# CADTH Approach and Common Drug Review Process for Reviewing SEBs

## Montreal, June 6 2016

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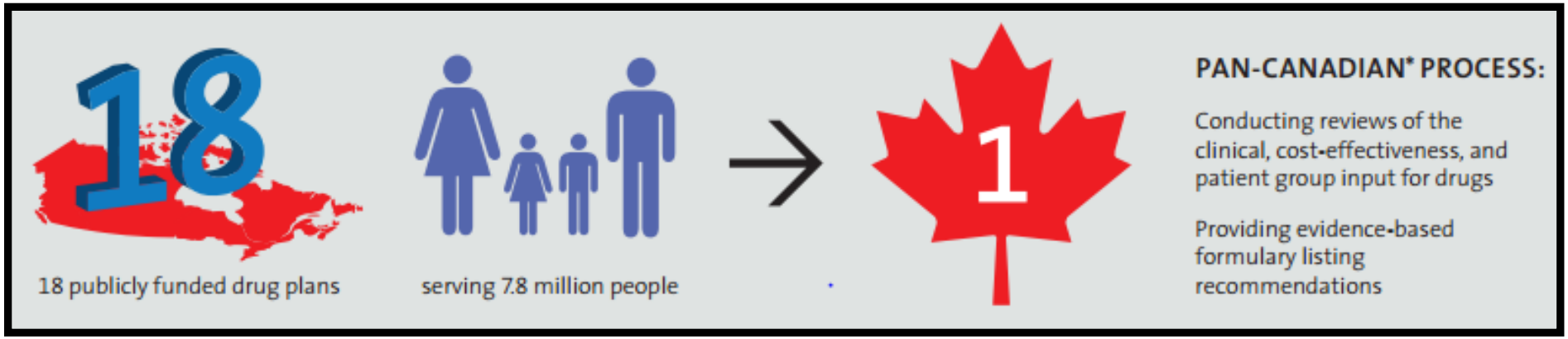
CADTH

# Outline of Presentation

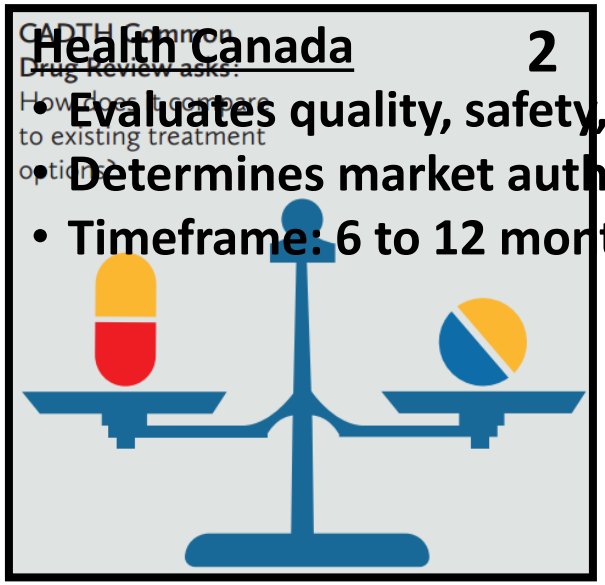
1. CADTH Common Drug Review (CDR)
    - Mandate, Scope, Key contributors
2. Why are SEBs reviewed by CDR?
    - Rationale, Benefits, Challenges
3. Overview of CADTH's process for SEBs
    - CADTH's experience with biosimilars
    - Submission requirements for biosimilars
    - Patient engagement
4. Conclusions and next steps

# CADTH Common Drug Review

- A pan-Canadian process that provides formulary listing recommendations to publicly-funded drug plans
  - *18 CDR-participating drug plans*
- Established in 2003 to reduce duplication across jurisdictions, maximize the use of limited resources, and enhance the consistency of drug reviews.
- Listing recommendations are provided by an appointed, national, expert advisory committee
  - *Canadian Drug Expert Committee (CDEC)*



# Regulatory Approval to Funding Decisions



**Health Canada**

- **Evaluates quality, safety, and efficacy**
- **Determines market authorization**
- **Timeframe: 6 to 12 months**

**Common Drug Review**

**Evaluates:**

- **Comparative effectiveness and cost-effectiveness vs. alternative treatments**
- **Timeframe: 5 to 6 months**

**6 to 12 months** | **5 to 6 months** | **Variable**

**Up to 3 months overlap**

**Recommendations (non-binding)**

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# What Drugs are Reviewed by CDR?

| Type | Description |
|---|---|
| **New Drug** | A new active substance that has not been previously marketed in Canada. |
| **New Indication** | A drug previously reviewed by CDR that has received an NOC for a new indication |
| **New Combination** | Two or more drugs that have not been previously marketed in Canada in that combination. |
| **SEBs** | Biologic drug demonstrating a high degree of similarity to an already authorized biologic drug (reference product). |

**Present since the inception of CDR in 2003**

**Pilot in 2009; Formally added in 2014**

**Out of scope:** Generic drugs, and line extensions as defined by CADTH for the purpose of CDR

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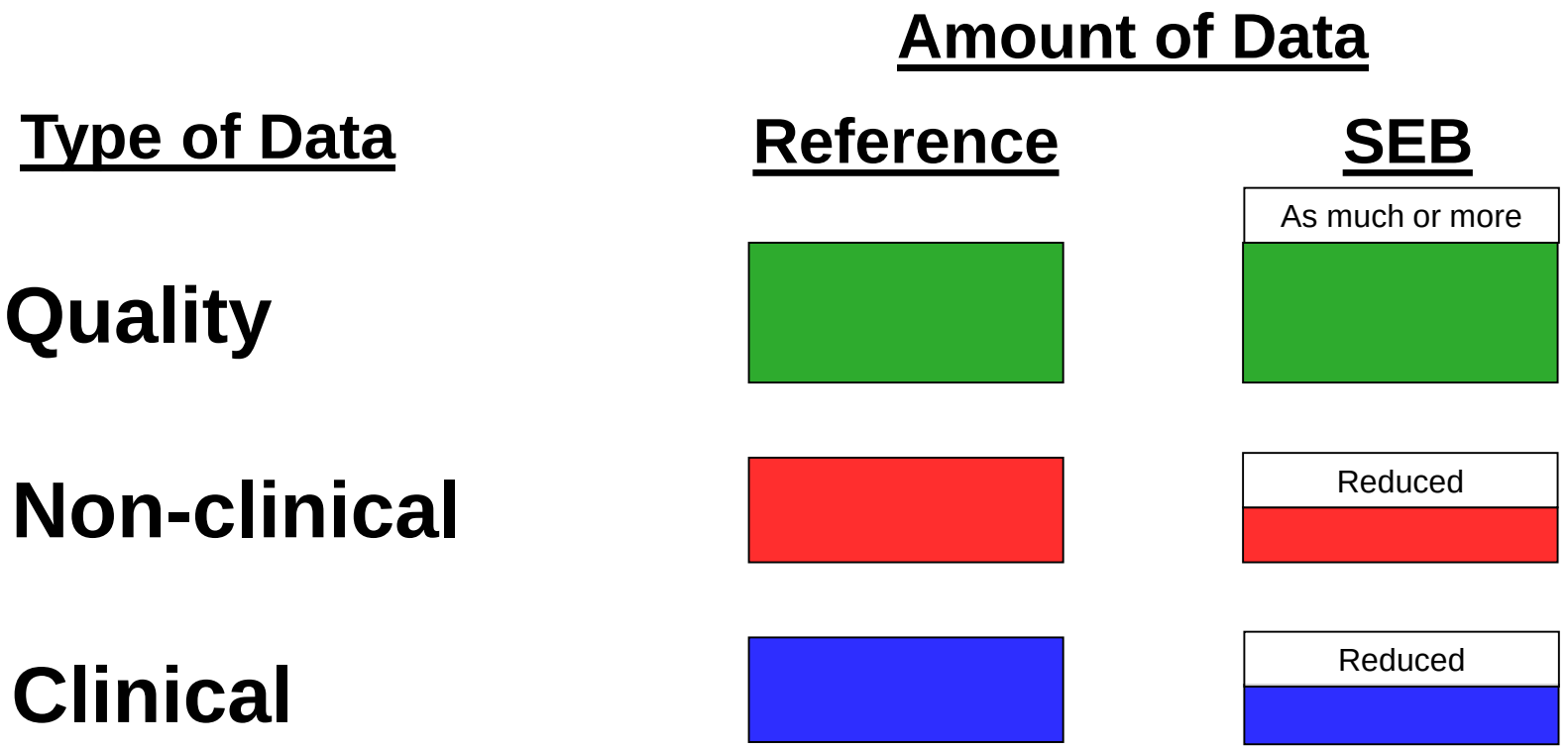
**CDR** = Common Drug Review; **NOC =** Notice of Compliance or Notice of Compliance with conditions.

# Subsequent Entry Biologics




*Adopted from: Beford 2013. Regulation of Subsequent Entry Biologics: Policy Considerations*

# Why are SEBs reviewed by CDR?

**Rationale for CDR Review**

Drug plans have requested that SEBs be reviewed through the CDR process for two main reasons:

1. SEBs are not generic versions of the reference product
2. Comparative cost of a biosimilar and reference product still requires evaluation after market authorization

**Benefits of CDR Review**

- Avoids duplication of reviews by multiple drug plans
- Single source for coordinating submission requirements, application screening, and patient group involvement
- Resources and experience:
  - CADTH can produce a concise, publicly-available report that addresses the relevant information needed for a listing decision

# HTA Challenges with SEBs

- Lack of robust evidence to assess comparative effectiveness and cost-effectiveness using traditional HTA approaches.
  - Reduced clinical data package
  - Indications granted based on extrapolated data.
  - RCT evidence is minimal or absent for many indications.
  - Unlikely to be sufficient clinical data for robust PE analysis
- Lack of consistent procedures across HTA agencies
- CADTH developed CDR submission requirements to help address the issues noted above.
- **Out of scope:** Interchangeability and substitutability of SEBs is an implementation issue for the CDR-participating drugs plans.

# CADTH Experience with SEBs

## Pilot Program for SEBs (2009)

- **Goal:** Determine the CDR submission requirements and establish an evaluative framework
- **Structure:** SEBs would be filed and reviewed as though they were submissions for new drugs
- **Duration:** Planned evaluation after three SEB reviews

## Issues with Pilot Program

- Only one submission received (Omnitrope; recombinant HGH)
- Absence of targeted requirements for SEB submissions
  - *Challenging for drug manufacturers to plan/prepare*
- Lack of clarity in the deliverable from CDEC (an advice document with or without a recommendation)
  - *Challenging for the drug plans to implement*



**CADTH Environmental Scan:** http://www.cadth.ca/media/pdf/ES0284_SEBs_es_e.pdf

# CADTH Experience with SEBs

## Pending Increase in SEBs (noted in late 2012)

- Large increase in the number and complexity of SEBs.
- CADTH and drug plans agreed that SEBs must be formally incorporated into the CDR process.

## CADTH Environmental Scan (2013)

- Current practices for regulatory evaluation of SEBs
- Current frameworks used by other HTA agencies
- Obtain additional information regarding the number of SEB submissions pending in the future

Canadian Agency for Drugs and Technologies in Health

Issue 43 • January 2014

Subsequent Entry Biologics — Emerging Trends in Regulatory and Health Technology Assessment Frameworks

*Environmental Scan*

This *Environmental Scan* is not intended to provide a comprehensive review of the topic. Results are based on selected published literature, grey literature, and other publicly accessible information from the websites of various health technology assessment (HTA) agencies and drug regulators. This report is based on information gathered as at October 2013.

**Background**

Subsequent entry biologics (SEBs), also referred to as "biosimilars" or "follow-on biologics" in some jurisdictions, are biologics that are similar to, and would enter the market subsequent to, an approved innovator biologic.[1] Biologics are a class of drug derived through living organisms.[2] The high cost of biologics has created a demand for SEBs as a cost-saving alternative.[3] The majority of biologics are used to treat chronic diseases such as cancer, rheumatoid arthritis, and diabetes. The Canadian Generic Pharmaceutical Association estimates that, in 2010, biologic drugs accounted for 14% of the Canadian pharmaceutical market, costing the Canadian health care system $3 billion.[4] Biologics are expected to represent 20% of the pharmaceutical market over the next decade; this will result in significant financial pressure on health care budgets. The impending expiration of patents for many biologics is also a significant driver of SEB development.[5]

In 2010, Health Canada unveiled its regulatory guidance for the entry of SEBs into the Canadian market.[5] The availability of SEBs in Canada offers the potential to decrease health care expenditures and provide patients with access to additional treatment options. However, the introduction of SEBs presents unique regulatory and reimbursement challenges. Unlike the more common, small-molecule drugs, biologics generally exhibit high molecular complexity, and are sensitive to changes in manufacturing practices.[2] SEBs are not identical to their innovator products because their chemical characteristics cannot be precisely duplicated during the manufacturing process. Therefore, SEBs may have unique efficacy, immunogenicity, and safety profiles that are distinct from their innovator products.[1]

**Findings**

The purpose of this Environmental Scan is to provide an overview of the SEB landscape in order to understand the implications for Canada and the world. This information could assist drug policy decision-makers, as well as stakeholders, in developing approaches to address key issues related to the review and reimbursement of SEBs.

**Objectives**

This Environmental Scan will address the following questions, which are grouped under three sub-topics:

A. **SEB Regulatory Trends for Key Regulators (Health Canada, the European Medicines Agency [EMA], Medicines and Healthcare Products Regulatory Agency [MHRA], Food and Drug Administration [FDA])**
- What has been the trend for SEBs among regulatory agencies around the world?
- What is the current standard of approval for SEBs by Health Canada?
- What has been the trend for SEB approvals and recommendations around the world?

B. **Biopharmaceutical Industry Pipeline for SEBs**
- How is the SEB pipeline evolving?
- What is the current and predicted market volume of SEBs, and their financial impact?
- How have SEBs been considered for pricing?

C. **HTA Reimbursement Frameworks for SEBs**
- How are SEBs currently reviewed by HTA and reimbursement organizations around the world?
- How are the requirements for the evaluation of SEBs evolving?
- What has been the trend for SEB recommendations and advice from HTA agencies around the world?

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**CADTH Environmental Scan:** http://www.cadth.ca/media/pdf/ES0284_SEBs_es_e.pdf

# CADTH Experience with SEBs – formal CDR review process

## First mAB SEB review by CDR (December 2014)

**Recommendation:**

CDEC recommends that Inflectra (infliximab) be listed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, if the following conditions are met:

**Conditions:**

- For use in patients for whom infliximab is considered to be the most appropriate treatment option.
- List in a manner similar to Remicade.

# CADTH Experience with SEBs

- Two recently completed SEB reviews
- Both have multiple approved indications

| Brand | INN | Indications |
|---|---|---|
| Basaglar | insulin glargine | Type 1 and 2 diabetes mellitus |
| Grastofil | filgrastim | Prevention or treatment of neutropenia in various indications |

**Grastofil (filgrastim) Recommendation**
**Of-Note**
CDEC noted that a patient being treated with Neupogen should be considered for switching to Grastofil, following a consultation between the patient and his or her physician

# CADTH SEB Requirements

**Submission Requirements**

- SEBs will undergo 'Tailored CDR reviews'
  - Completion of SEB submission template
- Other requirements are similar to non-SEB submissions, but with additional sections of the CTD

**Tailored CDR Review vs. Standard CDR Review**

- **Tailored review:** Appraisal of the clinical evidence and PE evaluation filed by the manufacturer using a template specific to the type of product under review
- **Standard review:** CDR conducts a systematic review of clinical evidence and an appraisal of the manufacturer's PE evaluation.

**Why a Tailored-Review for SEBs?**

- Most efficient use of resources without compromising quality.

# CDR Submission Template for SEBs

- Template created to address the unique aspects SEBs
  - Combines a summary of key data, regulatory opinion(s), cost information, patient input and drug plan listing status
  - Provides a concise overview of relevant information and will be publicly available
  - Template completed jointly by the applicant and CDR

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Common Drug Review
Subsequent Entry Biologic
Submission Template

**Template for a Subsequent Entry Biologic Submission**

**Instructions for Manufacturers**

Please read the instructions below and consult the recommended documentation before completing the template. If you have any questions regarding the CDR submission filing process or requirements, please email requests@cadth.ca with the complete details of your question(s).

**Before Completing the Template:**

- Please review the following documents to ensure an understanding of the CDR procedures and submission guidelines:
  - *Procedure for the CADTH Common Drug Review* (August 2014)
  - *Submission Guidelines for the CADTH Common Drug Review* (August 2014)
  - *CDR Updates* (webpage) for any applicable information.

**Completing the Template:**

- Complete all sections of the Subsequent Entry Biologic Submission Template with the exception of sections 5, 6.4, 8 and Appendix 3, which will be completed by the CDR reviewers.
- Do not exceed the page limitations in sections 4.1, 4.2.3, 4.3, 4.4, and 6.
- Do not write in sections labelled "To be completed by CDR reviewers."
- Use 11-point Calibri font for text outside tables and 10-point Calibri font for text inside tables.
- References must be provided in the following format:
  - In-text citations must be numbered in order of appearance.
  - A numbered reference list must be provided in the Citing Medicine format at the end of the document in the References section.
- Save the completed template as a Word document using the following file name structure: BrandName_Template

**Submitting the Template to CDR:**

- Incorporate the completed subsequent entry biologic (SEB) submission template saved as a Word document into a complete package of category 1 requirements in electronic format on a CD, DVD, or USB flash drive.
- Please consult the *Submission Guidelines for the CADTH Common Drug Review* for details on how to file the submission package.

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**SEB Template:** http://www.cadth.ca/media/cdr/templates/tailored-review/Subsequent_Entry_Biologic_Template.docx

# Patient Group Input for SEBs

1. Impact of the condition on patients and caregivers
   - Severity of symptoms, impact on quality of life
   - Emotional and financial burden
2. Patients' experiences with the reference product
   - Benefits, harms, issues with access
3. What are the expectations for the SEB?
   - Perceived advantages or disadvantages of the biosimilar
4. Comments on potential ways SEBs can be used
   - Opportunity to comment on substitution issues
   - Outside scope of CDR review
   - CADTH performing secretariat function to facilitate communication between patient groups and drug plans

# Interchangeability and substitution issues

- Interchangeability is implementation issue for the drug plans and is out of scope for the CADTH Common Drug Review.
- CADTH can assist drug plans in gathering and appraising evidence related to switching using other product lines.
- CDR review of an SEB can incorporate switching data when available
- 2015 CADTH Rapid Response report:
  - *Switching from Innovator to SEB Infliximab: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines*

# Conclusions and Next Steps

- SEBs pose a number of unique challenges for HTA agencies
  - CADTH developed a process that should permit a fair, unbiased, evaluation of SEBs to meet the needs of the CDR-participating drug plans.
- Monitor international approaches for reimbursement evaluation and decision-making related to SEBs.
- Continue to observe Canadian policy developments within Health Canada and the CDR-participating drug plans.
- Plan to re-evaluate process
  - Timelines TBD

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