Equivalence vs. Non-Inferiority
Regulator's View

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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.”

⇒ 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
“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