First Latin American Educational Workshop on
Similar Biotherapeutic Products

20 January 2015, Sheraton Maria Isabel Hotel & Towers, Mexico City, Mexico

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GaBI
Educational
Workshops

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Biosimilars – totality of evidence for regulatory approval

Vladimir Hanes, MD

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

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Biosimilars – Totality of Evidence for Regulatory Approval

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What are Biosimilars?

FDA Definition*

- The biological product is ***highly similar*** to the reference product notwithstanding minor differences in clinically inactive components;

And

- There are ***no clinically meaningful differences*** between the biological product and the reference product in terms of the safety, purity, and potency of the product

EU Definition**

- A biosimilar is a biological medicinal product that contains a ***version of the active substance*** of an already authorised original biological medicinal product (reference medicinal product).

- A biosimilar demonstrates ***similarity*** to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise

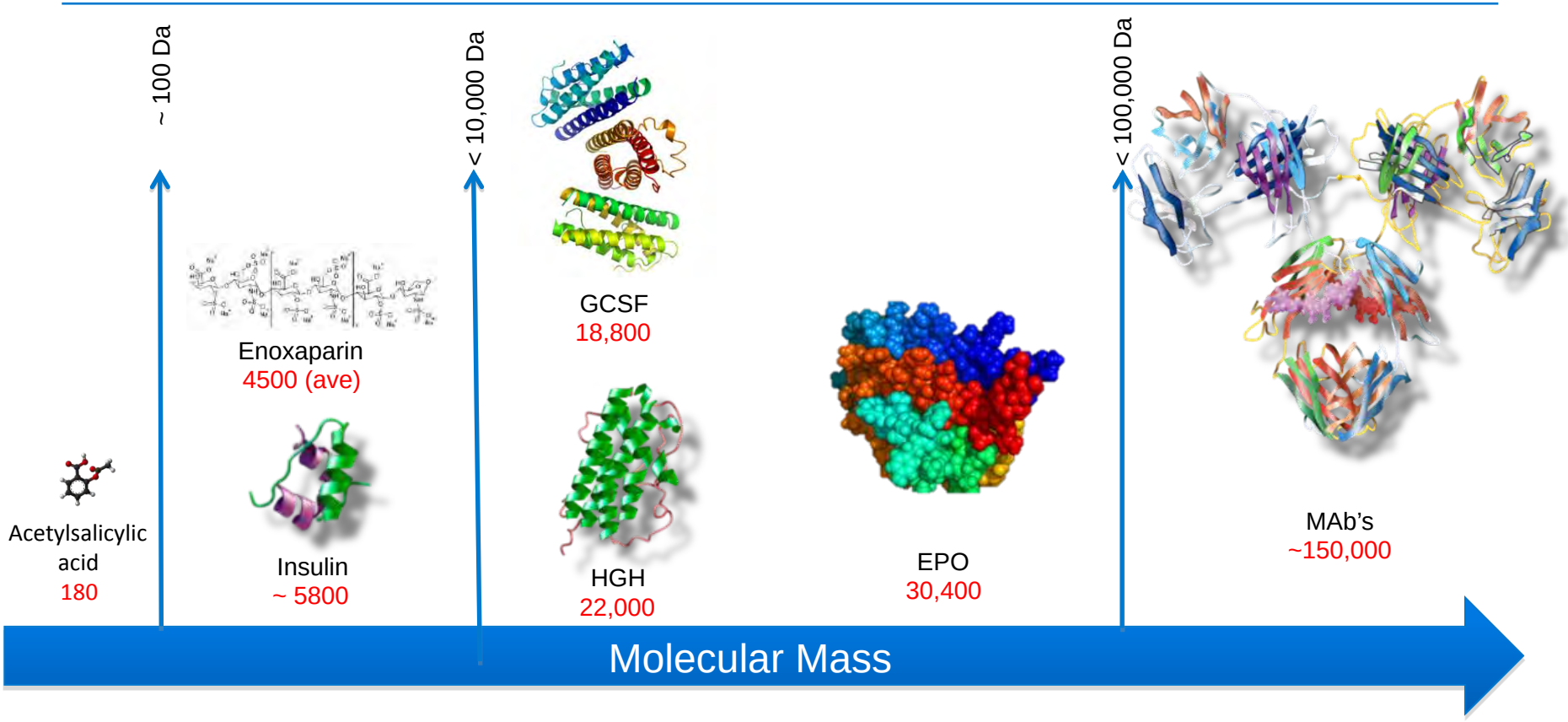
*Biologics Price Competition and Innovation Act, 42 USC 262(i)(2); see also, 42 USC 262(k)(2)
**Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1
(emphasis added)

What are Biosimilars?

Mexican Law (Bis 2, 2011)*	• Medicamento biotecnológico biocomparable, al medicamento biotecnológico no innovador que demuestre ser biocomparable en términos de seguridad, calidad y eficacia al medicamento biotecnológico de referencia.
Translation	• Biocomparable Biotechnological Medicine – a non-innovator biotechnological medicine that is shown to be biocomparable in terms of safety, quality and efficacy to a reference biotechnological medicine.

*Diario Oficial de la Federación, Adición de ARTÍCULO 2o, XIII Bis 2, 19/10/2011; http://dof.gob.mx/nota_detalle.php?codigo=5214882&fecha=19/10/2011

Generics and Biosimilars

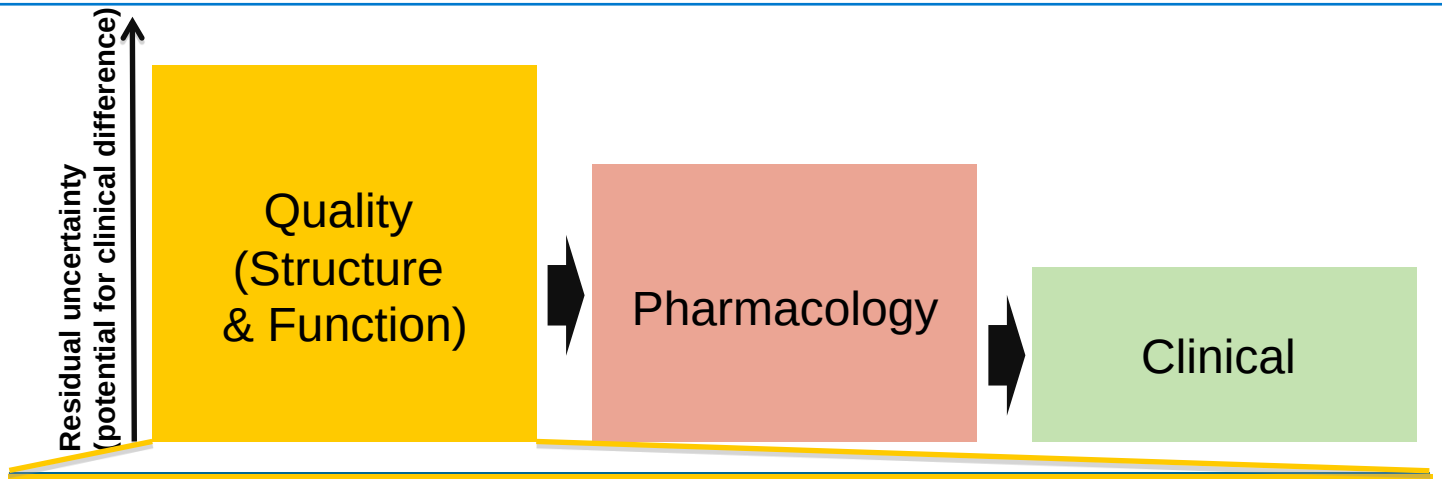


Generics | **Biosimilars 1.0** | **Biosimilars 2.0**

Same Structure = Same Function

Similarity in Structure

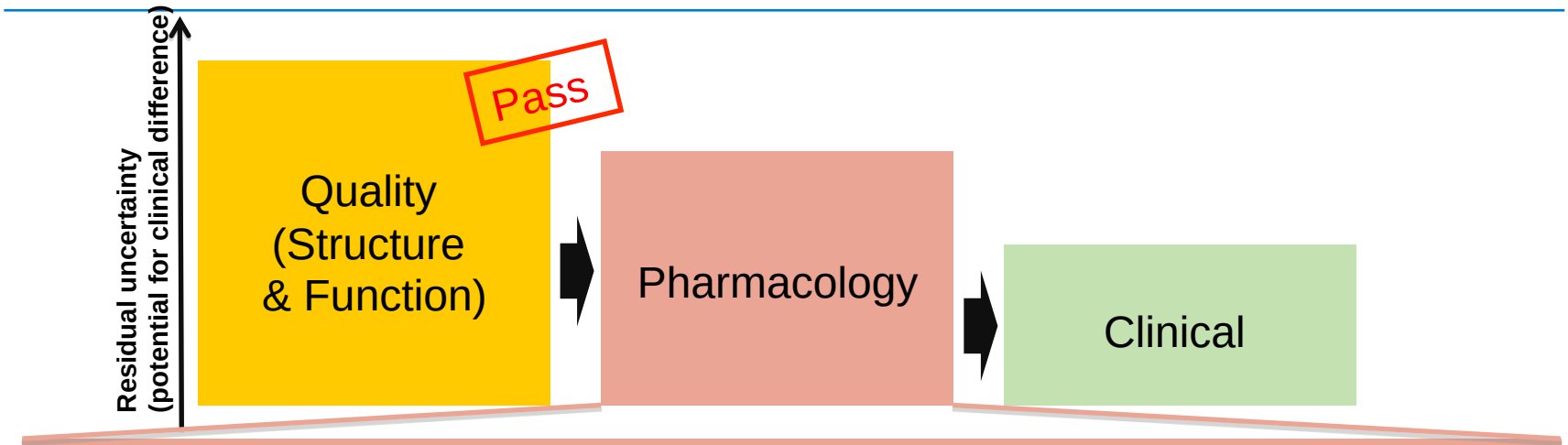
Stepwise Assessment for Totality of Evidence



- Same amino acid sequence and potency
- Minor differences in glycosylation and post-translation modifications – relevance of differences determined through assessments of function with sensitive assays
- Should match all effector functions regardless of potential contribution to mechanism of action

Difference in effector function = not highly similar therefore not biosimilar
Such a molecule or process should be re-engineered

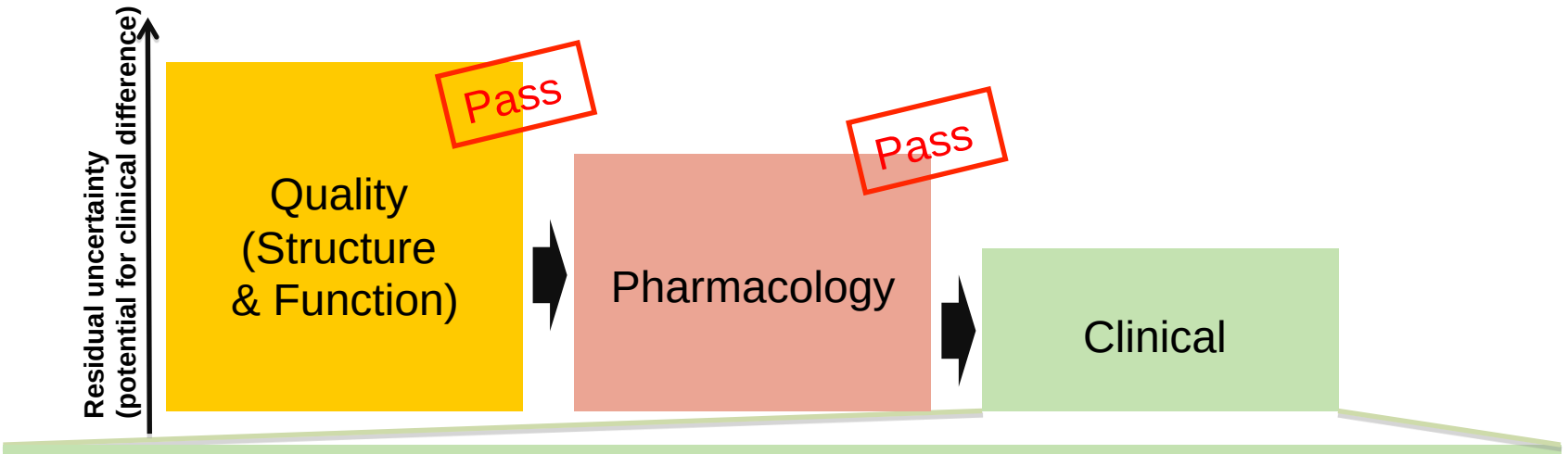
Stepwise Assessment for Totality of Evidence



- PK (pharmacokinetics) in healthy volunteers is generally the most sensitive population to assess kinetic similarity
- Equivalent PK (generally 90% CI to be within 80-125% as standard) establishes same dose as reference product assuming equivalent potency and functions
- PD (pharmacodynamics) with dose-response equivalence can infer clinical efficacy if sensitive and relevant marker is available

PD markers should be clinically relevant to inform efficacy

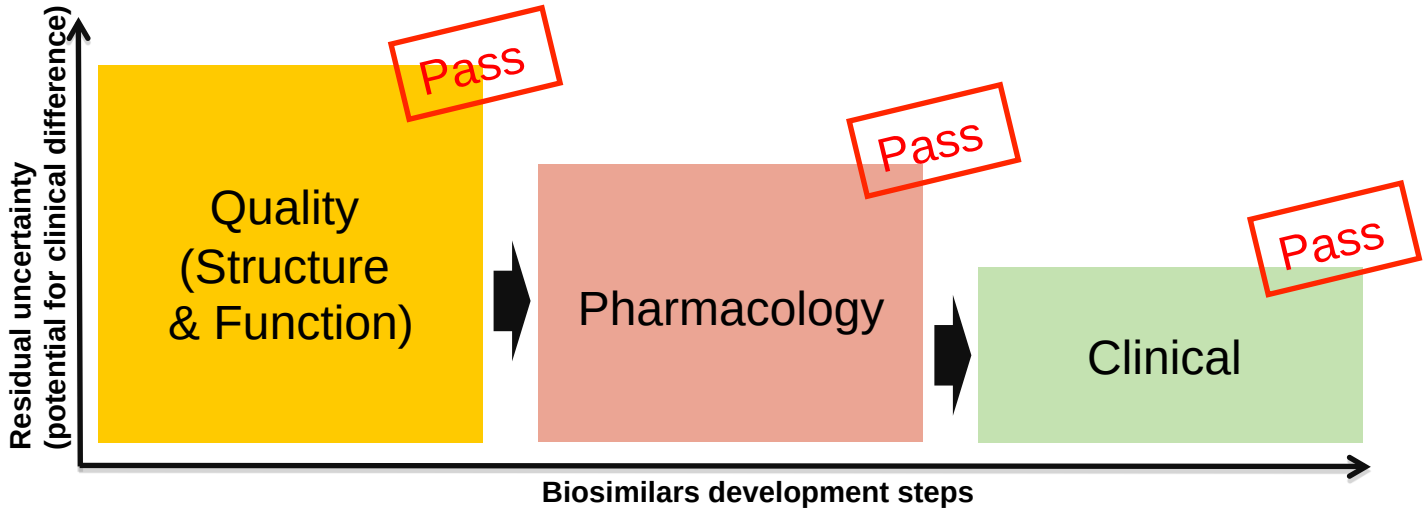
Stepwise Assessment for Totality of Evidence



- Clinical Efficacy confirmed in a randomized, blinded, head-to-head study in a sensitive population with sensitive endpoint(s)
- Clinical Safety confirmed in at least one sensitive patient population (e.g. use as monotherapy); enough exposures/time
- Immunogenicity assessed with drug tolerant assays in sensitive population (e.g. no immune suppression or concomitant chemotherapy)

Demonstration of no clinically meaningful differences is a BPCIA requirement
The patient population and endpoints are important for physician and patient confidence

Stepwise Assessment for Totality of Evidence

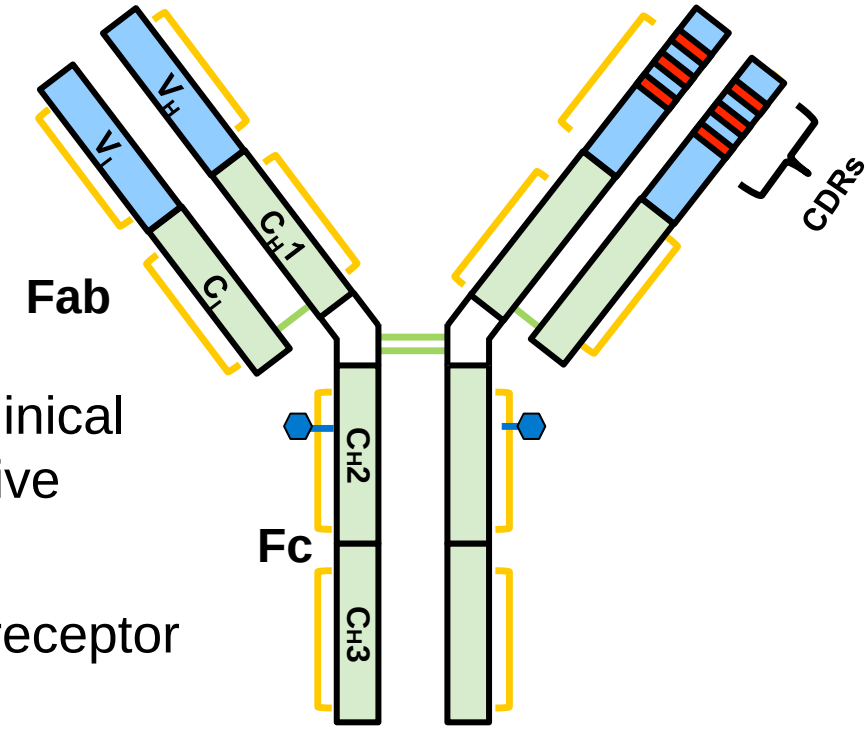


Each step has critical contribution to Totality of Evidence

- Each step should rely on most sensitive state-of-art capabilities
- No step can refute/overcome significant differences in other development steps
- Should satisfy all three steps to demonstrate biosimilarity

Case Studies for Monoclonal Antibodies (mAb)

CHO expressed humanized IgG1



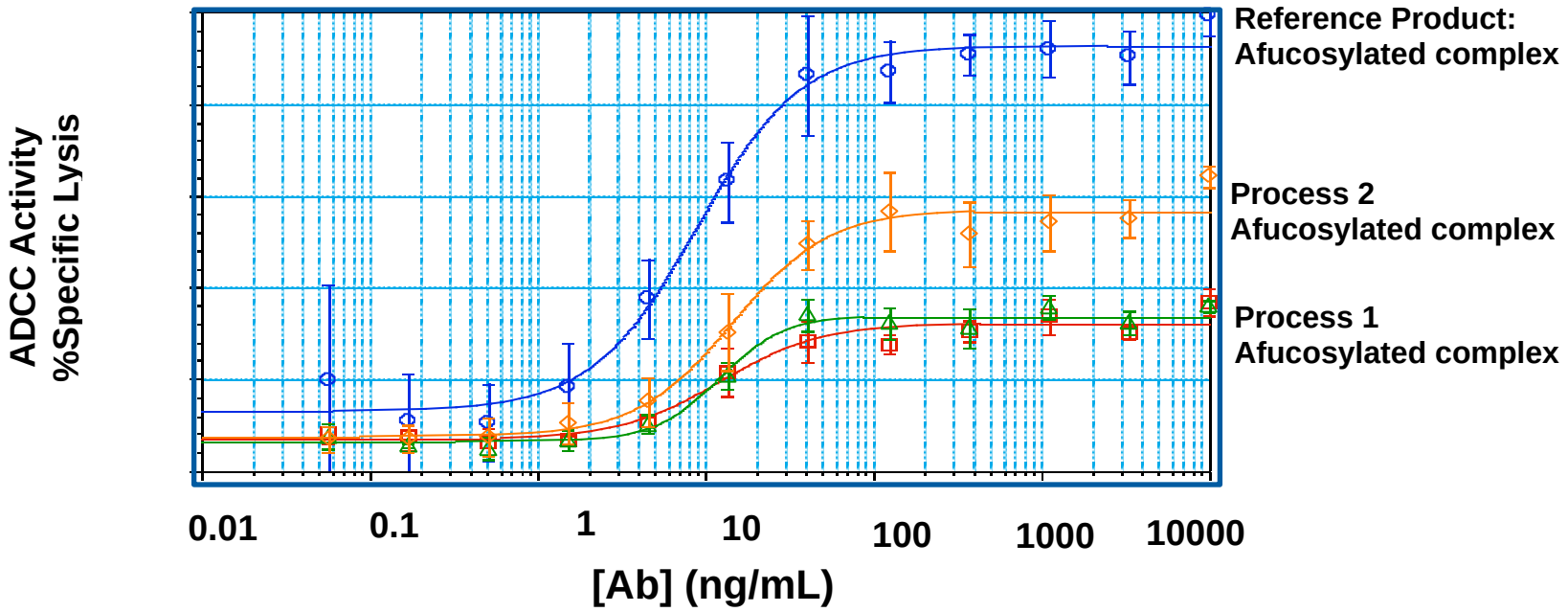
Key analytical attributes that affect clinical attributes were assessed with sensitive assays

- Binding & inhibition of cell surface receptor
- Induction of ADCC activity

Case Study 1 – Problem identified

Analytical differences leading to decreased ADCC activity

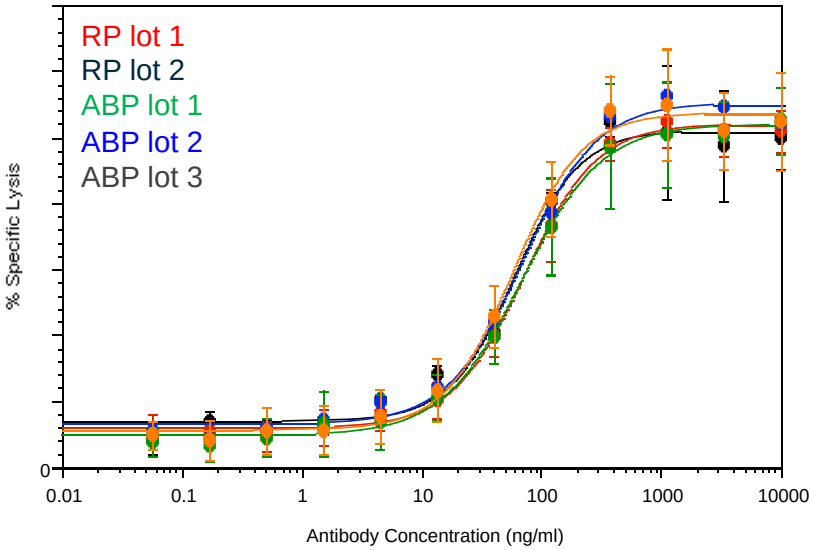
Significant clone screening and process development activities could not achieve matching ADCC profile



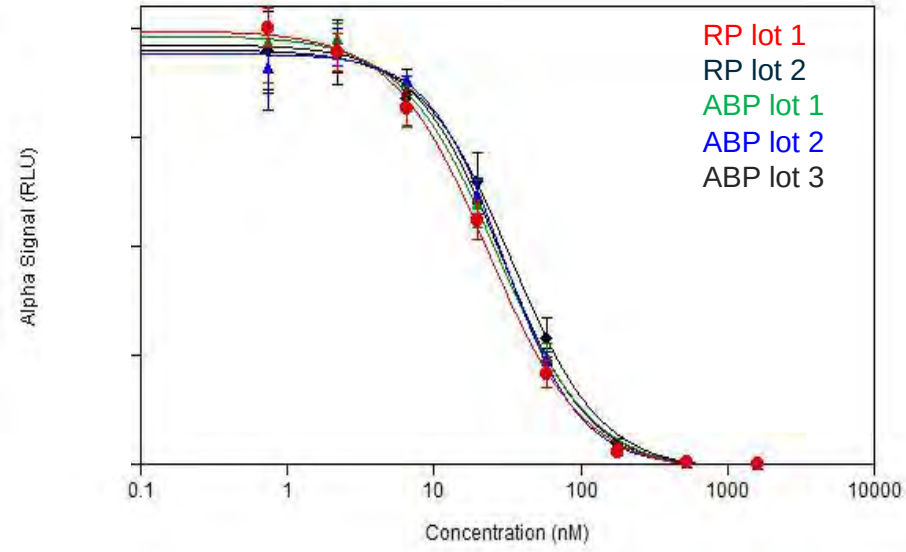
Case Study 1 – Problem resolved
New Biosimilar Candidate

- New candidate (different host cell line) showed high degree of similarity in glycan profile, in particular total afucosylated species
- Glycan profile corresponded to high degree of similarity with respect to FcγRIIIa binding and ADCC functional assays

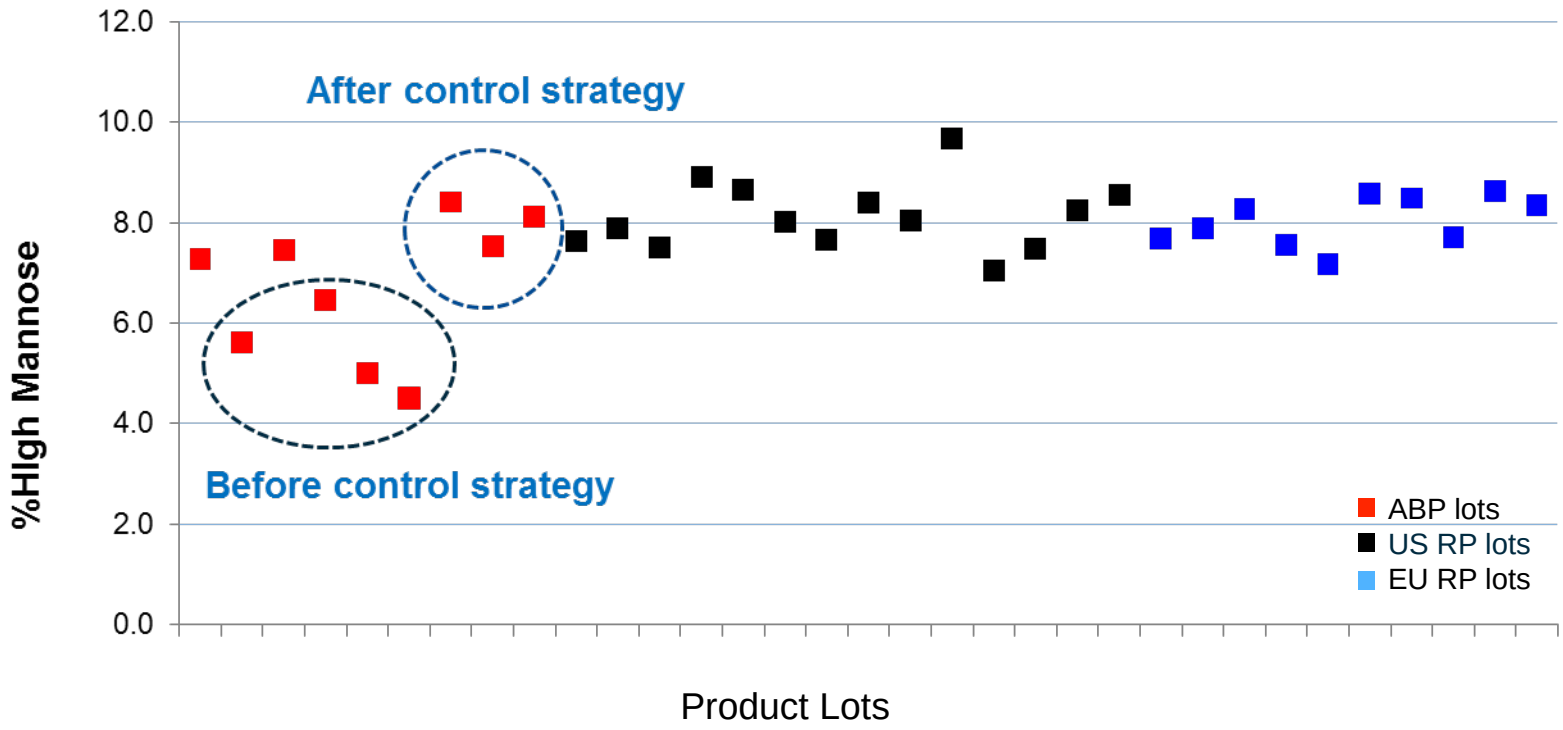
ADCC



FcγRIIIa

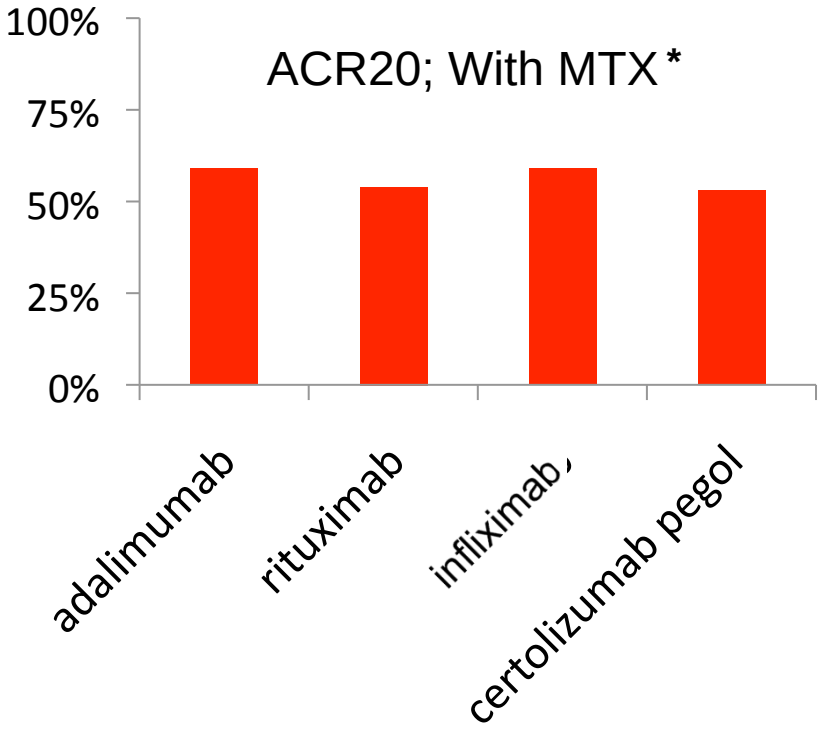


Case Study 2 – Problem identified
High Mannose Level



Desired High Mannose Level Achieved Through Control of a Key Trace Element

Case Study 3 – Problem identified
Clinical endpoint sensitivity

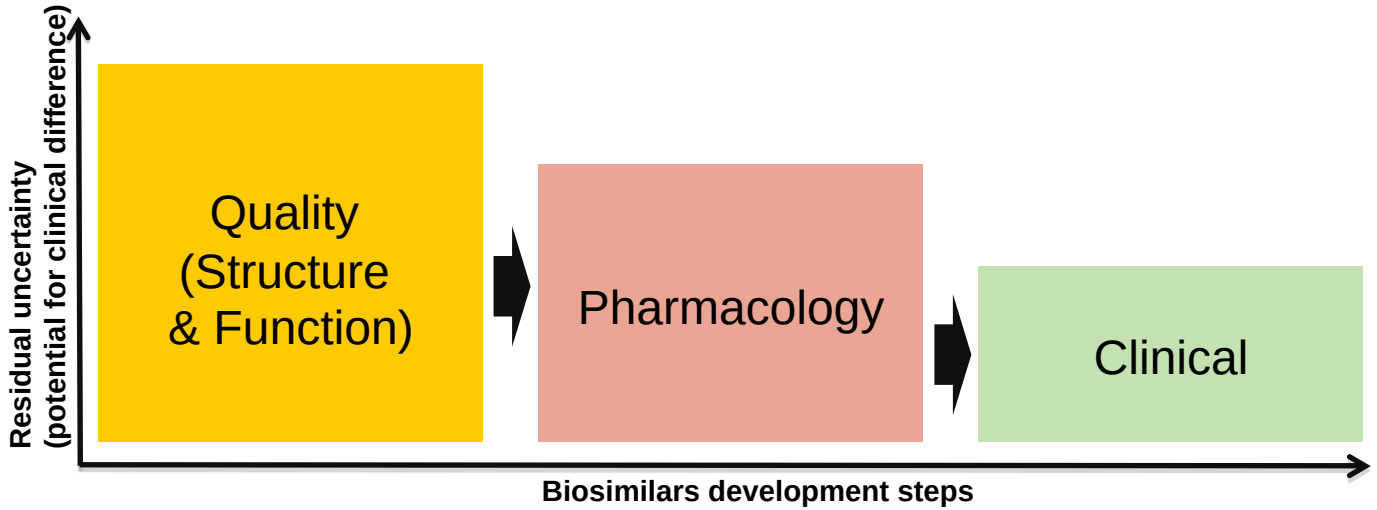


- ACR20 – clinical endpoint common for drug approvals in rheumatoid arthritis
- Four very unique molecules including different MoA show similar efficacy
- ACR20 alone may not be sensitive to fully inform extrapolation to other indications

Clinical study is critical to demonstrate the clinical equivalence; no 'unseen' aspects of the molecule altering efficacy, safety, or immunogenicity profile.

***ACR20 data at 12 month come from US prescribing information for each molecule, generated in separate development programs.**

Biosimilars – Totality of Evidence for Regulatory Approval



- Each ‘step’ removes uncertainty when conducted with rigor
- One step cannot be used to overcome a failure in a different step
- Basis for regulatory approval, but beyond that framework for patient and physician confidence

Totality of evidence will gain regulatory approval;
Science-led robust regulatory standards will expand confidence of physicians and patients in biosimilars!

Thank You

Questions ?