



Canadian IP Law News | June 2008



Subsequent Entry Biologics – How They Affect Your Patenting Strategy

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Health Canada recently released a draft guidance document, for public comment only, in respect of a proposed regulatory approval process for Subsequent Entry Biologics (SEBs).¹ This guidance document is the first step in the development of a comprehensive regulatory system to address SEBs that will, in all likelihood, also include regulatory amendments.

Since its release, the guidance document has been the subject of considerable public commentary. Key elements are briefly described below:

- **Definition of SEB:** Health Canada describes biologic products as those derived through the metabolic activity of living organisms. These products are listed on Schedule D of the *Food and Drugs Act* (i.e., blood products, cells and tissues, gene therapies, vaccines, etc.). An SEB is defined as a biologic product that would enter the market subsequent to, and “similar” to, an approved innovator biologic product. Such products could rely, to some extent, on the safety and efficacy data of an approved innovator product where they could demonstrate similarity with the approved product.
- **Proposed Regulatory Framework:** Health Canada proposes to utilize the existing regulatory framework for pharmaceuticals and biologics (i.e., Part C, Division 8 of the *Food and Drug Regulations*) with some modification. A manufacturer of an SEB will be required to submit a New Drug Submission, which may be based on reduced clinical data where the manufacturer can demonstrate similarity between the SEB and a chosen reference product.
- **Similarity:** The guidance document indicates that a manufacturer must demonstrate comparability/similarity through extensive data, including side-by-side characterizations of the SEB and the reference product. Manufacturers will be required to demonstrate that the SEB and reference product are comparable in terms of quality, safety, and efficacy. It is important to note, however, that manufacturers will not be required to demonstrate that the two products are identical. Rather, the manufacturer will be required to establish that the two products are similar enough that the existing knowledge of both products sufficiently indicates that any quality attribute differences should have no adverse impact on the safety or efficacy of the SEB.
- **Reference Product:** The reference product should be an approved biologic product marketed in Canada. The Minister of Health may, however, consider an approved reference product from another jurisdiction upon request. The reference product should have “a suitable

¹ Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), available at <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/consultation/seb-pbu/2008-tc-tm-eng.php>.

duration and volume of marketed use such that a demonstration of similarity will bring into relevance a substantial body of acceptable data dealing with safety and efficacy.” An SEB cannot be used as a reference product for subsequent submissions since it will not have been authorized on the basis of a complete quality and clinical data package.

- Indications: An SEB will not be readily granted approval for all of the indications of the reference product. The indications granted will depend on the data provided by the manufacturer.
- Product Monograph: A manufacturer of an SEB cannot rely on the product monograph of the reference product.

Implications for Intellectual Property Protection of Biologics in Canada

In Canada, innovators of drug products have three main routes to prevent (for a limited period of time) “generic” versions of their drugs from entering the Canadian marketplace: through a patent infringement suit under the *Patent Act*; through the data protection provisions under the *Food and Drug Regulations*, or through the *Patented Medicines (Notice of Compliance) Regulations*.

Generally speaking, biologic products tend to have a lengthy patent prosecution and regulatory approval period thereby providing a shorter period of exclusivity in the marketplace if relying on the *Patent Act* alone for protection. Moreover, patent infringement suits are often protracted and expensive. Additional market exclusivity protection through the *Food and Drug Regulations* and the *Patented Medicines (Notice of Compliance) Regulations* is, therefore, particularly appealing for innovators of these products.

Under the *Food and Drug Regulations*, a drug that meets the definition of an innovative drug under c.08.004.1 (i.e., a drug that contains a medicinal ingredient not previously approved in a drug by the Minister that is not a variation of a previously approved medicinal ingredient, such as a salt, enantiomer, solvate or polymorph), is eligible for an 8-year data protection period, or 8 ½ years for a drug with clinical studies in pediatric populations. This means that competitors wishing to directly or indirectly compare their “generic” product to the innovator’s product are prevented from receiving market authorization during this period.

The guidance document does not specifically address the issue of data protection in respect of biologics. It does, however, state that “all laws, patent and intellectual property principles outlined within the *Patent Act*, *Food and Drug Regulations (Data Protection)*, and *Patented Medicines (Notice of Compliance) Regulations* are applicable to SEBs” thus suggesting that the data protection restrictions will apply to SEBs.

Several issues, however, may arise in respect of the application of the data protection provisions to biologics. Complex biologics may contain large molecules that differ from a previously approved product by just a few amino acids or nucleotides, but have significantly different effects. It is unclear whether these “slight” differences in the sequence of the product will be viewed by Health Canada as “variations” or as a distinctly different “innovative” product. In effect, the question arises as to whether biologics should be defined by their physico-chemical properties, biologic function, or both. These issues have never been meaningfully addressed since no regulatory approval process for SEBs currently exists; however, with many biologics approaching the end of their patent exclusivity period and work currently underway by Health Canada to develop a regulatory process for SEBs, the application of the data protection provisions in the context of biologic products will no doubt be further debated and clarified by Health Canada and/or the Federal Court.

The guidance document also suggests that manufacturers of SEBs will be subject to the requirements under the *Patented Medicines (Notice of Compliance) Regulations*. Currently, when

an innovator files a new drug submission, or a supplemental new drug submission, it may list patents on the Patent Register in respect of the product to which the submission pertains if the patent claims: a medicinal ingredient, a formulation or change in a formulation that contains a medicinal ingredient; a dosage form or change in the dosage form; and a use of the medicinal ingredient or change in the use. The claim for the medicinal ingredient may be chemical or biological in nature. Any subsequent submission seeking regulatory approval based on a direct or indirect comparison to the innovator's product must address each patent listed on the Patent Register in respect of the innovator's product before regulatory approval will be granted.

The guidance document implies that manufacturers of SEBs will be required to address patents listed on the Patent Register in respect of their chosen reference product. There is, however, some uncertainty as to how the provisions of the *Patented Medicines (Notice of Compliance) Regulations* will accommodate the unique characteristics of most biologics. For example, how will a medicinal ingredient be defined or viewed in the context of biologic products? Will a biologic product used to create another substance *in vivo*, which then carries out a therapeutic function be considered a medicinal ingredient? Once again, these issues will need to be clarified, either through Health Canada, legislative amendments and/or by the Federal Court.

Lastly, the current scheme under the *Patented Medicines (Notice of Compliance) Regulations* excludes process patents. In the context of biologic products, however, manufacturing processes are often critical to biologic production. Accordingly, in order to protect and foster innovation in this area, any proposed regulatory pathway for SEBs must ensure adequate protection for biologics utilizing these processes for the purposes of developing innovative medical treatments. This issue will likely have to be addressed through legislative amendments rather than through guidance for industry if protection beyond what may be available under the *Patent Act* is to be afforded.

Strategies for Innovators of Biologic Products:

The draft guidance document is the first step in the development of a regulatory pathway for SEBs in Canada. With an increasing number of biologics coming off patent in the near future, the interest in the development and regulatory approval of SEBs is likely to increase.

In comparison to chemically synthesized drugs, there are relatively few patents listed on the Patent Register in relation to approved biologics. Innovators have not yet had to deal with competition in relation to "similar" products, nor have they had to deal with the intense judicial scrutiny in relation to eligibility for patent listing under the *Patented Medicines (Notice of Compliance) Regulations* as have innovators of chemically synthesized drugs. With the real possibility of SEBs entering the marketplace, innovators of biologic products may, however, wish to leverage the various regimes available to them in order to strategically maximize opportunities for protection of their products in the future.

Innovators have a prime opportunity to consider their patenting strategies in conjunction with opportunities for data protection early on in the development of their biologic products to maximize the period of exclusivity available in the marketplace. Patent filing and claim drafting strategies that are layered in multiple applications, and over time, generally afford greater flexibility in this regard. The objective is to ensure that if eligibility for data protection exists, patents can also be eligible for listing on the Patent Register in such a way so as to not preclude downstream products from eligibility for data protection and patent listing.

Given that reservations exist as to the extent of protection the *Food and Drug Regulations* and *Patented Medicines (Notice of Compliance) Regulations*, as they are currently drafted, will afford innovators of biologics, innovators need to advocate their interests, particularly in the context of legislative or policy debate, through participation in Health Canada's consultation processes.