GaBI Educational Workshops

3rd Colombian Educational Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

30 April 2019, Hilton Bogotá, Colombia

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- Division Manager, Clinical Review Division – Haematology/Oncology, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Biologics and Genetic Therapies Directorate, Health Canada

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

PPCI
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Pharmacological studies (PK/PD) to assess biosimilar medicinal products

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Pharmacological Studies (PK/PD) to Assess Biosimilar Medicinal Products

Jian Wang, MD, PhD
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3rd Colombian Educational Workshop on Regulatory Assessment of Biosimilars
April 30, 2019, Bogotá, Colombia

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Highlights

- General introduction to Biosimilars
- Step-wise approach to demonstrate similarity
- Comparative clinical PK data are required
- Comparative PD data are desirable (if feasible) and
- Can help to reduce residual uncertainty

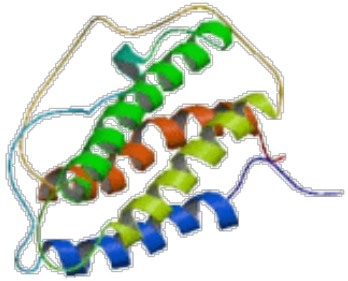
Pharmaceuticals vs. Biologics

Small Molecule

Acetyl-salicylic acid
~180 daltons
21 atoms

Biologics

Insulin
51 amino acids
~5,800 daltons
788 atoms



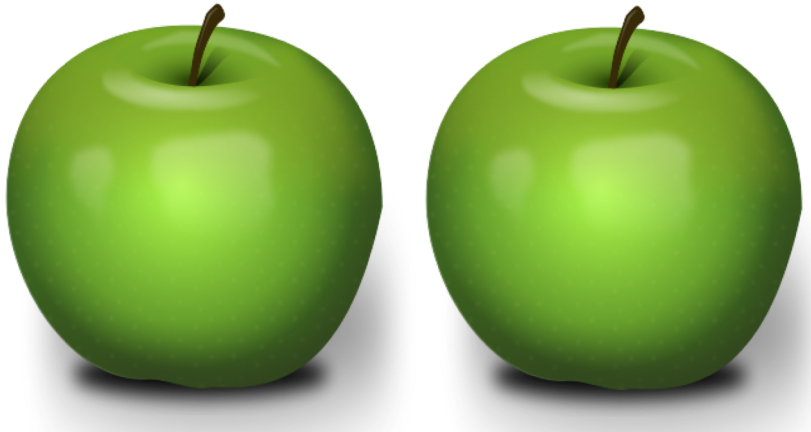
Erythropoietin
165 amino acids
~34,000 daltons
2611 atoms

IgG1 antibody
~1300 amino acids
~150,000 daltons
>20,000 atoms

Unlike small-molecule generic drugs, biosimilars are large, complex protein molecules that cannot be absolutely identical to the original product

Biosimilars are similar to the reference

... but not identical to the reference



Biosimilars

Different cell lines

Different manufacturing processes

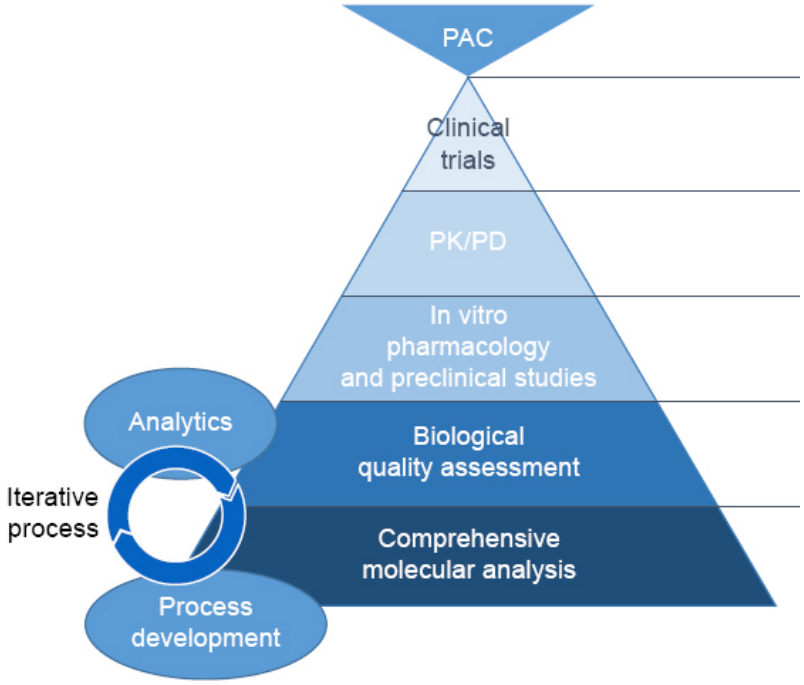
Generics

- A biosimilar is a biological product that is *highly similar* to a biologic that is approved for sale on local market

Highlights and Key Concepts

- To support regulatory approval, guidance/policy requests comparisons to be made to the reference:

1. *Analytical/Structural analyses*
    i. *Critical Quality Attributes*
2. *Functional analyses*
    i. *in vitro, cell-based studies*
3. *Non-clinical studies*
4. *Human clinical trials*
    i. *PK/PD, safety and efficacy*



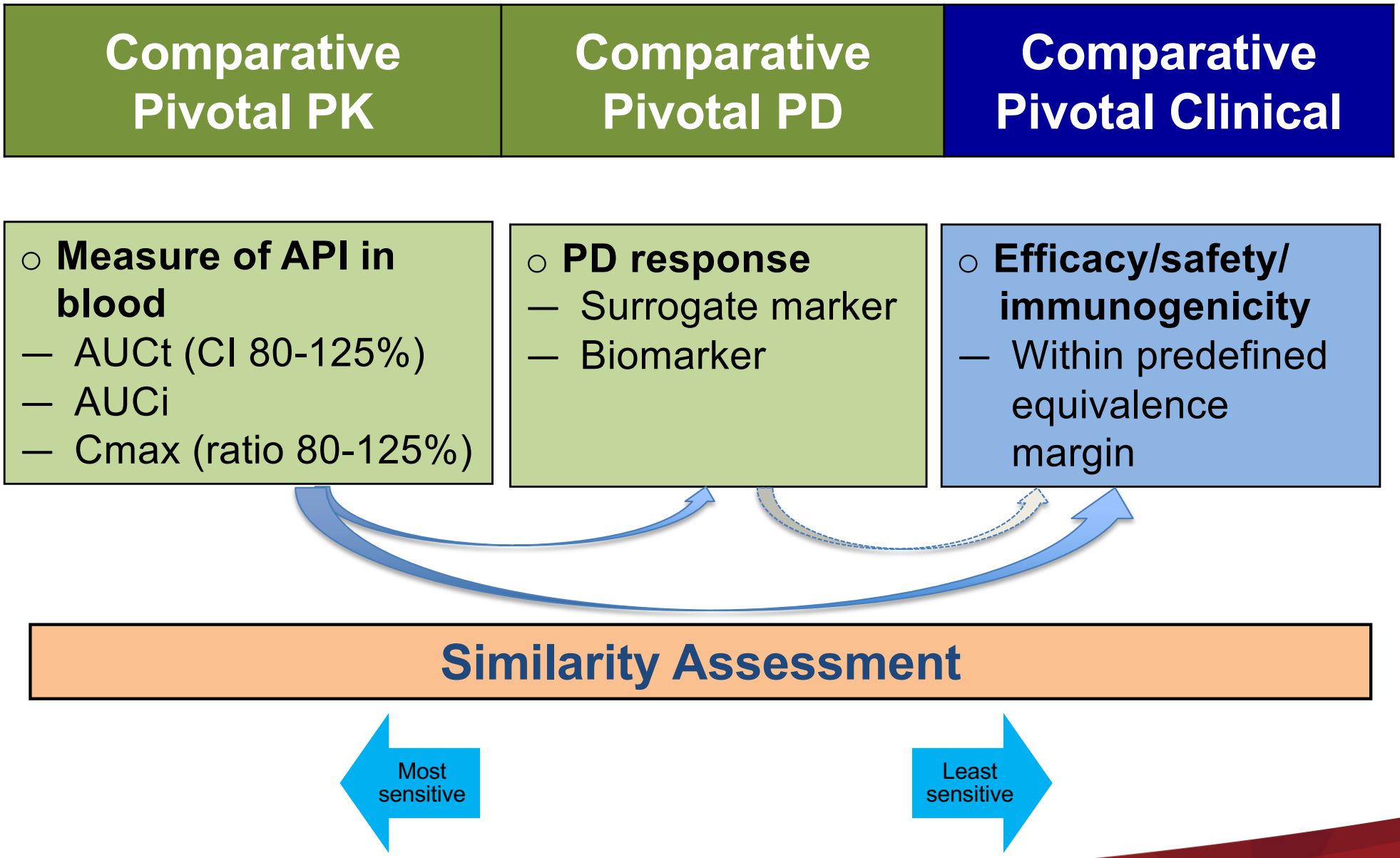
Biosimilar Clinical Program

- The innovator has established efficacy and safety for each indication
- The purpose of the clinical program is to show that residual uncertainty from quality assessment does not cause clinically meaningful differences in efficacy, safety and/or immunogenicity in the sensitive population

Critical Quality Attributes: Clinical Impacts

Quality Attribute		PK	Efficacy	Safety/ Immunogenicity
Structure	High-order structure	**Variable effect (product dependent)**	Misfolding or truncation can lead to lower efficacy	Misfolding can lead to ADA formation
	Aggregates	**Lower absorption and bioavailability**	Variable impact on Fcγ binding	Higher aggregates can lead to ADA formation
	Charge heterogeneity	**Variable effect (product dependent)**	Can impact potency (depending on source)	
Content	Protein concentration		Can impact dose/potency	Can impact safety
Glycosylation profile	High mannose	**Longer half-life with higher mannose**	Higher FCγRIII and ADCC with higher mannose	Can elicit immunogenic response
	Fucosylation		Higher FcγRIII and ADCC with lower fucose	Can elicit immunogenic response
Biological activity	Binding to Fcγ receptors		Variable impact on ADCC	
	FcRn affinity	**Higher FcRn affinity with longer half-life**	Variable impact on CDC	
Process impurities	Host cell DNA			Can elicit immunogenic response

Comparative Clinical Development Paradigm



Comparative PK/PD Studies

The goal of the clinical PK/PD is to rule out unacceptable PK/PD differences that could indicate the presence of significant structural and functional differences

PK/PD studies can also be used to

- Bridge gaps for using multiple non-domestic references
- Justify reducing subsequent clinical studies (e.g., insulin, filgrastim)
- Monitor immunogenicity during comparative clinical trials (e.g., altered PK)
- Establish bioequivalence between different strengths and formulations of biosimilars
- Demonstrate bioavailability for the different routes of administration
- Establish evidence for extrapolation of indications (e.g., cancer vs RA; adult vs paediatric)

Comparative PK Studies

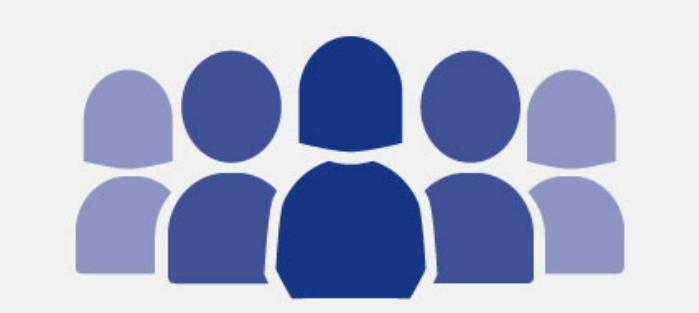
- Comparative clinical PK data are required
- Comparative PK studies should be conducted in a setting that is reflective of the clinical situation and/or is **sensitive** to detect differences between the biosimilar and the reference
- Comparative PK studies should be planned on the basis of the characteristics of the reference product, including its mode of action, safety profile and pharmacokinetic properties, such as
  - target-mediated disposition,
  - linear or non-linear PK,
  - time-dependency, and
  - half-life

Comparative PK Studies

- The most sensitive PK study design to detect potential differences is the single dose cross-over design (short half-life)
- Route of administration is an important factor to consider in the design and conduct of comparative PK studies
  - Use of a route that requires an absorption step is recommended (if applicable)
- In any PK study, anti-drug antibodies should be measured in parallel to PK assessment using appropriate sampling time points.

Comparative PK Studies: Study Population

- In general, the PK study can be conducted in healthy volunteers
- But … healthy volunteers may not always reflect the PK parameters of patients…
  - receptor expression
  - receptor sub-types
  - pathophysiological process of disease
  - patient status
  - Safety concerns
- Therefore, comparative PK studies may also be conducted in patient population



Comparative PK Studies: Study Design

- The principles of study design, statistical methods and criteria of acceptance for small molecules are used as a general guidance for biologics

In a single dose study

- AUCt (90% CI 80-125%)
- AUCi (90% CI 80-125%)
- Cmax (90% CI or ratio 80-125%)

When the IV route of administration is involved, additional parameters (Tmax, T1/2, CL, Vd or Vss) might also be investigated.

Comparative PK Studies: Study Design (Con't)

The cross-over, single dose design can be limited by the properties of the biologics

- long half-life
- formation of antidrug antibody (ADA)

Alternatively, parallel and/or multiple-dose design could be considered.

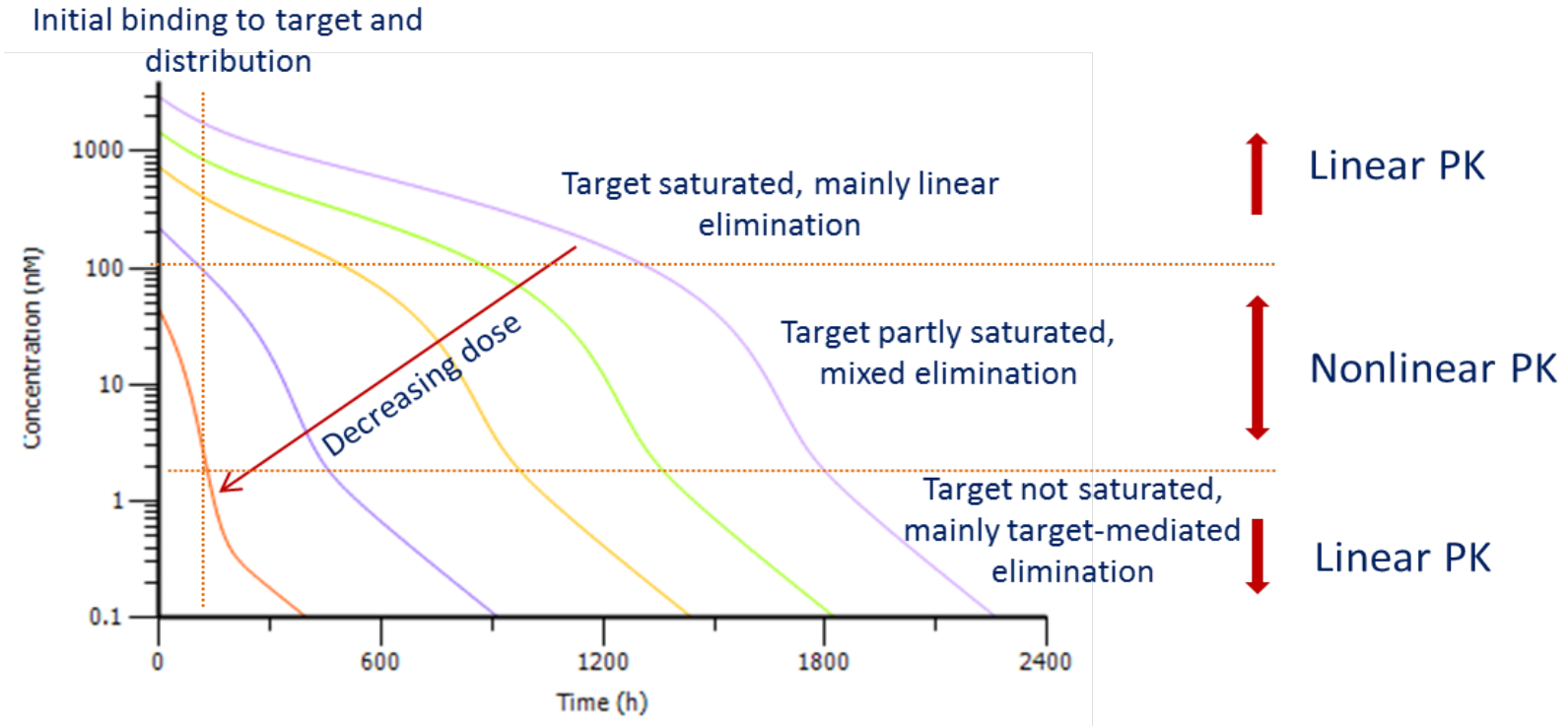
In a multiple dose study

The primary parameters should be the truncated AUC after the first administration until the second administration (AUC0–t) and AUC over a dosage interval (AUCτ) at steady state.

Secondary parameters are Cmax and Ctrough at steady state. The Ctrough at steady-state should not be less than 80%.

Clinical PK for Biosimilars: Special Concerns-TMDD

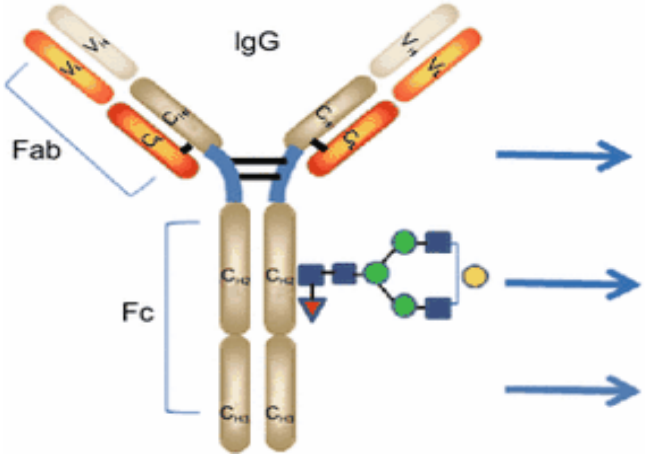
Many biologics, including mAbs, cytokines, and growth factors, display target mediated drug disposition (TMDD)



Considerations for drugs displaying TMDD:

- What is the sensitive dose for detecting PK differences?
- Should a clinically therapeutic dose or a sub-therapeutic dose be chosen?
- Is it ethical to administer patients at a sub-therapeutic dose?

Clinical PK for Biosimilars: Consideration for mAbs



Binding ligands	Relation to PK
Antigen	Target mediated disposition; charge/PI mediated clearance; off-target binding
Glycan receptor	Glycan mediated clearance and tissue distribution
FcRn	IgG recycling for long half-life

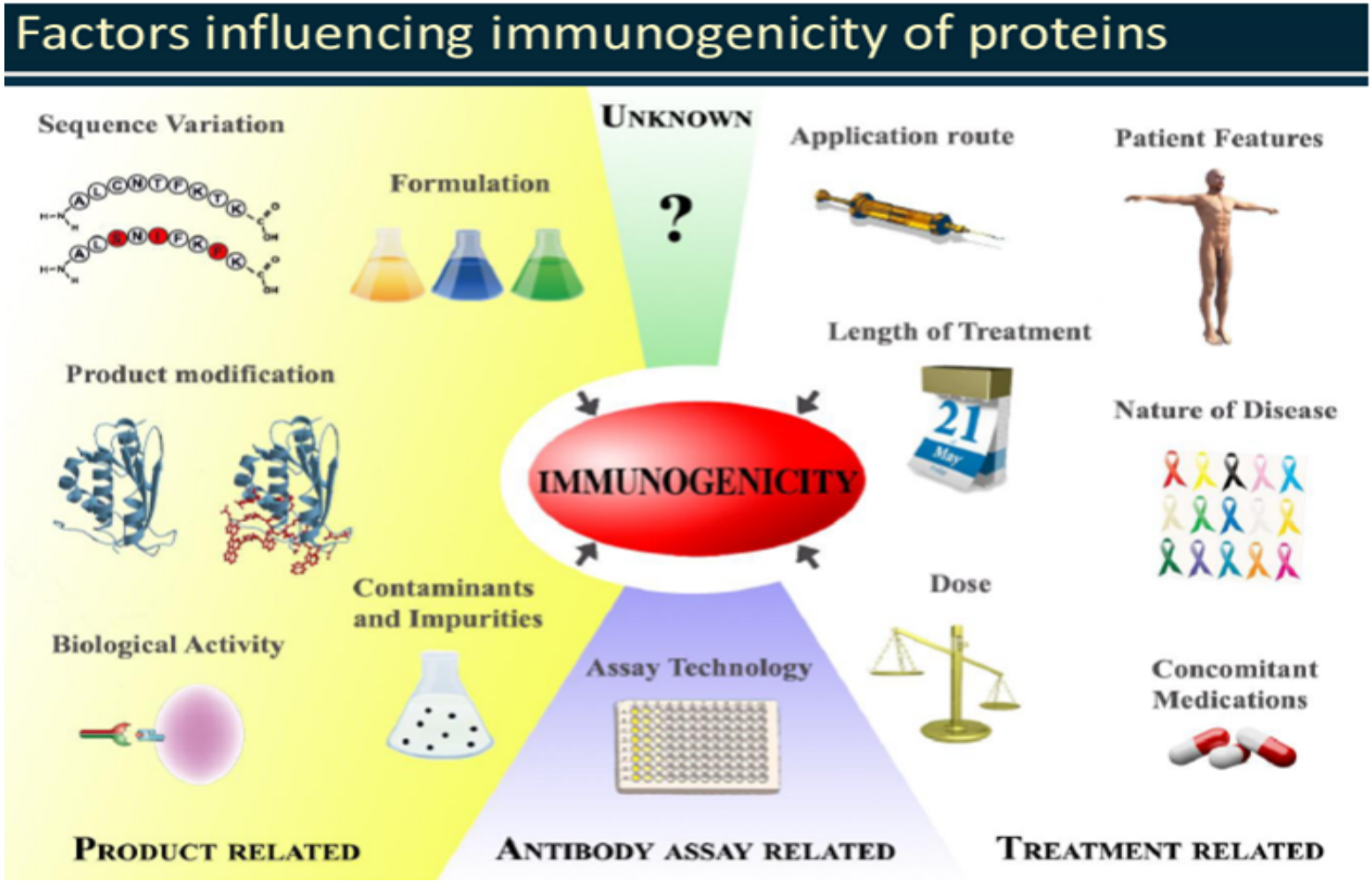
Liming Liu, January 2018, Volume 9, Issue 1, pp 15–32, Protein & Cell

Critical quality attributes can influence the pharmacokinetics (PK) of a mAb and therefore, may have a direct impact on biosimilarity

- FcRn mediated recycling is the primary determinant of an IgG antibody's PK properties, e.g., half-life.
- Glycosylation on mAb can have a significant impact on the PK of these molecules.
- High mannose content affects mAb half-life.
- Variation of isoelectric point (pI) values by 1–2 units is likely to impact the PK of mAb.

Clinical PK for Biosimilars: Immunogenicity

Most biologics induce some level of anti-drug antibodies (ADAs) and these ADAs may have undesirable clinical effect on pharmacokinetics, efficacy and/or safety, including immunogenicity.



Taken from: http://bcn2012.europeanbioanalysisforum.eu/slides/day%202/ii%20biosimilars/4_sauerborn.pdf.

PopPK Used to Assess Biosimilarity

PopPK studies are being used in demonstrating comparability for biosimilar mAbs, for example:

1. To reveal if there is any appreciable difference in the population PK parameter estimates between the biosimilar and the reference based on the Analysis of covariance.

2. To compare the exposure between formulations manufactured at two sites with the aim of showing ‘no differences’ between their pharmacokinetic parameters.

3. To evaluate PK consistency / similarity between the biosimilar and the reference product, using a nonlinear mixed effects approach based on the literature-reported population PK model with data from the comparative clinical study.

In these cases, the model played only a peripheral role.

Comparative Pharmacodynamic Studies (PD)

Comparative PD data are desirable (if feasible) and can help to reduce residual uncertainty

Following factors should be considered:

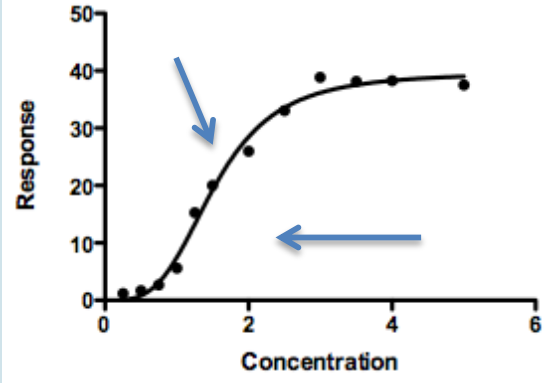
- Availability of PD biomarker/surrogate marker
- Relevance of the PD surrogate to the mechanism of action
- Correlation between the PK and PD values
- Quantitative relationship between the surrogate and clinical endpoint
- Sensitivity to detect clinically meaningful differences

Comparative PD Study: PD Surrogates

Biologics	PD Surrogate
Filgrastim (G-CSF)	Absolute neutrophil count (ANC)
Insulin	Euglycaemic clamp test (glucose)
Alpha interferons	Early viral load reduction
Epoetin	Hemoglobin levels
Teriparatide	Bone mineral density (BMD)*
Follicle stimulating hormone (r-hFSH)	Number of oocytes retrieved*

*PD parameters should be investigated as part of the “phase III trial”

Comparative PD Study: Sensitivity

Clinical sensitivity	Assay sensitivity	Dosing sensitivity
PD values should be sensitive to PK changes PD endpoints used should be clinically relevant, e.g., absolute neutrophil count (ANC) for a biosimilar G-CSF and be clinically validated	Dose in the steep part of the dose-response curve should be considered 	A therapeutic dose for patients may induce a ceiling effect in healthy volunteers, thus masking potential differences • A lower dose may be required

Comparative PD Study: Special Considerations

- PD parameters are generally investigated in the context of combined PK/PD studies or part of clinical trials
- Comparative PK/PD studies may provide useful information on the relationship between dose, systemic exposure, as well as safety and efficacy
- For most mAbs, there are no sensitive PD markers to confirm comparability between the biosimilar and the reference, and to be used to reduce the clinical studies
- Comparative in nature (95% confidence intervals to be used)

Comparative PD Studies: Endogenous Level

- If the biologic being studied is produced endogenously, the baseline endogenous levels in blood (plasma) should be measured and approximated, and
- These levels should be subtracted from the total concentrations measured from each subject after the drug product has been administered, so that the calculated pharmacokinetic parameters is based on the additional concentrations provided by the treatment.
- If a baseline correction results in a negative plasma concentration value, the value should be set equal to 0 before calculating the baseline-corrected AUC.

PK/PD Endpoint Parameter Acceptance Limits

Based on each agencies' regulatory guidance,

PK Endpoint

- The FDA considers that the 90% CI of the relative mean Cmax, AUCt and AUCi of the test to the reference should be within 80% to 125%.
- Health Canada considers that the 90% CI of the relative mean AUCt and the 90% geometric mean ratio of Cmax of the test to the reference should be within 80% to 125%.
- The EMA considers that the 90% CI of the relative mean Cmax and AUCi of the test to the reference should be within 80% to 125%.

PD Endpoint

- The FDA considers that the 90% confidence interval for the mean ratio (test to reference) should be within the predefined acceptance limits of 80–125%.
- The EMA and Health Canada considers that the 95% confidence interval for mean ratio (test to reference) should be within the predefined acceptance limits of 80–125%.

Conclusions

- The biosimilar is structurally and functionally (highly) similar to the reference product.
- Residual uncertainty from quality assessment should not cause clinically meaningful differences in efficacy, safety and/or immunogenicity.
- Comparative pharmacokinetic (PK) studies designed to demonstrate a comparable PK profile are always required for biosimilars.
- For products with a reliable PD marker, a high quality and sensitive PD study (usually combined with PK) may be better than an efficacy study in terms of detecting differences in efficacy between the biosimilar and the reference product.

Thank you

Merci

Gracias

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