



BIOTECCanada Principles for the Safe Introduction of Subsequent-Entry Biologics (SEBs) into the Canadian Healthcare System

The term Subsequent-Entry Biologic (SEB) is used by Health Canada to describe “a biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product.” The agency is currently considering the regulatory process by which such products would be granted a marketing licence in Canada.

BIOTECCanada supports the creation of a regulatory pathway for the regulation of SEBs that incorporates processes and requirements that ensure patient safety will be protected. BIOTECCanada members have developed this set of principles that the biotechnology industry believes should guide the introduction and regulation of SEBs in the Canadian marketplace.

Background and Definitions:

Interest in SEBs has been stimulated by the expiration of patents on several of the first biological therapies to be introduced. Manufacturers of SEB products believe that these products should receive marketing approval with fewer clinical trials by reliance on comparisons to similar innovator molecules. As a result, efforts are either completed or underway in several jurisdictions to define specific regulatory pathways for SEBs. Scientists around the world are engaged in considerable debate as to the appropriate regulatory requirements for approval of these products. A regulatory framework for “biosimilars” has been implemented in the European Union and several biosimilar products have been approved by the European Medical Evaluation Agency (EMA). The United States Congress is currently considering legislation that would create a separate regulatory pathway within the Food and Drug Administration (FDA) for SEB products.

Canadian policy on SEBs remains undefined. The Health Canada *Fact Sheet on Subsequent Entry Biologics* currently states that “Subsequent-entry Biologics are subject to the same regulatory requirements for biologics submitted as a New Drug Submission (NDS), although the extent of clinical trial data required may be different than that of the innovator’s product.”

Biologic Therapies: Biologic therapies have been marketed for a range of serious and life-threatening diseases such as cancer, diabetes, multiple sclerosis, rheumatoid arthritis and rare metabolic disorders. They include such diverse protein products as monoclonal antibodies, cytokines, protein hormones, gene therapies, vaccines, and blood and blood components. Biologic therapies are complex molecules derived from unique living organisms and cell lines making them complicated to produce. The molecules themselves are composed of a large number of molecular components and are of a large molecular weight. Small differences in the production of biologics can yield vastly different products with unique implications for patient safety.



Due to the complexity of the molecular structure and manufacturing processes of biologic products, SEBs can never definitively be called identical to innovator products; unlike “generic” versions of traditional pharmaceuticals. Health Canada, the EMEA and the FDA have all agreed that SEBs can only be called similar to the innovator product.

1. Patient Safety must be the primary concern of the SEB regulatory framework.

Canadian patients should not have to accept greater risks or uncertainties when using a subsequent entry product, and they deserve a regulatory framework that ensures SEBs are as safe to use as innovator products. Health Canada should take the following steps to ensure the highest levels of patient safety.

SEBs must have an acceptable safety profile: Substantial clinical trial data are required to demonstrate a satisfactory safety profile for each SEB product. Biological therapeutics have the potential to cause an “immunogenic” response, wherein the body produces antibodies to attack and neutralize the medicine, rendering the drug ineffective. On occasion, immunogenicity can trigger the antibodies to attack not only the medicine, but any similar substance occurring naturally in the patient’s body. Thus, the immunogenicity profile of an SEB must be well-characterized and clinically compared to the immunogenicity profile of the innovator product to avoid subjecting patients to potential adverse effects from immune reactions. Even very small process changes in the manufacture of a biologic product can result in significant changes in the clinical and immunogenic properties of the product. Therefore all innovator process changes are carefully evaluated and this risk taken into account when the documentation for such a change is developed, and for some process changes this also implies investigating immunogenicity in clinical trials. Immunogenicity is unpredictable and can often only be observed through the generation and evaluation of substantial clinical trial data.

- **SEBs are Not Interchangeable with Innovator Products:** Given the complexity of biologic products and the potential for significant immunogenicity and clinical response differences, SEB products cannot be declared interchangeable with innovator products. Doctors and patients should remain free to select the most appropriate biological therapy based on the patients’ needs and history of safe use and clinical response. Decisions to substitute one similar product with another should only be made on the basis of a physician’s express decision.

Each Biologic Product Must Have a Unique Product Name: Each SEB product must have unique and distinguishable brand names and a distinct name under the International Non-proprietary Names (INN) Program of the World Health Organization. Given the fact that SEB products are not identical to innovator products and could have significantly different

clinical outcomes for patients, post-market safety surveillance demands that patients, physicians, pharmacists, and nurses be able to readily distinguish similar biologic therapies on the basis of their names. A unique name will assist in the accurate prescribing and dispensing of similar products and supports pharmacovigilance efforts that must be able to trace an adverse event to the specific product of origin. Without distinct names, patients, physicians and pharmacists could become confused leading to inadvertent product substitution, consequent fluxuations in response and complications in adverse event tracking.

Strict Post-Market Surveillance Must Be Followed: Pharmacovigilance of SEB products must conform to the same rigorous standards as those used for innovator products. The traceability of products must be assured through unique names. Repeated, uncontrolled switching between similar products must be avoided in order to ensure adequate safety surveillance.

2. SEB Products Require Unique Regulatory Considerations

The Health Canada *Fact Sheet* recognizes the unique regulatory challenges associated with SEB products and it details a substantial set of information that *may* be required for Health Canada to consider an NDS for an SEB product. The regulatory framework for the approval of subsequent entry biologic products must achieve the same level of rigour in terms of safety, purity, and potency as applied by Health Canada for the original approval of innovator products. BIOTECanada members believe that the regulatory requirements for SEBs must be clear, specific and transparent at all levels of the Canadian health care system and should be developed according to the following principles.

- **Bioequivalence and Pharmacodynamic Studies Are Not Sufficient:** Bioequivalence studies are not adequate to establish safety and efficacy for subsequent-entry biologics. Bioequivalence studies evaluate drug levels in plasma, not the pharmacological effects of the drug, and are designed to test the same compound from two sources not similar compounds. Similarly, pharmacodynamic studies alone are not adequate to establish the safety and efficacy for subsequent-entry biologics. Clinical endpoints, both safety and efficacy, must be assessed for subsequent-entry biologics. Substantial clinical trial evidence and data, beyond pharmacokinetics and pharmacodynamics, are a fundamental requirement for evaluating and demonstrating the safety and effectiveness of a subsequent entry biologic, and such evidence must be generated for each individual SEB in order to qualify it for regulatory approval.

Complete Chemistry and Manufacturing Package Needed: Given the unique nature of biologic manufacturing processes, the manufacturing processes for SEB products must be



fully validated and cannot rely on innovator chemistry and manufacturing data for approval. Experience has shown that small manufacturing changes can result in significant differences in safety and efficacy for biologic products. As the original developer, the innovator has extensive knowledge of critical product process parameters and quality attributes pertaining to the production of the molecule and a greater understanding of the impacts of subtle manufacturing changes. Methods used by manufacturers to demonstrate product safety and effectiveness after a small manufacturing process change to an established and well-characterized process are not necessarily sufficient to demonstrate safety and efficacy of a subsequent entry biologic made by a different manufacturer using a different process – just as additional testing (including clinical testing) is necessary and required when innovators develop complete new manufacturing processes for an already approved product.

- **Specific Clinical Requirements Needed:** Given the complexities of the biological products and the diseases they treat, Health Canada must specify what clinical studies are necessary to meet the standard of “substantial clinical evidence” as required by Food and Drug regulation C.08.002 (h) or “sufficient clinical data” as stated in Health Canada’s Fact Sheet. The clinical package should demonstrate the safety and efficacy of the SEB including an understanding of its dose / response in order to allow for appropriate use of the medicine. Health Canada should consult with scientific experts, industry, patients and international regulatory authorities in the establishment of these regulatory requirements. Health Canada should establish guidance for each biological product category (e.g. somatropins, interferons, erythropoetins, etc.), as has been successfully adopted by the European Medicines Evaluation Agency (EMA) for the regulation of biosimilar products.
- **Reference Product Must Be Defined for Biologics:** The current definitions for “Canadian reference product” and “pharmaceutical equivalent” as found in Division 8 of the Food and Drugs Regulations, and regulation C.08.002.1 of the Food and Drug Regulations are not applicable to subsequent entry biologics. Distinct definitions of those terms will need to be defined specifically for SEB products. If for the purposes of filing an abbreviated regulatory data package, a SEB manufacturer seeks to compare the SEB product to an innovator product, then that innovator product must have been reviewed by Health Canada to establish an understanding of the product’s safety and efficacy, and subsequently approved by Health Canada. If no Canadian reference product has been reviewed and approved by Health Canada, then the product should proceed through the regulatory system as an innovative New Drug Submission, adhering to all requirements for the licensing of innovator biologics.

Unique Labelling and Product Monograph: Health Canada should grant SEB products a distinct label from the innovator product. Patients, physicians, pharmacists and provincial



formulary bodies should be fully aware of the data that were used to license a medication. The clinical data used to approve the product should be fully described, and the unique safety data must be included. If data generated with the innovative product are included and/or relied upon for the SEB approval, this must be clearly specified to ensure prescribers and patients fully understand the origin of the data. The approved indication(s) for the SEB should be that which was studied with the SEB, not simply an extrapolation of the approved indications from the innovator product.

3. Regulatory Approvals for SEB Product Must Respect and Protect Innovator Intellectual Property

The biotechnology industry relies on strong patent protection in order to secure the substantial financing necessary to bring innovative new therapies to market. Health Canada must ensure that any new regulations or guidelines promulgated to define the regulatory regime for Subsequent Entry Biologics does not weaken the provisions of the Patented Medicines (NOC) Regulations or Food and Drugs Data Protection Regulations.

Data Protection Triggered for SEBs: BIOTECCanada believes that under the Food and Drugs Act and Regulations, data protection must be triggered whenever a subsequent-entry manufacturer proposes submitting a regulatory data package based upon an existing product in the Canadian marketplace. The Government of Canada recently established eight years of data protection for novel therapeutics, including biologics, in Canada. Given the long development times necessary for biologic therapies, data protection is a key incentive to manufacturers to the introduction of novel products. BIOTECCanada also recommends that Health Canada establish appropriate data protection for innovative biologics in order to align with the longer data protection timelines in the European Union (11 years) and in the United States (12 years proposed).

Intellectual Property Rights: No SEB product should be approved until all statutory patent and other intellectual property protections are no longer available for the innovator product to which the SEB product is compared for the purposes of submitting a reduced regulatory package. Any regulatory pathway must also respect existing trade secret protections for the innovator product. The process must also ensure that appropriate incentives are preserved for innovator manufacturers to conduct research on new indications for the innovative product.

4. Health Canada should thoroughly consult with Canadian stakeholders, including manufacturers and patients, on the process for the introduction of SEBs in the Canadian marketplace, and should establish a clearly defined regulatory pathway.



A transparent regulatory process builds confidence. Establishment of a balanced and rigorous science-based regulatory pathway for SEBs requires consideration of complex scientific, legal, social and economic issues. The European Union established the approval process for biosimilars only after thorough public dialogue. The United States is currently engaged in public debates about the regulation of these products. Given the complexity of biological therapies and the potential implications for patient safety, Canadians deserve a robust public process and clear regulations for the introduction of SEBs including the publication of proposed regulatory changes in the *Canada Gazette*. In the interim while these regulations are being developed Health Canada should not approve any SEB products unless submitted with a full data package as for an innovator.

Philip Schwab, Ph.D.
Vice President, Industry Relations
BIOTECCanada
Tel: 613-230-5585 x 225
Fax: 613-563-8850
Philip.schwab@biotech.ca
www.biotech.ca

