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Considerations on Subsequent Entry Biologics (SEBs or biosimilars)

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Points for discussion

- What are SEBs? Is the name important?
- Differences between pharmaceuticals and biologicals: scientific and regulatory concepts in the Canadian context
- Differences between pharmaceuticals and biologics
- Terms used: substitutability, interchangeability
- Concerns regarding safety and follow-up
- Extrapolation and issues that may be raised
- Are SEBs safe, effective and of high quality?
- Some specific comments
- Jurisdictional issues and approaches
- Conclusions

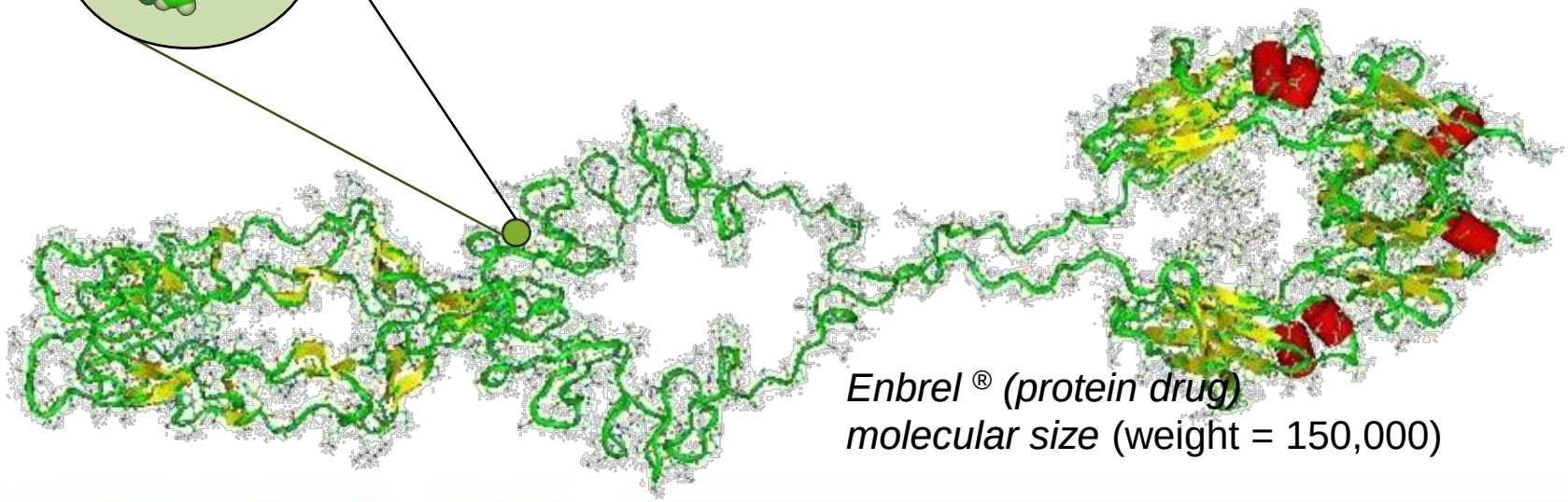
What are SEBs? Is the name important

- SEBs are “copies” of original drugs, in a manner similar to “generic” drugs
- The name distinguishes them from generics because:
  - Generics must be identical to the reference product
  - SEBs are highly similar to the reference chosen
  - As all biologicals, SEBs are synthesized in living cells, are highly complex and may have some variation in each batch that is manufactured
  - At least one clinical study is needed to compare the SEB to its reference
  - The label and package insert are, for the most part, unique to each product
  - Once found acceptable, each SEB becomes a self-standing drug product in its own right, and must be treated as such

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

Examples of biological products: hormones, blood products, cytokines, growth factors, vaccines, gene/cellular therapies, fusion proteins, monoclonal antibodies, etc.

Sensipar ® (chemical drug)
molecular size (weight = 393)



Enbrel ® (protein drug)
molecular size (weight = 150,000)

Differences between Pharmaceuticals and Biologics

	Pharmaceuticals	Biologics
Method of synthesis	Chemical	Living organism or cells
Molecular Size	Small/er	Large/er
Structure	Usually fully known	Complex, frequently partially unknown
Susceptibility to contamination during manufacturing	Low	High
Sensitivity to physical factors (e.g., heat, light)	Low	Higher
Manufacturing methods	Relatively simple	Complex

Differences between SEBs and Generics

	SEBs	Generics
Regulatory Pathway	NDS	ANDS
Drug Substance	Similar to reference	Identical to reference (Pharmaceutical equivalence)
Comparative non-Clinical	Required	Not required
Comparative PK/PD	Similar PK/PD profile	Formal declaration of bioequivalence
Comparative Clinical Trial	At least one	Not required
Efficacy/Safety	No meaningful therapeutic difference	Therapeutic equivalence
Indication extrapolation	Case by case	Automatic
Interchangeability	Generally no	Generally yes

Regulatory Pathways for Biosimilars

- It is widely accepted by global regulatory agencies and the biotech industry that biosimilars cannot be identical copies of the innovator products
- Inherent differences require different regulatory considerations and guidelines tailored to biosimilars
- Many countries as well as the WHO have published guidance documents on how to regulate biosimilars
- In Canada, biosimilars are regulated as New Drugs by comparison with a reference product previously authorised and marketed in Canada

Substitutability, interchangeability

- Different countries and parties use these terms to mean different things or more or less to express the same concept
- Definition in dictionary is very similar for both terms: the use will depend on the “legal” definition for each region or jurisdiction
- Overall, experience with SEBs/biosimilars is accumulating internationally
- Each country has dealt with any administrative and health care issues within the limits allowed by their own systems
- Not all uses for an SEB are authorised in each country: depends on the authorities to regulate a specific therapeutic area.
- The decision to treat with an originator (reference product) or a SEB is considered to be a health care decision, between a patient and her/his physician
- True therapeutic interchangeability generally requires specially designed studies

Concerns with Automatic Substitution/ Interchangeability

- **Quality:** Two biologics cannot be exactly the same. Minor differences in the production of biosimilars can lead to profound differences in clinical activity and side effect profiles that may not become apparent until the product is in widespread use
- **Safety:** As a consequence of their complexity and their impurity profiles, automatic interchangeability of biologics or biosimilars could give rise to different (and sometimes unexpected) clinical consequences
- **Immunogenicity:** The immunogenicity of biosimilars cannot be fully predicted using preclinical/clinical studies. Repeated switches between the biosimilar(s) and an originator's product may increase immunogenicity with potentially negative effects
- **Reliability of post-market traceability:** Is necessary when an adverse drug reaction occurs

Post-market traceability: Biosimilars Made by Many Companies

Sandoz, the generic drug division of Swiss drug giant Novartis AG, is determined to lead the biosimilar field

Amgen Inc, the world's largest biotechnology company, and generic drugmaker Watson Pharmaceuticals Inc will work together to develop and sell biosimilar versions of several biotech cancer drugs

Pfizer, the world's biggest pharmaceutical firm, will work with Biocon, India's largest biotech company, to bring "biosimilar" insulin treatments to market

Merck & Co is to develop its own version of Pfizer's ageing arthritis drug Enbrel with a South Korean manufacturer, Hanwha

Korean electronics giant Samsung had entered into a biosimilars joint venture with US biotechnology company Biogen Idec

Apotex Inc., the largest Canadian-owned generic pharmaceutical company and Intas Biopharmaceuticals Limited of India have extended their business agreement to develop a biosimilar version of pegfilgrastim (PegG-CSF)

Interchangeability declaration by Health Canada

- Health Canada does not declare interchangeability: the approach is the same in this regard for generics as well as for biosimilars (Subsequent Entry Biologics (SEBs) in Canada
- Health care system: Interchangeability remains a Provincial decision
- In Clinical Practice**:** The decision to treat a patient with an originator's product or a biosimilar is within the authority of a qualified healthcare professional, and in the best interest of his/her patient/s
- In a 2010 letter to Provincial Drug Plans concerning its guidance on the market authorisation of SEBs, Health Canada stated as follows:
  - SEBs are not "generic" biologics and market authorisation of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug
  - Reminding drug plans that, as a result of manufacturing drift, Health Canada "… does not support automatic substitution of an SEB for its reference drug …"

Extrapolation

- Extrapolation consists in extending the use of a product to other related uses without specific studies
- Extrapolation is based on a set of principles that allows this to happen due to:
  - The high similarity demonstrated between two products
  - Minor, usually unimportant differences between two products may have clinical impact if not well defined
  - Similar mechanism of action for each condition or use considered for extrapolation
  - Mechanism of the disease/s to be treated by the SEB
  - Similarities in clinical experience
  - Type and design of the clinical trial/s, population and endpoints that are measured
  - Other elements such as route of administration, dosage and regimen, etc.

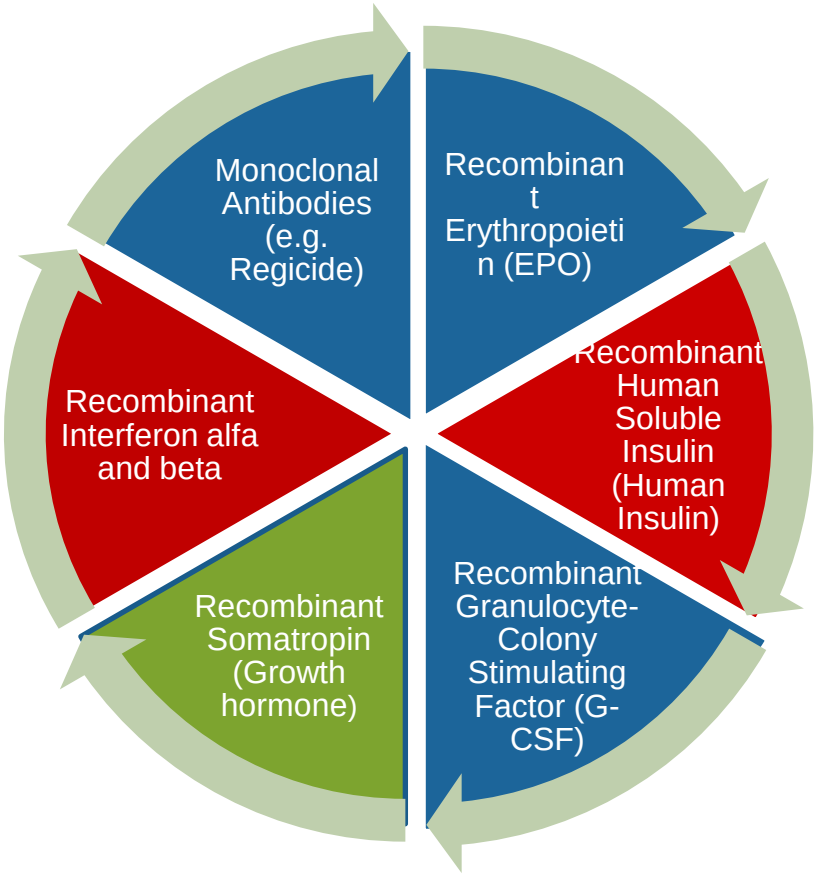
Are SEBs safe, effective and of high quality?

- SEBs are safe, effective and of high quality
- The quality information in the submission to the regulator is double: compares the SEB to the originator (reference biologic) and demonstrates the quality of the product itself
- Clinical trials are comparative between the reference and the SEB
- Comparisons are done simultaneously
- There are rules for conducting these clinical trials
  - Best population (most “sensitive”)
  - Best endpoints for studies (most “sensitive”)
  - Equivalence trial design
  - Non-inferiority is not as desirable
- Must have own labelling

Are SEBs safe, effective and of high quality?

- Similar immunogenicity
- Similarity in safety and immunogenicity compared with the reference product from a sufficient number of patients (> 100 patients) and a sufficiently long study duration (e.g., minimal follow-up period for chronically administered agents should be one year)
- Same/similar post-market requirements as the reference and any other biological
- At least, one clinical study to evaluate immunogenicity
  - Consider: the immunogenicity profiles observed with the reference product; both the severity of consequences and the incidence of immune response; population in which immune responses with adverse outcomes most likely to occur (e.g., more likely to observe immune responses in patients with autoimmune diseases than patients with malignancies)
  - Demonstrate that immunogenicity is not increased

Types of SEBs (Biosimilars)



First Canadian Authorized SEB: Omnitrope

Same Indications as Canadian reference product

Adult

- Authorized: Treatment of adults with either adult onset or childhood onset GHD

Pediatric

- Authorized: Treatment of children with growth failure due to growth hormone deficiency (GHD),
- **Not authorized** (Non-Canadian indications: Prader-Willi Syndrome, Small for Gestational Age, Turner Syndrome, and Idiopathic Short Stature)

Interchangeability vs. Substitutability (Global)

In the EU, decisions on the interchangeability or substitution of biosimilars and originator biologics are not made by EMA but at each national level (Fifteen nations have prohibited automatic substitution)	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 doesn't declare interchangeability neither for generics nor for biosimilars. Interchangeability remains a provincial decision in Canada.

Conclusions

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
	Non-clinical and clinical studies are reduced and are based on the residual uncertainty of the SEB product and history of the reference
	Extrapolation of Indications is case by case
	Automatic substitution is not recommended
	Risk Management Plans and Post-market monitoring are required

Thank You

Questions?

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