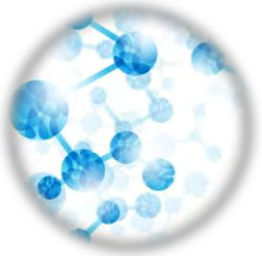


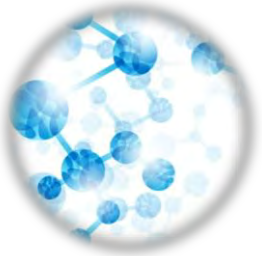
Professor Andrea Laslop, MD, Austria

- Head of Scientific Office, Austrian Agency for Health and Food Safety, Austria

GaBI Educational Workshops

First INVIMA Educational Workshop on Assessment of SIMILAR BIOTHERAPEUTIC PRODUCTS

14 June 2016, Hilton Bogotá, Colombia



Clinical and non-clinical assessment of biologicals/biosimilars

Professor Andrea Laslop, MD

14 June 2016

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

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Clinical and non-clinical assessment of biologicals/biosimilars

Andrea Laslop
Scientific Office, AGES, Vienna, Austria

Generics and Biosimilars Initiative (GaBI) Workshop on Biosimilars
14th June 2016, Bogota, Colombia

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*

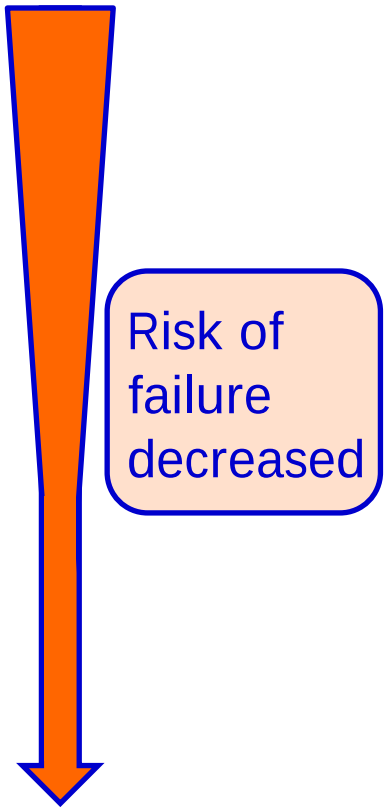
Overview

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

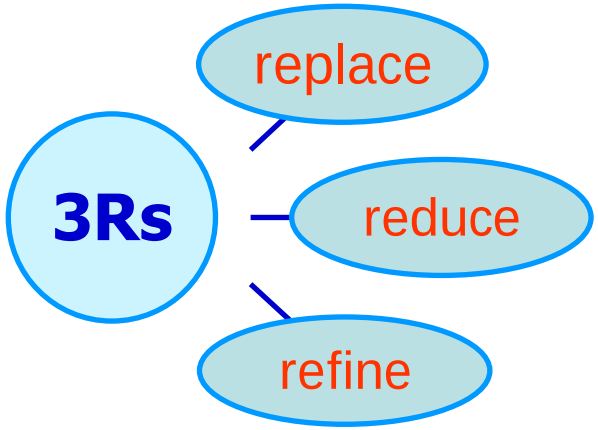
Non-clinical program

- **Important in vitro data:**
  - 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:** if at all, then ⇒
- According the



- **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** ⇨
    - For i.v. admin primary end-point **AUC** CI 80-125% (is it adequate?)
  - at the
    - For s.c. admin as co-primary endpoints **AUC & Cmax**
  - same time
    - Secondary PK endpoints Tmax, Ctrough clearance, etc.
  - **measure PD**
    - Secondary PD endpoints unspecific & supportive (e.g. CRP, ESR)

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 PD surrogate endpoints are available
  - E.g. ANC for filgrastims, insulin clamp study for insulins, viral load for interferon α, MRI for interferon β

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 **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**
  - **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 drug
  - **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

Efficacy/Safety studies

- Part of the full safety database is normally necessary **pre-marketing**
  - Substantial differences could be detected, e.g. in immunogenicity
    - However, at best a trend for difference to be discerned
    - Studies not powered for precise evaluation of similarity in safety
  - If the molecules are highly similar at quality level ⇨ role of impurities, host cell proteins, other unknown factors?
  - (Absence of) signals especially important when new expression systems or excipients are used in the manufacturing process

Clinical comparability aspects

How to justify extrapolation?

- Strong scientific rationale
- Supported by the **same mechanisms of action** (active site) or the **same receptors** involved in the various indications
- 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 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

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, 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

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??
  - How to collect immunogenicity data and when (post-marketing)?
  - 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