Clinical Development of Biosimilars: Overcoming Challenges

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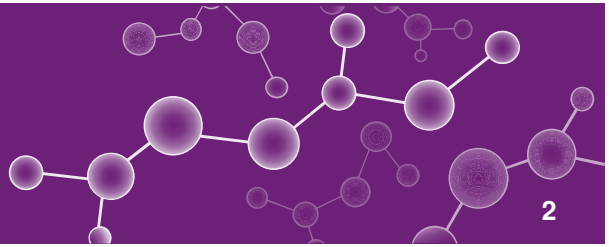


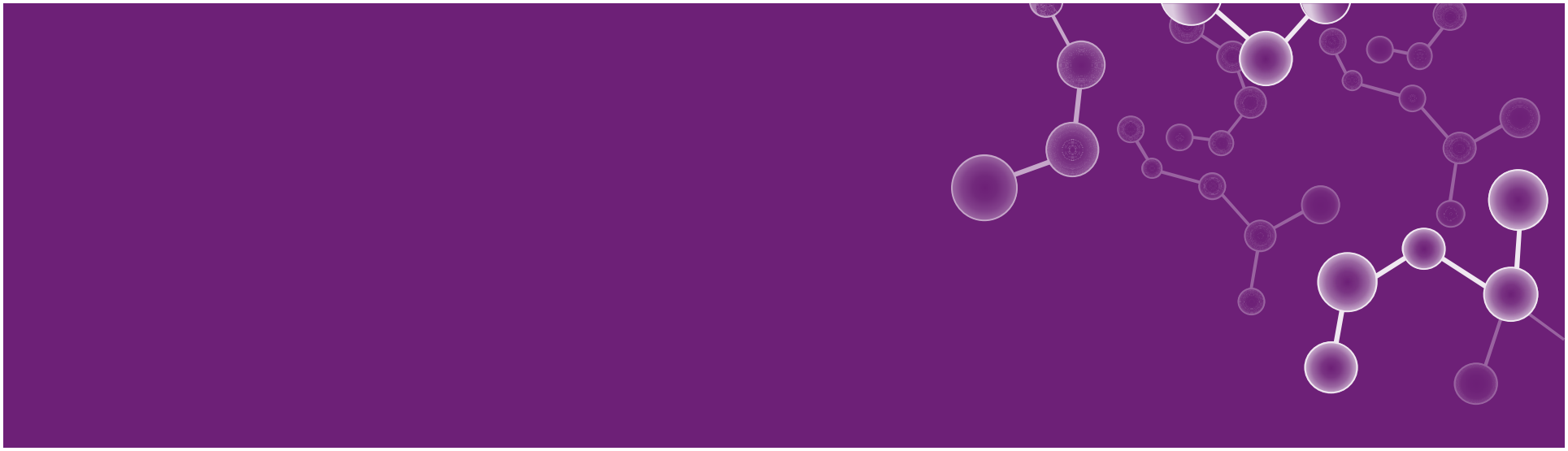
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Agenda

- **Biosimilars: How are they different**
- **Challenges in Clinical Development**
- **Quintiles for Biosimilars**

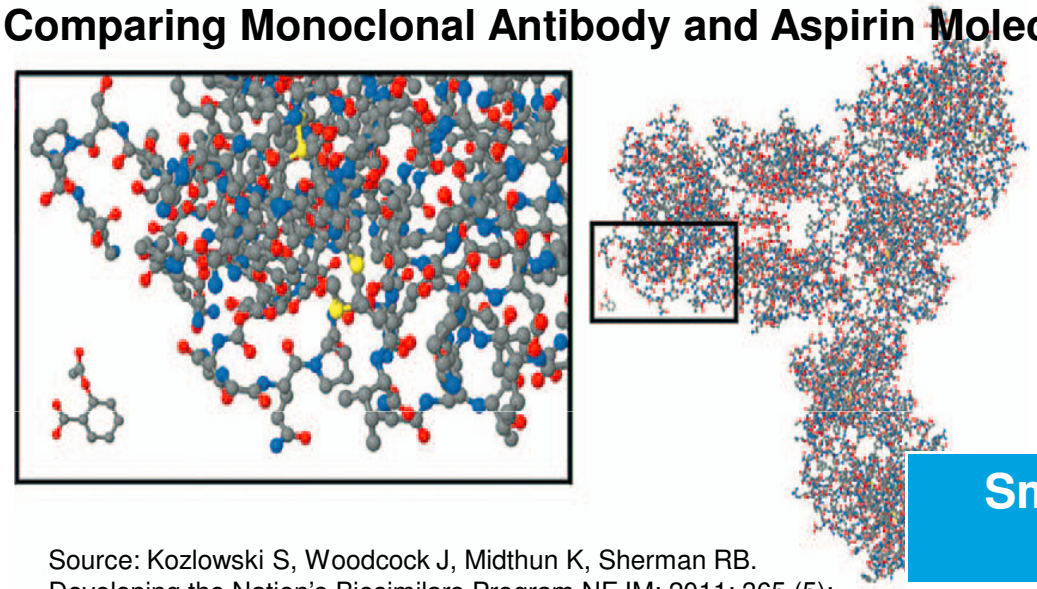




Biosimilars: How are they different

Biosimilars: How are they Different

Comparing Monoclonal Antibody and Aspirin Molecule



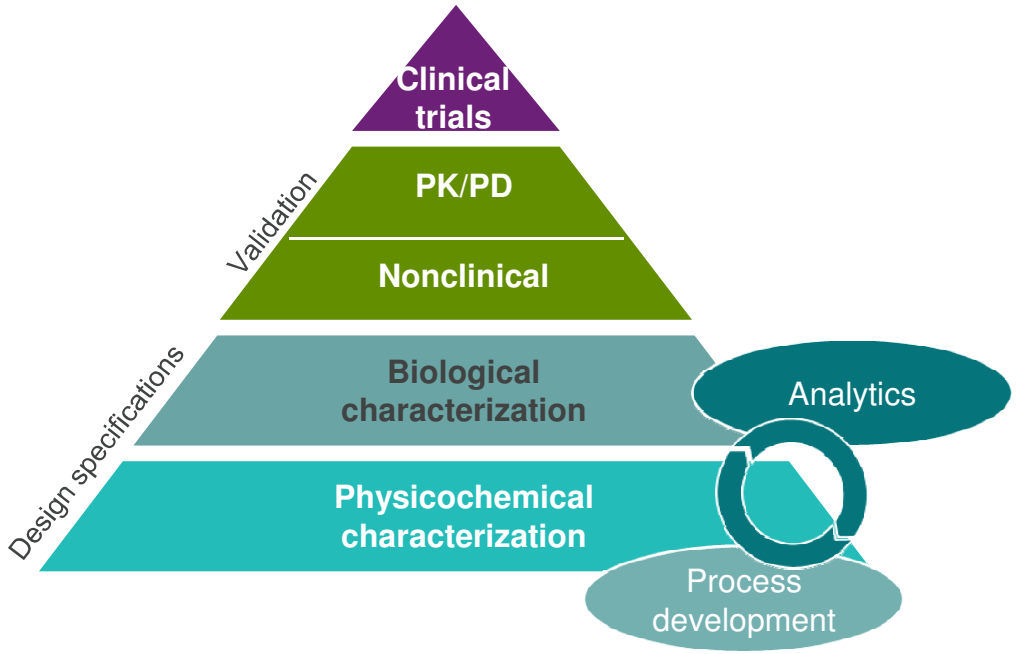
Source: Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the Nation's Biosimilars Program.NEJM: 2011; 365 (5): 385-388.

Small Molecule Generics	Biosimilars
Identical copies (i.e., same qualitative and quantitative composition)	No identical copies- just highly similar
Proof of quality and bioequivalence	Full quality dossier + comparability data
No substantial clinical data required	Appropriate pre-clinical & clinical comparability data (abbreviated vs. NCE/NBE)

QUINTILES

Biosimilars Development: Basic Principles

Robust quality comparability data and thorough knowledge of reference product first step in establishing biosimilarity. May require multiple iterations in early-stage development.



Source: McCamish M and Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther* 2012; 91(3): 405–417.

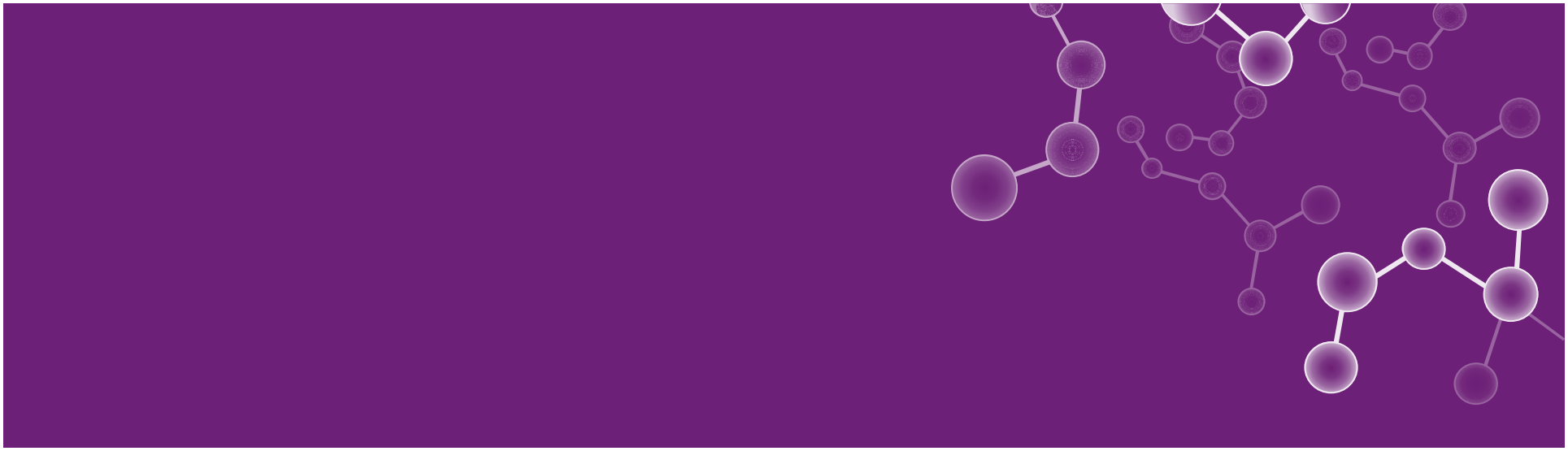
Biosimilars Development: Basic Principles

- **Step-by-step sequential development**, evaluating **residual uncertainity** at end of each step, designing next step accordingly,



- **Totality of evidence**, case by case **risk based approach** tailored to individual product

- Always prudent to have a dialogue with regulators early in development



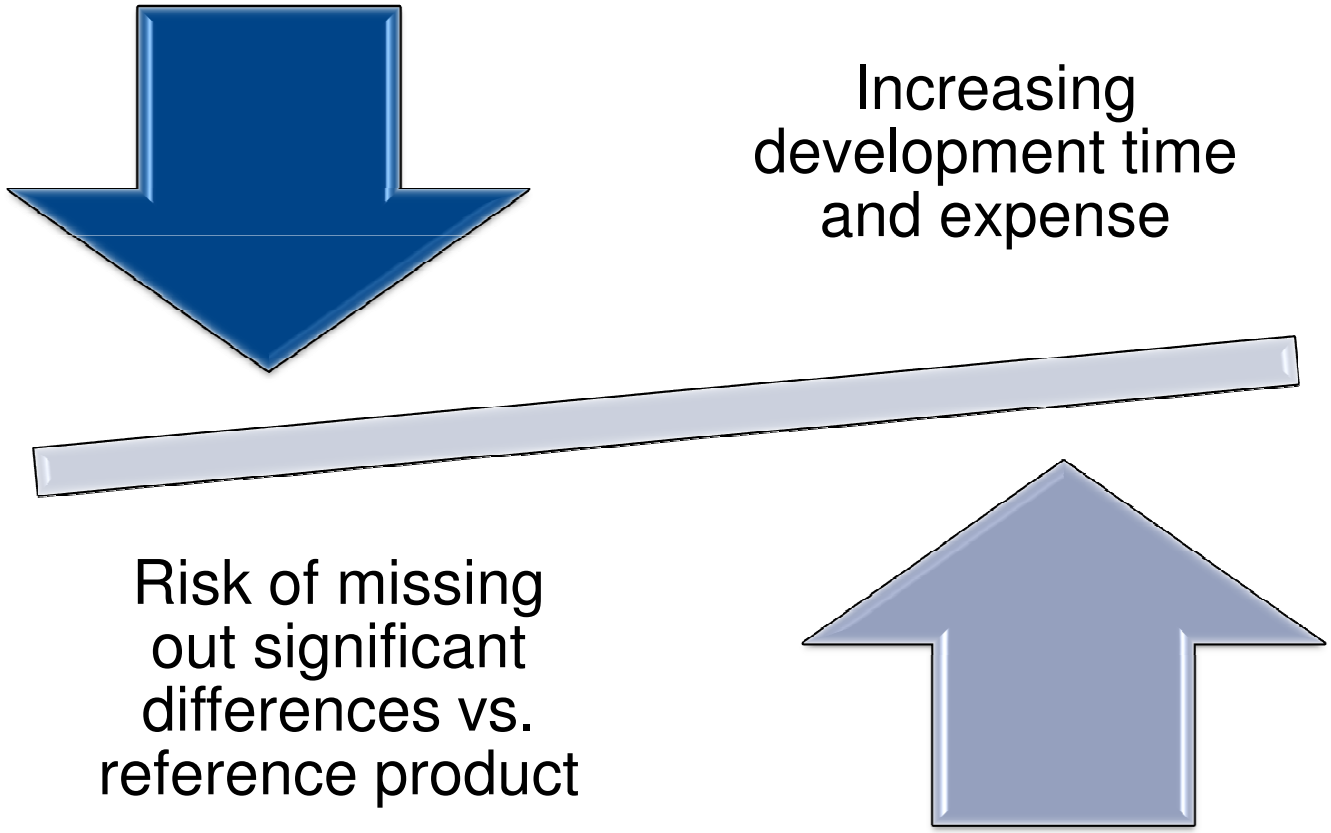
Challenges in Clinical Development

Key Challenges in Biosimilars Clinical Development

- Extent of clinical data requirement
- Clinical pharmacology studies
  - Confirmatory PK/PD studies
- Immunogenicity
- Choice of reference products, designing global programs
- Choice of indication/ study population
- Study design
- Study end-points
- Extrapolation of clinical data across indications
- Accessing patients for biosimilars clinical trials
- Establishing interchangability

Extent of Clinical Program

Tough Balancing Act



Extent of Clinical Program

Determined by Reference Product:

Nature and complexity

(Extent of) clinical experience, how well is PK, PD, MoA understood, accepted surrogate markers of clinical efficacy

Safety issues, including risk of immunogenicity, consequences of immunogenicity (e.g. suppressing endogenous protein)

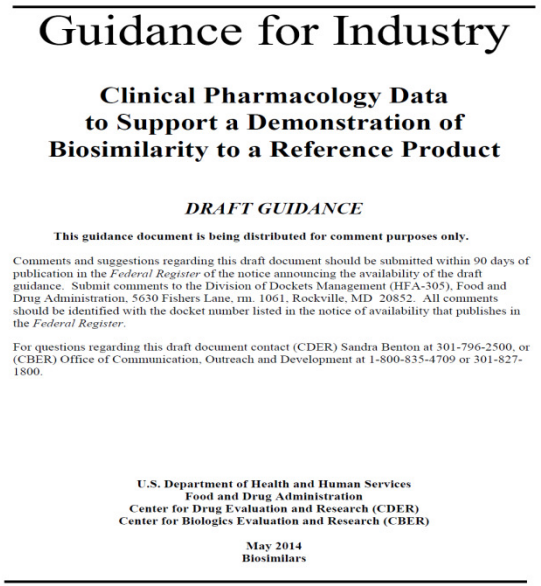
Determined by Biosimilar Product:

Robustness of quality comparability data, residual uncertainty at the end of quality and pre-clinical comparability studies

Extent of Clinical Program

Parameter	Filgrastim	Epoetin	Rituximab
Clinical Experience	Extensive	Extensive	15 years +
MoA, PK	Well understood	Well understood	Yes, not fully
Routes of Administration	SC, IV	SC, IV	IV infusion, SC (recent)
Indications	Multiple	Multiple	Multiple
Surrogate Marker for Clinical Efficacy	ANC	Hb	-
Immunogenicity	No significant risk	Low incidence, severe consequences	1.1 to 23%, across indications
Clinical Requirements	Limited	Extensive	Extensive

Clinical Pharmacology Studies



Guidance for Industry

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500, or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Biosimilars

Clinical pharmacology studies are normally a critical part of demonstrating biosimilarity b supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar and the reference product. These studies provide the data that describ degree of similarity in drug exposure between the proposed biosimilar and the reference product. In addition, clinical pharmacology studies often include PD endpoints (both therapeutic and toxic) and pharmacometric analysis to assess whether or not there are clinically meaningful differences between the proposed biosimilar and the reference product. If done well, they can add to the totality of the evidence, reduce residual uncertainty, and thus guide the need for and design of subsequent clinical testing to successfully support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity. Clinical pharmacology data may be an important component of the scientific justification supporting extrapolation of clinical data to one or more additional conditions of use.[7]

Clinical Pharmacology Studies

Type of clinical pharmacology studies appropriate for the given biologic:

- Healthy volunteers or patients
- Cross over or parallel group
- Single dose or multiple dose
- Route of administration
- Dose: therapeutic range, ascending linear portion of dose-response curve
- PK parameters- equivalence criteria
- PD end-points- single, multiple parameters, equivalence criteria

Confirmatory Pharmacokinetic/ Pharmacodynamic (PK/PD) Studies

- Could replace evidence for comparable efficacy in select cases

- Possible only when pre-requisites met:
  - PK & PD of Reference biologic well characterized
  - At least 1 PD marker validated as clinical efficacy surrogate
  - Relationship between dose/exposure, relevant PD marker(s) and response/efficacy established

- Where feasible, may be regulator's preferred option due to better sensitivity

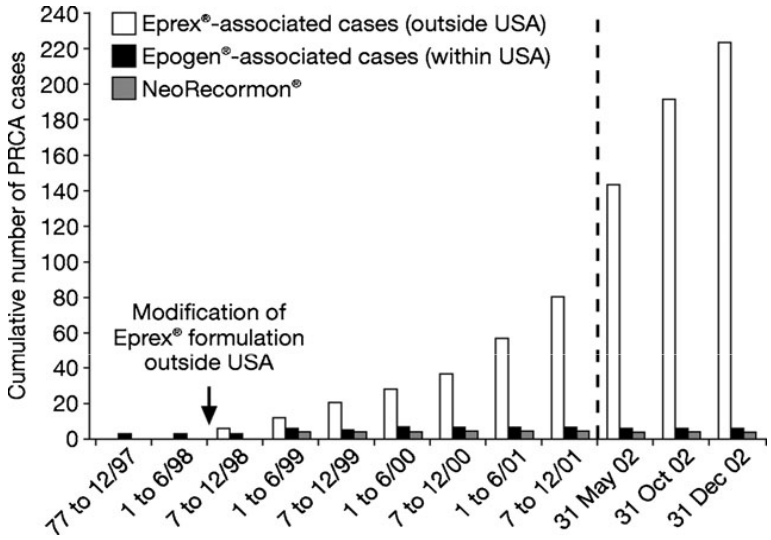
- Some examples:
  - Euglycemic clamp studies for biosimilar insulins (& insulin analogues)
  - Absolute neutrophil count and CD34+ cell count for biosimilar filgrastim

- Robust comparability on CMC and *in vitro* functional assays and comprehensive clinical PK & PD study(ies) characterizing exposure as well as multiple pharmacodynamic parameters (both therapeutic and toxic): address additional safety & immunogenicity requirements post approval

Immunogenicity

Case Study 1

- Significant increase in incidence of antibody PRCA between 1998-2003



- CKD patients, 1 particular brand of EPO through SC route (other 2 brands unaffected)

- Breakdown of natural immune tolerance & formation of neutralizing antibodies against recombinant & endogenous EPO

- SC route contraindicated → reduction in incidence of PRCA

Source: Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. *Nephrol Dial Transplant 2005; 20: vi3–vi9*

Immunogenicity

Case Study 1

- Coincided with a “minor” change in formulation: replacement of HSA (stabilizer) with glycine + polysorbate 80 in 1998

- Possible triggers:
  - ? Micelle formation from polysorbate 80 and epoietin alfa
  - ? Leachates from rubber stoppers breaking B-cell tolerance via an adjuvant effect
  - ? Increased levels of aggregates during storage (within specifications)

Immunogenicity is difficult to predict, can result from “minor” variations, can have serious consequences

Immunogenicity

Case Study 2

- Clinical trial of biosimilar epoetin in CKD anemia patients, SC administration
- 2 of 337 randomized patients developed neutralizing antibodies to EPO, both on biosimilar
- Study terminated
- Root cause traced to increased tungsten exposure in PFS

Case Study 3

- Somatropin biosimilar, initial clinical studies showed high incidence of anti-hGH and anti-HCP antibodies (~ 60% subjects).
- No clinical consequences: similar growth recorded in children with and without antibodies.
- Root cause traced to increased HCP levels. Additional purification steps introduced.

Immunogenicity

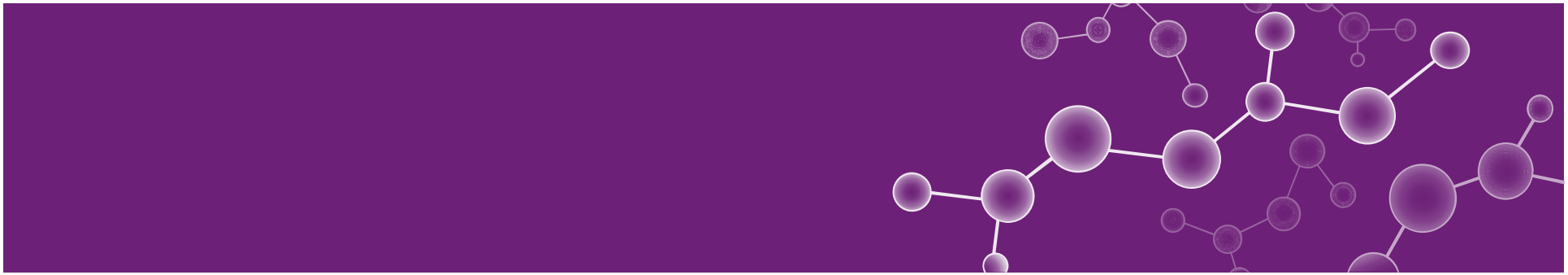
- Immunogenicity can be demonstrated only in human studies, of adequate size and duration

- Extent of data, duration and timing of study(ies) depends up on :
  - Analytical similarity between reference product and proposed biosimilar
  - Known incidence & clinical consequences of immune response for reference product

- Evaluate immunogenicity in sensitive populations

- Evaluate for both occurrence of antibodies, as well as clinical consequences

Questions?



Choice of Reference Product

Comparability exercise requires:

- All studies comparative against RMP
- *RMP authorized in MA jurisdiction*
- RMP authorized on basis of complete dossier
- Same RMP throughout development



Choice of Reference Product: Global Development Programs

- Possible to employ Reference product from another jurisdiction for some studies
  - > EMA Draft Guideline on Similar Biological Medicinal Products, CHMP/437/04Rev1 (May 2013)
  - > US FDA Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Feb 2012)

- Pre-requisites:
  - > Analytical studies & at least 1 human PK/PD study against local Reference
  - > Establish acceptable bridge between different References
  - > Duration/ extent of marketing experience

Choice of Reference Product: Global Development Programs

- Pre-requisites (continued):
  - Product approving regulatory authority with similar scientific & regulatory standards
  - Relationship between license holders in different jurisdictions, manufactured in same facilities
  - Manufacturing facility approving regulatory authority with similar scientific & regulatory standards

- Have a dialogue with regulators beforehand

Choice of Reference Product: Global Development Programs

- 3 way comparative physico-chemical & biological characterization studies

Establish Comparability Across Reference Products

- 3 way comparative PK & PD studies

- 2 way comparative clinical safety & efficacy study

Extrapolation of Clinical Data Across Indications

Possible to have biosimilar licensed for more indications than those evaluated in development program. Scientific justification based on:

- MoA in each indication
  - Target/ receptor(s) for each activity
  - Binding, dose-response, pattern of molecular signaling
  - Relation between product structure & target/receptor(s) interactions
  - Location and expression of target/ receptor(s)
- PK and bio-distribution in different patient populations
- Expected toxicities in different patient populations



Extrapolation of Clinical Data Across Indications

INFLIXIMAB BIOSIMILAR EMA APPROVAL

Approval of 1st mAb biosimilar in EU. Extrapolation granted across different TAs!

"Based on the robust comparisons of the physicochemical and *in vitro and ex vivo biological analyses*, *Inflectra was considered biosimilar to the reference product Remicade. These data, in combination with clinical data demonstrating pharmacokinetic and therapeutic equivalence in rheumatology conditions, allow for extrapolation to all other indications of Remicade. In addition, the Applicant will conduct a randomised, double-blind, parallel-group comparative study between Inflectra and Remicade in patients with active Crohn's disease."*

Extrapolation of Clinical Data Across Indications

INFLIXIMAB BIOSIMILAR HEALTH CANADA APPROVAL

"The sponsor requested authorization for all of the indications and uses currently authorized to Remicade. Remicade is currently authorized for indications and uses in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. Comparability between Inflectra and the reference product was established based on comparative chemistry and manufacturing studies, and comparative non-clinical studies. .....

The indications for psoriatic arthritis and plaque psoriasis were granted on the basis of similarity and the absence of meaningful differences, between Inflectra and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and on clinical experience with the reference product. Scientific rationales submitted by the sponsor were found to be adequate to support extrapolation to the indications and uses pertaining to psoriatic arthritis and plaque psoriasis; however, extrapolation to indications and uses pertaining to Crohn's disease and ulcerative colitis could not be recommended due to differences between Inflectra and the reference product, that could have an impact on the clinical safety and efficacy of these products in these indications. ....."

Extrapolation of Clinical Data Across Indications

Indication	Remicade Label	Biosimilar Label- EMA	Biosimilar Label- HC	Biosimilar Studies
Rheumatoid Arthritis (RA), adults, DMARD non-responders	√	√	√	√
RA, adults, severe active, DMARD naive	√	√	√	X
Adult Crohn's Disease	√	√	X	X
Paediatric Crohn's Disease	√	√	X	X
Ulcerative Colitis	√	√	X	X
Paediatric Ulcerative Colitis	√	√	X	X
Ankylosing Spondylosis	√	√	√	√
Psoriatic Arthritis	√	√	√	X
Psoriasis	√	√	√	X

Questions?

