Health Canada Santé Canada

Canada

Regulatory Framework for Subsequent Entry Biologics (SEBs) in Canada

CAPRA Montreal Dinner Meeting
April 7th 2016

YOUR HEALTH AND SAFETY... OUR PRIORITY.

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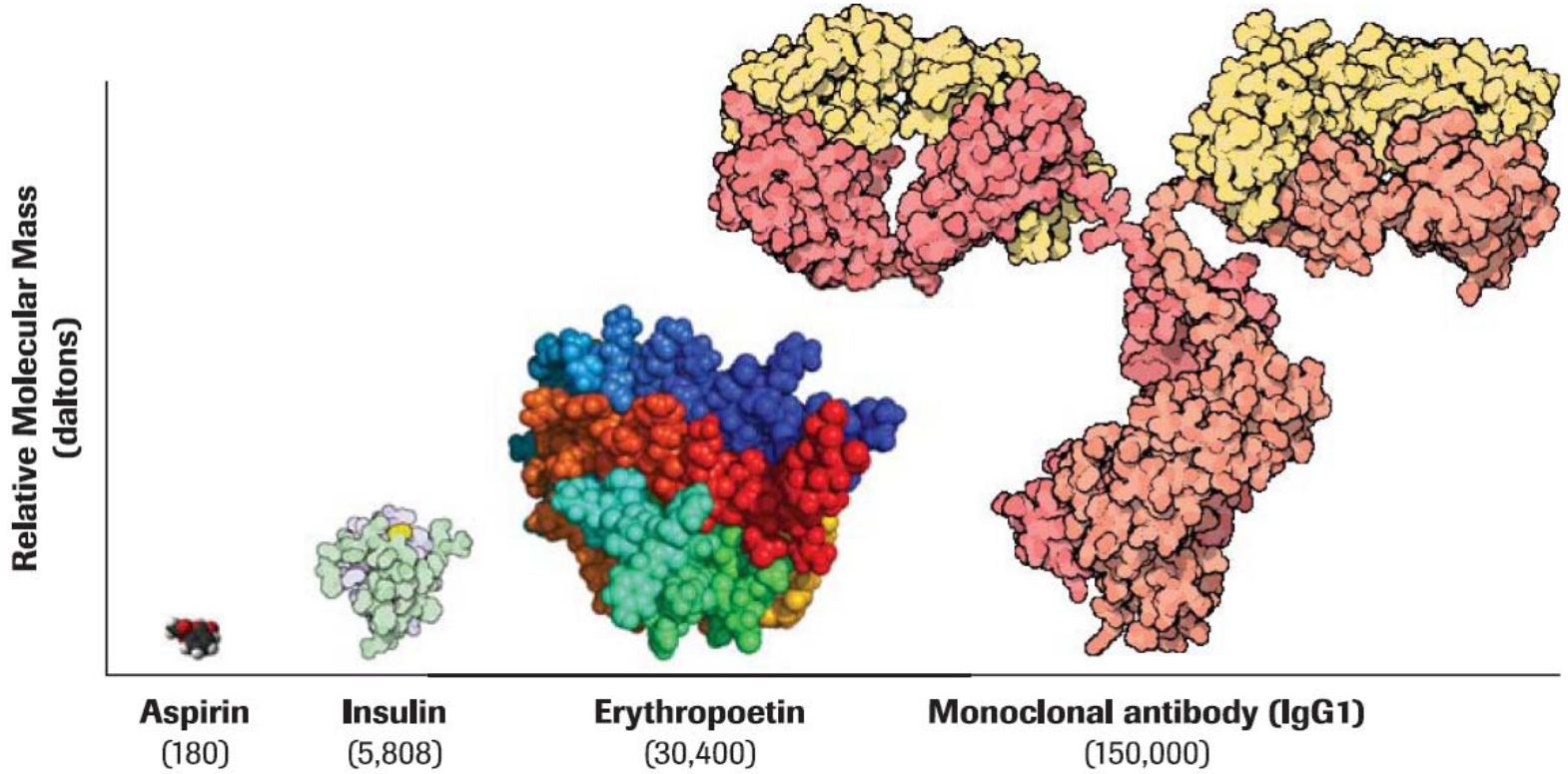
Overview of Presentation

- Biologics and Subsequent Entry Biologics (SEBs)
- Canadian Regulatory Framework for SEBs
- SEB Submission Requirements
- Revisions to Health Canada's SEB Guidance
- Jurisdictional Approaches to SEB (Biosimilar) Regulation

Biologics and Subsequent Entry Biologics (SEBs)

Biologics

Biologics, unlike pharmaceuticals, are derived from a variety of expression systems (e.g. human, animal, microorganism, cell culture) or produced using recombinant DNA technology.



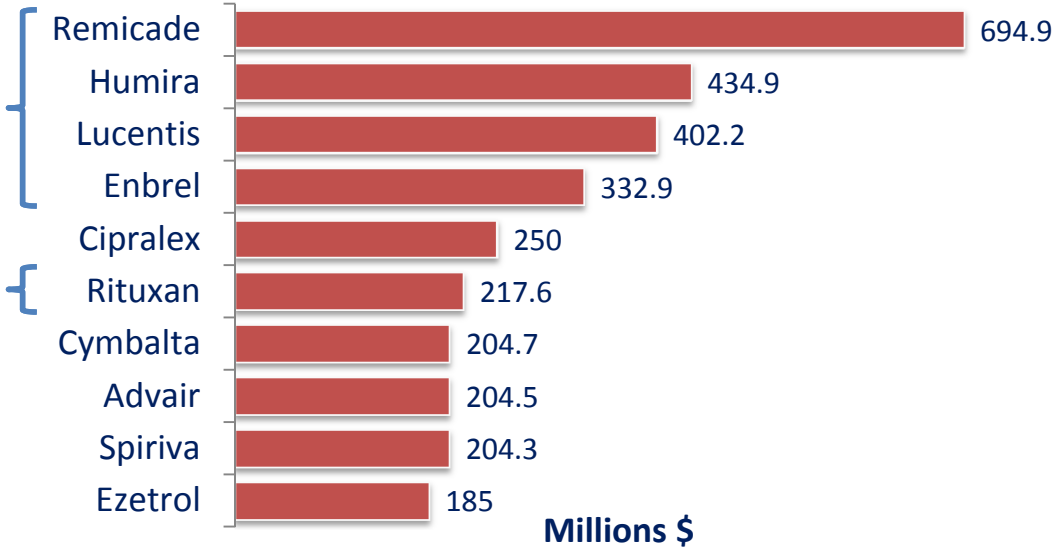
Revers and Furczon, CPJ, 2010, 143:134
http://cph.sagepub.com/content/143/3/134

Differences Between Biologics and Pharmaceuticals

Biologics	Pharmaceuticals
Large molecular weight	Low molecular weight
Species specific	Species independent
Immunogenic	Non-immunogenic (generally)
Degraded	Metabolized
Exaggerated pharmacology	Toxicity
Target-mediated drug disposition	Non-target-mediated drug disposition

Biologic Sales in Canada

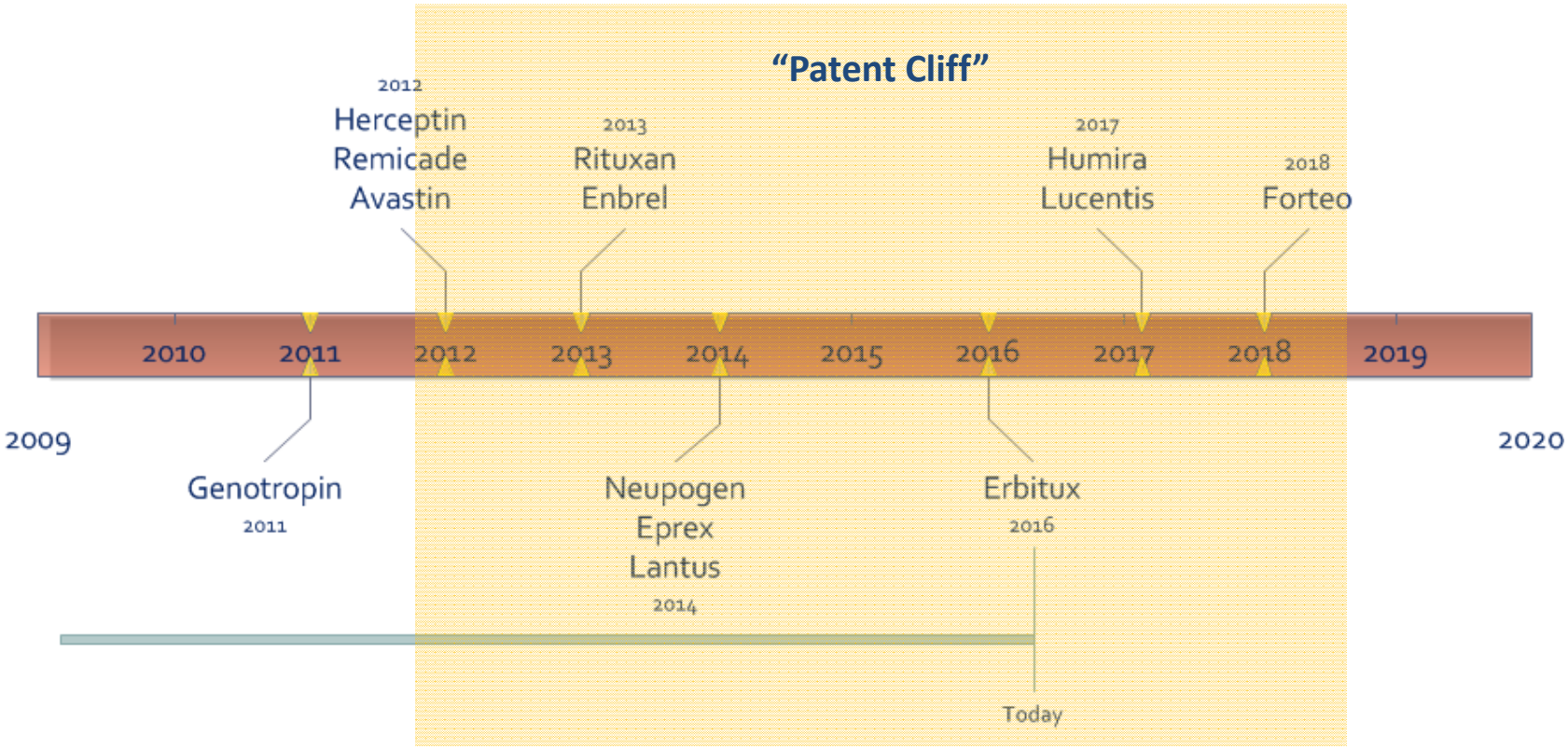
Top selling drug products in Canada, 2012



- **Biologics made up 5 of the top 10**
  - **Expiring patents for all 5!**

Adapted from Industry Canada - https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html

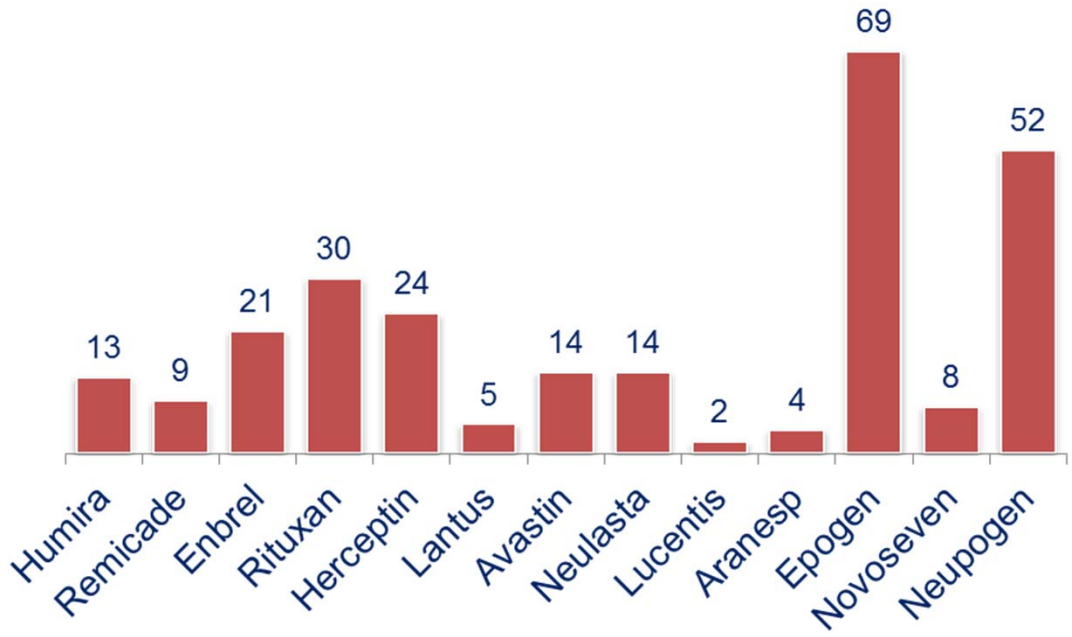
Biologic Patent Expiry in Canada



Information gathered from CIPO - http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/Home

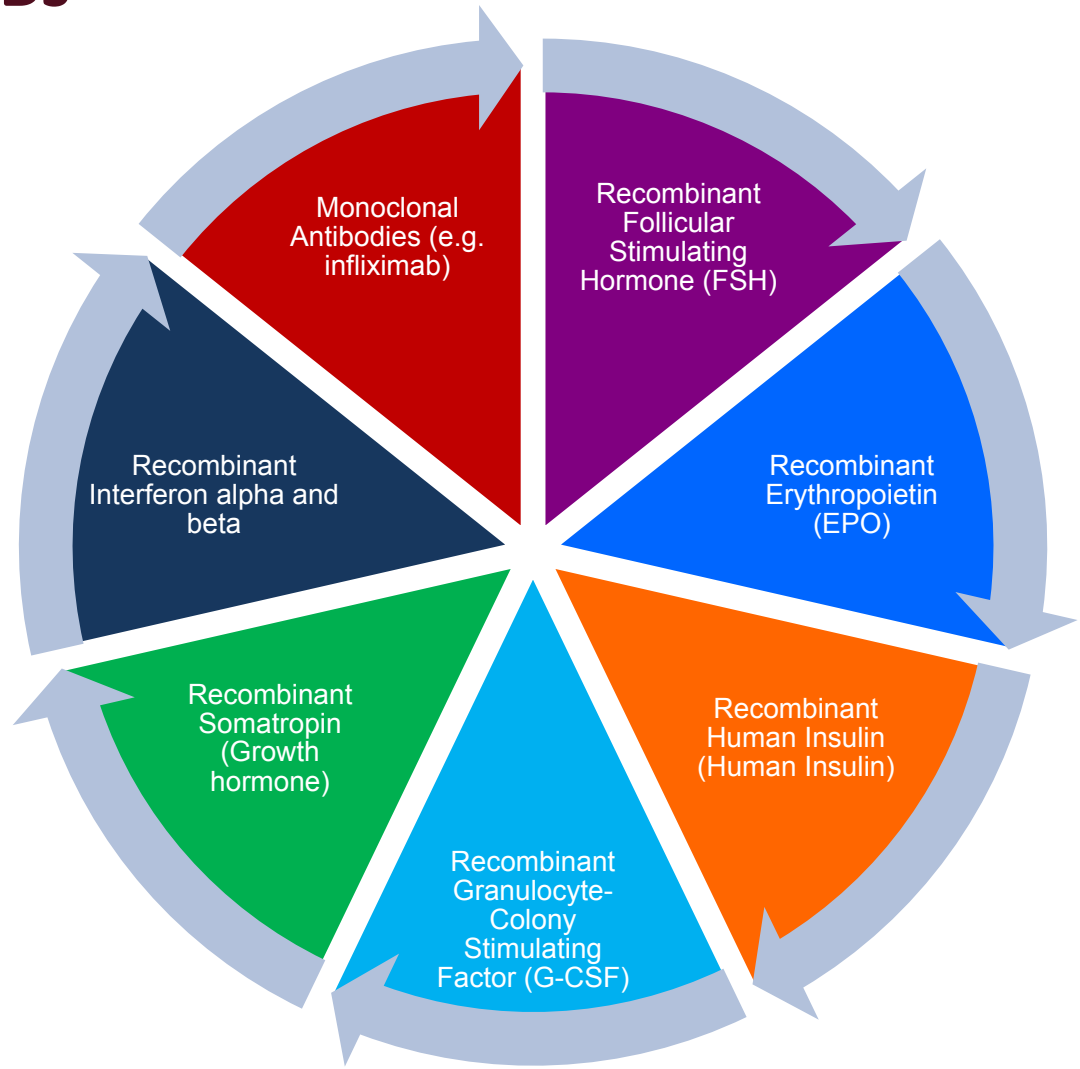
Biosimilar Development Pipeline

- **Today, there are numerous biosimilar development programs underway**
  - **Multiple programs for each of the top selling biologics**



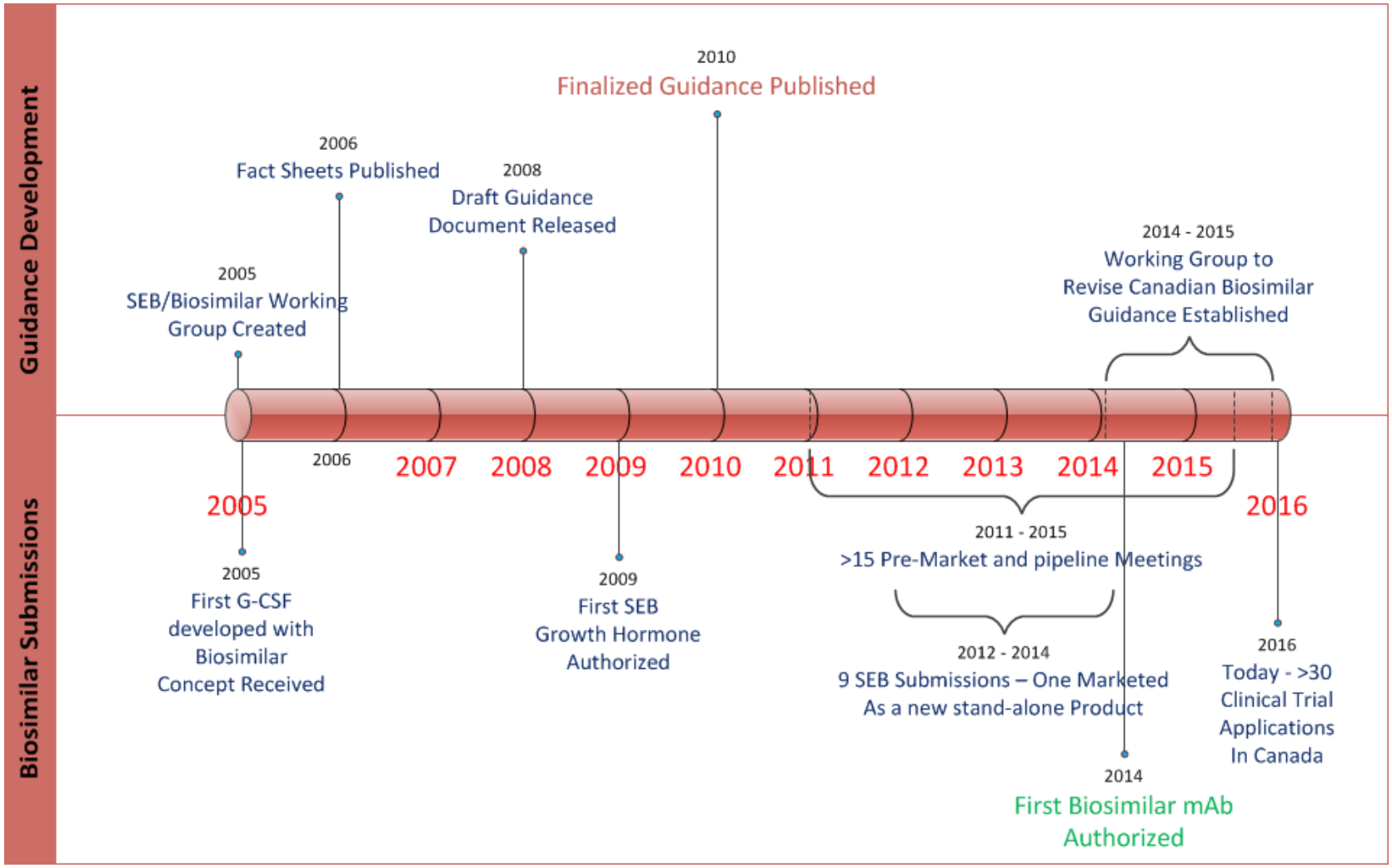
Adapted from: BioProcess International, 2013, 11(6):16-23
US Federal Trade Commission

Types of SEBs



Canadian Regulatory Framework for SEBs

History of SEB Regulation in Canada



What are Biologics?

No specific definition for “biologic” in the Canadian Regulations

- Products listed on Schedule D of the *Food and Drugs Act, which includes* individual products, product classes, references to particular sources, and methods of production, are termed biologics.

- Essentially unique relative to pharmaceuticals as they are derived from metabolic activity of living organisms, are inherently more variable, and are large and structurally complex.

- “The Process is the Product” is often used to describe the importance of application of risk management throughout the process such as for pathogens in starting materials or the growth of adventitious agents such as viruses during manufacturing.

Regulations for Biologics

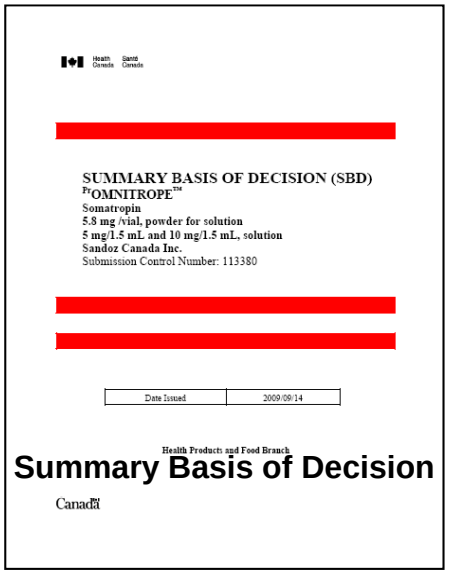
- ***Food and Drugs Act***
  - Schedule D – Biologic Drugs List
  - Section 12 - Requirement that the premises in which the drug is manufactured and the process and conditions of manufacture therein are suitable to ensure that the drug will not be unsafe for use.

- ***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

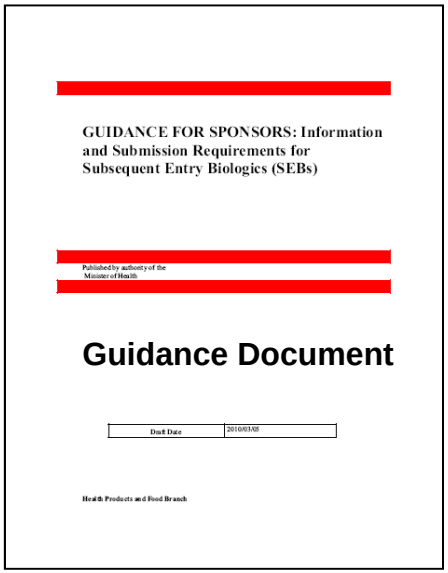
SEB Regulatory Framework

Applicable to amendment

Applicable to SEBs without amendment
- C.08.002(2)
- C.08.004.1(3)(a) & (3)(b)



Possible without policy
- NOC (Sept 14, 2009)



Provides transparency
- Draft March 27, 2009
- Final March 5, 2010
- Revised 2016

Subsequent Entry Biologic

A biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug (RBD).

An SEB relies in part on prior information regarding safety and efficacy due to the demonstration of *similarity* to the RBD.

The demonstration of similarity can be the basis for accepting a reduced clinical data package.

Also referred to as “biosimilar” internationally.

Regulations for SEBs

Same pathway as for New Drugs:

(a) Regulatory pathways

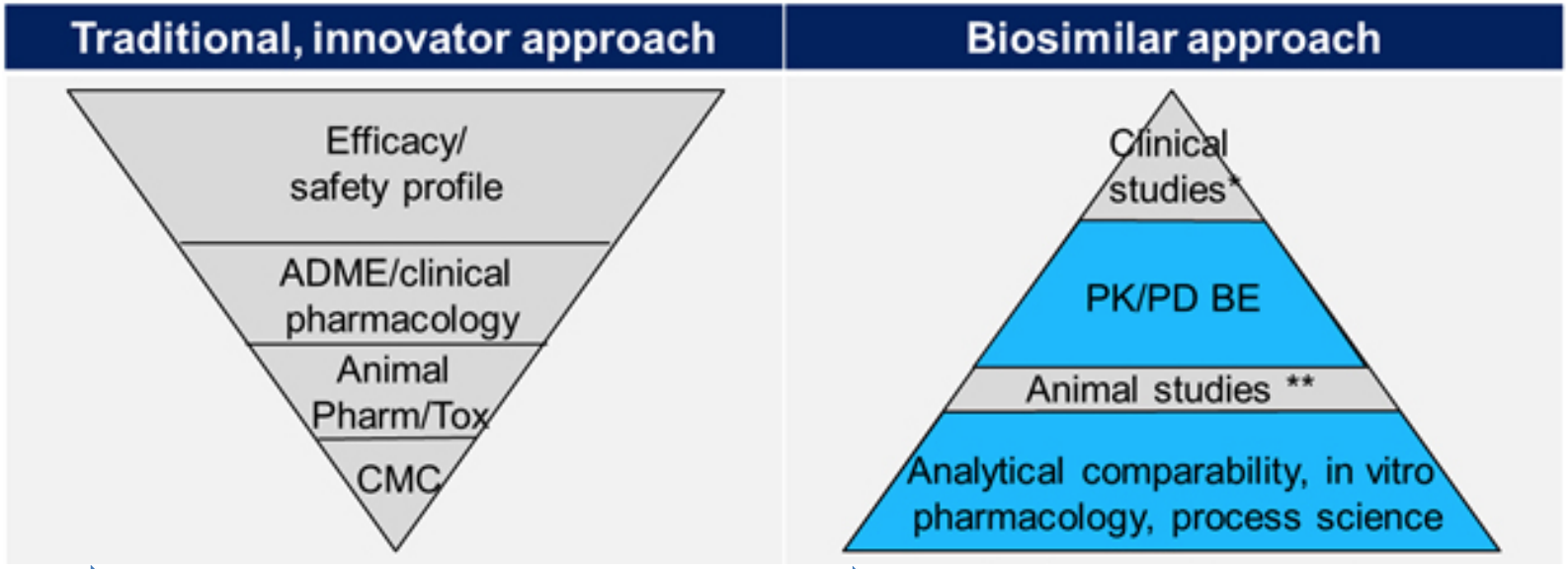
- C.08.002 New Drug Submission pathway
- ~~C.08.002.1 Abbreviated New Drug Submission pathway~~

(b) Intellectual property protections

- C.08.004 (*6 years data protection/8 years market exclusivity*)
- Patented Medicines (Notice of Compliance) Regulations (*patent linkage*)

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

Innovator vs. SEB Approaches



Establish de novo efficacy/safety

Establish similarity to the reference drug

Adapted from http://www.santo.kz/en/doctors/publishing/european-experience-with-biosimilars/

SEB Development

- 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.

SEB Submission Requirements

Submission Packages: Innovator vs. SEB

Quality

Drug substance
- Manufacture
- Characterisation
- Control
- Reference standard
- Container
- Stability

Drug product
- Description
- Development
- Manufacture
- Control
- Reference standard
- Container
- Stability

Nonclinical

Pharmacology
- Primary pharm.
- Secondary pharm.
- Safety pharm.
- Interactions

Pharmacokinetics
- ADME
- Interactions

Toxicology
- Single dose
- Repeat dose
- Genotoxicity
- Carcinogenicity
- Reproduction
- Local tolerance

Clinical

Pharmacology

Pharmacokinetics
- Single dose
- Repeat dose
- Special populations

Efficacy and safety
- Dose finding
- Schedule finding
- Pivotal
  - Indication 1
  - Indication 2
  - Indication 3

Immunogenicity

Risk Management Plan
- PvP

Submission Packages: Innovator vs. SEB

Quality

Drug substance
- Manufacture
- Characterisation
- Control
- Reference standard
- Container
- Stability

Drug product
- Description
- Development
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Nonclinical studies

Pharmacology
- Primary pharm.
- Secondary pharm.
- Safety pharm.
- Interactions
- Pharmacokinetics
- ADME
- Interactions

Toxicology
- Single dose
- Repeat dose
- Genotoxicity
- Carcinogenicity
- Reproduction
- Local tolerance

Clinical studies

Pharmacology
Pharmacokinetics
- Single dose
- Repeat dose
- Special populations

Efficacy and safety
- Dose finding
- Schedule finding
- Pivotal
  - Indication 1
  - Indication 2
  - Indication 3

Immunogenicity
Risk Management Plan
- PvP

Demonstration of Similarity

Comparison of Drug Substance and/or Drug Product

- Physicochemical properties
- Biological activity
- Immunochemical properties
- Specifications
- Stability

Reference Biologic Drug

Decision to Issue a Notice of Compliance for an SEB

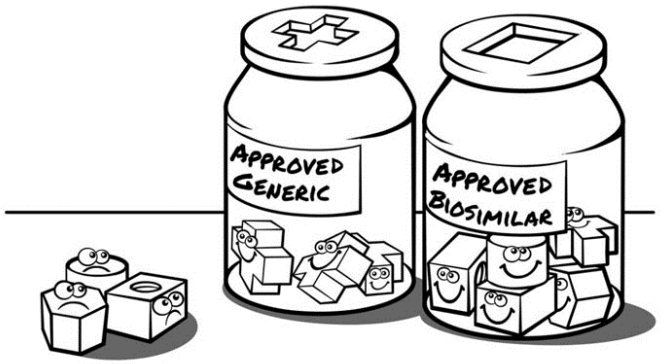
A final determination to issue an NOC is based upon a benefit/risk decision after considering all of the safety, quality and efficacy data submitted by the sponsor.

- **Note:** This is not different than what is done for all new drugs.

Key Messages

- SEBs rely on comparator in addition to their own safety, quality and efficacy data

- SEBs ≠ generic biologics



www.coalesce.co.uk

- SEBs are not linked to their reference products in the way of generic pharmaceuticals
  - They cannot claim "pharmaceutical equivalence", "therapeutic/clinical equivalence", or "bioequivalence"
  - SEBs are "New Drugs" according to the Food and Drugs Regulations

Revisions to Health Canada's SEB Guidance

Update: Guidance Review

- The SEB-WG has performed an internal review of the *2010 Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)*.

- The review was based on experiences over the past five years as well as international developments in the regulation of SEBs.

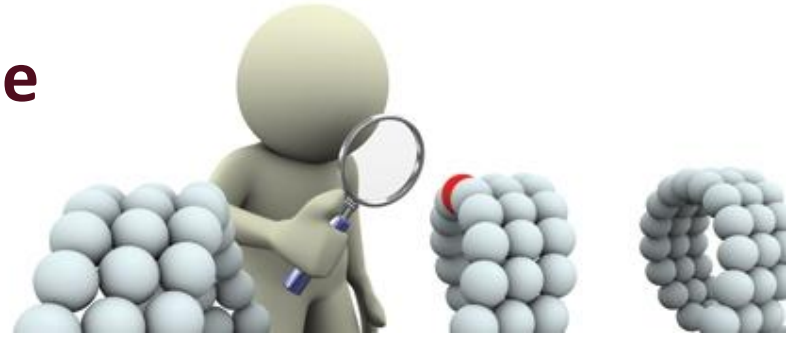
- Many of the proposed revisions reflect guidance provided by Health Canada to SEB sponsors in relation to submissions or queries.

Key Revisions to the SEB Guidance

Selection of the Reference Biologic Drug:

SEB Guidance 2010	Revised SEB Guidance 2016
➢ Sponsor must name the reference biologic drug authorized in Canada to which the SEB will be subsequent. ➢ The submission should explicitly explain the link between the non-Canadian reference and Canadian products.	➢ Provide clarity on establishing a link between the non-Canadian reference and Canadian reference biologic drug: - The non-Canadian reference biologic drug should have the same medicinal ingredient(s), dosage form(s) and route(s) of administration as the Canadian version. - Rationale and/or clinical study or bioavailability/bioequivalence study may be requested.

Key Revisions to the SEB Guidance



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Non-Clinical Studies

SEB Guidance 2010	Revised SEB Guidance 2016
➢ Appropriate comparative non-clinical studies should be conducted as per ICH S6(R1). ➢ In vitro studies and in vivo studies; at least one repeat-dose toxicity study.	➢ Comparative non-clinical studies could be replaced by a single arm non-clinical study in a relevant species prior to the first-in-human study, if similarity is well established by analytical/biological characterization and extensive in vitro studies.

Key Revisions to the SEB Guidance

Clinical Studies

SEB Guidance 2010	Revised SEB Guidance 2016
➢ Comparative PK studies using acceptable criteria for the determination of similarity. ➢ Design of comparative clinical trials and clinical comparability margins of the primary efficacy endpoints should be given careful consideration and justified on clinical grounds. ➢ Equivalence trials are preferred over non-inferiority trials.	➢ The most **sensitive population**, in which potential differences between an SEB and a reference product can be most easily detected and study outcomes can be used to support extrapolation of indications, should be considered in clinical trial design. ➢ The use of a **clinically relevant and sensitive endpoint** to detect potential differences.

Key Revisions to the SEB Guidance

Immunogenicity

SEB Guidance 2010	Revised SEB Guidance 2016
➢ Immunogenicity should be evaluated using appropriately designed clinical studies with state-of-the-art methods, taking into consideration the potential impact on both efficacy and safety. ➢ A rationale on the strategy for testing immunogenicity should be provided. ➢ Assay methods should be validated, and able to characterize antibody content and type of antibodies formed (neutralizing Abs and Abs with cross-reactivity).	➢ Methods used should be **sensitive** to detect differences in immunogenicity between the reference drug and the SEB.

Key Revisions to the SEB Guidance

Post-Market Requirements

SEB Guidance 2010	Revised SEB Guidance 2016
➢ ADR reporting is required post-market under section C.01.016 of the Food and Drug Regulations. ➢ Periodic Safety Update Reports (PSURs) should be submitted in the pharmacovigilance plan.	➢ Periodic benefit-risk evaluation reports (PBRERs) or PSURs should be submitted and be consistent with ICH E2C(R2). ➢ Labelling changes for product class type-specific safety information. ➢ Under certain circumstances, HC will consider for review a SNDS for an SEB that relied on the previously demonstrated similarity provided in the original NDS to support a change.

Key Revisions to the SEB Guidance

Extrapolation

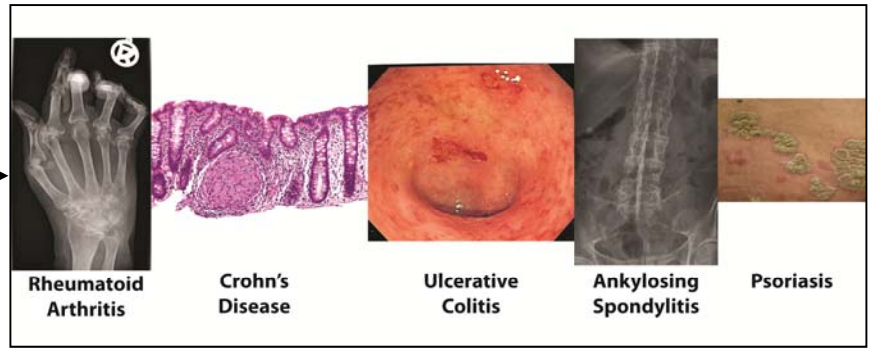
Revised SEB Guidance 2016
➢ A new section on indication extrapolation was added.

Indication Extrapolation

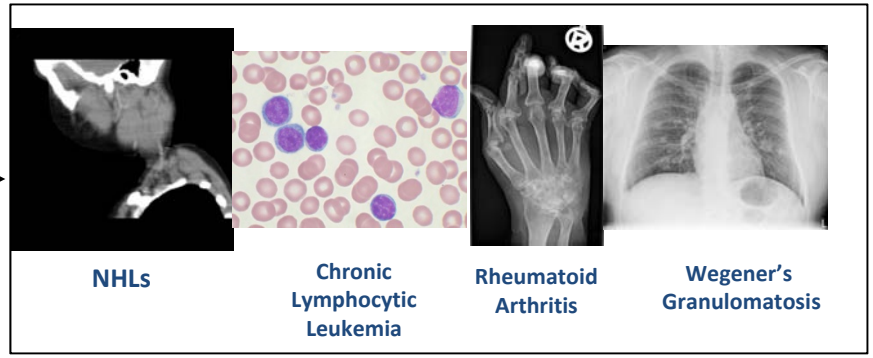
A single biologic may be indicated for use in a variety of diseases…

Infliximab

Indicated diseases



Rituximab



Considerations for Extrapolation

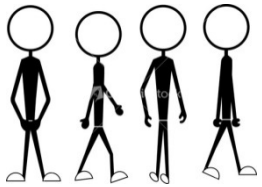
- The innovator has established efficacy and safety for each indication.
- An SEB does not have to re-establish the *de novo* benefit/risk provided it can be considered highly similar from a CMC perspective.
- The purpose of the clinical program should be to establish that minor (acceptable) differences between two products do not cause clinically meaningful differences in efficacy and/or safety.
- This may not require the investigation of the SEB in all of the indications → clinical data or rationales may address the principles that HC uses to determine whether extrapolation is appropriate.
- However, certain factors should be taken into account and may require a clinical study/ies…

Extrapolation Checklist

- The product similarity is demonstrated through a detailed and comprehensive comparative product characterization.
- There is a good understanding of the mechanism(s) of action of the biological product, and the similarities and differences in the mechanism(s) of action that play a role in each of the indicated conditions for which a sponsor applies.
- There is also a good understanding of the pathophysiological process(s) of the indicated diseases, and the differences and similarities between them.
- The safety profiles in the respective conditions and/or populations are comparable.
- There is adequate clinical experience with the reference drug.

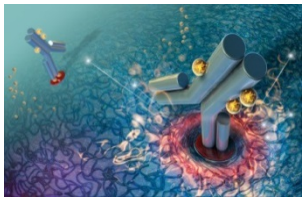
Factors to Be Considered for Extrapolation

STUDY POPULATION: AGE, SEX & ETHNIC ORIGIN

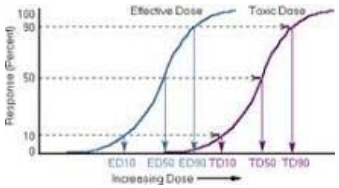


PIVOTAL TRIAL DURATION, ROUTE OF ADMINISTRATION & DOSAGE RANGE

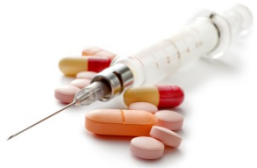
SAFETY & IMMUNOGENICITY PROFILE



PK/PD PROFILE



MONOTHERAPHY & COMBINATION THERAPY



Key Revisions to the SEB Guidance

Consultation with the Biologics and Genetic Therapies Directorate

Revised SEB Guidance 2016
➢ A new section which promotes early consultation with Health Canada, as well as the launch of three year pilot for SEB Scientific Advice Meetings to allow for discussion of an SEB with Health Canada early in the development process.

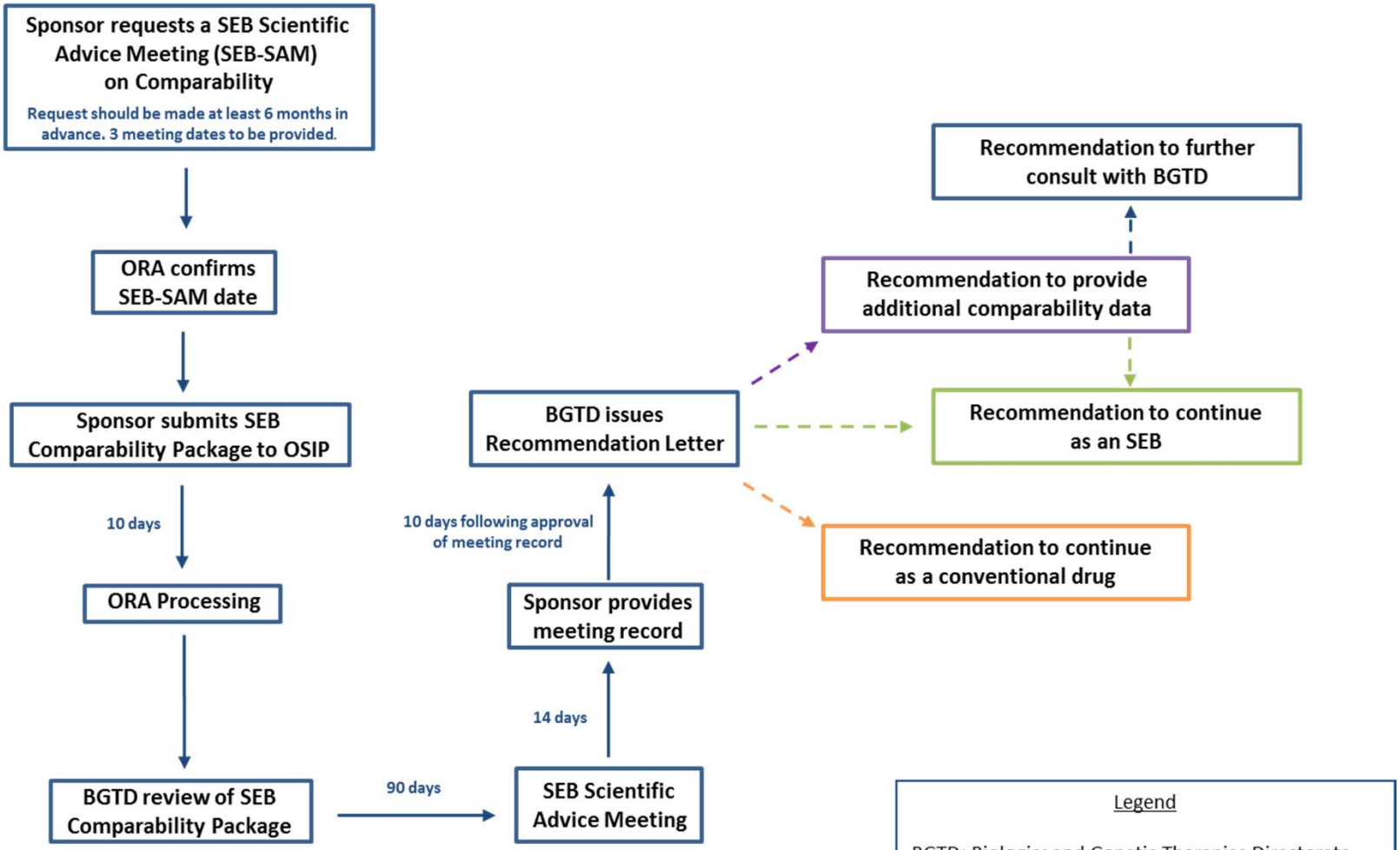
SEB Scientific Advice Meeting (SAM) - Issue of Timing

- Health Canada's experience with the regulatory review of SEBs has triggered the need to implement a step-wise review approach for these products.

- Pre-submission meetings for SEBs occur late in the development process, thereby leaving both sponsor and Health Canada to deal with the consequences of not understanding the chosen development path.

- The timing of Health Canada's advice is not in-line with that of other regulators (i.e. U.S FDA and EMA), that allow for a step-wise review approach.

SEB Scientific Advice Meeting (SAM)



SEB Scientific Advice Meeting (SAM)

The SEB-SAM will:

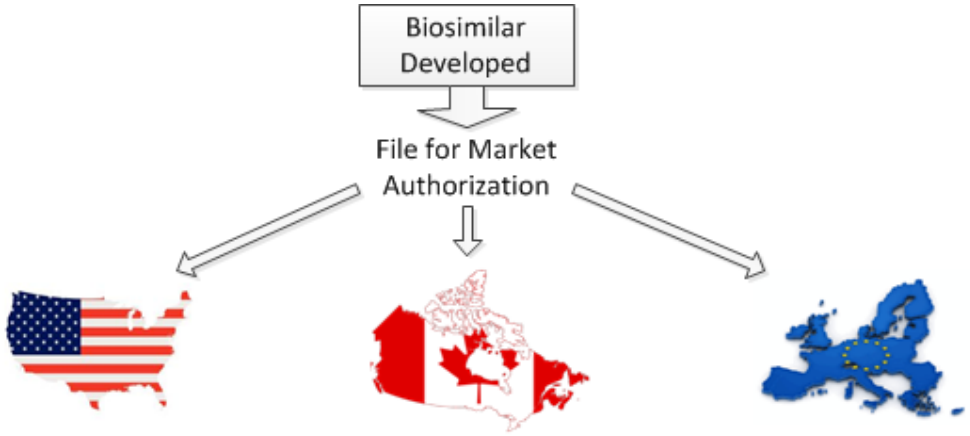
- provide the SEB sponsor with a clear mechanism to seek advice from Health Canada early in the SEB development process;
- provide an opportunity to thoroughly review the comparability package to determine the degree of similarity between the SEB and RBD;
- further align a step-wise review approach which mirrors the SEB drug development process – similar to approaches used by U.S. FDA and EMA;
- allow for Health Canada to recommend whether the SEB sponsor should a) continue as a SEB submission, or b) file as a traditional new drug.

Moving Forward

- External consultation launched from December 7, 2015 to February 15, 2016.
- Health Canada will consider comments received and prepare a final SEB Guidance for publication.

Jurisdictional Approaches to SEB (Biosimilar) Regulation

International Pathways for Biosimilars



- Legislative Pathway for the approval of Biosimilars
- Public Health Services Act 351(k) abbreviated licensure pathway
- declaration of biosimilarity or interchangeability possible

- Reviewed and Authorized under the same regulations as New Drugs
- No specific abbreviated legislative pathway
- FDA & R – C08.001
- Guidance for Subsequent Entry Biologics (SEBs) sets out SEB policy
- Regulated as a New Drug after approval – no link to reference

- Regulatory framework grounded by legal basis for the authorization of similar biological medicines
- Requirements set forth in Article 10(4) of Directive 2001/83/EC and annex
- Various guidelines for specific product types as well as overarching guidance

Interchangeability

FDA 	HC 	EMA 
While the FDA can designate a biosimilar as interchangeable with its reference originator product, the individual states govern the practice of pharmacy including drug substitution laws.	**Health Canada does not declare interchangeability neither for generics nor for biosimilars.** **Interchangeability remains a provincial decision in Canada.**	In the EU, decision on the interchangeability or substitution of biosimilars and originator biologics is not made by EMA but at each national level. (Fifteen nations have prohibited automatic substitution)

Concerns with Automatic Interchangeability

- **Quality:**

  Two biologics cannot be exactly the same.

- **Safety:**

  As a consequence of their complexity and their impurity profiles, could give rise to different and/or unexpected clinical consequences.

- **Immunogenicity:**

  Cannot be fully predicted using preclinical/clinical studies. Repeated switches between the biosimilar and the originator product may increase immunogenicity with potentially negative effects.

- **Reliability of post-market traceability:**

  Is necessary when an adverse drug reaction occurs.

Summary

- SEBs are not “generic” biologics; they are regulated like other new biologics (as NDS).
- SEBs are compared with a suitable reference in a stepwise approach, and authorization is based on the demonstration of similarity to the reference drug.
- SEB submission package can be reduced, and is based on the residual uncertainty of the SEB product and history of the reference product.
- Extrapolation is possible when the appropriate data and rationales are provided (case-by-case).
- Biosimilar regulatory pathway in Canada differs from other regulatory jurisdictions (e.g. FDA and EMA).
- HC published the SEB guidance document in 2010, and the revised draft SEB guidance was issued in 2016. As new scientific information become available, regulatory requirements and recommendations for SEB will continue to evolve.

SEBs Authorized in Canada

Product name	Active Substance	Therapeutic area	Authorization date
Omnitrope	somatropin	Growth hormone deficiency in adults and children	20 Apr 2009
Remsima	infliximab	Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis	15 Jan 2014
Inflectra	infliximab	Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis	15 Jan 2014
Omnitrope	somatropin	Small for gestational age (SGA) Small for gestational age (SGA) Turner Syndrome (TS)	08 May 2015
Basaglar	insulin glargine	Type 1 diabetes mellitus Type 2 diabetes mellitus	01 Sep 2015
Grastofil	filgrastim	Prevention/treatment of neutropenia in various indication	07 Dec 2015

Thank you
Merci

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