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# Clinical and non-clinical assessment of biosimilars

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# Clinical and non-clinical assessment of biosimilars

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10 October 2018

Austrian Medicines and Medical Devices Agency, Vienna, Austria

Generics and Biosimilars Initiative (GaBI), together with Ministry of Health & Prevention, UAE, Dubai

# Disclaimer

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

- The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CHMP or reflecting the position of the CHMP or the Austrian Medicines Agency

# Overview

- Non-clinical comparability aspects
  - In vitro and in vivo studies
- Clinical comparability aspects
  - PK/PD studies
  - Efficacy and safety studies
  - Extrapolation of indications

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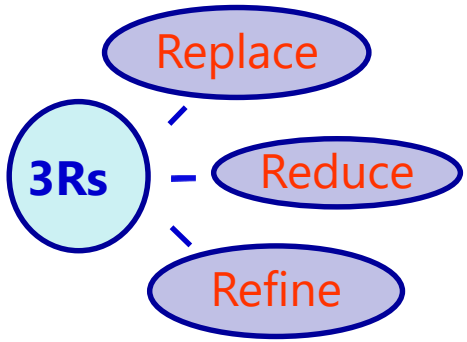
# Non-clinical data package

## Biosimilarity at non-clinical level

- **Step-wise and risk-based approach**
  - **Step 1** – in vitro studies:
    - **Step 2** – determine level of concern
      - **Step 3** – in vivo studies:
        May be needed, but only in rare specific situations, e.g. with novel excipients, new expression systems


Not, when no relevant species or model exist

**No off-target in vivo toxicity studies ! Principle of**



# Non-clinical data package

## Biosimilarity at non-clinical level

- **Step-wise and risk-based approach**
  - In most instances **in vitro** studies considered sufficient
    - Highly important data for both biosimilarity and extrapolation
    - PD fingerprinting approach – use a variety of test systems to confirm the results from several aspects
    - Various cell types and assays (consider high sensitivity, but also physiological conditions)
    - Often overlap with the quality part of the dossier

# Non-clinical data package

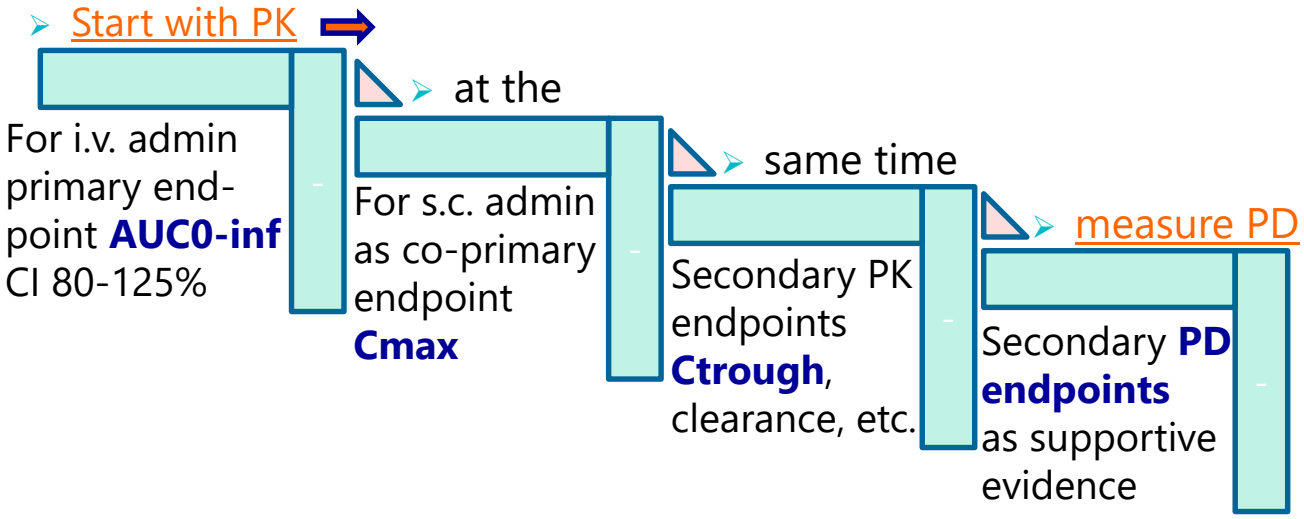
## If differences at non-clinical level are observed

- **Questions** to be asked:
  - Is there a plausible rationale (based on the quality characterisation)?
  - Do the differences concern a major pathway/mode of action?
  - Could further investigations using either more sensitive assays or under more physiologic conditions be helpful?
- **Conclusion** should take into account that
  - All non-clinical findings need to be interpreted in the context of clinical results and vice versa ⇨ principle of **"totality of data"**
  - Often no formal statistical evaluation of non-clinical tests

# Clinical data package

## Biosimilarity at the clinical level – PK/PD

- **Step-wise** approach to clinical comparability




- Studies usually powered for primary PK comparison
- Importance to characterise the elimination phase !

- Usually one single-dose PK/(PD) study in **healthy volunteers**
  - Sensitive dose in steep part of dose/ exposure curve
  - Less variability in exposure (e.g. via target-mediated clearance)
  - For some molecules not acceptable due to toxicity (e.g. rituximab)

# Clinical data package

## If differences at PK level are observed

- **For PK/PD** – results outside equivalence limits, due to e.g.
  - Study not sufficiently powered ?
  - Variability higher than expected ?
  - Higher content/concentration of drug substance in test/reference batches ?


- Variability
  - May be difficult to anticipate (due to scarce PK data of the originator product)
  - Impacts on sample size
  - Cross-over design may reduce/eliminate the impact of variability
  - Further decrease in variability by using only men ?
- When an additional efficacy trial is performed, limited **PK/PD sampling** in the patient population can "qualitatively" confirm the results from HVs
  - Enables assessment of PK after repeat administration

# Clinical data package

## Biosimilarity at the clinical level – PD/efficacy

- As standard approach, in many instances (e.g. biosimilar monoclonal antibodies) a phase III study demonstrating equivalence in clinical endpoints is required
- Do we always need **phase III efficacy trials?** ⇨ **NO!**
- In some cases **PD data** can establish equivalent efficacy
  - E.g. for molecules like biosimilar erythropoetin, G-CSF, insulin, interferons α and β, low molecular-weight heparins, teriparatide,….?
  - Requires in general a validated PD surrogate endpoint (for complex molecules with several modes of action surrogate parameters are not sufficiently reliable and validated)
  - PD then co-primary with PK, study powered for PD equivalence margin
  - Possible way forward for orphan biosimilars ?

# Clinical data package

## Biosimilarity at the clinical level – efficacy

- In general, the comparison of biosimilar with reference is less sensitive at the clinical level than at the quality/in vitro level
- This also applies along the step-wise comparison from PK to PD to clinical efficacy and safety
  - Ways to **strengthen the low sensitivity** of the clinical comparison: use the ⇨
    - Most appropriate model
    - Most homogeneous/sensitive population
    - Most sensitive dose (two doses?)
    - Most sensitive endpoint
    - Most accurate definition of the equivalence margin, based on both statistical and clinical grounds (non-inferiority acceptable only in exceptional cases)

# Clinical data package

## Biosimilarity at the clinical level – safety

- Pre-approval – demonstrate a **similar safety profile** to the reference
  - Judged in descriptive terms only (no hard equivalence criteria)
  - Special attention on differences in expression systems, impurities and immunogenicity
    - Normally **12 months comparative data** requested
    - For products with low immunogenic potential 6 months data pre-authorisation acceptable
      ⇨ Complete by collection of further 6 months data post-marketing
- Lower immunogenicity (lower ADA levels) of the biosimilar can be accepted
  - Artificially increased efficacy with potentially higher rates of other adverse events?
    - Separate comparison of the efficacy profiles between biosimilar and reference in both subgroups of patients with / without ADAs
      ⇨ Acceptable if patients without antibodies show comparable efficacy

# Clinical data package

## If differences at efficacy or safety level are observed

- **For efficacy** – results outside equivalence limits
  - Study not sufficiently powered?
  - Variability higher than expected?
  - Clinical relevance of the finding?

Provide additional PD data ?

- **For safety** – imbalances in results
  - Chance finding ?
  - Difference in antigenicity, impurities?
  - Artefact due to assay variability, difference in sensitivity?

Propose stringent RMP ?

# Extrapolation

## General aspects on extrapolation

- Extrapolation is the **most important principle for biosimilars** (and the most contentious one)
- Extrapolation as a concept is not new ⇨
  - Applied for generics, biosimilars, paediatric indications, other populations
  - Changes of manufacturing process for biological medicines
- Change in manufacturing leads to a **new version of the active substance**
  - This corresponds to the definition of a biosimilar
  - Typically, clinical data not required to substantiate manufacturing changes
- Extrapolation should be done in the light of the **totality of data**
- Implemented in all biosimilar products approved until now

# Extrapolation

## Justification based on cautious approach

- The **mechanism of action** is key to extrapolation
  - In vitro assays more sensitively characterise the MoA than clinical study
  - If the **same mechanisms of action** (active site) or the **same receptors** are involved (e.g. erythropoetin, filgrastim) ⇨ extrapolation straightforward
  - Additional non-clinical **or** clinical data (e.g. functional assays, PK or PD parameters and/or efficacy/safety data) may have to be **generated if** ⇨
    - Different active sites or different receptors are involved which may have a specific impact in different therapeutic indications (e.g. Fcγ receptor functions)
    - Studied therapeutic indication is not relevant for the others in terms of efficacy or safety (e.g. extrapolation from RA to oncology indications)
    - Different safety profile (e.g. immunogenicity) is expected in different therapeutic indications

# Summary

## How to enable a tailored development program for biosimilars

- Under the umbrella term of the **totality of data/ evidence**
  - New (statistical) approaches to comparison of critical quality attributes?
  - Further reassurance from functional data (in vitro, clinical PD)?
  - Waiving of clinical phase III efficacy and safety studies?
  - Strengthened post-marketing collection of safety/immunogenicity data?

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# Thank you for your interest and time