Chapter 19

Regulation of Subsequent Entry Biologics

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OBJECTIVES

- Understand what subsequent entry biologics (SEBs) are and the complexities associated with their approval
- Understand the Canadian regulation of SEBs
- Understand the information and data required to support a New Drug Submission (NDS) for an SEB
- Understand patent linkage and data protection in the context of SEBs
- Learn the differences between Canadian, EU and US regulation of SEBs

LAWS, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER

- Food and Drugs Act
- Food and Drug Regulations
- Patented Medicines (Notice of Compliance) Regulations
- Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)
- Guidance Document: Patented Medicines (Notice of Compliance) Regulations
- Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations

Introduction

Biologics

A biologic drug, or simply a biologic, is a protein-based therapeutic that is derived from, or produced using, a living organism. More specifically, Health Canada defines a “biologic” as a drug that is listed in Schedule D of the Food and Drugs Act (F&DA). Schedule D lists both individual products (e.g., insulin and interferon) and product classes that are defined by their activity (e.g., immunizing agents), source (e.g., drugs, other than antibiotics, prepared from microorganisms) or method of preparation (e.g., drugs obtained by recombinant DNA procedures).

Health Canada has recognized that biologics are significantly more variable and structurally complex than small molecule chemical entities (SMCEs).

Subsequent Entry Biologics

Health Canada has adopted the term “subsequent entry biologic” (SEB) to describe a biologic that enters the Canadian market subsequent to a version previously authorized for sale in Canada, with “demonstrated similarity” to that previously authorized biologic. The biologic to which the SEB is compared is called a “reference biologic drug.”

The demonstrated similarity referred to in the definition of an SEB relates to similarity in the quality attributes of the two biologics determined by analytical and biological characterization. Once similarity is demonstrated, it can be concluded that: 1) any differences in quality attributes between the two biologics should have no adverse impact on the SEB’s safety or efficacy; and 2) nonclinical and clinical
data generated with the reference biologic drug are relevant to the SEB.

Comparison to EU and US

The term SEB is analogous to the term “biosimilar,” which is used by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) to describe subsequent entry or follow-on biologics.

In the EU, a “biosimilar” is defined by EMA as a biologic medicine “similar” to a biological reference medicine, with no significant differences between the products in safety or efficacy. According, the EMA definition includes a requirement that the biosimilar have a safety and efficacy profile similar to that of the reference product. Likewise, in the US, a biosimilar is defined as a biologic that is “highly similar” to a reference product, with no clinically meaningful differences between the products in safety, purity and potency.

The key difference in the Canadian definition of an SEB from the EU and US definitions of biosimilars is that it does not incorporate the concept of clinical similarity.

Regulation of Subsequent Entry Biologics in Canada

In Canada, the approval of both SMCEs and biologics are regulated by the Food and Drug Regulations (FDR).

In March 2010, Health Canada released a final version of its Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (SEB Guidance), which outlined an approval pathway for SEBs in Canada. While Health Canada previously stated that it intended to amend the FDR to provide a comprehensive legal basis for the approval of SEBs, it instead opted to regulate SEBs solely through guidance documents. To this end, the SEB Guidance states that SEBs are subject to the FDR for authorization and oversight and that conformance with the SEB Guidance, along with other guidance for biologics, should enable SEB sponsors to satisfy FDR requirements.

In particular, conformance with the SEB Guidance is said to allow a sponsor to comply with the following pivotal sections of Chapter C of the FDR:

“C.08.002 (1)(a): No person shall sell or advertise a new drug unless the manufacturer has filed with the Minister a New Drug Submission (NDS) relating to the new drug that is satisfactory to the Minister.

C.08.002 (2): A New Drug Submission shall contain sufficient information and material to enable the Minister to assess the safety and efficacy of a new drug.”

In other words, the SEB Guidance provides information on the safety and efficacy information required to support a New Drug Submission (NDS) for an SEB.

Health Canada accompanied the release of the SEB Guidance with amendments to Guidance Document: Patented Medicines (Notice of Compliance) Regulations (NOC Regulations Guidance) and Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations (Data Protection Guidance), which were amended to state that the current patent linkage and data protection laws were applicable to SEBs. Patent linkage and data protection are discussed in more detail later in this chapter.

Comparison to the EU and US

The creation of the Canadian SEB approval pathway differed from that of the EU and US biosimilar pathways, which were enabled through legislation rather than guidance documents. The EU biosimilar pathway was enabled by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. However, as in Canada, the details of the EU biosimilar pathway are largely set out in guidance documents developed by EMA.

In the US, the biosimilar pathway was enabled by Title VII of the Patient Protection and Affordable Care Act of 2010 (US act). The US act is more substantive than the equivalent EU enabling legislation and provides the secretary of the Department of Health and Human Services (DHHS) the authority to issue guidance on the licensing of biosimilars. In February 2012, FDA issued Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.

Reference Biologic Drug

Similar to a generic pharmaceutical drug, an SEB is a biologic that is approved based on a reduced clinical and nonclinical data package, which relies in part on the prior clinical or nonclinical data of a reference biologic drug. The reduced data package is justified by a demonstration of the SEB’s similarity to the reference biologic drug.

The SEB Guidance outlines a number of factors a sponsor must consider when selecting a candidate for an SEB and its corresponding reference biologic drug. The SEB sponsor must select a suitable candidate and reference product, and the onus is on the SEB sponsor to demonstrate the biosimilarity of the SEB to the reference product. The following should be considered when making the selection:

Ability to be Extensively Characterized

The most important consideration when selecting an SEB candidate and reference biologic drug is the ability of the biologics to be extensively characterized to allow for their comparison.

Health Canada stated in an early draft version of the SEB Guidance that it intended to develop guidance documents that would provide specific information about the data required to characterize and establish similarity for particular
biologics or classes of biologics. In the final SEB Guidance, Health Canada abandoned this approach and instead recommended that sponsors refer to the molecule- or class-specific guidance documents developed by EMA’s Similar Biological (Biosimilar) Medicinal Products Working Party, deeming that the scientific principles set out in these guidance documents are consistent with those of Health Canada.

While the SEB Guidance does not limit biologics eligible to be authorized as SEBs to those addressed in a molecule- or class-specific guidance, biologics addressed in an independent guidance are likely to be deemed acceptable as SEB candidates capable of characterization and comparison. These include each of the following biologics, which are the subject of molecule-specific EMA guidance documents:

- somatropin
- recombinant granulocyte-colony stimulating factor
- recombinant human insulin
- recombinant erythropoietin
- low-molecular-weight-heparins
- recombinant interferon alpha

The somatropin guidance document was one of the first molecule-specific guidelines released by EMA. Somatropin is the active ingredient of Sandoz Canada Inc.’s Omnitrope, which was the first SEB approved in Canada. Health Canada released its Summary Basis of Decision for the approval of Omnitrope (Omnitrope SBD) in September 2009. The Omnitrope SBD will be referenced throughout the remainder of this chapter to provide context to the principles outlined in the SEB Guidance. While the Omnitrope SBD was published prior to the release of the final SEB Guidance, it provides insight into the data required to support an SEB submission and into the decision-making process of Health Canada.

In addition, EMA has adopted guidance documents for a variety of biosimilars:

- Similar biological medicinal products
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues
- Similar biological medicinal products containing recombinant follicle-stimulating hormone
- Similar biological medicinal products containing interferon beta
- Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues
- Similar biological medicinal products containing recombinant erythropoietins
- Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Future guidance potentially may be gained from product class-specific guidance documents developed in the US. The US act provides authority to the DHHS secretary to release product class-specific guidance documents, including a guidance stating that a particular product or product class does not lend itself to the approval of a biosimilar. The SEB Guidance espouses a principle of international harmonization, which makes future guidance documents released in the US relevant to the Canadian context.

Approved and Marketed in Canada

The SEB Guidance states that the reference biologic drug should be approved and marketed in Canada. The SEB sponsor is required to name the authorized reference biologic drug to which the SEB is compared and will be subsequent. In the case of Omnitrope, the reference biologic drug Genotropin was approved in Canada, but never marketed there. This suggests that exceptions may be made to the “marketed in Canada” requirement.

While the reference biologic should be approved and marketed in Canada, a foreign proxy may be used in the comparative studies. This allows a sponsor to use data generated in other jurisdictions to avoid Canada-specific testing.
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However, if a sponsor wishes to use a foreign proxy, the following must be considered:

- The submission must establish a link between the Canadian reference biologic drug and the foreign proxy, including a demonstration that the two drugs are marketed by the same innovator company and in the same dosage form.
- The foreign proxy must be associated with sufficient data to support the submission.
- The foreign proxy must be from a jurisdiction that has a relationship with Health Canada.
- The foreign proxy must be widely marketed in a jurisdiction that formally adopts International Conference on Harmonisation (ICH) guidelines and has regulatory standards and principles similar to those of Canada.

As noted above, Genotropin was never marketed in Canada, which indicates that a foreign proxy was used for the comparison exercise for Omnitrope.

**Comparison to the EU and US**

The ability to use a foreign proxy of the reference product in the comparability exercise is possible in both Canada and the US. In the EU, the reference product must be used as the reference in the comparability exercise. The reference product also must be approved already on the EU market for the comparator product to be approved, once demonstrating comparability. Data generated from products authorized outside the community may be used only for supportive information.

In the US, the authorization of biologics is regulated by the *Public Health Service Act (PHS Act)*. The US act defines a “reference product” as the single reference biologic product licensed under subsection (a) of the *PHS Act* against which a biosimilar is evaluated in a submission for authorization of the biosimilar. If there is an approved reference product, it must be used in the comparability exercise.

**Significant Safety and Efficacy Data**

The *SEB Guidance* defines a “reference biologic drug” as a “biologic drug authorized on the basis of a complete quality, nonclinical, and clinical data package, to which an SEB is compared in studies to demonstrate similarity.” SEBs are excluded from this definition since they are approved on the basis of a reduced data package. This exclusion is implicitly stated in the *SEB Guidance*.

The *SEB Guidance* suggests that to be a suitable reference drug, a biologic should be associated with a body of safety and efficacy data that goes beyond that used to support its authorization. It notes that the reference biologic drug should have an “accumulated” body of data and a “substantial body of reliable data.” Thus, when selecting a reference biologic drug, an SEB sponsor must consider whether the reference biologic drug is associated with a substantial body of postapproval safety and efficacy data.

The case of Omnitrope suggests that Health Canada will consider safety and efficacy data from other jurisdictions when assessing the body of accumulated data of the reference biologic drug.

**Same Dosage Form, Strength and Route of Administration**

The *SEB Guidance* states that the SEB’s dosage form, strength and route of administration should be the same as those of the reference biologic drug.

The Omnitrope SBD demonstrates that deviation from the requirement of identical dosage form and strength may be allowed, if supported by data. Two dosage forms and strengths of Omnitrope that differed from the reference product were approved. Approval was based on data from pivotal safety and efficacy trials and comparative pharmacokinetic (PK)/pharmacodynamic (PD) data.

**Comparison to the EU and US**

The EU also requires that the pharmaceutical form, strength and route of administration of a biosimilar be the same as those of the reference biologic drug. However, EU guidance specifically allows exceptions, such as those seen with the Canadian Omnitrope submission, when additional data are provided to support the comparability exercise.

The US act requires a biosimilar submission to demonstrate that the biologic product’s route of administration, dosage form and strength are the same as those of the reference product. The US act does not allow for changes from the reference product in regard to the administration, dosage form and strength.

**Information Requirements for New Drug Submission (NDS)**

Section C.08.002 of the *FDR* requires a sponsor seeking authorization for a new drug to submit an NDS containing sufficient information and material to enable the minister of health (minister) to assess the new drug’s safety and efficacy. The *SEB Guidance* provides recommendations on the information required to meet this requirement for an SEB submission.

**Quality**

Like an NDS for a standard new biologic drug, an NDS for an SEB must include a full chemistry and manufacturing (C&M) data package. In addition, it must include comprehensive data demonstrating the SEB’s similarity to the reference biologic.
The comparison exercise should include a complete, side-by-side characterization that is a comparison of the biologics’ physicochemical properties, biological activity, immunochemical properties, purity, impurities, contaminants and quantity. The SEB Guidance provides a high-level description of considerations for each aforementioned comparison exercise and encourages sponsors to consider the concepts set out in ICH Q5C\(^4\) and ICH Q6B\(^5\) when developing and conducting the comparability exercise.

The SEB Guidance notes that it may be possible to carry out the quality comparability studies using the formulated drug products if the excipients do not limit the characterization assays’ sensitivity. However, in other cases, studies at the drug substance level will be required. If comparison at the drug substance level is required, and the reference drug substance is isolated from the reference drug product, additional studies should be conducted to demonstrate that the isolation process does not alter the drug substance.

The Omnitrope SBD provides little detail as to the quality comparability data submitted in support of the Omnitrope submission. The decision does conclude that a reduced clinical package is justified based on the comparison of the Omnitrope "drug substance and drug products" to the reference product, Genotropin.\(^4\) This suggests that comparisons were made at both the drug substance and drug product levels.

**Comparison to the EU and US**

The quality considerations set out in the SEB Guidance are similar to those in the EMA Quality Guidance.\(^6\) For example, as in Canada, the EU requires a submission for marketing authorization of a biosimilar to include a full quality dossier and data supporting the similarity of the biosimilar and reference biologic drug.

FDA has issued Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product.\(^7\) SEB Guidance, the Omnitrope SBD suggests that exceptions may be made to this rule.

**Clinical Studies**

Clinical trials involving SEBs are regulated in the same manner as trials for SMCEs and novel biologics. Accordingly, Clinical Trial Applications must be submitted for all trials involving SEBs, in accordance with the principles outlined in Chapter 6 Clinical Trials and Good Clinical Practice.

The SEB Guidance outlines the types of studies that typically will be required to support an SEB submission. These studies are discussed below.

**Pharmacokinetic Studies**

Comparative PK studies should be carried out to demonstrate similarity in the PK characteristics of the SEB and reference biologic drug. The SEB Guidance recommends PK studies be carried out in the relevant patient population (i.e., the patient population for which the product will be...
indicated). However, exceptions may be made where justifi-
able and no undue risk exists. In the case of Omnitrope, Health Canada accepted PK studies conducted in healthy volunteers.

Pharmacodynamic Studies
Comparative PD studies should be carried out to demon-
strate similarity in the PD characteristics between the SEB and reference biologic drug. The SEB Guidance notes that for certain molecules (e.g., recombinant human soluble insulin), only comparative clinical safety trials may be required. Equivalence trials are preferred over noninferiority trials, but in some situations, the use of noninferiority trials may be justified. Sponsors are, however, cautioned against relying solely on noninferiority trials because such reliance will make it difficult to extrapolate efficacy demonstrated for one indication to other indications. Sponsors should be aware that if the efficacy trials demonstrate a clinically meaningful superiority of the SEB candidate over the refer-
ence biologic, Health Canada will no longer consider the candidate to be an SEB.

Sponsors are encouraged to consult the EMA molecule-
and class-specific guidance documents for information pertaining to the clinical requirements for specific molecules.

The Omnitrope SBD provides greater insight as to the scope and type of clinical efficacy information required to support an SEB submission. A single pivotal Phase III efficacy study, consisting of three sequential sub-studies, was submitted in support of the efficacy of Omnitrope. All three sub-studies were conducted in the same cohort of 89 subjects in clinical sites in Poland and Hungary. Only the first sub-study, which lasted nine months, was comparative in nature. The single comparison trial was supplemented with two single-arm, long-term safety and efficacy trials carried out in sites in Poland, Hungary and Spain.

While clinical requirements will differ for different biologics and classes of biologics, the following observations can be made from the clinical data presented in the Omnitrope SBD:

• A single comparison study may be sufficient to demonstrate similar efficacy between an SEB and reference biologic candidate.

• Similar efficacy can potentially be demonstrated with a small sample size. The single Omnitrope comparison trial involved 89 patients, with 44 patients receiving Omnitrope and 45 patients receiving Genotropin.

• Non-comparative studies may be used to support similarities in efficacy and safety. In the case of Omnitrope, the first sub-study of the pivotal Phase III trial was the only comparative study. The remain-
ing two sub-studies in the pivotal trial and the two additional long-term safety studies were not comparative in nature.

• Data from the Canadian population may not be required. None of the Omnitrope clinical trials were conducted in Canada. Upon initial review of the clinical efficacy and safety data, Health Canada requested additional information to allow it to assess the efficacy and safety of Omnitrope in the Canadian population. The Omnitrope sponsor was able to satisfy this request with a re-analysis of the trial data using different national standards.

Comparison to the EU and US
The nonclinical and clinical requirements outlined in the SEB Guidance are similar to those set out in the EMA Clinical Guidance. There is further similarity between the clinical requirements of the two jurisdictions because, as noted above, the SEB Guidance directs sponsors to the EMA molecule-
and class-specific guidance documents, which outline clinical requirements for specific molecules and classes. Due to these similarities, in many cases, SEB sponsors may rely on clini-
cal data filed in support of an EU biosimilar submission, in support of a Canadian SEB submission.

One difference between the Canadian and EU guidance documents is that the EMA Clinical Guidance recognizes that, in some cases, efficacy and safety trials will not be required if comparability PK/PD studies have been con-
ducted, and the biologics are sufficiently characterized. The SEB Guidance seemingly mandates that safety and efficacy trials be conducted, with the exception of certain conditions where only safety trials will be required.

FDA issued Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. This guidance provides an overview of the clinical requirements regarding the biosimilar and reference product.

Approved Indications
The SEB sponsor may apply for one or more clinical indications for which the reference biologic is authorized. Each indication should be supported by clinical safety and effi-
cacy data. However, in certain circumstances, approval for an indication may be granted without clinical efficacy data, if justified, e.g., if comparative PK/PD data can sufficiently bridge the indication to another indication supported by clinical data.
Omnitrope was approved for both indications for which its reference product Genotropin was authorized, namely treatment of growth hormone deficiency (GHD) in children and adults, even though it was only tested in the paediatric population. Health Canada deemed it acceptable to extrapolate the paediatric data to the adult population due to the similarity between quality characteristics of Omnitrope and Genotropin and the similar pathology of GHD in the two populations.\(^5^1\)

According to the SEB Guidance, approval may be sought for an indication not held by the reference biologic drug if full clinical trial data are provided in support of the novel indication.\(^5^2\)

**Comparison to the EU and US**

The EU position with respect to authorization of a biosimilar in association with the indication(s) of its reference biologic drug is the same as that in Canada. Safety and efficacy must be demonstrated in association with each indication, but in certain instances, it may be possible to extrapolate therapeutic similarity shown for one indication to another indication.\(^5^3\) In the US, it appears that efficacy must be “demonstrated” for each indication.\(^5^4\) Without further guidance, it is unclear whether an extrapolation based on supporting data would be deemed to be a demonstration of efficacy.

The ability to seek approval for indications not associated with the reference biologic appears to be unique to Canada. EU guidance does not appear to cover approval for novel indications. The US act does not allow such an approval, because it mandates that a sponsor demonstrate in a biosimilar submission that the reference product had been previously approved for the indication that is being sought.\(^5^5\)

**SEBs Are not “Generic Biologics” or Interchangeable Products**

The SEB Guidance states that SEBs are not “generic biologics” and that the authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug. No further information is provided in the SEB Guidance regarding the interchangeability or substitutability of an SEB for its reference biologic or how SEBs will be dispensed by pharmacists. However, in a question and answer document that accompanied the release of the SEB Guidance, Health Canada released the following warning against interchangeability:

Health Canada does not support automatic substitution of a SEB for its reference biologic drug and recommends that physicians make only well-informed decisions regarding therapeutic interchange.\(^5^6\)

While Health Canada provided the above recommendation, it has stated that it will ultimately leave decisions regarding interchangeability up to the provinces.\(^5^7\)

To date, the majority of provinces have not made formal decisions as to whether they will allow postapproval declarations of interchangeability. At least one province (Alberta) has decided that SEBs will not be eligible for review as interchangeable products.\(^5^8\)

**Patent Linkage and SEBs**

As with SMCEs, the grant of a Notice of Compliance (NOC) for an SEB in Canada is linked to the patent status of the reference biologic drug. According to the SEB Guidance, this linkage is regulated by the existing Patented Medicines (Notice of Compliance) Regulations (PM(NOC) Regulations)\(^5^9\) and the related NOC Guidance, which was amended in March 2010 to implicitly state that SEBs fall within the scope of the PM(NOC) Regulations. A brief discussion of the application of the PM(NOC) Regulations to SEBs is set out below, while a more comprehensive
description of the PM(NOC) Regulations can be found in Chapter 15 of this book.

The amended NOC Guidance states that SEBs fall within the ambit of Section 5 of the PM(NOC) Regulations because a submission for an NOC for an SEB will compare the drug with, or make reference to, another biologic drug marketed in Canada as described by Section 5 of the PM(NOC) Regulations. In other words, a sponsor who files a submission for the authorization of an SEB is a “second person” within the meaning of the PM(NOC) Regulations and is subject to all of the requirements placed upon a second person.

Under the PM(NOC) Regulations, the minister of health maintains a register of patents (the Patent Register) that is analogous to FDA’s Orange Book, which lists patents that are relevant to authorized innovative drugs. A “first person” who files an NDS, or a supplement to an NDS, may submit to the minister a list of patents that relate to the submission for addition to the Patent Register. For some time, the minister has been listing patents on the Patent Register against biologics, including patents listed against recombinant proteins (e.g., filgrastim, r-met Hu G-CSF) and monoclonal antibodies (e.g., rituximab). These patents were listed even though at the time there was no pathway in place for the approval of a subsequent product.

Patents eligible for listing on the Patent Register contain a claim for the medicinal ingredient, the formulation that contains the medicinal ingredient, the dosage form or the use of the medicinal ingredient. A notable exclusion to this list is patents containing claims to a method of isolating or producing a medicinal ingredient. Claims of this type are of greater significance to biologics than to SMCEs because biologics are in part defined by their method of production (i.e., biologics are defined as drugs “isolated” from living matter or “produced” in living cells). For example, as set out above, Schedule D of the FDC Act classifies drugs obtained by recombinant DNA procedures as biologics. Despite the importance of method and process claims to the protection of biologics, Health Canada opted not to amend the listing requirements of the PM(NOC) Regulations to encompass these types of claims.

The PM(NOC) Regulations require a second person who files a submission for a drug that compares the drug to the reference drug to address the patents listed on the Patent Register against the reference drug. Accordingly, a second person that files a submission for authorization of an SEB must address any patents listed on the Patent Register against the reference biologic drug as required by the PM(NOC) Regulations. The process of addressing the listed patents is the same as that for SMCEs, which is discussed in Chapter 15 of this book.

Comparison to the EU and US

There is no system of patent linkage in the EU for either SMCEs or biologics.

In the US, SMCEs and biologics are regulated under different acts, namely the Federal Food, Drug, and Cosmetic Act (FDC Act) and the PHS Act, respectively. The Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act), which is the American equivalent of the PM(NOC) Regulations, only applies to drugs approved under the FDC Act.

Instead of amending and expanding the scope of the Hatch-Waxman Act to encompass drugs approved under the PHS Act (i.e., biologics and biosimilars), the US act created a complex new system for resolving patent disputes arising from a biosimilar submission. The system will be discussed summarily to highlight the differences between the US and Canadian systems.

The system under the US act involves several exchanges of information between the biosimilar sponsor and the reference product sponsor that are triggered by the filing of a sponsor’s submission for approval of a biosimilar. Throughout the process, the parties exchange information pertaining to: 1) the manufacture of the biosimilar; 2) patents the parties allege are infringed or believe may be infringed; and 3) factual and legal bases from the parties regarding the infringement/non-infringement and validity/invalidity of the identified patents.

The primary difference between the US and Canadian schemes is that, unlike the linkage system in Canada, the scheme under the US act does not link the approval of the biosimilar to the reference biologic’s patent status, because it does not permit an automatic stay of the approval of the biosimilar submission. The US act does, however, require the biosimilar sponsor to provide notice to the reference product sponsor 180 days before market entry. In certain circumstances, the reference product sponsor may, in response, seek a preliminary injunction to prevent the sale of the biosimilar. Therefore, the US scheme does not provide a true system of patent linkage, because there is no automatic stay prohibiting approval while the patent issues are decided.

Another distinction between the Canadian and US systems is that the scope and type of patents at issue in the US are more encompassing than in Canada. Since, under the US act, any patent that may be infringed may be at issue, patents having method claims may be subject to litigation. In contrast, such claims are not eligible for listing on the Patent Register in Canada and, consequently, are irrelevant to proceedings under the PM(NOC) Regulations.

In summary, the Canadian patent linkage system for SEBs is unique because it provides a true linkage between the approval of the SEB and the reference biologic drug’s patent status. Neither the EU nor the US has a similar system for biologics.
Data Protection of the Reference Biologic

The SEB Guidance states that SEBs are subject to the existing data protection provisions under C.08.004.1 of the FDR (the Data Protection Provisions). The Data Protection Guidance, which provides guidance with respect to the Data Protection Provisions, was amended by Health Canada in March 2010 to implicitly state that these provisions apply to SEBs.

The Data Protection Provisions provide periods of “data exclusivity” and “market exclusivity” for “innovative drugs.” The data exclusivity period is the interval in time during which a sponsor is prevented from filing a submission for an NOC for an SEB that compares the SEB to an innovative reference biologic drug. In Canada, a sponsor may not file a submission for an SEB until six years after the day on which the first NOC for the innovative biologic reference drug was issued.

The market exclusivity period is the interval during which the minister is prevented from approving the SEB submission and issuing an NOC for it. In Canada, the minister is prevented from approving the SEB until eight years after the day on which the first NOC for the innovative biologic drug was issued. This period may be extended by six months if the innovative drug sponsor has provided the minister with the description and results of clinical trials relating to the use of the innovative drug in relevant paediatric populations.

For the purpose of these exclusivity periods, Health Canada defines an innovative drug as a drug that contains a medicinal ingredient not previously approved in a drug by the minister and that is not a variation of a previously approved medicinal ingredient. The Data Protection Guidance states that an SEB will not be considered an “innovative drug.”

It is important to note that exclusivity is afforded only to “innovative drugs” and not simply to any drug that is issued an NOC based on a submission comprising a complete data package. This may be an important consideration for an SEB sponsor when selecting a suitable reference biologic drug, because one potential reference biologic may be an “innovative drug” subject to periods of exclusivity, while a subsequently approved product may not. Accordingly, it is recommended that sponsors consult the register of innovative drugs maintained by the minister prior to selecting a reference product.

Comparison to the EU and US

The Canadian market exclusivity periods for SEBs are shorter than those afforded to biosimilars in both the EU and the US.

In the EU, biosimilars are afforded eight years of data exclusivity and 10 years of market exclusivity. The period of market exclusivity may be extended by a year in the event of the authorization within the first eight years of a new indication that represents a significant clinical benefit in comparison with existing therapies. The exclusivity afforded in the EU is also more expansive than that in Canada because it applies to any reference product to which a biologic is compared, regardless of whether it is “innovative.”

In the US, the data exclusivity period afforded to biosimilars is only four years. However, more importantly, a 12-year market exclusivity period is afforded to biologics, which is four additional years of protection compared to Canada. As in the EU, there is no equivalent to the Canadian requirement that the reference biologic be “innovative.”

The US act also provides a period of interchangeable exclusivity for the first biosimilar to be declared interchangeable with a reference product, in which no other biosimilar may be declared interchangeable. This period can extend up to one year after first commercial marketing of the first interchangeable biosimilar.

Summary

- The approval of SEBs in Canada is regulated by Health Canada under the existing FDR. Health Canada has published the SEB Guidance to inform SEB sponsors of how to comply with the FDR.
- Many of the principles in the SEB Guidance addressing quality, nonclinical and clinical issues are similar to those established in EU guidance documents. Since the SEB Guidance allows a sponsor to utilize a foreign proxy for the reference product in comparability studies, in many cases data filed in support of an EU submission may be used in support of a Canadian SEB submission.
- SEBs are subject to the existing patent linkage regulations established by the PM(NOC) Regulations. Accordingly, an SEB sponsor is required to address any patents listed on the Patent Register against the reference biologic drug at the time of filing the SEB submission.
- SEBs are subject to the existing data protection provisions established by the FDR. Accordingly, innovative biologics are afforded six years of data exclusivity and eight years of market exclusivity.

References

4. C.R.C., c. 870 (the “FDR”).
7. Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations, 8 March 2010 (the "Data Protection Guidance”).
11. Op cit 1, s. 2.1.3.
12. Op cit 5, s. 1.3.8.
13. Op cit 1, s. 2.6.
24. Op cit 3, SEC. 7002, ss. (k)(8)(D) and (E).
25. Op cit 1, s. 2.1.3.
26. Op cit 20, p. 4, s. 3.
27. Op cit 1, s. 2.1.3.1.
28. Op cit 10, s. 2.2.
29. 42 USC 201 ("PHS Act”).
31. Op cit 1, p. 3, s. 1.4.
32. Ibid, p. 5, s. 2.1.3.
33. Ibid, s. 1.2.
34. Ibid, s. 2.1.3.
35. The Omnitrope reference product Genotropin was approved in Canada in the form of 1.5 mg, 5.8 mg and 13.8 mg powders for solution, which corresponded to final concentrations after reconstitution of 1.3 mg/mL, 5 mg/mL and 12 mg/mL, respectively. In addition to the 5.8 mg powder for solution, two dosages and strengths of Omnitrope that differed from the reference product were approved, namely 5 mg/1.5 mL and 10 mg/1.5 mL solutions. The authorization of the 5 mg/1.5 mL solution was based on data from the pivotal safety and efficacy trials, and the 10 mg/1.5 mL solution was approved based on comparative PK/PD data that demonstrated similarity to the 5.8 mg powders for solution of Omnitrope and Genotropin.
36. Op cit 10, s. 2.2.
38. Op cit 1, p. 7, s. 2.3.1.
41. Op cit 20, s. 3.1.5.
42. Op cit 10.
43. ICH Q5c: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.
44. Op cit 1, p. 13, s. 2.3.2.2.
45. For example, the Omnitrope submission provided two PD studies. One of the studies did not compare Omnitrope to the reference biologic drug but rather compared Omnitrope to an international reference standard (Omnitrope SBD, supra note 21, s. 4.1). Similarly, the only repeat-dose toxicity study presented in the Omnitrope submission was not comparative in nature but was nevertheless deemed to meet the nonclinical requirements (Omnitrope SBD, supra note 21, s. 4.1).
47. Op cit 20, s. 3.3.2.
49. Ibid, p. 5, s. 4.2.
50. Op cit 1, s. 2.3.2.1, p. 12.
51. Op cit 21, s. 3.3.2, p. 14.
52. Op cit 1, s. 2.3.2.1, p. 13.
53. Op cit 10, p. 3, s. 1.
59. Op cit 10, s. 2.1.
60. Op cit 5, s. 1.3.6.
63. SOR/93-133 (the “PM(NOC) Regulations Guidance”).
64. Ibid, s. 4.
65. 21 USC 301 (the “FD&C Act”).
67. Op cit 3, SEC. 7002, ss. (1).
69. For example, several somatropin products have been approved in Canada based on complete data packages; the first approved product
was Serono Canada Inc.’s Saizen. While Saizen was likely an “innovative drug” at the time of its authorization, subsequently approved somatropin products would likely not be considered innovative.


73. Op cit 3, SEC. 7002, ss. (k)(7)(B).

74. Ibid, SEC. 7002, ss. (k)(7)(A).

75. Ibid, SEC. 7002, ss. (k)(6).