Subsequent Entry Biologics: Federal and Provincial Policy Considerations in Canada

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Abstract

In January 2014, the biotechnology and pharmaceutical industry in Canada experienced a monumental federal regulatory decision—Health Canada approved a subsequent entry biologic (SEB) of Janssen Biotech Inc.’s REMICADE®. SEBs are developed with reference to a marketed originator biologic product once the respective patent has expired; SEBs and their reference biologic drugs (RBDs) are similar but not identical, therefore adding a level of additional regulatory complexity not associated with small molecule drugs and their generic counterparts. The SEB, coined REMSIMA™ and INFLECTRA™ (marketed by Celltrion Inc. and Hospira Inc., respectively) was the first to be approved post-finalization of Health Canada’s Guidance for Sponsors in 2010. REMSIMA™/INFLECTRA™ was also the first monoclonal antibody (mAb) SEB approved in Canada. Monoclonal antibodies are of the largest, most complex biologic therapeutics. Federal regulatory requirements for the approval of an SEB are less than what is required for a new innovative biologic, which has lead clinicians and other health practitioners to question the comparability of the safety and efficacy profiles based on minor differences between an SEB and its RBD. This paper will examine current federal and provincial policies related to SEBs and suggest future approaches, mainly regarding: federal regulatory requirements, pharmacy-level interchangeability, and naming. Federal and provincial regulatory authorities need to develop and implement effective policies that balance the promotion of price competition while preserving health outcomes; the adoption of SEBs should be encouraged, only if such promotion does jeopardize patient health. Health Canada should consider adopting the use of Greek suffixes to differentiate between SEBs and their RBDs and develop new manufacturing change policies specific to SEBs to address “drift”. Provincially, interchangeability should not be supported until robust patient-level switching data is available.
Introduction

Canada’s biopharmaceutical regulatory framework has been under considerable pressure from the emergence of less costly subsequent entry biologic medicines. SEBs have posed substantial policy problems - while they have the potential to reduce healthcare expenditure, current regulations are inadequate to properly address patient safety and maintain health outcomes. In this paper I will argue that Canada needs to adopt enhanced manufacturing data requirements and more stringent naming guidelines. In addition, provinces should not allow interchangeability based on the current, limited level of available SEB-RBD switching data.

Biologic medicines have provided patients with effective therapeutic options for the management of complex diseases where traditional small molecule drugs often lose their response or are simply ineffective. The importance of biologics in the clinical setting has been well established, however, they are substantially more costly. In the nine provincial jurisdictions analyzed by the Canadian Institute for Health Information (CIHI) in 2012, an average of $17,782 was paid per beneficiary on anti-TNF-α biologics for the treatment of inflammatory diseases. Biologics place a substantial burden on public drug programs and private insurance providers. In 2010, biologics constituted over $3 billion in health care costs representing 14% of the total pharmaceutical market. Biologic medicines have driven spending on prescription drugs largely due to the increased use of monoclonal antibody cancer therapies and immunosuppressants. From 2007 to 2012, anti-TNF-α agents contributed to more than half (54.8%) of the growth in drug program spending
across Canada, with an average annual growth rate of 28.1%. The high cost of biologic drug development and manufacture, improved outcomes and the decline in development of novel therapies has led to large increases in prices. For example, the recently approved SOVALDI® (sofosbuvir; Gilead Inc.) will carry a lofty price tag of $55,000 (CDN) for a one-time 12-week cycle for the treatment of hepatitis C. This price does not include additional costs to the patient/insurer, such as combination therapies, wholesaler upcharges, pharmacy upcharges or drug dispensing fees. The cost pressures of biologics on private, public, and individual payers has led to the increased need for similar lower cost alternatives, subsequent entry biologics.

The first biologics on the Canadian market are beginning to lose their patent protection, creating a market for SEBs. Subsequent entry biologics are therapeutics developed with respect to a reference biologic drug (RBD) once the patent on the RBD has expired. SEBs must demonstrate adequate similarity to the RBD, but are not identical, hence the commonly referred to term biosimilars. SEBs cannot simply be thought of as generics; generics are copies of small molecule drugs where equivalence can be determined through analytical testing in the absence of clinical data. Biologics are derived from living cells using recombinant DNA through complex manufacturing processes. Some smaller biologics, such as human growth hormones are derived using bacterial cells, whereas more complex agents such as monoclonal antibodies (mAbs) are developed using mammalian cells. Mammalian derived protein therapeutics undergo modifications within cells that are not applicable to those derived in bacterial cells. The slightest change in manufacturing can lead to product variation, with unintended and unknown clinical consequences.
Concern has arisen due to the fact that RBDs and their SEB versions are manufactured using different cell lines and under slightly different conditions, subjecting them to inherent variation. Biologics such as mAbs, can be thousands of times larger than small molecule drugs such as Aspirin (150,000 Daltons vs. 150 Daltons). The size and complexity of these molecules enables multiple potential sources of structural variation. This molecular complexity has lead to discussion over how minor differences between RBDs and their SEBs will affect health outcomes: immunogenicity (an unwanted immune response; loss of response or adverse immune reaction), and the safety and efficacy profiles of an SEB and its RBD.

Through expected price reductions of 20-40%, SEBs may enable better access to effective biologic medicines and provide substantial savings to public drug programs, private drug insurers, and individual patients. However, these benefits do not come free of concern and new policy challenges. Physician groups, patient groups, and innovator companies have expressed apprehension towards the level of comparability that is required by federal regulatory authorities. Reduced clinical data requirements have contributed to the debate over the validity of current clinical trial data i.e. the level of clinical comparability between an SEB and its RBD.

Federal Regulatory Requirements

In 2010, Health Canada published its Guidance for Sponsors on SEB products, outlining the recommended data requirements for SEB submissions. The
requirements for SEB applications fall in the middle of the spectrum between
generic requirements and that of an innovative biologic therapeuetic. A manufacturer
may submit an SEB application with reference to a marketed originator product
(synonymous with RBD) using a combination of analytical testing, biological assays,
non-clinical and clinical studies. For instance, an innovative product may require
robust phase I, II, and III clinical trial data, whereas an SEB may be granted
marketing approval based just one phase III efficacy study and one phase I study,
highly reducing development costs, and incentivizing and promoting competition.
This was the case of the recently approved SEB of Janssen Biotech Inc.’s REMICADE®
(infliximab), REMSIMA™/INFLECTRA™. The two SEB products, which are identical,
were approved by Health Canada in January 2014. The study molecule was given
brand names INFLECTRA™ (marketed by Hospira Inc.) and REMSIMA™ (marketed
by Celltrion Inc.). Although REMSIMA™/INFLECTRA™ was not the first SEB to be
approved by Health Canada, it was the first complex monoclonal antibody, posing
greater clinical, regulatory, legal and pharmacy-level policy considerations; it is
easier to ensure molecular similarity between smaller biologic RBDs and SEBs that
are not derived from mammalian cells, as they do not undergo complicated
intracellular processing alterations resulting in SEB-RBD variability. In 2009, Health
Canada approved an SEB of Sandoz’s OMNITROPE® —a human growth hormone
derived from bacterial cells. This approval occurred prior to the finalization of the
Guidance for Sponsors by Health Canada in 2010. Due to its smaller size and
complexity, OMNITROPE® did not pose the same level of policy considerations as
those involved in mAb SEBs; bacterial cells are limited to the amount of molecular modification.

In the case of REMSIMA™/INFLECTRA™, non-inferiority (statistically not efficaciously inferior) with respect to REMICADE® was demonstrated in only 302 patients with rheumatoid arthritis\textsuperscript{10} and 128 patients with ankylosing\textsuperscript{11} in shortened 30-week clinical trials. These trials were both smaller in size and shorter in duration than those generally conducted with innovative biologics in rheumatology.\textsuperscript{12} In a recent study assessing the attitudes and perceptions towards SEBs among Canadian rheumatologists, it was found that only 30.9\% of those surveyed agreed or strongly agreed that they would prescribe an SEB if available, and conversely 39.5\% disagreed or strongly disagreed.\textsuperscript{14} While meeting the demands of federal regulatory authorities, current SEB clinical trial data does not appear to fully appease clinician data requirements. Many physicians have expressed concern over the real world effectiveness of SEBs, as well as differences in immunogenicity and adverse event profiles.\textsuperscript{14} Physician-regulator disconnect has occurred federally surrounding the phenomena known as indication extrapolation, and provincially where public drug programs are grappling with the task of denoting what level of similarity will be required to support SEB-RBD interchangeability policies. This disconnect will not have significant impact until the use of SEBs is legislatively enforced. Until then, the decision to use an SEB or RBD will be based on the clinical judgment of a physician. Provincial governments should be cautious in mandating the use of SEBs until there is enough data to generate support from a significant majority of physicians, as it subsequently mandates
extrapolated indications. Otherwise, significant autonomy will be removed from the clinical setting with regards to clinician judgment.

**Indication Extrapolation**

REMSIMA™/INFLECTRA™ was granted four originator indications (those held by its RBD, REMICADE®) of rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (PsO), and ankylosing spondylitis (AS) based on only one phase III (RA) and one phase I (AS) clinical trial. Indications of PsA and PsO were granted for the SEB in the absence of clinical data. Health Canada granted these extrapolated indications based on similarities in pathophysiology, pharmacokinetic profiles, dosage administered and routes of administration as those found in patients with RA or AS. However, originator (REMICADE®) indications of ulcerative colitis (UC) and Crohn’s disease (CD) were not granted for REMSIMA™/INFLECTRA™ based on differences between the SEB and RBD that could not be ruled out as a possible mechanism of action specific to these diseases. It is interesting to note that the European Medicines Agency (EMA) recommended the approval of all the aforementioned indications in June of 2013. Similarly to Health Canada and the EMA, the U.S. Food and Drug Administration (FDA) has also provided direction for sponsors to justify requests of indication extrapolation. As of January 2015, the FDA has not approved REMSIMA™/INFLECTRA™, and subsequently has not made any decision with regards to indication extrapolation. In the United States, REMSIMA™ was the first SEB monoclonal antibody to be filed through the FDA’s
Biologics Price Competition and Innovation Act of 2009 (BPCIA, 2009). Comparably, the justification for indication extrapolation is similar between the U.S. and Canada. Significant areas that differ between Canadian and U.S. federal regulation are mostly limited to the requirements/pathway for interchangeability, based on differences in federal-state jurisdictional authority between the two countries.

**Interchangeability and Substitution**

Interchangeability refers to the given authority of a pharmacist to dispense a different medication than what is prescribed by a physician, usually a financial-based decision without the physician’s consent. Similarly, substitution refers to the act of automatically substituting a prescribed product for another, usually done on the basis of a medical decision requiring physician consent. Based on the inherent variation between SEBs and their RBDs, stakeholders have expressed concern over the interchange between the two, mainly as a result of the limited trial size and lack of interchange data. Healthcare professionals remain uncertain if an interchange between the two products will maintain safety and effectiveness and avoid immunogenicity. Patient organizations such as the Arthritis Society have expressed agreement with scientific viewpoints against interchangeability or ‘therapeutic substitution’ and they believe that such viewpoints should be adopted by Health Canada and incorporated in federal, provincial, territorial, and private payers drug reimbursement. Health Canada has stated that “SEBs are not generic
biologics”, and that “[a]uthorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug”. However, Health Canada has also responded to further stakeholder recommendations in agreeing that specialized clinical studies may be used to support interchangeability. In doing so, Health Canada outlined the need for physicians to make informed decisions regarding interchangeability, as specialized studies may lose relevance over time due to separate manufacturing changes between an RBD and SEB, referred to as “manufacturing drift”. While there has been expressed stakeholder discontent regarding interchangeability, the authority rests with the individual provinces to designate products as such. Provinces could consider carefully worded legislation allowing pharmacists to substitute an RBD with an SEB only in patients who have not previously been treated with the RBD, in addition to giving the prescribing physician notice of the substitution. Until robust switching data between an SEB and RBD is available, provinces should not allow interchange between the two products in patients already receiving the RBD. Inflammatory diseases are incredibly complex; treatment is usually targeted to achieve clinical remission rather than cure. A loss of response or immune reaction due therapeutic interchange could pose significant economic and quality of life consequences to the patient, and create economic pressures on already stressed healthcare resources.

In the United States, SEB and brand-name manufacturers have agreed to support legislation that would support automatic substitution where a physician has been notified within a “reasonable” timeframe. Unlike Health Canada, which does not have the authority to deem products interchangeable, the FDA has a regulatory
pathway, outlining the authority to designate an SEB and RBD interchangeable under the 351(K) pathway of the Public Health Services (PHS) Act. Furthermore, state-level legislation may differ with regards to the process of physician notification regarding interchange. The difference in federal-provincial policy-making in Canada compared to the United States surrounding pharmaceutical interchange presents the need for increased federal-provincial channels of communication. Data submitted to Health Canada will be required by the provinces to make informed evidence-based policies and formulary decisions.

**Addressing “Drift”**

Manufacturing quality is highly controlled and regulated by Health Canada; any changes in production require the manufacturer to submit supporting data and must comply with outlined conditions. Acceptable limits are set by Health Canada to which a single product can differ before and after a manufacturing change is made. With respect to a single product, manufacturing changes more often than not have minimal clinical implications due to stringent federal data regulatory requirements. However, when an SEB and RBD are considered, the two companies would individually submit confidential information to regulatory authorities regarding production changes. Over time, if each company makes multiple manufacturing changes, each product with respect to their previous version would remain within the acceptable limits outlined by Health Canada, yet may become less similar to their SEB/RBD counterpart and continually “drift” apart.
The main area of concern with regards to drift coincides with the level of interchangeability that is determined by the provinces. Multiple manufacturing changes and subsequent compounded minor differences between an SEB and RBD may result in larger clinically meaningful differences if a patient is switched between the two products. Consider four manufacturing changes that result in 5 nearly identical products: 1, 2, 3, 4 and 5. All five products (variations of the SEB OR RBD) would be within the acceptable difference limits when considering the previous version i.e. 1 to 2, 2 to 3, 3 to 4, and 4 to 5, maintaining the clinical safety and efficacy that product 1 was approved on. After four manufacturing changes to both the SEB and the RBD, product 5 of the SEB and product 5 of the RBD may exhibit differences between the two that fall outside the acceptable limits outlined by Health Canada for a single biologic product. These differences would be based on compounded variation between the two products after multiple manufacturing changes. Federal and provincial regulatory authorities should discuss the potential level of interchangeability that may be authorized. If the provinces express interest in interchangeability at some point in the future, then Health Canada should begin creating new manufacturing change policies surrounding SEBs. If two products are interchangeable, it would be ideal that manufacturing change submissions to Health Canada require the new version not only to be compared with the pre-manufacturing change version, but with its current marketed RBD. This would ensure the products remain clinically similar. Without this coordination of policy, patients may be exposed to future unknown clinical risks, such as immunogenicity, adverse events and loss of efficacy.
Clinical and Economic Considerations

SEBs will provide important therapeutic options to promote competition in provinces faced with unsustainable pharmaceutical expenditures. However, the federal government has carefully outlined the regulatory requirements for SEBs as to promote innovation and economic development. Policies developed in Ontario will be specifically interesting as the province will have to balance the potential savings with the promotion and continued expansion of the pharmaceutical and biotechnology sector in the greater Toronto Area. This region is home to more than 163 biotechnology companies, and over 50 global pharmaceutical/biotechnology firms. The life science sector in Toronto is a major economic growth driver. The adoption of SEBs, and ultimately the savings associated with their increased use, comes down to two factors: physician’s perception of the products’ safety and efficacy (their willingness to prescribe) and the extent to which payers mandate their use through formulary decisions. The prior is more likely affect the adoption of SEBs in the early stages in Canada, as the latter will take time to develop effective, evidence-based policies. It is expected that both an SEB and its RBD will be listed when an SEB becomes available. Once marketed, tiered formularies are possible for new patients. This refers to a patient’s access to an originator product over an SEB, either through higher co-pays or physician-noted medical rationale.

Federal Naming Responsibilities
Health Canada has not established a new International Non-Proprietary Name (INN) for REMSIMA™/INFLECTRA™. The current INN remains infliximab, identical to the INN of the RBD - REMICADE®. Greek suffixes for SEB INNs have been used in other regions, as illustrated by Epoetin Alpha and Epoetin Zeta in Europe. Greek prefixes or suffixes would ensure that inappropriate interchange is avoided, and safety and health outcomes are properly monitored through effective pharmacovigilance programs. Pharmacovigilance programs monitor safety events associated with drugs, as controlled clinical trials often do not capture real world event likelihoods. Such programs are increasingly more important for SEBs as current clinical data is more limited than that of innovative products. Without a prefix or suffix, there remains a level of subjective interpretation on part of the pharmacist if the prescribing physician has written the INN rather than the brand name, which could result in inappropriate interchange.

Conclusion

Along with the EMA and U.S. FDA, Health Canada has established timely regulatory guidance surrounding SEBs. There are similarities and differences between regulatory requirements based on the structure of the varying political/regulatory systems. However, a demand for continued policy innovation exists in Canada regarding federal-provincial channels of communication with respect to SEB policy development, as well as considerations of SEB naming. The federal government should adopt the use of Greek prefixes and suffixes, and
implement new regulatory requirements for SEB manufacturing changes. Provincial
governments across Canada will have to make important decisions with regards to
formulary listings and interchangeability; they should not mandate
interchangeability until robust clinical data establishing the safety and efficacy of
switching between an SEB and RBD has been demonstrated. All policies must
carefully balance potential savings, the economic growth of Canada’s
pharmaceutical and biotechnology sectors, and most importantly patient outcomes.
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