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Clinical and non-clinical comparability for biologicals/biosimilars

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GENERICS AND BIOSIMILARS INITIATIVE
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European Medical Societies Roundtable on Biosimilars – Comparability, Extrapolation, Interchangeability and Substitution, Pharmacovigilance

Clinical and non-clinical comparability for biologicals/biosimilars

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European Medical Societies Roundtable on Biosimilars
12th January 2016, Brussels, Belgium

Disclaimer

- *I attend this conference as an individual expert, and do not represent the CHMP or the Austrian Medicines Agency*
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Overview

- Non-clinical comparability aspects
  - In vitro and in vivo studies
- Clinical comparability aspects
  - PK/PD studies
  - Efficacy and safety studies
  - Specific aspects on global development
  - Biosimilars of orphan products

Biosimilarity – general aspects

Development is a step-wise approach

1) Comparability at the **quality** level is key
2) Comparability at the **non-clinical** = functional level to give reassurance on similar effects
3) Comparability at the **clinical** level can and must be strengthened by a number of factors to be considered
   - Most homogeneous/sensitive population
   - Most sensitive dose (two doses?)
   - Most appropriate model and statistical approach
   - Most accurate definition of the equivalence margin

Non-clinical comparability aspects

Non-clinical program

- **Step-wise and risk-based approach**
  - Step 1 – In vitro studies:

    always necessary, always first
    most informative (functional assays for PD fingerprinting!)

  - Step 2 – determine level of concern

  - Step 3 – In vivo studies:

    may become necessary, e.g. with novel excipients

Non-clinical comparability aspects

Non-clinical program

- **Important in vitro data:**
  - In general, comparative studies of in vitro function, e.g.
    - Comparative binding to target antigen(s)
    - Comparative binding to Fc receptors and complement
    - Fab-associated functions (neutralization, receptor activation or receptor blockade)
    - Fc-associated functions (ADCC and CDC, complement activation
- **Animal data:** according the **3Rs** ⇨ if at all, then
  - **No studies in non-relevant species**
  - or without a relevant model

No off-target tox studies !

Clinical comparability aspects

PK/PD studies

- **Step-wise** approach to clinical comparability
  - Start with PK ⇨ PD can be measured at the same time
- For PK in some instances **AUC** as primary endpoint (CI 80-125%) is sufficient (i.v. administration)
- Otherwise **Cmax** as co-primary endpoint
- Secondary PK endpoints
  - Tmax, Ctrough, clearance, etc.

Clinical comparability aspects

PK/PD studies

- May provide pivotal equivalence data in some cases
- **No further phase III trial** necessary
  - When **PD surrogate endpoints** are available
  - E.g. ANC for filgrastims, insulin clamp study for insulins, viral load for interferon α, MRI for interferon β
- Biosimilar heparins rely on PD comparison only (no PK)
- Otherwise rather unspecific PD parameters as secondary endpoints provide supportive evidence
  - E.g. levels of various immunocompetent cells, CRP, ESR, etc.

Clinical comparability aspects

Efficacy/Safety studies

- Pivotal clinical trials are still needed in many instances (such as biosimilar antibodies)
- For **efficacy** – demonstration of **equivalence**
  - Especially for more complex molecules with several modes of action and where no good and single surrogate parameter exists
  - Also due to uncertainties in concluding on the absence (or presence) of clinical relevance of observed quality differences
  - However, the clinical trial is less sensitive than in vitro studies
  - Choice of the **clinical disease model**
    - Consider how to define a realistic equivalence margin
    - Population and concomitant therapy with lowest background noise

Clinical comparability aspects

Efficacy/Safety studies

- Overall the biosimilar should have the **same safety** profile as the innovator drug
  - Improved safety (e.g. lower immunogenicity) may be acceptable
- Part of the full safety database is necessary **pre-marketing**
  - Significant differences to be detected, e.g. in immunogenicity
  - Due to impurities, host cell proteins, other unknown factors?
  - Especially when new expression systems or excipients are used in the manufacturing process

Clinical comparability aspects

Safety database for biosimilars

- **Further safety data** to be delivered **post-marketing**
- Traceability of products is crucial
- Challenges in collection of reliable information on products and batches
  - Cooperation of clinicians most important
  - No agreed naming system yet
  - WHO Biological Qualifyer (BQ) scheme
    - Proposal for globally recognised unique identification code
    - 4 letter code as a complement to the INN
    - Currently not accepted by all regulators

Clinical comparability aspects

Considerations on global development

- Comparability at the clinical level is not expected to be significantly influenced by **ethnic factors** (are not different between treatment arms)
  - Acceptance of trials from other regions, other populations
  - As long as additional factors are respected in order to have a clinical model representative of the EU standard of care
  - E.g. adequate background treatment, adequate reference product, adequate GCP conditions of the study

Clinical comparability aspects

Considerations on global development

- **International dialogue of regulators**
  - International Pharmaceutical Regulators Forum (IPRF) – Working group on biosimilars (chair: Korea)
    - Representatives from Europe, North & Latin America, Asia, Africa + WHO
    - Inform, discuss and converge the legal, regulatory and scientific framework
  - Biosimilar cluster: t-cons between EMA (BMWP)-FDA-HC-PMDA
  - Parallel scientific advice between EMA and FDA
- **Harmonization** of regulatory requirements
  - Increase efficiency and consistency of regulatory decision taking
  - Facilitated by acceptance of **reference products** and **trial data** from different regions

Clinical comparability aspects

Biosimilars of orphan drugs

- **Feasibility challenges**
  - The number of patients will definitely preclude a statistical definition of "hard" equivalence margins
  - This will also preclude a reassuring safety database pre-licensing
  - PD surrogate endpoints often not available
  - Can PK comparison alone be sufficiently reassuring?
  - Additional challenges for extrapolation to other indications
- Weight of evidence on the **quality** (physicochemical and biological) **and** pre-clinical = **functional** in vitro comparison

Summary

Biosimilars are moving ahead

- **Challenges/changes** to be discussed
  - New approaches to comparison of critical quality attributes?
  - No more clinical phase III efficacy and safety studies required??
  - Where, when and to which extent to get the safety/immunogenicity data from?
  - How best to justify extrapolation to other indications?
  - How to reach global convergence?
- **Final goal** is to provide faster access of patients to affordable biological medicines at a sustainable price

Thank you for your attention