GaBI Educational Workshops

30 April 2019, Hilton Bogotá, Colombia

3rd Colombian Educational Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

Extrapolation of biosimilars

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

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3rd Colombian Educational Workshop on Regulatory Assessment of Biosimilars

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Principles of extrapolation of indications in the EU

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Disclaimer

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- 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

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- General considerations on extrapolation
- Extrapolation as addressed in guidelines
- Specific examples of extrapolation for various molecules
  - Erythropoetin
  - Filgrastim
  - Monoclonal antibodies – examples:
    - Infliximab
    - Etanercept
    - Rituximab
- Summary

The concept of extrapolation

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General considerations on extrapolation

- For biosimilars extrapolation is the most important feature
  - Relevant for abridged development with potential savings
- However, it is also the most contentious issue
- Addressed in many biosimilar guidelines
  - Overarching GL, general GLs, GL on biosimilar monoclonal antibodies, product-specific GLs
- Implemented in all biosimilar product approvals until now
- Various approaches ("comparability exercises") may lead to same SmPC label of biosimilar products with the same INN

The concept of extrapolation

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Extrapolation as a concept is not new

- Is a well-established scientific and regulatory principle frequently applied in regulatory decisions, e.g. for
  - Generics and biosimilars
  - Paediatric indications and other special populations
  - Changes in the manufacturing process of biological medicines
- The latter is the most relevant example for biosimilars
  - Comparability exercise (pre- vs. post-change product) to ensure that efficacy and safety can be expected to be the same
  - Change in manufacturing leads to new version of the active substance (= definition biosimilar)
    - Typically, clinical data not required to approve manufacturing changes

The concept of extrapolation

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The mechanism of action is key to extrapolation

- Mediated by functional molecular moieties in disease-specific manner
  - Characterisation by suitable assays more sensitive than clinical studies
- If **same mechanisms of action** (active site) or **same receptors** (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 be required ⇨
  - Different active sites are present in the product or it reacts via different receptors (e.g. Fcγ receptors) which are involved in different indications
  - 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) in different therapeutic indications

Extrapolation in guidelines

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Reference to extrapolation in biosimilar guidelines

- Overarching guideline on similar biological medicinal products
  - If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification

Guideline on similar biological medicinal products
CHMP/437/04 Rev 1

- General guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical & clinical issues

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
EMEA/CHMP/BMWP/42832/2005 Rev1

  - The reference product may have more than one therapeutic indication
  - Extrapolation of clinical data to other indications could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required
  - Extrapolation should be considered in the light of the totality of data

Examples of extrapolation

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Erythropoetin: extrapolation renal anemia ⇨ oncology

- All licensed biosimilar epoetins have the same amino acid sequence as their reference product
- Complex molecules (glycosylation!) but well characterised
- For all licensed biosimilar epoetins high similarity in molecular structure and biological activity was observed
- The pharmacological effect is mediated by the same receptor and same mode of action in all indications
- Renal anemia is the more sensitive model than chemotherapy-induced anemia (high similarity in efficacy and safety incl. immunogenicity was demonstrated)
- Risk of PRCA esp. observed with s.c. administration (extrapolation from s.c. to i.v. possible, but not the other way round)

Examples of extrapolation

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Filgrastim: extrapolation neutropenia ⇨ stem cell mobilisation

- Rather simple molecules (non-glycosylated!) and well characterised
- For all licensed biosimilar filgrastims high similarity in molecular structure and biological activity was demonstrated
- The pharmacological effect is mediated by the same receptor (CSF3R) and same mode of action in all indications
- Once PK profiles of biosimilar and reference product shown to be similar ⇨ ensures equivalent exposure
- Immunogenicity is very low for filgrastim
- In post-marketing experience no problems as regards efficacy and safety

Examples of extrapolation

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Infliximab: extrapolation rheumatological disorder (RA) ⇨ inflammatory bowel disease (IBD)

- Binds 2 different ligands with 2 different modes of action
  - Soluble TNFα and transmembrane TNFα
  - Fab part of the antibody: transduces the major mode of action, binds both sTNFα and tmTNFα, blocks the binding to their receptors
  - Fc part of the antibody: is primarily activated after binding to tmTNFα, induces additional mechanism of action like ADCC and CDC
- According to the guideline on biosimilar monoclonal antibodies ANY mechanism of action that could potentially be involved in claimed indications should be studied

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues
EMA/CHMP/BMWP/403543/2010

  - **In vitro assays** should broadly cover all functional aspects of the mAb
  - Even though some may not be essential for therapeutic mode of action

Examples of extrapolation

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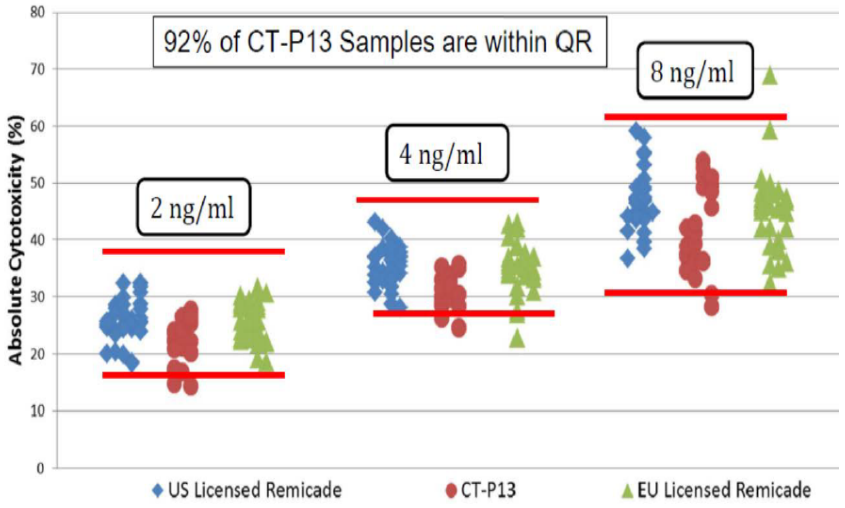
Infliximab – Remsima: extrapolation RA ⇨ IBD

- Extensive battery of in vitro tests showed comparable activities except
  - Lower percentage of afucosylated glycoforms ⇨ this led to
    - Lower binding to FcγRIIIa/b ⇨ and in consequence to
      - Lower ADCC
- This 20% lower ADCC activity was observed in a most sensitive and artificial in vitro test system
  - Jurkat cells as target cells (expressing abnormally high levels of tmTNFα) and NK cells as effector cells
  - Is this relevant for the clinical situation?

Figure 9. ADCC of CT-P13, US-licensed Remicade, and EU-approved Remicade Using NK Cells as Effector Cells



Source: CDER Clinical Review Template on CT-P13, available at www.fda.gov

Examples of extrapolation

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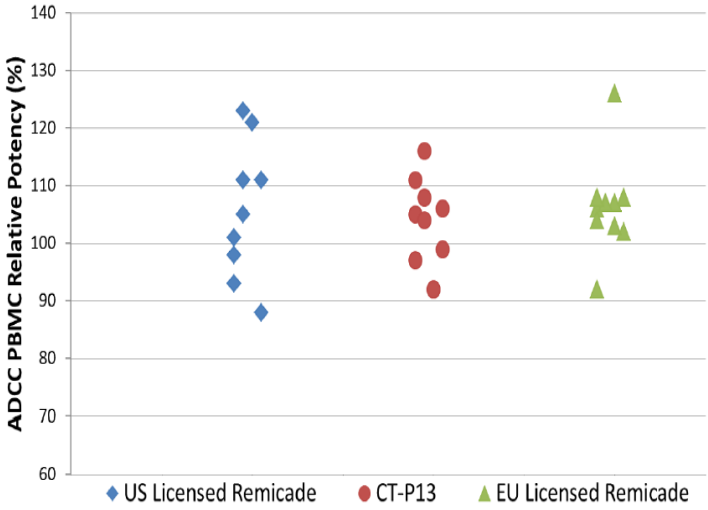
Infliximab – Remsima: extrapolation RA ⇨ IBD

- In physiologic conditions difference in afucosylated glycoforms was not clinically relevant

  - In NK cell assay with use of serum or whole blood or with PBMCs as target cells ⇨ no differences in binding/ADCC observed

  - In LPS-stimulated monocytes as target cells ⇨ no ADCC response with either product (role of ADCC in inflammation seems limited!)

Figure 8. ADCC of CT-P13, US-licensed Remicade, and EU-approved Remicade Using PBMC as Effector Cells



Source: CDER Clinical Review Template on CT-P13, available at www.fda.gov

  - No difference in induction of regulatory macrophages by PBMCs, nor in suppression of T cell proliferation and promotion of wound healing in cultured colorectal epithelial cells

  - Comparable dose-dependent inhibition of apoptosis and IL-6 & IL-8 secretion in inflammatory model of human intestinal epithelial cell line

Examples of extrapolation

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Infliximab – Remsima: extrapolation RA ⇨ IBD

- **Conclusion:** based on the totality of evidence the CHMP agreed to extrapolation with approval of all indications
  - Biosimilarity established at the level of
    - Quality data: comparable structure
    - Non-clinical assays: comparable functions
    - Clinical data: comparable PK and PD profiles in 250 patients with ankylosing spondylitis and comparable results on efficacy, safety and immunogenicity in 606 patients with rheumatoid arthritis
- All data provided convincing evidence that the observed difference in afucosylated species is not clinically relevant

Examples of extrapolation

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Etanercept – Benepali: extrapolation RA ⇨ PsA

- Comparable quality/non-clinical data on
  - TNFα binding, LT-α3 binding, TNFα neutralisation cell-based assay
  - Ligand binding to FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcRn, C1q
  - ADCC and CDC assay, apoptosis activity assay (tmTNFα)
- Slightly higher afucosylated glycan content (~2-fold) and slightly higher affinities to FcγRIIIa/b
  - In relation to infliximab (set at 100%) ADCC in RMP Etanercept is < 5% and in Benepali < 5-10% ⇨ not considered clinically relevant
- ADCC even less important (compared with infliximab) for the mode of action of etanercept in both arthritic and psoriatic indications ⇨
  - Primary mode of action: competitive inhibition of TNFα binding to cell surface TNF-receptors (mimics TNF-R), preventing TNFα-mediated signal transduction
- Extrapolation granted from rheumatic to psoriatic arthritis and others

Examples of extrapolation

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Rituximab: extrapolation rheumatology ⇨ oncology

- Interaction with same receptor (transmembrane CD20) results in different cell-specific effects ⇨ extrapolate to different indications?
- Pre-requisites:
  - Additional (non-)clinical studies, investigating, e.g. depletion of CD20 positive cells by ADCC, CDC and/or apoptosis
  - Due to possible differences in the clearance (target-mediated) and the mechanism of B-cell depletion (depending on whether malignant or autoimmune-reactive B-cells are targeted), a clinical bridge should be established, e.g. via an additional PK/PD study in patients with NHL
  - Phase III study in RA is acceptable, sensitive population, no cytotoxic co-medication, less variability in amount of tumour burden and consequently target-mediated clearance
- Totality of evidence allows extrapolation in both directions

Summary on extrapolation

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Key messages

- Extrapolation is essential for the success of biosimilars
  - Major issue for health care
  - To be done on the basis of the totality of data
- Extrapolation is common in drug development
- Once the comparability on all levels of the product and in a suitable model has been demonstrated, extrapolation is the expectation
- Extrapolation is not done automatically (needs to be justified)
- Post-approval experience in “extrapolated” indications is good (always successful until now)

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Thank you for your attention !

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