


Canadian Biologics Regulatory Overview

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Presentation Topics

- **Terminology and Background**
- **Regulatory Framework**
- **Patent Issues**


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Terminology and Background

- **Definitions**
- **Innovator vs. “Generic”**
- **Debate over “Generic” Terminology**


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Definition of “Biologic”

- Drugs listed on Schedule D to the *Food and Drugs Act*:
 - individual products (e.g. “insulin”);
 - product classes (e.g. “immunizing agents”);
 - references to particular sources (e.g. “drugs, other than antibiotics, prepared from micro-organisms”);
 - methodology (e.g. “drugs obtained by recombinant DNA procedures”).


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Definition of “Biologic”

- Manufactured from animals, or micro-organism
- Derived from metabolic activity of organisms; more variable and structurally complex than chemical drugs
- Labile and sensitive to changes in manufacturing processes and conditions
- “the process is the product”
 - Much effort is focussed on manufacturing control and quality assurance


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“Generic” Biologics Terminology

- Many different terms used to refer to “generic” biologics
 - World Health Organization → “biosimilars”
 - F.D.A. (U.S.A.) → “follow-on protein products”
 - Health Canada → “subsequent entry biologics”
- Terminology is subject of great debate
 - *WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products*; Geneva, 4-5 September 2006


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Debate on “Generic” Terminology

- Health Canada’s position: “Generic Biologic” = follow on product after patent expiry, not true generic because biologics are not identical
- For biologics, the manufacturing process is critical to defining the final product
- Regulatory path for biosimilars may differ from innovator biologics
- Degree of similarity between biosimilar product and comparator is critical
- Concept of a biosimilar product is regulatory in nature
- At present there can be no true generic biologic


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Debate on “Generic” Terminology

- Health Canada is in the process of developing regulatory framework for “subsequent-entry biologics”
 - Issues under consideration:
 - nature of a Canadian reference of comparator;
 - impact of intellectual property issues on regulatory policy;
 - guidance on long term pharmacovigilance planning for biosimilars


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Innovator vs. “Generic”

- Innovator Biologic
 - original products;
 - usually first to receive approvals;
 - Innovator conducts original and extensive R&D;
 - full efficacy and safety testing.
- Biosimilar
 - Abbreviation for “similar biotech medicinal product”;
 - new type of generic biopharmaceutical approval in E.U. and associated products
- Biogeneric
 - Refers to any biologic considered generic, based on any criteria
- Subsequent Entry Biologics
 - Biologic similar to and entering market subsequent to an approved innovator biologic

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Regulatory Framework

- Entity Responsible for Regulation
- Regulation of Innovator (“stand alone”) Biologics
- Regulation of Subsequent Entry Biologics (“biosimilars”)
- Challenges in Regulation of Biosimilars
- Conclusion


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Entity Responsible for Regulation

- Biologics are regulated by Health Canada
 - The Biologics and Genetic Therapies Directorate (BGTD) regulates biologics under Divisions 1, 1A, 2, 4, 5 and 8 of Part C of the *Food and Drug Regulations*

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Health Canada Structure

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graph TD
    BGTD[Biologics and Genetic Therapies Directorate] --> CBR[Centre for Biologics Research]
    BGTD --> BRE[Biologics and Radiopharmaceuticals Evaluation Centre]
    BGTD --> CPRA[Centre for Policy and Regulatory Affairs]
    BRE --> BTD[Blood Tissues and Organ Division]
    BRE --> V[ Vaccines Division ]
    BRE --> Biotherapeutics[Biotherapeutics Division]
    BRE --> CED[Clinical Evaluation Division]
  
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Regulation of Innovator Biologics

- After issuance of NOC manufacturer must adhere to BGTD's Lot Release Program
 - Risk-based criteria for testing product before market release


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Regulation: Innovator vs. "Generic"

<p><u>Innovator</u></p> <ul style="list-style-type: none"> <input type="checkbox"/> BGTD governs regulation • Verification of: quality, safety, efficacy, benefits outweigh risk • Testing of intermediaries • On-site evaluations • NOC • DIN • Lot-Release Program 	<p><u>Subsequent Entry</u></p> <ul style="list-style-type: none"> <input type="checkbox"/> BGTD governs regulation • Subject to all of the current regulatory requirements for biologics • "New Drug Submission" (NDS) for review as a basis for seeking market authorization <ul style="list-style-type: none"> • Extent of information required may be different than for innovator
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Regulation of Biosimilars: “NDS”

- BGTD encourages participation in pre-submission meeting
- Submission requirements for SEBs will be determined on a case by case basis


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Regulation of Biosimilars: “NDS”

- Non-exhaustive list of submission requirements:
 - Complete chemistry and manufacturing data package
 - Rationale for the choice of the comparator innovator biologic with information on its safety and efficacy
 - Characterization information to show chemical and biological comparability
 - Pharmacodynamic data to demonstrate comparable bioactivity
 - Pharmacokinetic data to demonstrate comparable bioavailability
 - Immunogenic profile of the SEB in humans and its potential impact on safety and efficacy
 - Clinical package demonstrating safety and efficacy including:
 - comparative studies between the SEB and innovator products;
 - data for the innovator product in the public domain.


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Marketing Biologics in Canada

- A Notice of Compliance (NOC)
 - Review of chemistry and manufacturing data;
 - clinical data;
 - facility information contained in NDS
 - Testing of consistency samples (3-5 lots)
 - Pre-approval On-Site Evaluation of manufacturing sites
- An Establishment License
 - Issued on the basis of evidence of GMP compliance
 - The distributor (NOC holder) must have a Canadian Importer who holds an Establishment License


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Future: Regulation of Biosimilars

- A number of biologics will come off-patent worldwide in the next five years, and the patents for others such as insulin, human growth hormones, some interferons have already expired
- BGTD is working on developing a comprehensive regulatory framework for SEBs addressing the regulatory, legal and scientific issues related to SEBs


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Regulatory Challenges: Biosimilars

- Development of regulatory system for SEBs based on evaluation of reduced clinical data presents challenges to both manufacturers and regulators
- Assurance of safety, quality and efficacy closely tied to carefully controlled and highly reproducible manufacturing process


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Regulatory Challenges: Biosimilars

- After manufacturing change an innovator must demonstrate comparability of new product to old one
- Extent of testing will depend on:
 - Nature of proposed manufacturing change;
 - Design of scientifically sound study can be challenging.
- SEB manufacturer faces greater challenge:
 - Must develop their product;
 - Demonstrate comparability to comparable product for testing purposes.
- Challenges increase with:
 - Molecular size and complexity of product;
 - Number of biological activities of product.


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Regulatory Challenges: Biosimilars

- Should not be the same as for generic chemical pharmaceutical
- May or may not be simpler than for innovator biologics, with respect to the amount of clinical data needed to be generated with the new biosimilar product itself
- The extent of differences in requirements for biosimilars and innovator biologics will be decided on a case by case basis


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Regulation of Biologics/Biosimilars Conclusion


- Biologics regulation in Canada involves a carefully evolved and integrated approach
- The elements of the approach are typical of those used by many countries
- With a small population, limited resources and increasing workload, innovative strategies will be required for Canada to retain sovereignty in decision-making while coping with new technologies and many new biologic products

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Thank You

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