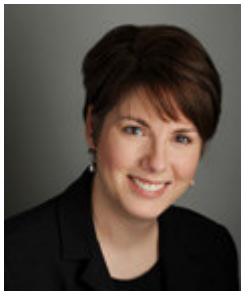

Health Canada Finalizes Regulatory Approval Process for Subsequent Entry Biologics

Tanya Weston

On March 5, 2010 Heath Canada released its "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics ["SEBs"][1] in order to enable sponsors to satisfy the information and regulatory requirements under the *Food & Drugs Act* and *Regulations* for the authorization of SEBs in Canada. The final guidance document has been the culmination of ongoing consultations since January 2008 resulting in the release of two prior draft documents. The final guidance document was released in conjunction with updated guidance documents relating to the *Patented Medicines (Notice of Compliance) Regulations* ["*PM(NOC) Regulations*"][2] and Data Protection under C.08.004.1 of the *Food & Drug Regulations*.[3]

Interestingly, Health Canada approved the first SEB in Canada prior to finalizing the guidance document. Sandoz Canada's Omnitrope™ product was approved on the basis of demonstrated similarity to Pfizer's Genotropin® product, an approved biologic for the treatment of growth hormone deficiency.[4]

Biologic products are defined as products derived through the metabolic activity of living organisms. These products are listed on Schedule D of the *Food and Drugs Act* and include blood products, cells and tissues, gene therapies, vaccines, etc. Health Canada defines an SEB as a biologic product that would enter the market subsequent to an approved innovator biologic product by relying, to some extent, on the safety and efficacy data of an approved innovator product where they could demonstrate similarity with the approved product.

The guidance document utilizes the existing regulatory framework for pharmaceuticals and biologics (i.e., Part C, Division 8 of the *Food & Drug Regulations ["Regulations"]*) and highlights the modified application of this framework to SEBs.[5] When seeking an authorization for sale, a

[1] **http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/notice-avis_seb-pbu_2010-eng.php.**

[2] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php.

[3] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/data_donnees_protection-eng.php

[4] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/nd_ad_2009_omnitrope_113380-eng.php.

[5] It is important to note that SEB's are not regulated as small molecules and as such are not subject to the abbreviated drug submission provisions. A sponsor of an SEB must file a new drug submission.

manufacturer of an SEB will be required to submit a new drug submission that may be based on reduced clinical data where the manufacturer can demonstrate similarity between the SEB and a chosen reference product that is a previously approved biologic. For the present context, a reference product is a biologic drug that has been authorized for use on the basis of a complete package of quality, clinical and non-clinical data. Similarity means that the existing knowledge of both products is sufficient to predict that any differences in quality attributes should have no adverse impact on safety or efficacy of the SEB.[6]

One of the more controversial aspects of the guidance document relates to the Minister of Health's willingness to consider an approved reference product from another jurisdiction as is currently also possible for generic chemically synthesized drugs under C.08.002.1 of the *Regulations*. In addition to other requirements, a sponsor of an SEB must demonstrate that the foreign reference product is suitable for the purposes of demonstrating similarity. More particularly, the sponsor must demonstrate that the foreign reference product is marketed by an innovator company that has approval to market the medicinal ingredient in the same dosage form in Canada. It should be noted that Sandoz Canada was successful in gaining market authorization for its Omnitrope™ product based on a comparison to Genotropin® as foreign reference product. Pfizer had received approval for Genotropin® but had not yet commenced marketing in Canada.

The guidance document and update to the guidance document on data protection are clear that Health Canada considers that SEBs will be subject to the same submission filing and approval restrictions of the data protection provisions in situations where they have relied on an "innovative drug."[7] The guidance document confirms that an SEB submission based on a comparison to a reference biologic that qualifies as an "innovative drug" will not be accepted within six years from the first market authorization of the reference product and actual market authorization will not be granted within eight years from said market authorization.[8] In the circumstances where an SEB submission is relying on a foreign reference product marketed by an innovator company that has approval to market the medicinal ingredient in the same dosage form in Canada, and whose approved Canadian product is eligible for data protection, the data protection provisions will apply, as noted above.

As noted in our June 2008 newsletter,[9] several issues may arise in respect of the application of the data protection provisions to SEBs. A chosen reference product may contain large molecules that differ from a previously approved product by just a few amino acids or nucleotides, but have

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[6] The guidance document indicates that a manufacturer must demonstrate similarity through extensive data, including side-by-side characterizations of the SEB and the reference product. Similarity will primarily be deduced from comprehensive quality studies. Manufacturers will be required to demonstrate that the SEB and reference product are comparable in terms of quality, safety, and efficacy.

[7] Part C.08.004.01 of the *Food & Drug Regulations* provides a term of protection for drugs that qualify as and "innovative drug." A manufacturer who wishes to obtain market authorization for its product on the basis of a direct or indirect comparison to an "innovative drug" is prohibited from filing its respective drug submission for a period of six years from the date the first market authorization was issued in respect of the "innovative drug." Market authorization for the drug making a direct or indirect comparison to the "innovative drug" will not be granted for a period of eight years. An additional six months protection is afforded to the "innovative drug" if its drug submission includes clinical trials in pediatric populations.

[8] An additional six months protection is provided if the reference product's submission has included clinical trials in paediatric populations.

[9] http://www.mbm.com/News/Quarterly%20e-Newletter/Articles/HTML/Jun%202008%20Articles/Biologics.html

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. The definition of an "innovative drug" in the *Regulations* was developed in the context of chemically synthesized drugs and, as such, is not well-suited to deal with complex biologics. Moreover, in situations where an SEB is demonstrating similarity to a foreign reference product whose approved Canadian product has received market authorization but has not commenced marketing in Canada, the data protection provisions may not apply, regardless of whether or not the product in question would be classified by Health Canada as an "innovative drug."[10]

The guidance document and update to the guidance document on the *PM(NOC) Regulations* is clear that manufacturers of SEBs will also be subject to the requirements under the *PM (NOC) Regulations*.[11] More particularly, a sponsor of an SEB that makes a direct or indirect comparison to a reference biologic will be required to address all patents listed on the Patent Register in respect of that reference product. The guidance documents also indicate that supplemental submissions in respect of an SEB for a change in formulation, dosage or use of a medicinal ingredient that relies on similarity to a reference biologic will also be captured under the *PM(NOC) Regulations*.

Interestingly, the guidance documents attempt to clarify situations where a foreign reference product is utilized. The documents indicate that where an SEB submission attempts to demonstrate similarity with a foreign reference product, the submission will be viewed by Health Canada as making a comparison to the approved Canadian product marketed in Canada, thus triggering the *PM(NOC) Regulations.* It is important to note, however, that the guidance documents do not address situations where the submission is based on a foreign reference whose Canadian product is approved but has not yet been marketed in Canada . This situation arose with respect Sandoz using Genotropin® in order to seek approval for Omnitrope™. In such a scenario, a sponsor of an SEB may argue that s.5(1) & (e) of the *PM(NOC) Regulations* are not met since the drug has not been "marketed in Canada". Given the uncertainty, this may encourage innovative drug manufacturers to market their drugs in Canada.

It is important to note that Health Canada acknowledges that the guidance document is intended to reflect Health Canada's policy within an existing regulatory framework. As such, the guidance document is an administrative instrument that does not have a "force of law". However, given the highly litigious nature of the regulatory approval process for chemically synthesized drugs, the application of this policy to biologics will no doubt be further debated and clarified by Health Canada and/or the Federal Court.

[10] See C.08.004.1(5) of the *Food & Drug Regulations*.

[11] Currently, when an innovator files a new drug submission, or a supplemental new drug submission, under the *PM(NOC) Regulations,* 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