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Principles of extrapolation of indications

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Principles of Extrapolation of Indications

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Extrapolation of indications

- Single greatest benefit of biosimilar development
- Most contentious issue

Extrapolation of data: not a new concept

Biosimilars: the science of extrapolation

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(*Blood*. 2014;124(22):3191-3196)

Extrapolation of data is already an established scientific and regulatory principle that has been exercised for many years, for example, in the case of **major changes in the manufacturing process** of originator biologicals. In such cases, clinical data are typically generated in one indication and, taking into account the **overall information gained from the comparability exercise**, may then be extrapolated to the other indications. In fact, the authors are **not aware of any case where additional clinical studies with the changed product in other or even all approved indications** have been provided by the marketing authorisation holders, or **have been considered necessary** by regulators.

Biologicals change during their life cycles



Schneider C. Ann Rheum Dis, 2013

Changes in the manufacturing process

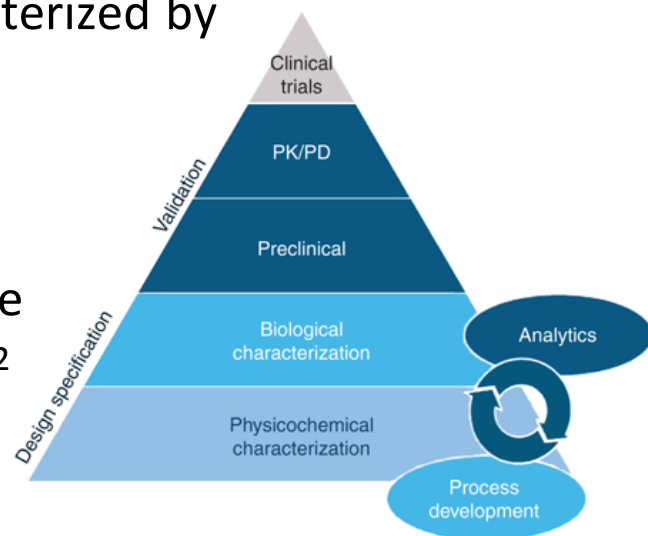
- Different versions of the active substance
- Comparability exercise (pre-change vs. post-change product) to ensure unchanged efficacy and safety

Comparability / Similarity: the basis for extrapolation

- Cornerstone is the **comprehensive characterisation and comparison** of physicochemical and functional characteristics
- Mechanism of action is mediated by the **functional moieties of the molecule**, which can usually be much better characterized by suitable assays than by clinical studies

➔ **Clinical trials address remaining uncertainties**

- **Scientific principles** for comparability exercise in the context of a change in the manufacturing process^{1,2} and for biosimilar development³ **are the same**

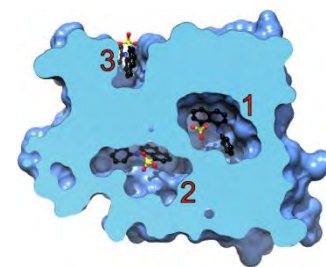


McCamish, *Clin Pharmacol Ther* 2012

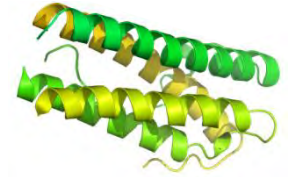
- 1 ICH Topic Q 5 E Comparability of Biotechnological/Biological Products (CPMP/ICH/5721/03)
- 2 Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues (EMA/CHMP/BMWP/101695/2006)
- 3 Guideline on similar biological medicinal products (CHMP/437/04 Rev 1)

Considerations for extrapolation

- Usually unproblematic when **same MoA/receptor** is involved and no unique safety concern
- Same receptor but **different target-cell specific downstream signalling** → no reason to request additional data
- **Different active sites** of the biological or **different target receptors** → additional data necessary (e.g. functional assays and/or PD parameters, clinical data)
- **Immunogenicity** must always be addressed



Filgrastim: extrapolation



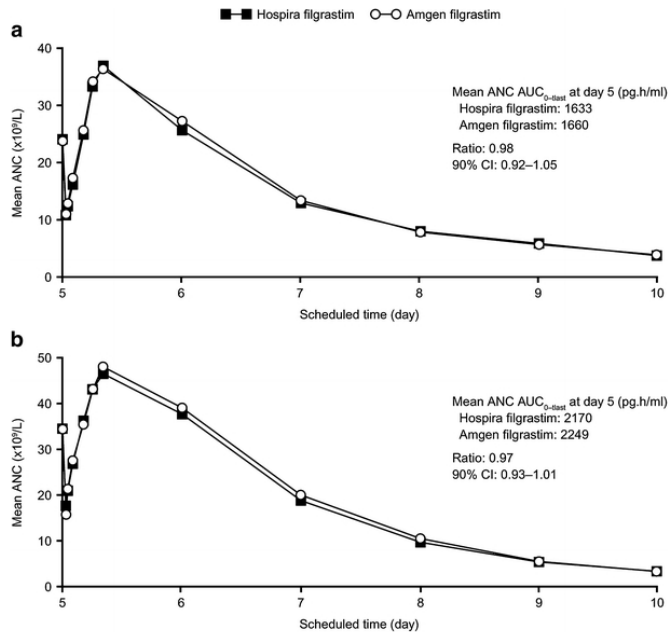
175 AA, 18.8 kDa

Concern: use for stem cell mobilisation in healthy donors

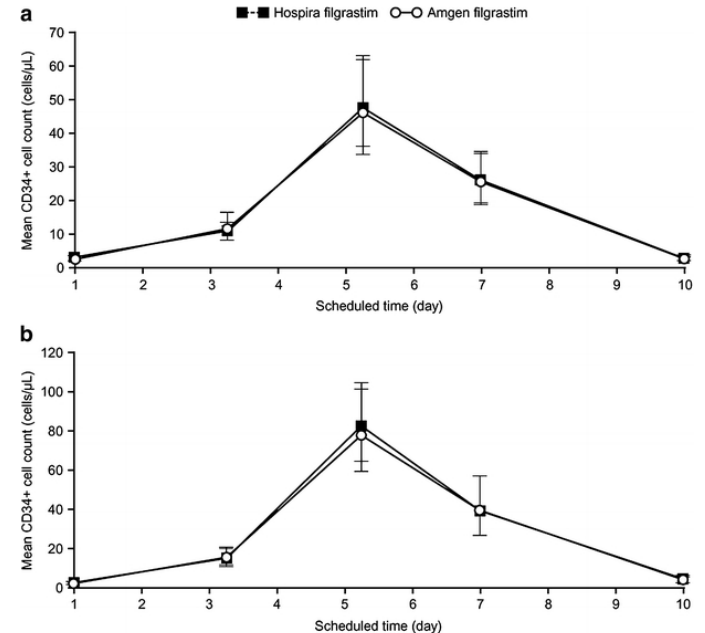
- Very well characterizable non-glycosylated protein
- Binding to CSF3R
- Data on stimulation of CD34+ cell count provide additional evidence for extrapolation from “neutropenia” to “stem cell mobilisation” indication
- Immunogenicity no particular issue
- Post-marketing studies confirmed efficacy and safety*

* (F Lefrère 2011, JC Ianotto 2012, A Publicover 2013, P Gascón 2013, M Schmitt 2014, P Reményi 2014)

Biosimilar filgrastim: PD data



Mean ANC over time in subjects given Hospira filgrastim or Amgen filgrastim; **a** 5-µg/kg dose group and **b** 10-µg/kg dose group. Data shown are geometric means. Samples taken outside each schedule timepoint window have been excluded. *ANC* absolute neutrophil count, $AUC_{0-tlast}$ area under the curve from time 0 to the last time point, *CI* confidence interval

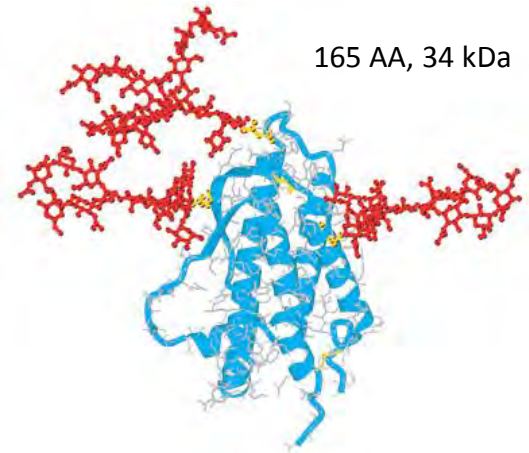


Mean CD34+ cell count over time in subjects given Hospira filgrastim or Amgen filgrastim; **a** 5-µg/kg dose group and **b** 10-µg/kg dose group. Data shown are geometric mean values with lower and upper 95% confidence intervals

Waller, Ann Hematol 2010

Epoetin: Extrapolation

165 AA, 34 kDa



Courtesy of M.B. Altmann and R.A. Davis, Oxford Glycoscience Institute, and P.M. Reut, NIBIT

Concern: use in cancer patients

- Complex glycoprotein but well characterizable
- Binding to EpoR
- Same MoA in haematopoiesis, regardless of the cause of anaemia
- Sensitive “model indication” to be studied: renal anaemia
- Risk of PRCA esp. with s.c. use in patients with renal anaemia
 - ➔ extrapolation of immunogenicity data from renal to chemotherapy-induced anaemia and from s.c. to i.v. use, not vice versa
- Post-marketing studies confirmed efficacy and safety*

* (G Lonnemann 2011 , L Kerkhofs 2012 , F Hörbrand 2013)

Biosimilar Epoetin alfa: characterisation studies

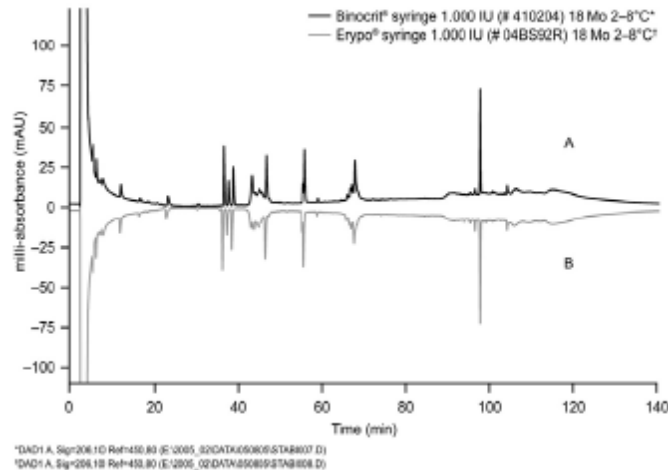


Fig. 1: Comparison of peptide mapping profiles

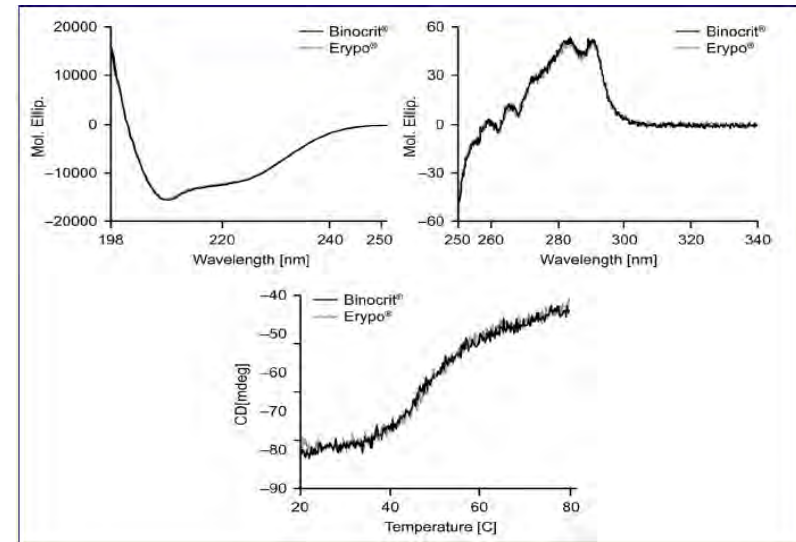


Fig. 2: Comparison of far- (top left) and near-ultraviolet circular dichroism-spectra (top right) of Binocrit® and epoetin alfa

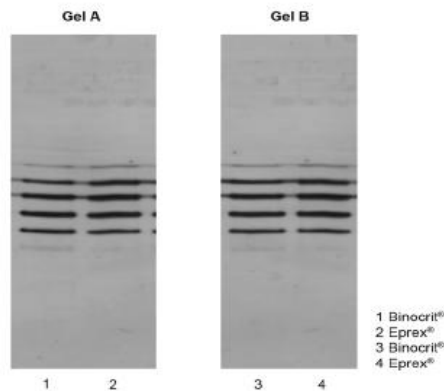


Fig. 3b: Comparison of the isoform pattern for Binocrit® and epoetin alfa by isoelectric focusing gel electrophoresis

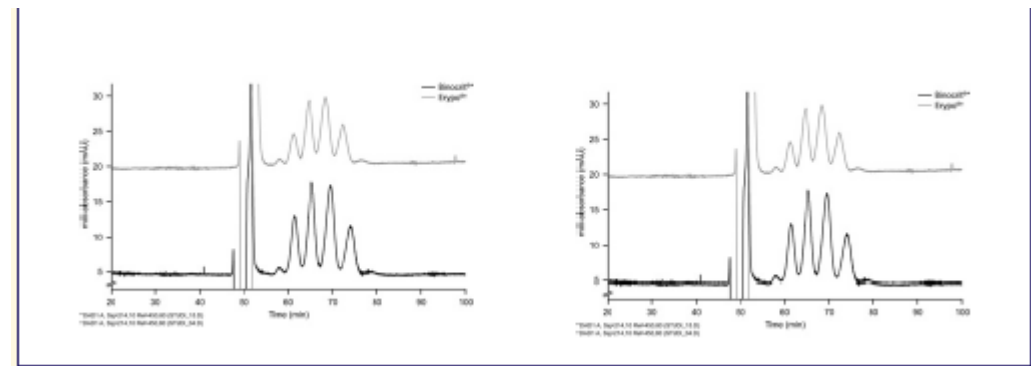
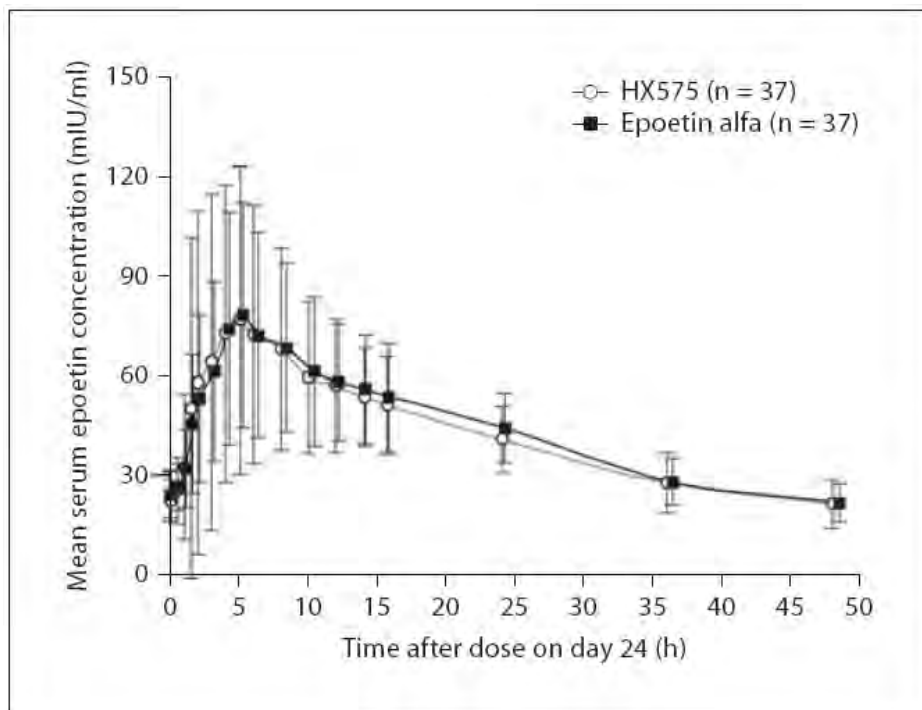


Fig. 3a: Comparison of the isoform pattern for Binocrit® and epoetin alfa capillary zone electrophoresis

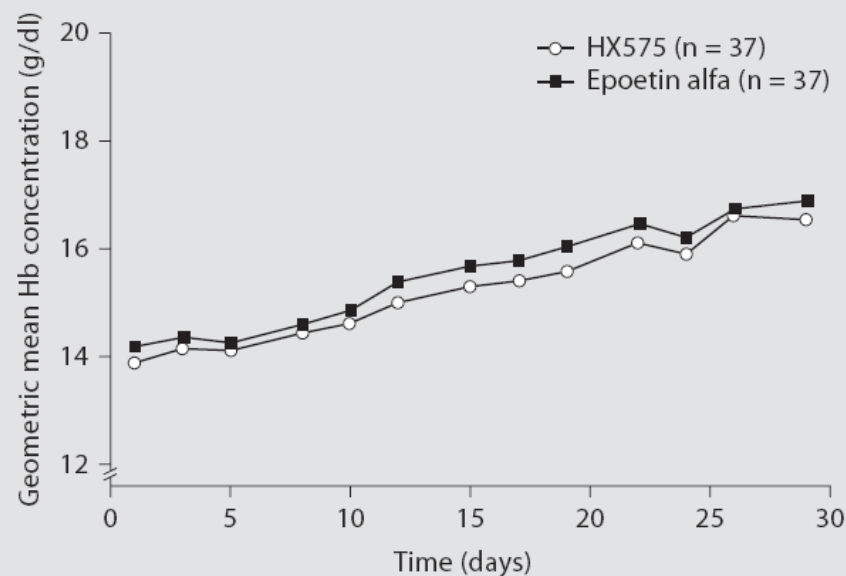
Biosimilar epoetin alfa: clinical studies

Multiple dose PK/PD study (SC)

Mean serum epoetin concentrations (\pm SD)



Mean Hb concentrations



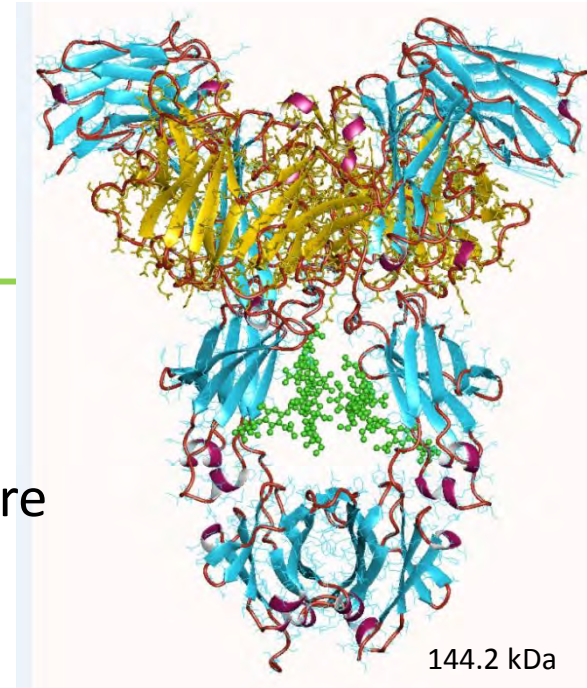
Sörgel et.al., Pharmacology 2009;83:122–130

Similar efficacy, safety and immunogenicity was confirmed in a clinical trial

Biosimilar Infliximab*

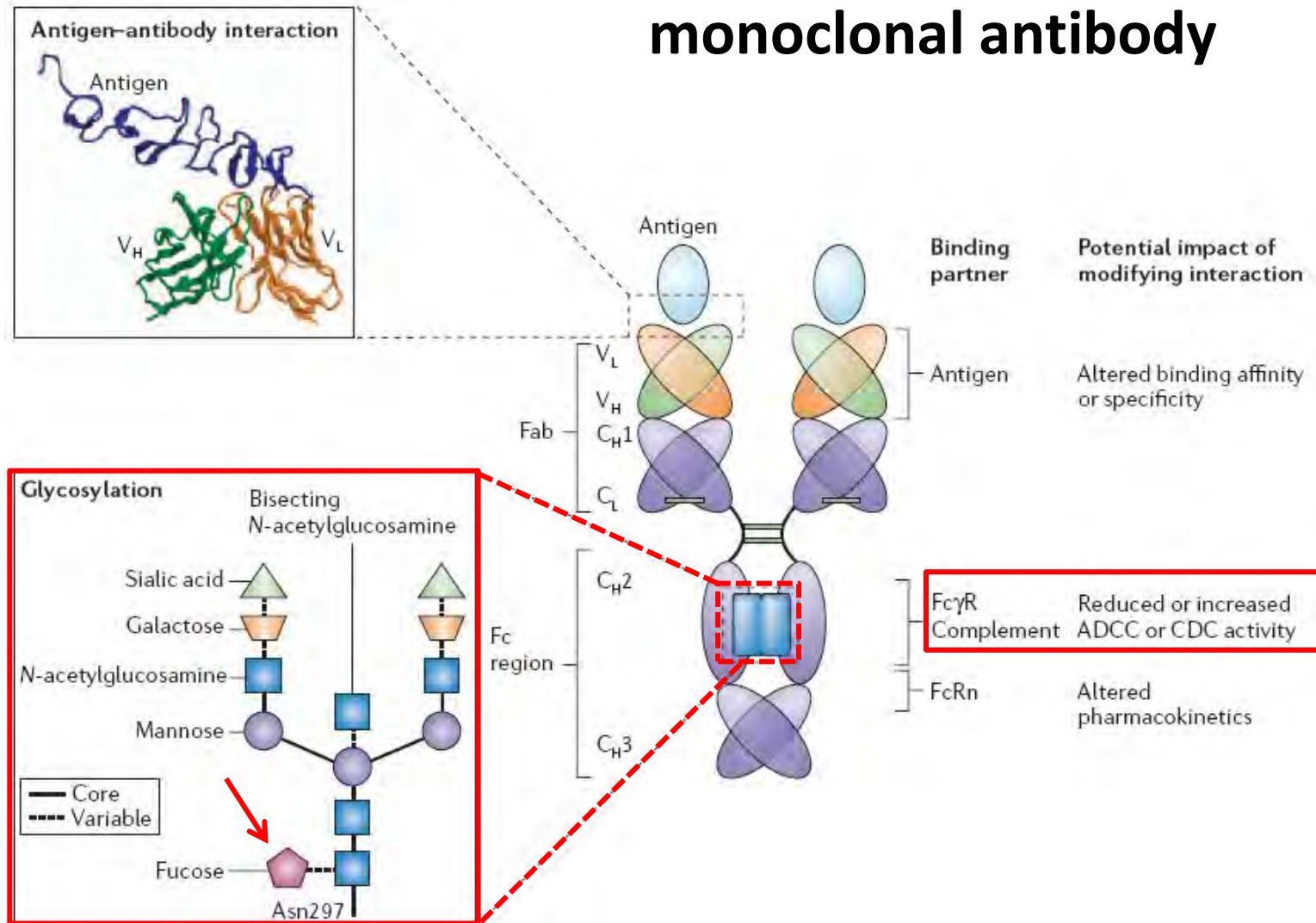
Concern: use in inflammatory bowel disease

- Identical primary, secondary and tertiary structure
- Comparable post-translational profiles
- Comparable *in vitro* functional characteristics
- Comparable pharmacokinetic profiles (250 patients with ankylosing spondylitis, 54 weeks, supportive efficacy and safety data)
- Comparable efficacy, safety and immunogenicity (606 patients with rheumatoid arthritis, 30+24 weeks)
- Small difference in afucosylated species



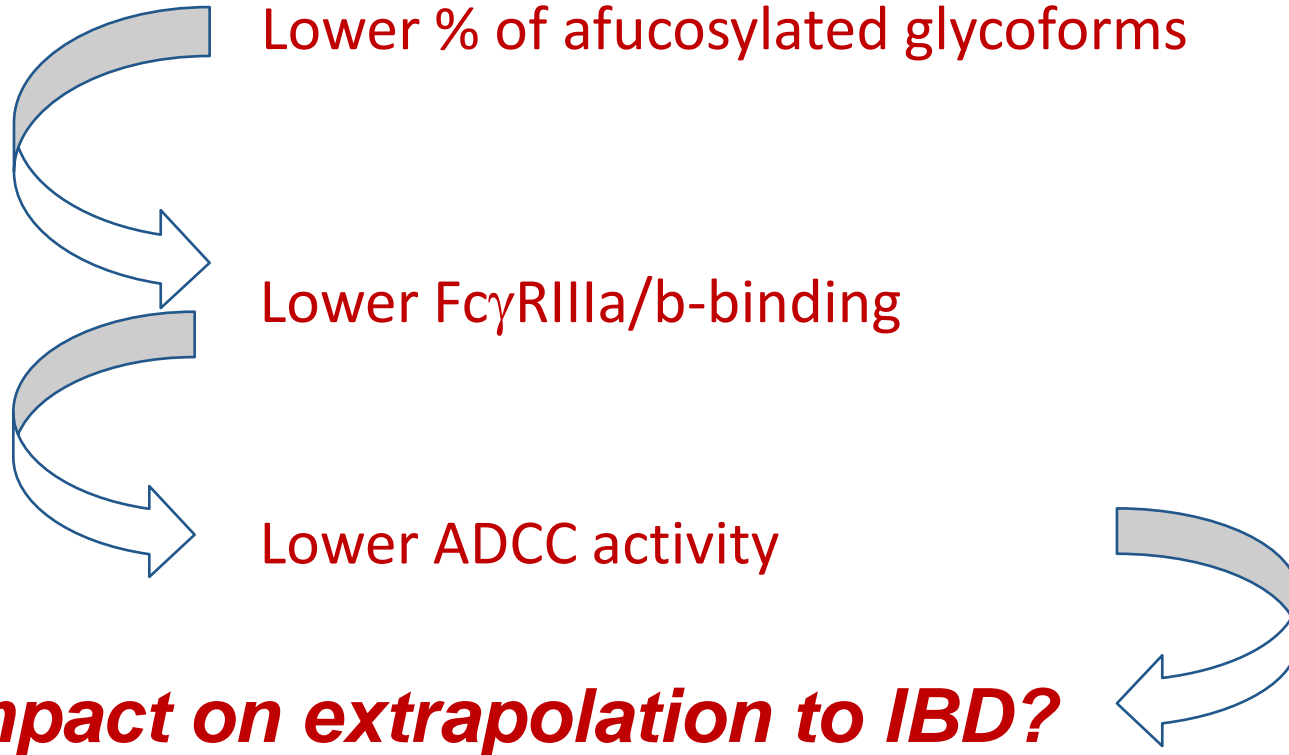
* See European Public Assessment Report on Remsima @ www.ema.europa.eu

monoclonal antibody



Carter PJ: Potent antibody therapeutics by design, *Nature Rev Immunol* 6, 343 (2006)

Biosimilar infliximab: functional studies



Infliximab: Relevance of difference in ADCC*

- 20% difference in ADCC activity observed in the most sensitive *in vitro* test using Jurkat cells (expressing abnormally high levels of tmTNF α) as target cells and NK cells as effector cells
- Difference in ADCC activity not seen in more physiological conditions
 - Adding diluted serum or whole blood to the NK-cell assay or using PBMCs abrogated the difference in ADCC
 - No ADCC response when using LPS-stimulated monocytes as target cells → ADCC likely limited in inflammation
 - No difference in binding to neutrophils (high levels of Fc γ RIIIb)
 - Similar blocking of TNF α effects on human epithelial cells (suppression of inflammatory cytokine secretion and inhibition of apoptosis)
 - Similar induction of regulatory macrophages, inhibition of T-cell proliferation and promotion of wound healing of human colorectal epithelium cells

CHMP decision on Extrapolation*

All indications of the reference product approved

- Neutralisation of sTNF α and tmTNF α mediates efficacy in RA and other forms of autoimmune arthritis
- By using a range of experimental models that are considered representative of the pathophysiological conditions and MoA of infliximab, convincing evidence has been provided that the observed difference in afucosylated species is not clinically relevant

* See European Public Assessment Report on Remsima @ www.ema.europa.eu

How is extrapolation addressed in the EPAR ?

Biosimilar filgrastim

Biograstim (2008)

Risk-benefit assessment

The only area of uncertainty is the mobilisation of peripheral blood progenitor cells because it is not known whether the efficacy in oncology can be fully extrapolated to this area of use. The uncertainty is due to the lack of complete understanding of the mechanism of peripheral blood progenitor cell mobilisation from the bone marrow. This issue has now been satisfactorily addressed by the RMP.

Extrapolation accepted
but with uncertainties

Accofil (2014)

Benefit-risk balance

PD, safety and efficacy) comparability exercises. The totality of the data provided from the quality, non-clinical and clinical comparability exercises support demonstration of biosimilarity of Accofil to Neupogen.

Extrapolation not
specifically addressed

Biosimilar infliximab

Remsima (2013)

2.6.3. Extrapolation of efficacy and safety

It is currently believed that neutralisation of sTNF and tmTNF is responsible of its efficacy in RA by preventing TNF from inducing TNFR-mediated cellular functions. It can also be accepted that the effects of infliximab blockade on synovial inflammation are comparable in different forms of arthritis. Such effects are also believed to play a role in psoriasis plaques. However, more mechanisms are likely

In conclusion, by using a range of experimental models that are considered representative of the pathophysiological conditions and putative mechanisms of action of infliximab, the Applicant has provided convincing evidence that the difference detected in the amount of afucosylated species has no clinically relevant impact on the efficacy and safety of CT-P13, in particular in IBD. Additional *in vitro* data from human intestinal cells are further supporting extrapolation of the clinical data to IBD.

Benefit-risk balance

Extrapolation of the pharmacokinetic, efficacy and safety data generated in the two clinical trials in RA and AS to the other indications of Remicade, including IBD, is considered possible based on the results of the extensive *in vitro* and *ex vivo* comparability data on all functionalities of the infliximab molecule, including several experiments especially relevant to IBD. It is further supported by increasing genetic and

Extrapolation
well justified

Summary and Conclusion

- Many physicians are worried about extrapolation of data in the context of biosimilars
- Extrapolation is not a new concept and is based on sound scientific principles
- Extrapolation must always be appropriately justified
- In case of remaining doubt, additional functional or clinical data are required or extrapolation cannot be granted
- Regulators in the EU take a careful approach in order not to jeopardize the safety and wellbeing of patients
- Explanation of the reasons for extrapolation granted by CHMP may be improved in the EPAR

Thank you very much for your attention!

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