inferiority trials

Draft Biosimilar MAb Guideline

- "Normally, similar clinical efficacy should be demonstrated in …..equivalence trials."
- "It may be difficult to define appropriate equivalence margins for pharmacodynamic equivalence based on clinical relevance."
- "Equivalence margins have to be defined *a priori* and appropriately justified."

WHO Guideline on Similar Biotherapeutics

Equivalence trials

- Preferred option
- Advantages
  - Confirm absence of a clinically meaningful differences
  - Provide good rationale for extrapolation of efficacy data to other indications of the reference product
  - Current experience is based on equivalence trials
- Disadvantages
  - Larger sample size needed
  - Finding of superiority would lead to formal failure of the study (although study may be adequate for stand-alone application)

WHO Guideline on Similar Biotherapeutics

Non-inferiority trials

- Should be justified
- Advantages
  - Smaller sample size
  - Finding of superior efficacy would not lead to study failure
- Disadvantages
  - Possibility of superior efficacy not excluded
  - Post-hoc justification of absence of clinically relevant superiority may be difficult
  - More difficult to extrapolate efficacy data to other indications of the reference product
  - No experience in the “biosimilar” setting

Revision of the General Guideline

- Considerations
  - Clearer advice needed
  - Equivalence trials preferred but may not always be feasible or necessary (e.g. oncology trials)
  - Demonstration of similar physicochemical characteristics, potency and PK (PD) profiles make superior efficacy highly unlikely

⇒ Personal suggestion: include wording from WHO Guideline