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GaBI Scientific Meetings

2nd MENA Stakeholder Meeting on **Regulatory Approval, Clinical Settings, Interchangeability and Pharmacovigilance of Biosimilars**

10 October 2018, Le Meridien Dubai, United Arab Emirates

Biosimilars: Canada's approaches to interchangeability, biosimilarity, extrapolation of indications and uses – a comparison to the US FDA

Jian Wang, MD, PhD, Canada

10 October 2018

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Canada

Biosimilars: Canada's Approaches to Interchangeability, Biosimilarity, Extrapolation of Indications and Uses – a Comparison to the US FDA

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Biologics and Genetic Therapies Directorate
Health Canada

2nd MENA Biosimilars meeting

Oct 10, 2018

Dubai, UAE

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Highlights

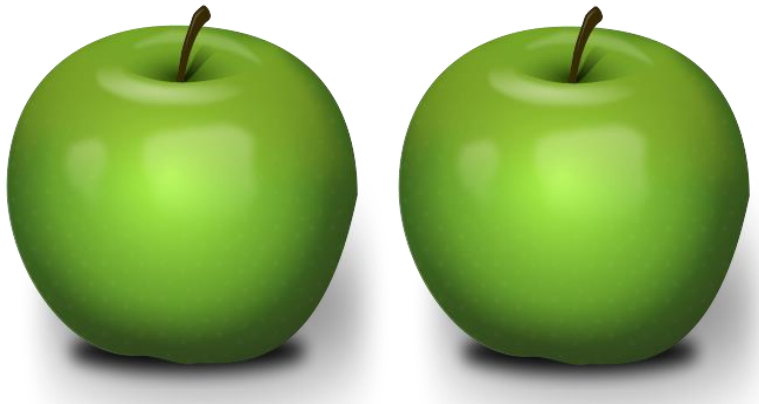
- A biosimilar is a biological product that is highly similar to a marketed biologic
- Biosimilarity is established on comparative analytical, nonclinical and clinical studies
- Sensitivity of clinical study design, study population/endpoint, analytical methodology is critical for demonstrating no meaningful differences
- Therapeutic indications for a biosimilar are based on the totality of evidence from the development program
- Interchangeability designation and standards are mandated by law in the US

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



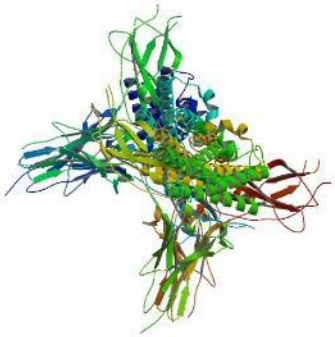
Generics

Different cell lines

Different manufacturing processes

Step-wise **Comparative** Approach for Biosimilars

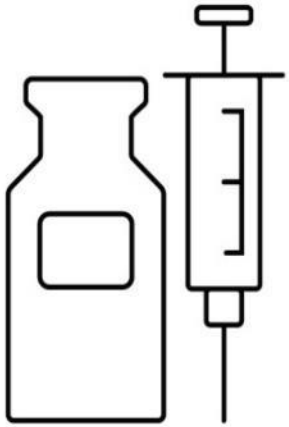
Sensitive in detecting differences

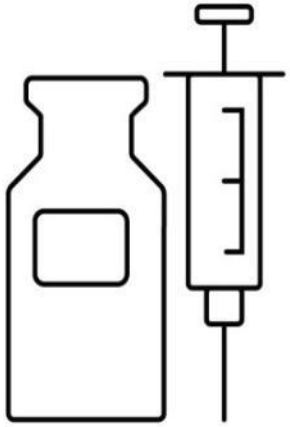


Comparative clinical studies
- Pharmacokinetic/pharmacodynamic
- Efficacy + safety + immunogenicity

Comparative non-clinical studies
- Pharmacodynamic
- Toxicology

Comparative quality studies
- Analytical: physical + chemical properties
- Functional: biological/pharmacological activity





Compare to what we know

Reference medicine **Biosimilar medicine**

Quality comparison forming the basis for Biosimilars

Address uncertainties stemming from earlier testing

Biosimilars

Demonstrating Similarity and No Clinically Meaningful Differences

Reference Product

	FDA	Health Canada
Regulatory pathway	Biosimilar 351(k) application	New Drug
Reference Product	US-licensed reference product	Accepts the use of a non-Canadian version of the Canadian authorised reference product from another jurisdiction for the full biosimilar program development
Bridging to the national product	Yes, if a non-US-Licensed Reference Product is used	Not required

Critical Quality Attributes: Extensive Quality Comparison

Quality Attribute	Methodology
Amino acid sequence and modifications	Mass spectrometry (MS), peptide mapping, chromatographic separation
Folding	S-S bonding, calorimetry, HDX and ion mobility MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence
Subunit interactions	Chromatography, ion mobility MS
Heterogeneity of size, charge, hydrophobicity	Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS
Glycosylation	Anion exchange, enzymatic digestion, peptide mapping, CE, MS
Bioactivity	Cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction
Aggregation	Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy
Impurities	Proteomics, immunoassays, metal & solvents analysis
Adventitious Agents	Sterility, qPCR, bioassays, clearance

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; can impact FcRn binding	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
	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

Number of Lot and Statistical Analysis

	FDA	Health Canada
Number of lot required for analytical assessment	At least 10 lots	Not stated
Statistical Analysis for Quality Data	Yes, issued in September 2017 3 tiers • tier 1 is equivalence testing, • tier 2 is the use of quality ranges, and • tier 3 uses a visual comparisons approach Withdrawn on 21 June 2018	Not specifically required

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)

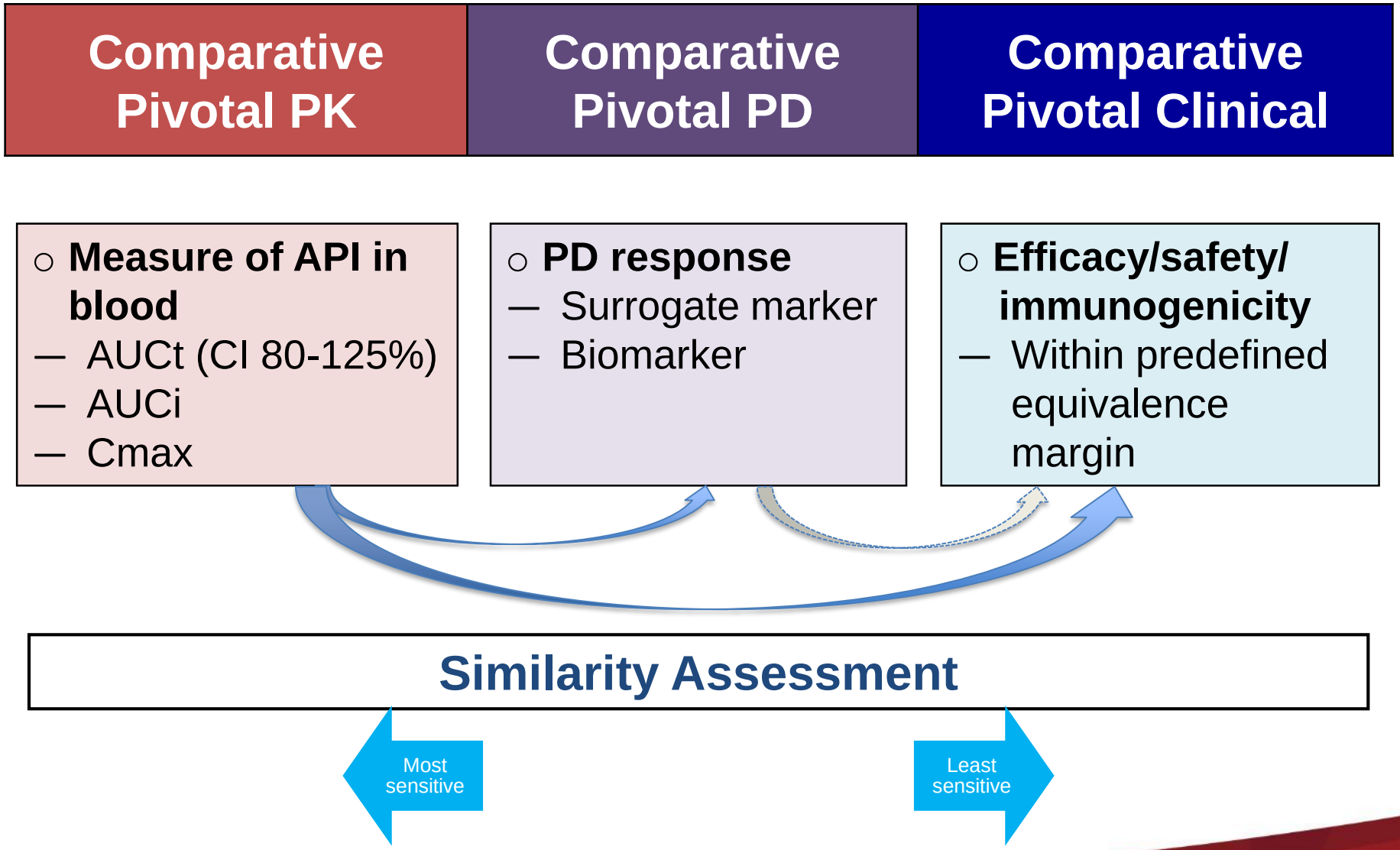
In vivo studies

- 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

Comparative Clinical Development Paradigm



Comparative Pivotal PK Studies

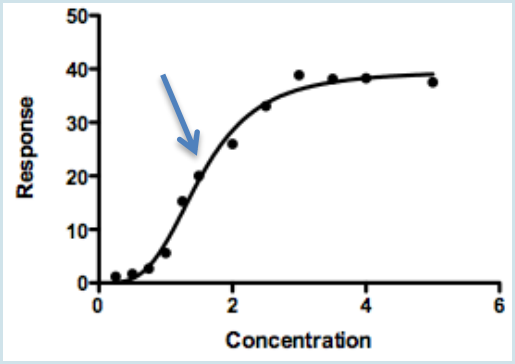
Design of Clinical PK Studies for Biosimilars

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

Comparative Pivotal PD studies

Sensitivity of Comparative PD studies

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

Clinical sensitivity	Assay sensitivity	Dosing sensitivity
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

PK/PD Endpoint Parameter Acceptance Limits

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%.

PD Endpoint

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

Comparative Pivotal Clinical Studies

- The innovator has established efficacy and safety for each indication.
- A biosimilar does not have to re-establish the *de novo* benefit/risk (provided it can be considered highly similar from a quality perspective).
- 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 a sensitive population.

Sensitive Clinical Study Population

Study population, endpoint, sample size and study duration should be adequately sensitive to detect differences between products, should they exist.

- A **homogeneous population** would give a better chance to detect potential differences between a biosimilar and its reference
- **Mechanism of action** is well-understood and representative
- Observed clinical effects are the **direct action** by the biosimilar or the reference without interference of other drugs
- The **effect size** should be large
- A large body of **historical data** is available for validation of study outcomes

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 or PFS as primary endpoint instead of OS in oncology trials for biosimilars.
- A new surrogate 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).

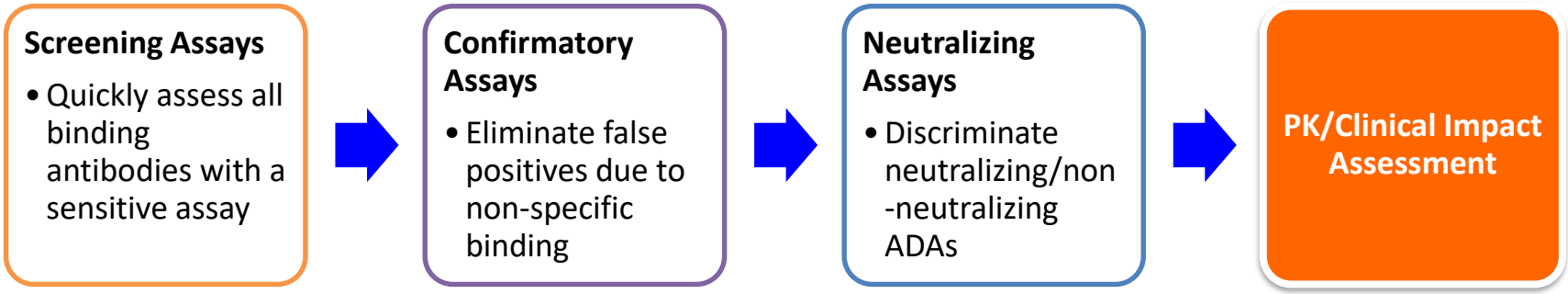
Potential Differences in Clinical Trial Design (Oncology)

	FDA*	HC*
Equivalence Margin	±15	±13.5
	asymmetric	symmetric
Confidence Interval (CI) for clinical endpoint	90%	95%
Statistical Power	90%	At least 80%
Study Population	Neoadjuvant	Adjuvant
Statistical Analysis on endpoint	Risk Ratio	Risk Difference
Study Endpoint	pCR	ORR

***Not real case (illustration only)**

Immunogenicity Assessment Strategy

- **Anti-drug antibody (ADA) is a key concern for biologics**
- Immunogenicity should be compared between the biosimilar and the reference in at least one clinical study that enrolled a sufficient number of patients for a sufficient period of time.
- Immunogenicity assessment strategy:



A biosimilar should not be more immunogenic than its reference in terms of ADA incidence or ADA concentration

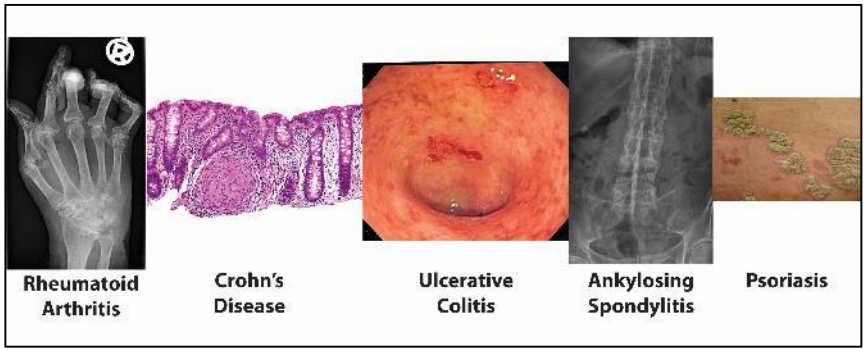
Therapeutic Indications for Biosimilars

A single biologic may be indicated for use in a variety of diseases…

Remicade (Infliximab)

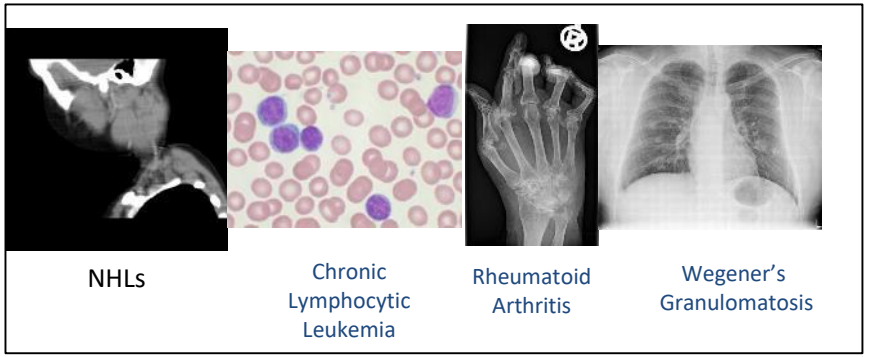
Authorized for

Indications



Rituxan (Rituximab)

Authorized for

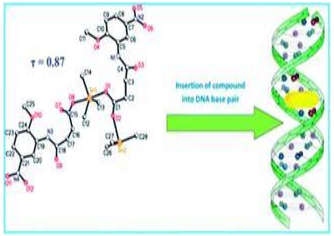


Authorization of Indications: Totality of Evidence

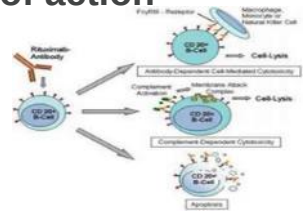
- The final authorized indications are not ‘extrapolated’ from one ‘single’ comparative clinical study.
- The decision to authorize the requested indications is dependent on the demonstration of similarity between the biosimilar and reference biologic drug based on data from comparative structural, functional, non-clinical, PK/PD and clinical studies and a detailed scientific rationale.
- The biosimilar manufacturer may choose not to seek all indications held by the reference, and
- Health Canada/regulatory agencies may decide not to authorize a biosimilar for a certain indication based on scientific and benefit/risk-based considerations.

Consideration for Granting Therapeutic Indications: Totality of Evidence

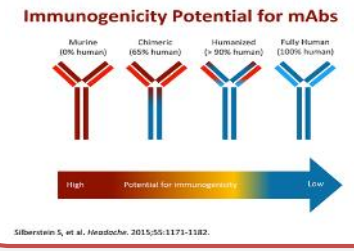
Physicochemical characterization



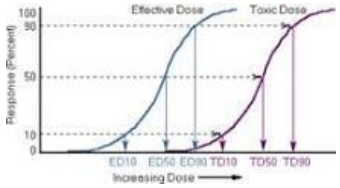
Biological activity/Mechanism of action



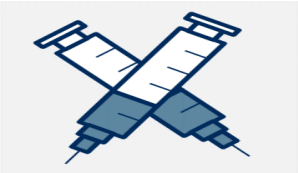
Safety/ Immunogenicity



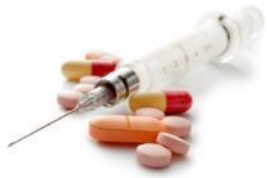
PK/PD Profile



Route of Admin & Dosage Range

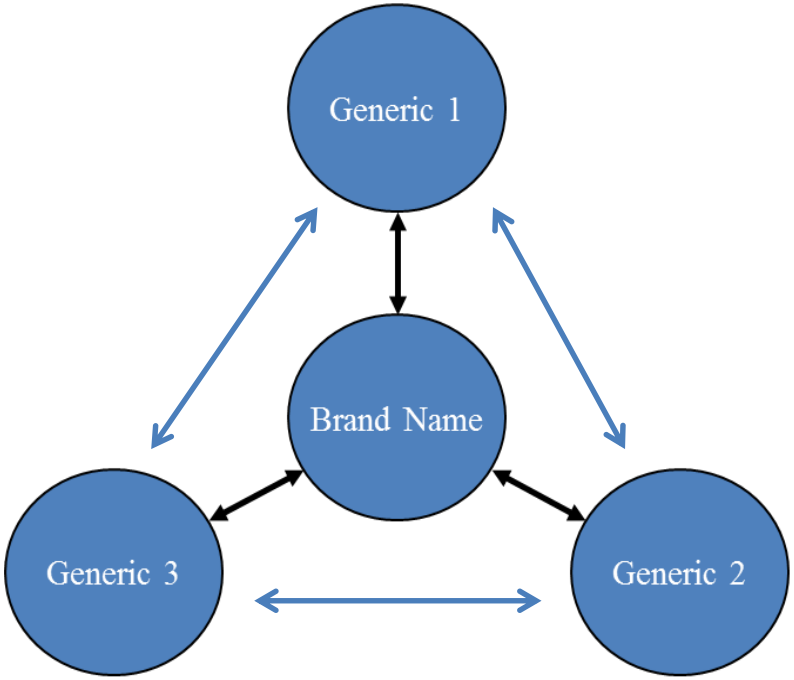


Monotherapy & Combination Therapy

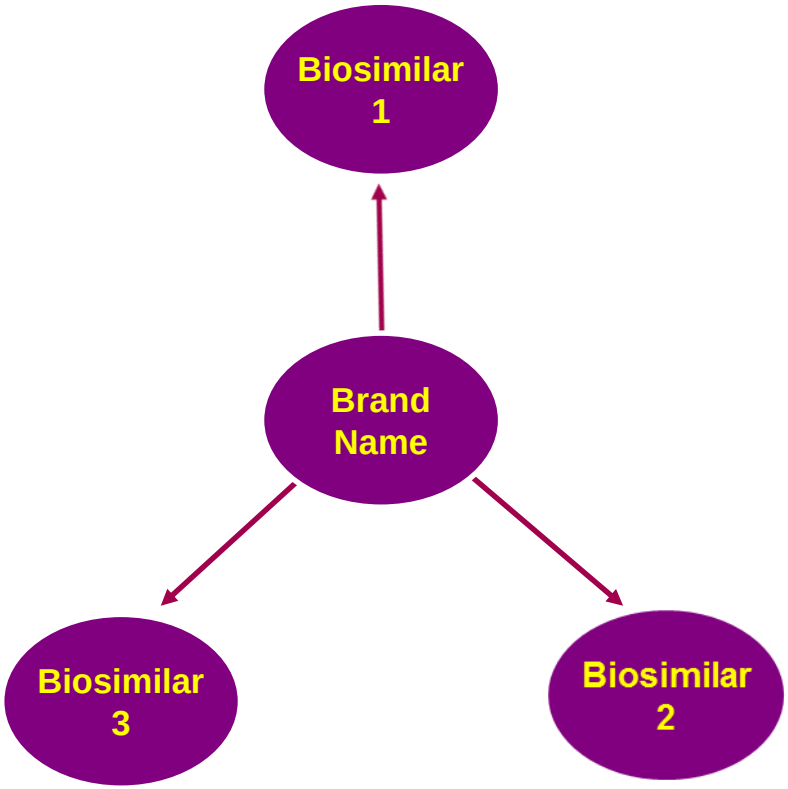


Biosimilars can receive all indications of the reference based on the totality of evidence obtained from all comparative studies

Interchangeability/Substitutability for Biosimilars



A generic can be automatically interchanged with the brand name product (and other generics)



A biosimilar could be switched with the brand name biologic by physicians

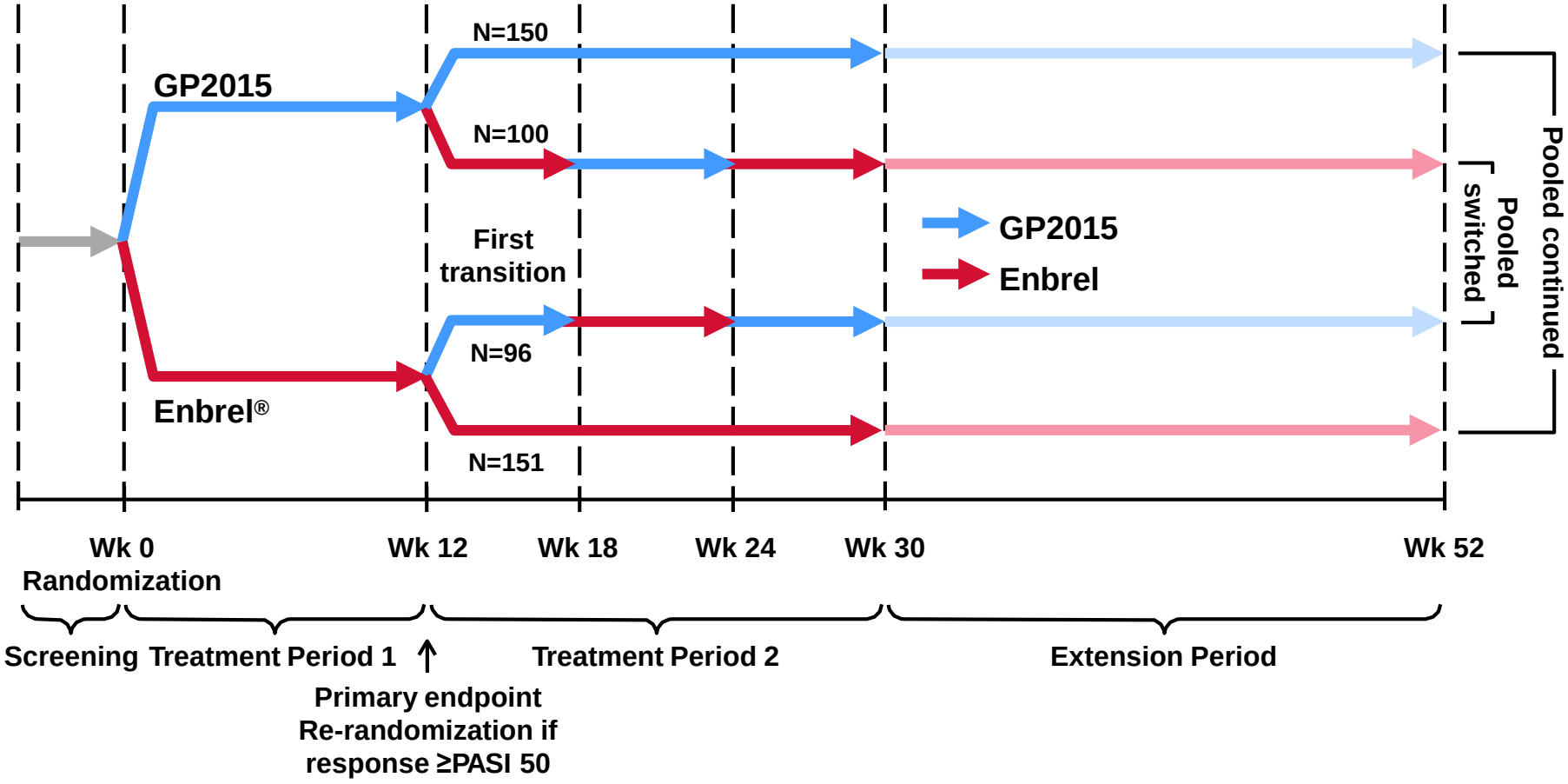
Interchangeability

Health Canada	US FDA
• Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug • The authority to declare two products interchangeable rests with each province and territory	• Interchangeability designation and standards are mandated by law • Draft guidance published by FDA in Jan. 2017 • Additional data requirements • No interchangeable biosimilar products licenced to date

FDA: Biosimilar and Interchangeable Products - Key Points

- **Different and distinct statutory** approval requirements for biosimilar vs. Interchangeable products (IC) products
  - IC product is **biosimilar**, and has additional data requirements
    - "**Expected** to produce the **same clinical result**… **any given patient**"
    - "Risk in terms of safety or diminished efficacy of **alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch"
  - These additional data elements allow FDA to evaluate whether the product is **one that may be substituted** for the reference product without consulting the prescriber
- FDA has described its thinking in guidance as to how the IC standards could be addressed though certain showings, data and information
  - Onus is on the Applicant to choose their approach, and provide adequate support for their approach in addressing these additional requirements

Compare Multiple Switches With Continued Treatment



- undergoing repeated switches (GP2015 and Enbrel) adopted from the Sandoz presentation to Arthritis Advisory Committee Meeting on July 13, 2016

Switching

Health Canada's position

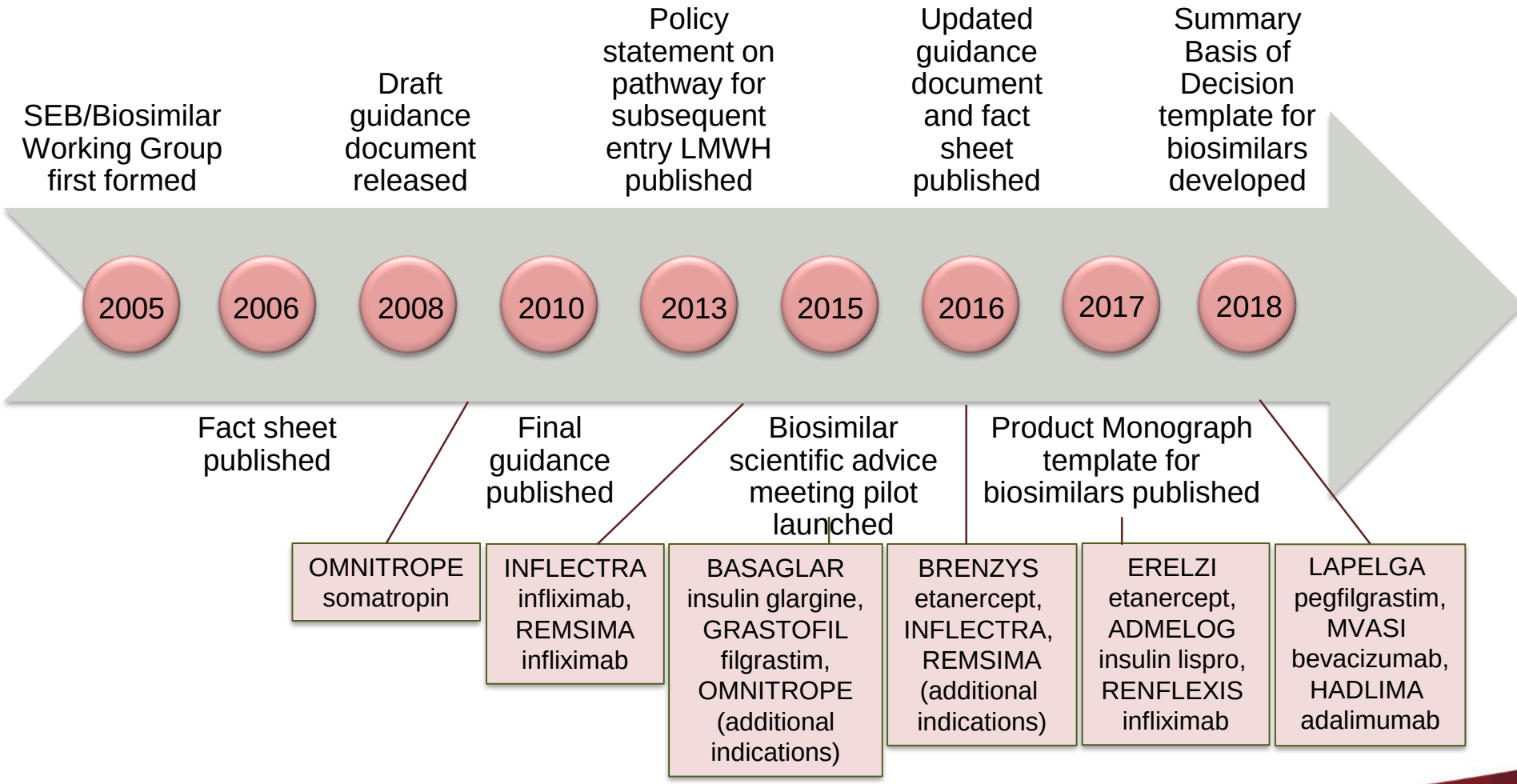
- Health Canada does not require switch study from a reference biologic drug to a biosimilar for the purpose of market authorization
- Health Canada recommends that a decision to switch a patient being treated with a reference biologic drug to a biosimilar, or between any biologics, be made by the treating physician in consultation with the patient and take into account any policies of the relevant jurisdiction

Conclusions

When Health Canada/regulatory agencies authorize the 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 may receive all or some therapeutic indications of the reference product

History of Biosimilars Regulation in Canada



Thank you

Merci

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