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Clinical and non-clinical assessment of biologicals/biosimilars

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First ASEAN Educational Workshop on Regulation and Approval of Biosimilars/Similar Biotherapeutic Products

Clinical and non-clinical assessment of biologicals/biosimilars

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Disclaimer

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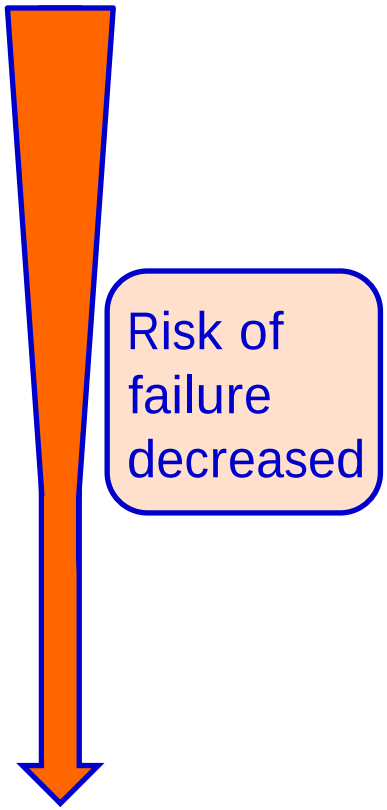
Overview

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

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 to be strengthened by a number of factors
   - Most homogeneous/sensitive <u>population</u>
   - Most sensitive <u>dose</u> (two doses?)
   - Most appropriate model and <u>statistical approach</u>
   - Most accurate definition of the <u>equivalence margin</u>
   - Most sensitive <u>timepoint</u> of primary assessment



Non-clinical comparability aspects

Non-clinical program

- **Step-wise and risk-based approach**
  - **Step 1** – <u>in vitro studies:</u>

    always necessary, always first, most informative
    functional assays in various test systems ⇨ PD fingerprinting!

  - **Step 2** – determine <u>level of concern</u>

    - **Step 3** – <u>in vivo studies:</u>

      may become necessary, e.g. with novel excipients,
      new expression systems

Non-clinical comparability aspects

Non-clinical program

- **Important in vitro data:**
  - Measurement of biological activity according to the properties of the product
  - In general, **comparative studies of in vitro function**, e.g.
    - Binding of ligand/receptor
    - Enzymatic or cell-based assays
    - Binding to target antigen(s) of mAbs
    - Binding to Fc receptors and complement
    - Fab-associated functions (neutralization, receptor activation or receptor blockade)
    - Fc-associated functions (ADCC and CDC, complement activation)

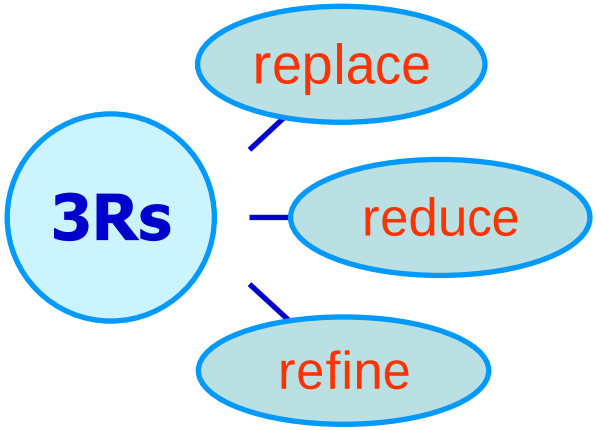
Non-clinical comparability aspects

Non-clinical program

- **Animal data:** only in rare specific situations, if at all, then

⇒

- According the **3Rs**



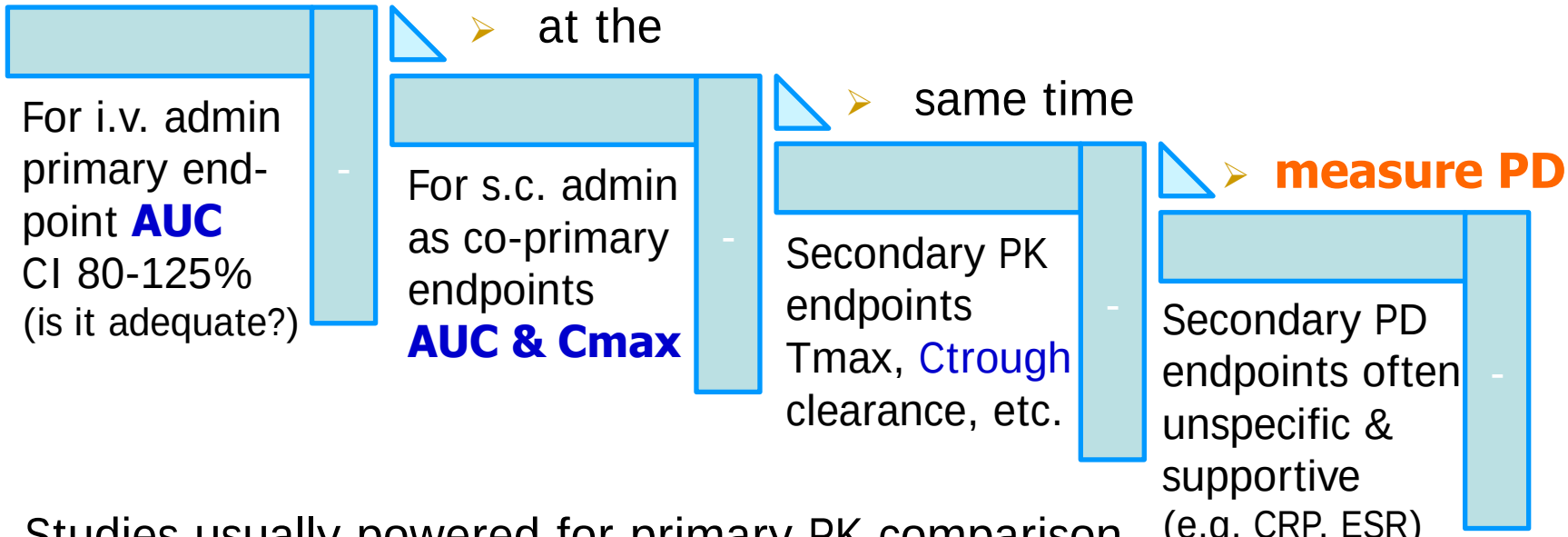
- **No studies in non-relevant species**
- or without a relevant model

No off-target tox studies !

Clinical comparability aspects

PK/PD studies

- **Step-wise** approach to clinical comparability
  - **Start with PK** ⇨
  - at the
  - same time
  - **measure PD**



- Studies usually powered for primary PK comparison
- In many instances ⇨ importance to characterise the elimination phase !

Clinical comparability aspects

PK/PD studies

- In some cases PD as pivotal data for equivalent efficacy
- **No further phase III trial** necessary
  - Requires a **risk-based approach**
  - When validated PD surrogate endpoints are available
  - PD then co-primary with PK, study powered for PD equivalence margin
  - E.g. ANC for filgrastims, euglycaemic clamp study for insulins, viral load for interferon α, MRI for interferon β, anti-FXa/FIIa for LMWH

But

- **Pivotal clinical efficacy trials** are still needed in many instances (such as biosimilar antibodies)

Clinical comparability aspects

Efficacy/Safety studies

- For **efficacy** – demonstration of clinical **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
- Careful choice of the **clinical disease model**
  - Considerations to strengthen the sensitivity ⇨ see above
  - In certain cases non-inferiority could be acceptable
  - **Confirmation** of biosimilarity observed in earlier steps

Clinical comparability aspects

Efficacy/Safety studies

- Overall the biosimilar should have the **same safety profile** as the innovator (studies are not powered for equivalence in safety !)
  - **Improved safety** (e.g. lower immunogenicity) may be acceptable
  - But ⇨ concerns of higher efficacy of the biosimilar
    - Could appear artificially increased due to lower levels of (neutralising) antibodies (ADAs)
    - In consequence higher rates of other adverse events could be possible
  - Comparison of the efficacy profile of biosimilar and reference in both subgroups of patients with / without ADAs
    - Acceptable if patients without antibodies show comparable efficacy

Clinical comparability aspects

How to justify extrapolation?

- Strong scientific rationale needed
- Supported by the **same mechanisms of action** (active site) or the **same receptors** involved in the various indications
- If different active sites or different target receptors are involved
  ⇨ additional data necessary
- Importance of the **overall data package**
  - **Quality** –
    differences in sugar moieties, antibodies, …
  - **Non-clinical** –
    receptor binding, PD cascades, cytotoxicity, ...
  - **Clinical** results –
    PK/PD studies measuring surrogate parameters, ...

Strongest weight on functional data

PD fingerprinting!

Clinical PK/PD?

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 are important (but often not available)
  - Can PK comparison alone be sufficiently reassuring?
  - Additional challenges for extrapolation to other indications
- Weight of evidence on **quality** (physicochemical and biological) **and** pre-clinical/**functional** in vitro comparison

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
- Use of non-EU/EEA reference product in clinical studies
  - Appropriate bridging data to be provided

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, approximate the legal, regulatory and scientific framework
  - Biosimilar cluster: t-cons between EMA (BMWP) – FDA – HC – PMDA
  - Parallel scientific advice between EMA and FDA
- **Convergence** of regulatory requirements
  - Increase efficiency and consistency of regulatory decision taking
  - Facilitated by acceptance of **reference products** and **trial data** from different regions

Summary

Biosimilars: where are we going? Evolution of the biosimilar paradigm

- **Challenges/changes** to be discussed
  - New approaches to comparison of critical quality attributes?
  - Tailoring of clinical evidence: how much phase III efficacy and safety data are required?
  - When and how to collect immunogenicity data (post-marketing)?
  - How to best 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