

The Advent of Subsequent Entry Biologics Biosimilars in Canada

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Author:

Patrick J. Mott, MSc.

Editors

Allison Hillier BA, MA
Heather Munroe, CTDP
Dave Solomon

Medical Illustrator

Nicole Beauvais-Holt

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Why This Program?

Biological Development

While medicines have existed for thousands of years, it was not until the 1970s and 1980s that research into recombinant DNA technology allowed scientists to produce specific proteins, or “biologics” for therapeutic use. The first example of these biologics was human insulin, developed and produced to help treat diabetes. More than thirty years later, we have access to hundreds of different biologic drugs, with world-wide sales exceeding \$100 billion dollars [1,2].

A New Era

As scientific advances expand the horizons for new and innovative biologics, the patents protecting the first generation of branded biologics are expiring, opening the door for copycat, or biosimilar drugs. Although these biosimilars are being integrated into national healthcare systems, they are significantly different from traditional generic drugs, in part due to the complexities of producing and marketing a biologic drug.

These differences are important, not only to prescribing physicians, but also to industry professionals, who must help support their customer's practices.

The Devil is in the Details

This Program has been developed to help you gain an understanding of what a biologic drug is, how it is produced, and how it is tested.

As well, you will examine the scientific, logistical, and regulatory difficulties facing biosimilar sponsors and learn how these biosimilar products will be evaluated by various regulatory bodies.

Throughout this program, you will find specific examples and insights into various biosimilar products and issues which have been associated with them.

We hope these materials will help educate, engage, and inspire you to face this new class of pharmaceuticals with a genuine concern for patient safety and therapeutic benefit.

Regulatory Developments

Each country has its own unique regulatory requirements for the approval of biosimilars. For that reason, we review a global overview of the status of biosimilars, as well as the relevant approval and regulatory processes.

Although Health Canada has already approved two officially recognized biosimilars, the guidance on expectations and requirements remains vague.

You will examine the current regulatory guidance for how biosimilars will be evaluated in Canada, and learn how they will be compared with innovator biologics. Understanding Health Canada's position on biosimilars, relative to other jurisdictions, will allow you to act as a resource for a wide variety of questions your customers might have.



Learning Objectives

Through this program, you will first examine what biologic drugs are, the science behind why they are difficult to produce, and why they may be difficult to replicate. Through Module 1, you will learn about:

- The definition of a biologic drug, and various real-world examples
- The differences between complex biological molecules and their small molecule counterparts
- How biologic drugs are produced, and how changes to the manufacturing process can affect the final product.
- Examples of biologic drugs that underwent unexpected changes when their manufacturing or formulation processes were altered.
- How a biosimilar drug is developed, and the challenges that might face the manufacturer of a biosimilar.

Once you have reviewed the scientific topics in Module 1, you will move on to the regulatory guidance that is in place throughout the world. In the first part of Module 2, you will examine different topics, including:

- The motivation behind the development and regulatory approval of biosimilars
- Different definitions and regulatory requirements of various regulatory bodies
- Examples of biosimilars that have been approved and marketed in different regions

Once you have an understanding of the international status of biosimilars, you will move on to examine Health Canada's specific regulations regarding SEBs, including:

- The key topics within Health Canada's guidance on SEBs
- Health Canada's official stance on the topic of SEBs,
- The requirements for an SEB to obtain regulatory approval
- The various classes of biosimilarity comparisons
- Key concerns that industry stakeholders have expressed regarding Health Canada's guidance on SEBs
- How the introduction of SEBs may affect your customer's practice

Taken together, this information will help prepare you to address the topic of SEBs with your peers and customers. Through these conversations, you will be able to provide a level of clarity in a field which is currently clouded by misconceptions and confusion.

Learning Tools

Throughout this program, we have added different tools to help support you as you learn about these important topics.



Key terms throughout this Program have been bolded on first appearance: you can find them in the Glossary at the end of each section if you need a refresher.



Did You Know? callouts will provide fun and interesting facts about the content. While these are not critical to learning the content, they can be used as interesting "conversation fodder" for future discussions.



At the end of each Section, we have provided In Summary review that should help recap what you have just read. If anything in these callouts doesn't seem familiar, we encourage you to review the Section to make sure you are comfortable with the content.



The Case Study icon alerts you to case examples further illustrating key concepts in that section.



Recall! callouts provide an important remind of topics that have already been covered, which are important to remember as you learn about new topics.



Insight for Your Customers provide talking points for customers. These high-level comments can be used to help respond accurately to customer queries or concerns.



The final piece of each Section is the Takeaway Gems. If you only remember one thing from that Section, make sure it's the Gems! These are a recap of the critical highlights that you can present to your customers to help inform their prescribing decisions.

While everyone learns at their own speed, we suggest planning for approximately 20 hours to complete this Program.

Once you have completed your learning, and are comfortable with the content, you will be tested with 50 multiple choice questions. These questions will examine your understanding of the content, as well as your ability to select appropriately worded responses to possible customer questions.

You will access the exam through the my CCPE portal at www.CCPE-CFPC.org

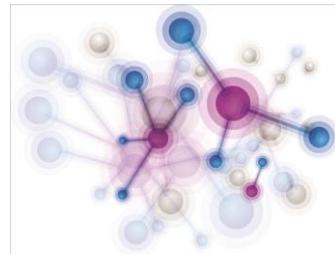


MODULE 1

The Background on Biologics



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Introduction

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In this Module we provide the context of why biologics are relevant to human therapy, the current market conditions, and lay out your learning objectives for both Module 1 and the Program as a whole.

Biologic Drugs: Then and Now

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To frame the issue of SEBs, you will examine exactly what a biologic is (and is not).

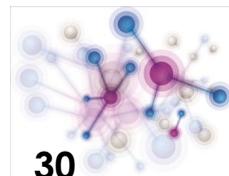
- A Step Back in Time
- A Comparison to Small Molecules
- David and Goliath: Size is Everything
- Biologics: Inherently Complex
- Biologics on the Market Today
- In Summary and Takeaway Gems

Let's Whip Up a Batch: The Making of A Biologic

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Producing a biologic drug requires many different steps, each of which adds a level of complexity that contribute to the final product's attributes. Understanding that production affects biologics on a molecular level emphasizes the care that must be taken in comparing innovator biologics and biosimilars/SEBs.

- Step One: Transcription
- Step Two: Translating RNA into Protein
- Step Three: Modification with all the Trimmings
- Step Four: 3D Folding for Function
- In Summary and Takeaway Gems



Monoclonal Antibodies: Y Not?

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Monoclonal antibodies are larger, more complex, and more complicated to produce than smaller biologics. Here we examine the structural and functional features of a monoclonal antibody to help frame the topic of replicating biosimilar antibodies.

- Overview of Antibody Structure and Function
- Two Arms for Holding... An Antigen
- The Crystalizable Fragment
- Cause and Effector Functions
- In Summary and Takeaway Gems

Designer Drugs: Developing a Biologic

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Designing and developing a biologic drug is complicated and intensive. Here we examine the steps to produce a biologic for therapeutic use.

- Step One: Identifying the Target
- Step Two: Designing the Gene in a Bottle
- Designing a Monoclonal Antibody
- Step Three: Choosing a Cellular Factory
- Step Four: From Cell to Syringe
- Changes Lead to Changes
- In Summary and Takeaway Gems

Cloning the Clone: The Development and Production Process for Biosimilars

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While the development and production process is similar for both an innovator biologic drug and a biosimilar, small changes in the respective development and production processes can impact the final products.

- The Process is the Product: The Active Pharmaceutical Ingredient And The Manufacturing Process
- In Summary and Takeaway Gems

Module 1 Summary

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Module 1 Glossary

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Module 1 References

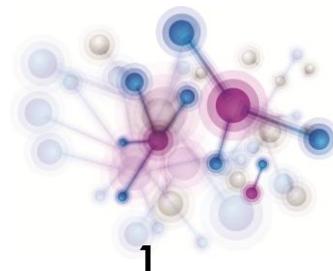
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MODULE 2

Regulating Biosimilars: Global Experience and Canadian Guidance



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Introduction

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In this Module we provide the introduction to biosimilars/SEBs, and the legislative landscape.

Biosimilars: The Big Picture

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By examining international examples of biosimilars and their regulation, you gain knowledge that will help prepare you to examine Health Canada's guidance.

- Global Uptake of Biosimilars
- A Summary of Key Events in the History of Biosimilars
- Different Jurisdictions, Different Names
- Global Regulatory Guidelines
- A State of Change: Biosimilars Across the World
- European Medicines Agency (EMA) Regulations
- Japan's Regulations
- US Food and Drug Administration (FDA) Regulations
- India's Regulations
- China's Regulations
- In Summary and Takeaway Gems

Canadian Eh? Regulation of Subsequent Entry Biologics in Canada

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Health Canada has prepared specific guidance regarding the comparison and approval process for SEBs in Canada, so you will examine the important regulatory points and how they will impact the innovator biologic and SEB.

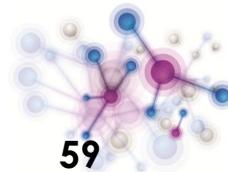
- Health Canada's Stance on SEBs
- Hmm, Which Reference Biologic to Choose?
- Six Important Policy Statements
- Rejection of Biosimilarity
- In Summary and Takeaway Gems

The Letter of the Law: Comparability Studies

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Properly understanding the key issues of SEBs requires an understanding of the specific tests that are and are not required for the submission of an SEB for regulatory approval in Canada.

- Show Me the Similarity (Through a Comparability Study)
- Group One: Physicochemical, Biological, Immunochemical
- Group Two: Purity and Stability
- In Summary and Takeaway Gems



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Clinical Studies and Post-Market Requirements

Although reduced, clinical testing will play an important role in determining if an SEB is truly similar. In this section you will examine the various types of clinical testing, and how they can support a claim of similarity.

- Pharmacokinetic Studies (PK studies)
- Pharmacodynamic Studies (PD Studies)
- Enforcing Proper Labelling
- In Summary and Takeaway Gems

Concerns Regarding Health Canada's Guidance

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Some industry stakeholders have expressed concerns regarding the lack of clarity in Health Canada's guidance on SEBs. To help prepare you to address these concerns, you will examine a breakdown of the various key concerns.

- Concern #1: Now You See Similarity, Now You Don't...
- Concern #2: What You Don't Know Can Hurt You
- Concern #3: How Long is Long Enough?
- Concern #4: What is Sensitive Anyways?
- Concern #5: Measuring Similarity
- Concern #6: Group Effect, or Individual Results
- Concern #7: Show Me the Reference (Material)!
- In Summary and Takeaway Gems

Implications for Healthcare Professionals: Extrapolation, Naming, and Interchangeability

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Understanding the difference between biosimilarity and bioequivalence is critical to understanding the application of SEBs in Canada.

- Pushing the Envelope: Extrapolation of Biologics Across Indications
- A New Frontier: Extrapolation in Europe
- What's in A Name?
- Similar but Different? Interchangeability and Substitution In Canada
- Provincial Positions on Interchangeability and Substitution
- Switching Treatments, Unintended Consequences?
- In Summary and Takeaway Gems

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