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GaBI Educational Workshops

23 June 2019, G Hotel, Penang, Malaysia

2nd ASEAN Educational Workshop on
REGULATORY CONSIDERATIONS FOR BIOSIMILARS

Canada's approach to non-clinical and clinical assessment of biosimilars

Jian Wang, MD, PhD

23 June 2019

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

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Canada's Approach to Non-Clinical and Clinical Assessment of Biosimilars

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

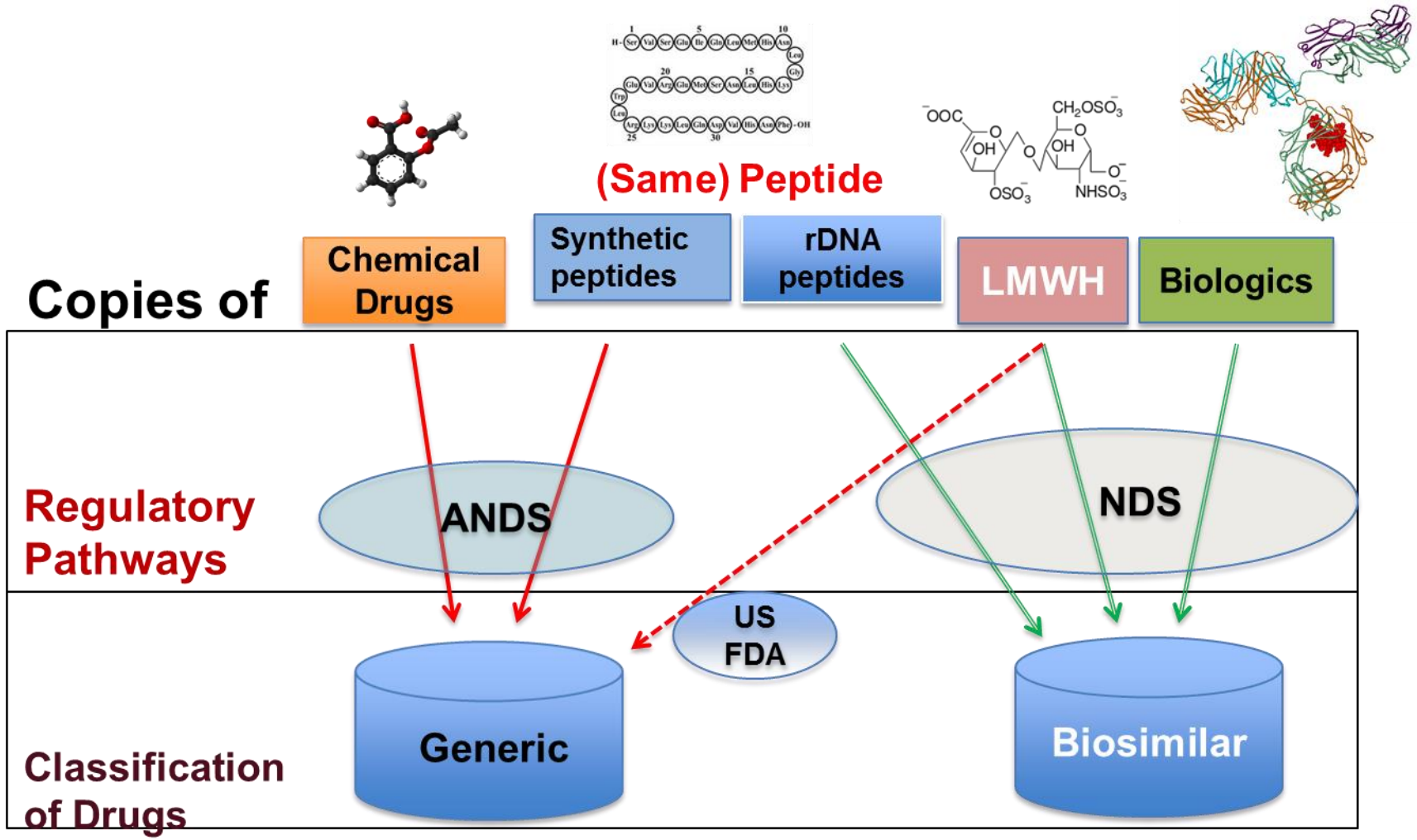
Regulations for Biologics in Canada

- ***Food and Drugs Act***
  - Schedule D – Biologic Drugs List
  - Section 12 - Requirement that the premises in which the drug is manufactured and the process and conditions of manufacture therein are suitable to ensure that the drug will not be unsafe for use.

- ***Food and Drug Regulations***, Part C: Drugs
  - Division 1 - General Requirements
  - Division 1A -Establishment Licensing
  - Division 2 - Good Manufacturing Practices
    - Annex to the GMP Guidelines, GMPs for Biologics
  - Division 4 - Schedule D (Biologic) Drugs
  - Division 5 - Clinical Trial Applications
  - Division 8 - New Drugs

- **Importantly, there are no regulations that establish an abbreviated authorization pathway for Biosimilars**
- **Canadian requirements are based on policy that allows for a reduced clinical package under certain circumstances**

Regulatory Pathways for Biosimilars in Canada

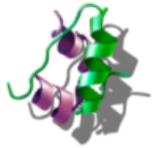


Pharmaceuticals vs. Biologics

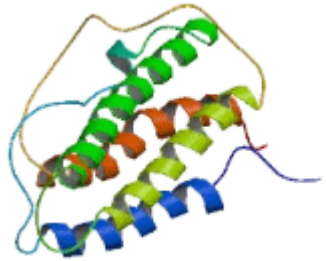
Small Molecule

Acetyl-salicylic acid
~180 daltons
21 atoms

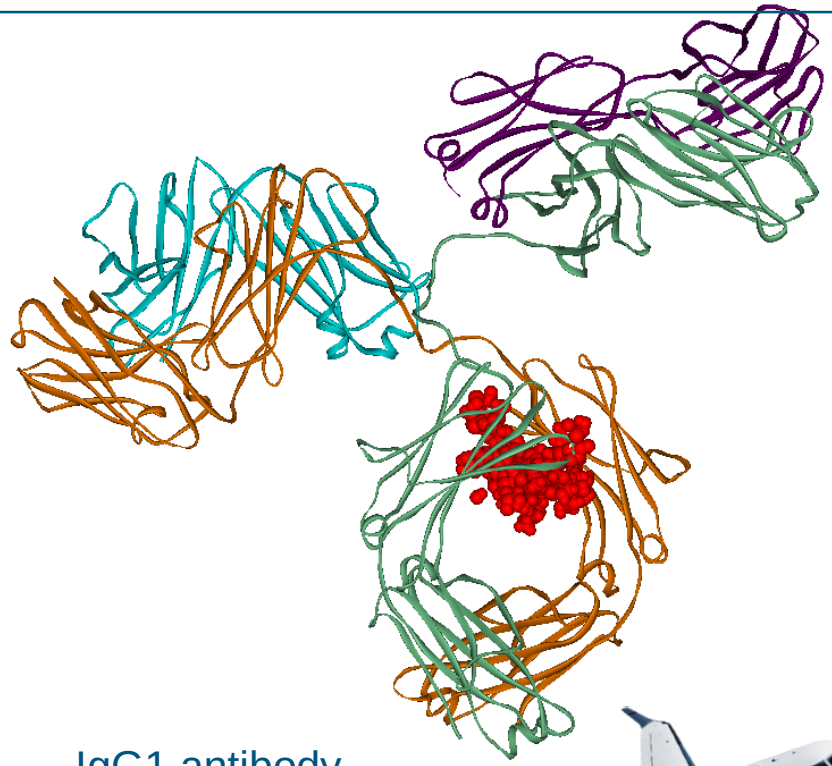
Biologics



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

More Data Required for Biosimilars than Generics

	Biosimilars	Generics
Regulatory Pathway	New Drug or biosimilar pathway	Generic
Drug Substance	Identical amino-acid sequence to reference	Identical to reference (Pharmaceutical equivalence)
Comparative Dissolution Profiles	**Not required (injectable)**	**Required at 3 pH levels**
Structure characterization	**Comparable to reference**	
Function characterization	**Comparable to reference**	
Non-Clinical Study	**Reduced and comparable to reference**	
PK Profile	**Comparable PK profile to reference**	**PK equivalence to reference**
PD Profile	**Comparable PD profile to reference**	
Efficacy	**No clinically meaningful differences in at least one indication**	
Safety/ Immunogenicity	**No clinically meaningful differences in at least one indication**	
Indication	**May receive all indications of Reference or additional study (switchable)**	**Receive all indications of Reference (interchangeable)**

Biosimilar Development Program

- The foundation of a biosimilar development program is based on the **extensive side-by-side structural and functional characterization of the biosimilar and the reference biological drug (RBD) to demonstrate similarity.**

- **Step-by-step sequential development program**, evaluating residual_uncertainty at each step.

- **Case-by-case based approach** tailored to individual product.

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
Glysoylation profile	High mannose	Longer half-life with higher mannose	Higher FCγRIII and ADCC with higher mannose	Can elicit immunogenic response
	Fucosylatio		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

Non-clinical Comparison

Comparative Non-Clinical Studies

Comparative non-clinical studies following principles recommended by ICH S6 (R1) to detect significant differences between the biosimilar and the reference

In vitro studies

- Extensive receptor binding studies and cell-based assays (considered to be more sensitive)

In vivo studies

- Animal PK/PD studies when feasible
- At least one repeat-dose toxicity study, including characterization of toxicokinetic parameters, conducted in a relevant species
- Other relevant safety observations (e.g., local tolerance), which can be made during the same toxicity study

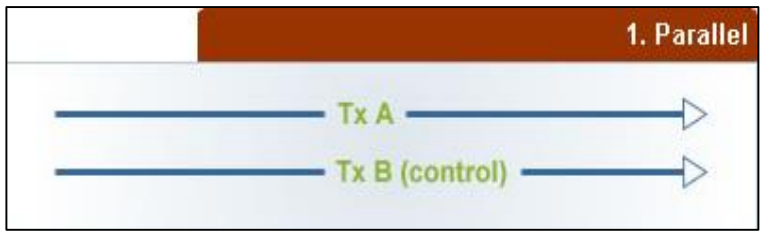
Future: Regulatory expectations for comparative toxicology studies have changed over time. Flexible approaches have been considered,

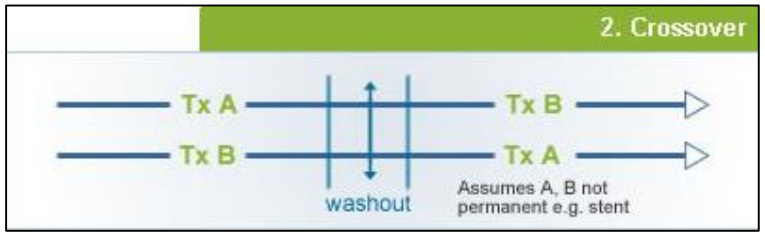
- Non-comparative animal studies
- *in vitro* studies only, if justifiable

PK/PD Comparison

Comparative PK Studies

- Comparative clinical PK data are required.
- The 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.
- The most sensitive PK study design to detect potential differences is the single dose cross-over design (short half-life).
- The cross-over, single dose design can be limited by the properties of the biologics. Alternatively, parallel and/or multiple-dose design could be considered.





www.esourceresearch.org/tabid/198/Default.aspx

Comparative PK Studies: Study Population

- In general, the PK study can be conducted in healthy volunteers
- However, 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

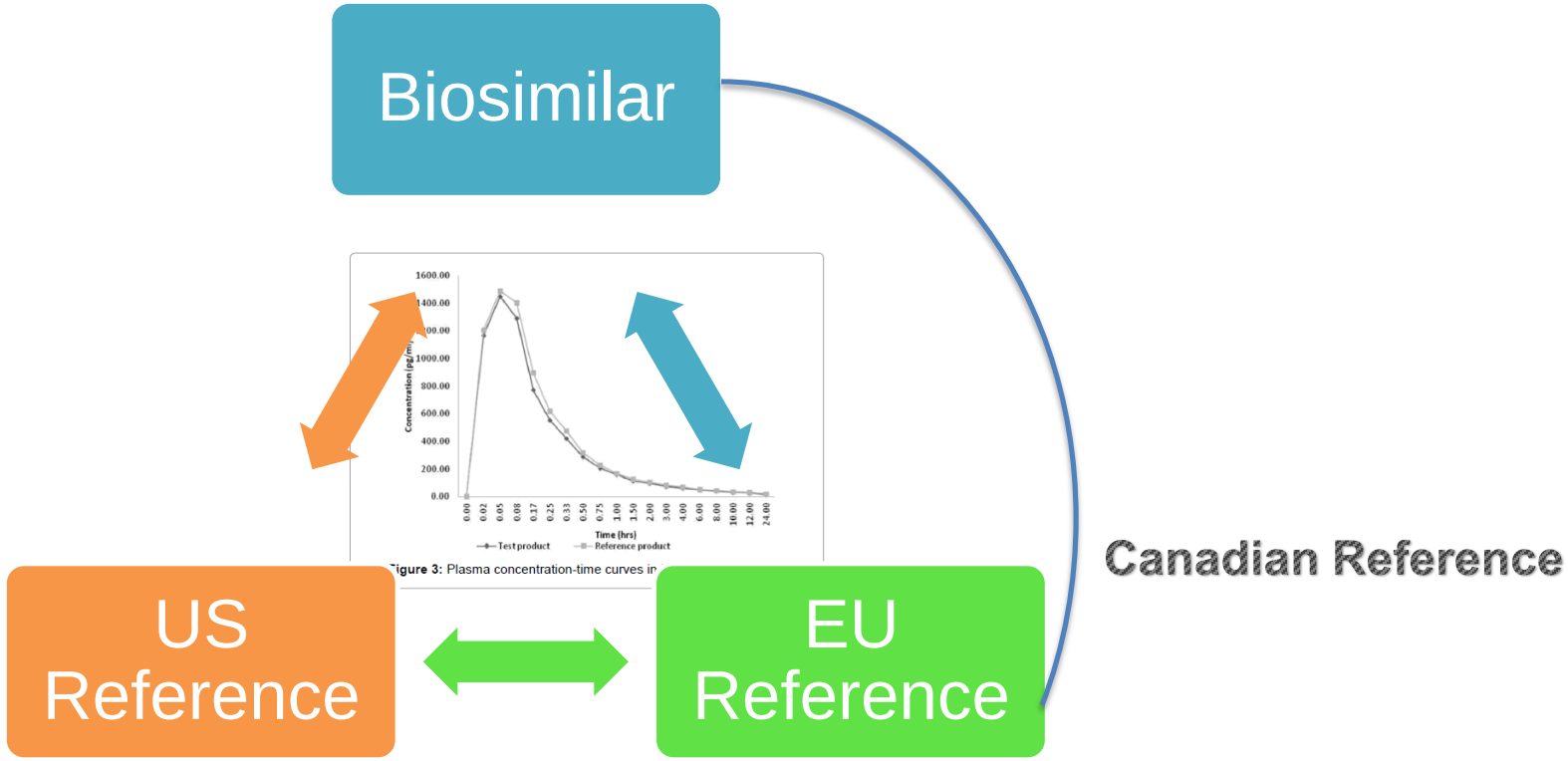
- Principles of study design, statistical methods and criteria of acceptance for small molecules are used as a general guidance for biologics

In a single dose study

- AUCt (90% CI, 80-125%)
- AUCi (not required in Canada)
- Cmax (90% ratio, 80-125%)

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

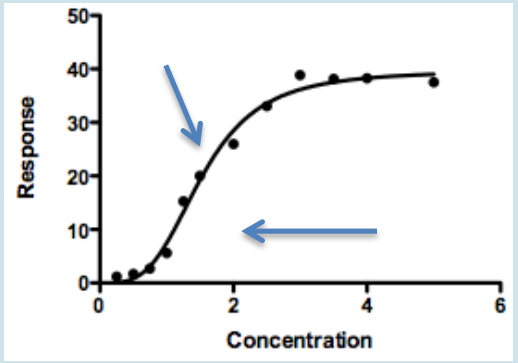
Comparative PK Studies: 3-Way Head to Head



- Submission usually contains 3-way comparisons
- Health Canada usually considers the comparison between the biosimilar and the reference that is deemed to be the Canadian reference
- 3-Way comparison is considered if both references are used in clinical studies

Comparative PD Studies

- **Comparative PD data are desirable (if available) and can help to reduce residual uncertainty**

Clinical sensitivity	Assay sensitivity	Dosing sensitivity
PD values should be sensitive to PK changes The PD surrogate should be relevant to the mechanism of action PD endpoints used should be clinically relevant e.g., absolute neutrophil count 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: 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”
- 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

PK/PD Endpoint Parameters: Not Harmonized

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% ratio 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 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%**

Clinical Comparison

Biosimilar Clinical Program

- The innovator has established efficacy and safety for each indication

- The purpose of the clinical program for biosimilars 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

Sensitive Clinical Study Population

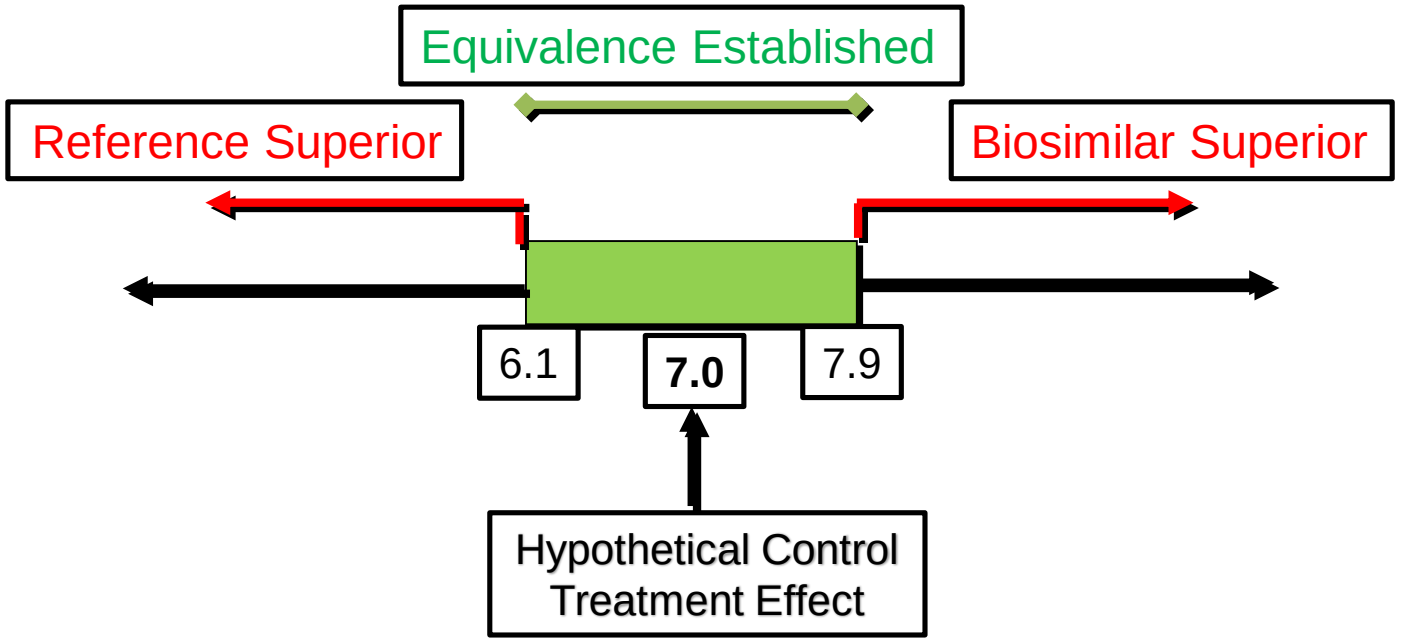
The comparative clinical study should be conducted in a sufficiently sensitive population that is representative of the authorized indications to detect differences between the biosimilar and the reference.

- A homogeneous population would give a better chance to detect potential differences
- Observed clinical effects are the direct action of the biosimilar or the reference without interference of other drugs (when feasible)
- A large body of historical data is available for validation of study outcomes (external validity)
- Mechanism of action is well-understood and represented in the population
- Effect size is known to be large

Equivalence Trial Design

Equivalence designs are preferred to Non-inferiority

- Margins are expected to be justified (clinical and statistical considerations)



In an equivalence trial, if the treatment effect falls between the predefined equivalence margin 6.1 and 7.9, the study would establish “equivalence” between the biosimilar and the reference.

If the treatment effect falls outside the 6.1 to 7.9 range, the study would fail to establish “equivalence” between the biosimilar and the reference.

Sensitive Clinical Study Endpoint

A sensitive study endpoint should be considered to improve the detection of potential differences between the biosimilar and the reference within the sensitive population.

- A study endpoint different from the innovator's original study endpoint(s) may be used, e.g., ORR as primary endpoint instead of OS in oncology trials for biosimilars.
- A new surrogate (e.g. pCR) or a more sensitive clinical endpoint identified in clinical practice may be acceptable, e.g., assess clinical response before the plateau phase for better sensitivity (time-dependent sensitivity).

Sensitivity of Clinical Assessment Time Points

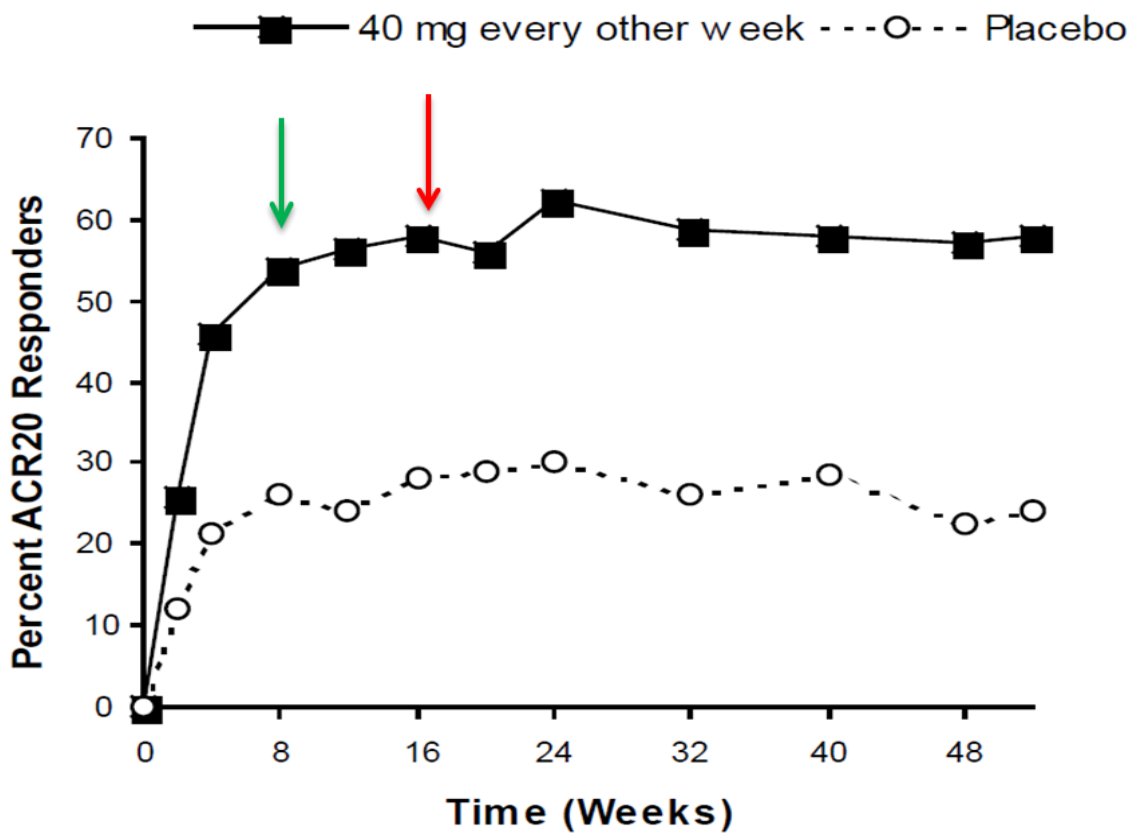
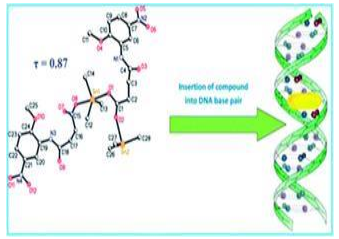


Figure 2. **Study DE019 ACR 20 Responses Over 52 Weeks**

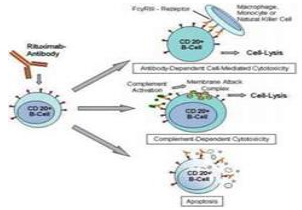
Extension of Indications: Totality of Evidence

The final authorized indications are not ‘extrapolated’ from one ‘single’ comparative clinical study. It is based on the totality of evidence.

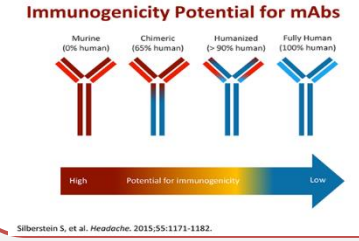
Physicochemical characterization



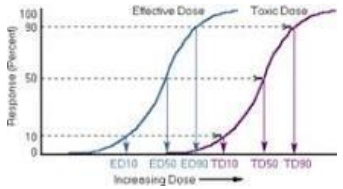
Biological activity/Mechanism of action



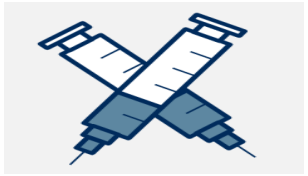
Safety/ Immunogenicity



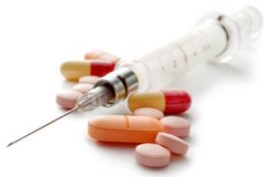
PK/PD Profile



Route of Admin & Dosage Range



Monotherapy & Combination Therapy



Biosimilars can receive all indications of the reference based on the totality of evidence obtained from all comparative studies

Extension of Indications: What Would Be Authorized

- A biosimilar sponsor is eligible to apply for the indication(s) and condition(s) of use that are held by the reference drug authorized in Canada.
- The biosimilar manufacturer may choose not to seek all indications held by the reference (most likely due to patent issue associated with the individual indication), and
- Health Canada may decide not to authorize a biosimilar for a certain indication based on scientific and benefit/risk-based considerations.
- After initial marketing authorization of the biosimilar, supplemental biosimilar submissions can be filed for new indications that are already held by the Canadian reference drug.
- Indication that is not held by the Canadian reference drug could be granted to the biosimilar sponsor with a full clinical development programme.

What is a biosimilar?

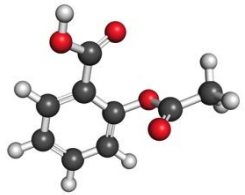
- A biosimilar is a legitimate copy of a biopharmaceutical, which no longer is protected by patent, that has:
  - Undergone rigorous analytical and clinical assessment, in comparison to its reference product, *and*
  - Been approved by a regulatory agency according to a specific pathway for biosimilar evaluation

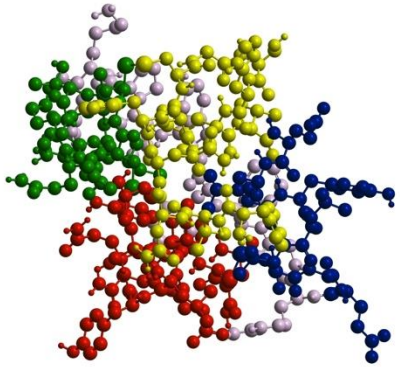
Generics and Biosimilars

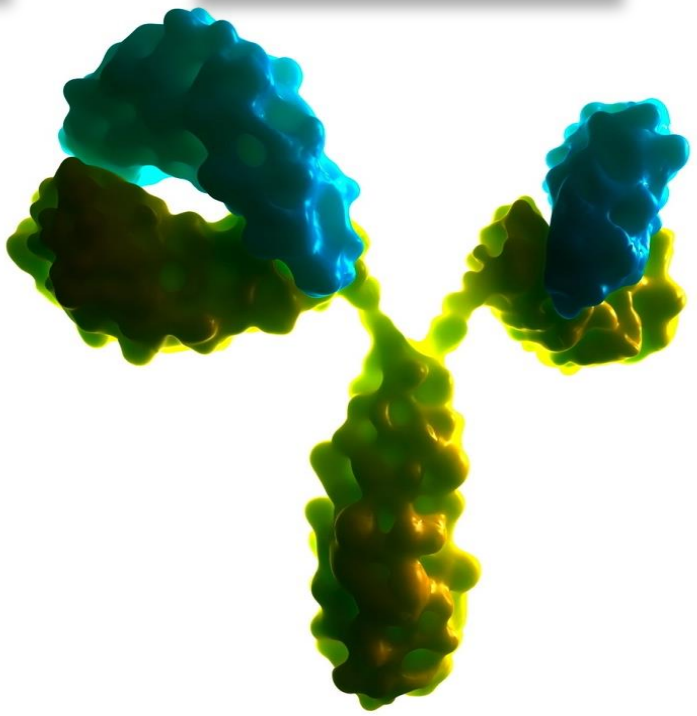
Generic

1st generation biosimilar

2nd generation biosimilar







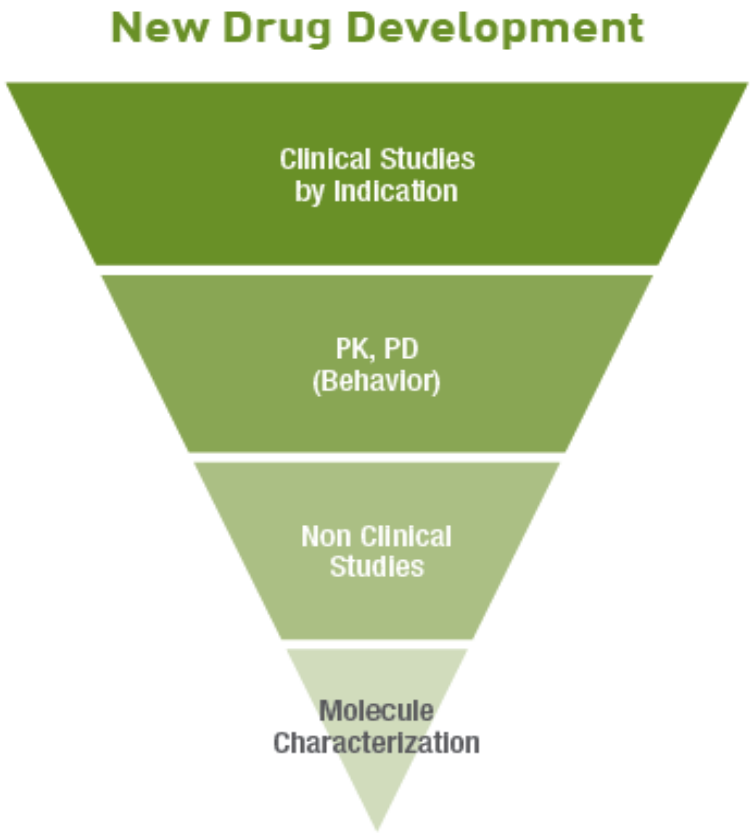
Aspirin (chemical)
180 daltons

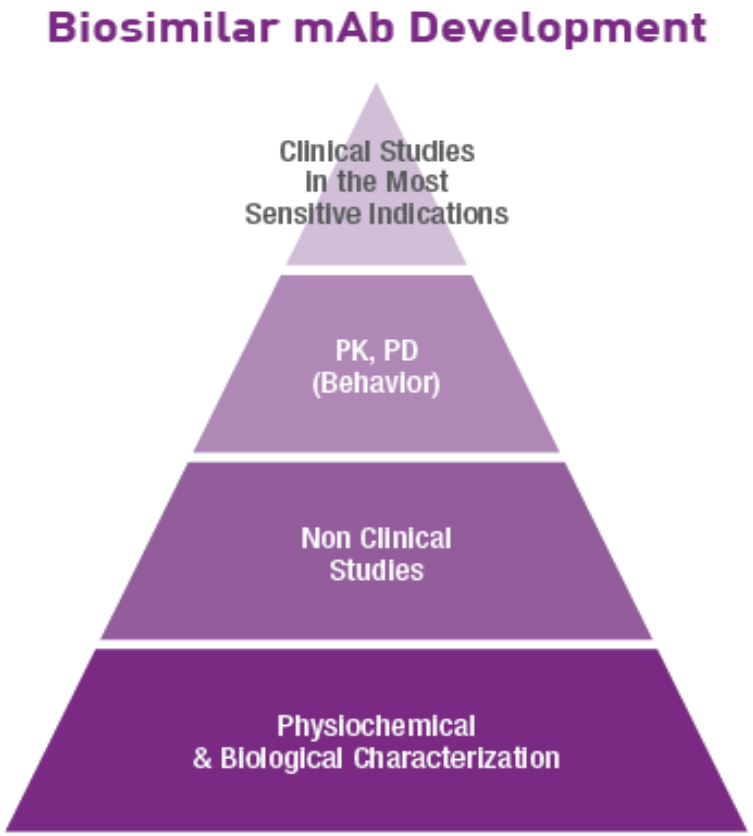
Insulin
5,700 daltons

mAb
~150,000 daltons

Comparison of Regulatory Requirements

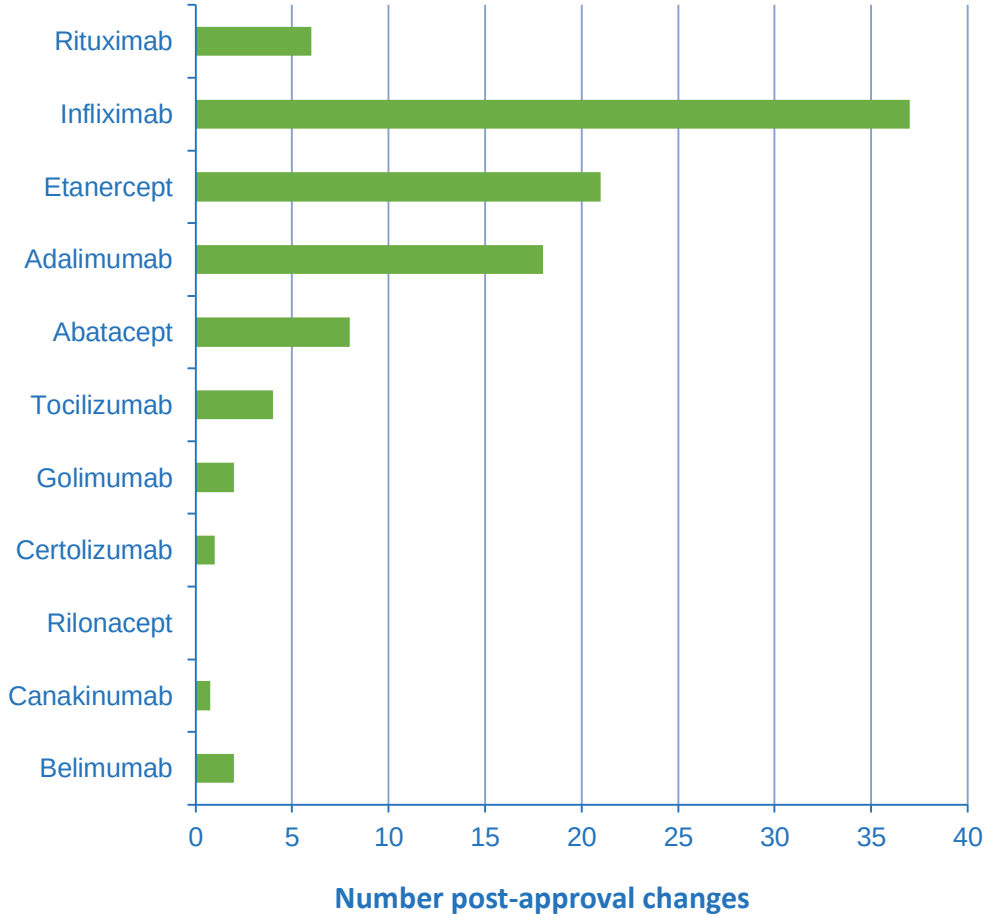
- The aim of a biosimilar development program is to establish ***"biosimilarity"*** based upon totality of evidence.





1. Guideline on similar biological medicinal products. European Medicines Agency 23rd October 2014.
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (Accessed October 2016).

Manufacturing changes have been a part of biologics all along



Schneider CK et al. ARD 2013;72:315–318

HC Authorized Biosimilars

2009

- Omnitrope (somatropin)
  - additional indications in 2015

2014

- Inflectra (infliximab)
  - Additional indications in 2016
- Remsima (infliximab)
  - Additional indications in 2016

2015

- Basaglar (insulin glargine)
- Grastofil (filgrastim)

2016

- Brenzys (etanercept)

2017

- Erelzi (etanercept)
- Admelog (insulin lispro)
- Renflexis (infliximab)

2018

- Lapelga (pegfilgrastim)
- Mvasi (bevacizumab)
- Fulphila (pegfilgrastim)

2019

- Truxima (rituximab)
- Ogivri (Trastuzumab)
- Brand name (bevacizumab)

Intellectual Property (IP) Hold

- Even the review decision is positive.
- If a declaration that the making, constructing, using or selling of the biosimilar would infringe any reference drug's patent that is the subject of an allegation, the submission will be placed on "Intellectual Property (IP) Hold" in Canada.

Conclusions

When Health Canada grants market authorization of a biosimilar, it means that,

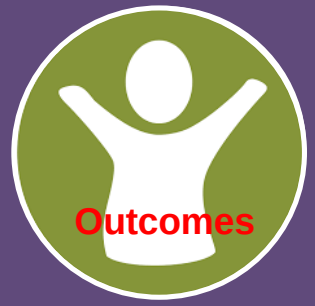
- The biosimilar has met all quality, safety, and clinical standards
- The biosimilar is structurally and functionally (highly) similar to the reference product
- Residual uncertainty from quality assessment does not cause clinically meaningful differences in efficacy, safety and/or immunogenicity
- The biosimilar can be safely used for all authorized therapeutic indications.

Potential Benefits of Using Biosimilars

Biosimilars offer stakeholders, including physicians, patients and payers - more choices when it comes to treatment options.

Potential Savings from the Use of Biosimilars

Providing more Affordable Options for Stakeholders



More Accessible and Improvement in Patient Outcomes

Reallocation of Resources to Other Areas of Patient Care

Thank you

Merci

Gracias

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