

# Health Canada Aims to Finalize its Biosimilar Pathway Guidances

by Adrienne M. Blanchard

**H**ealth Canada is continuing its consultation on the development of an appropriate framework for approving subsequent entry biologics (SEBs). Unlike the United States, the Canadian government has taken the position that it has the jurisdiction to issue approvals for SEBs, and that a new regulatory authority is not required in order to proceed with SEB approvals. Indeed, the first SEB was approved in Canada on April 22, 2009 under the new drug submission regulations of the *Food and Drug Regulations* (Section C.08.002(2)). As in the European Union (EU) and the United States, the first approved product in this country was Sandoz Canada's OMNITROPE, a follow-on version of GENOTROPE.

While Health Canada's position has been that it has authority to issue marketing approval without

a new set of regulations, it has been consulting on a guidance document setting out requirements for SEB manufacturers. The first guidance for consultation released in January 2008 was entitled "*Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics*." Over 2008, Health Canada engaged in consultations, and published a revised draft guidance on March 27, 2009 for further consultation. Comments were due by May 26, 2009.<sup>1</sup>

## Intellectual Property Concerns

Throughout consultations, the innovative industry expressed concerns that SEB manufacturers could bypass the provisions of two key sets of regulations that protect the intellectual property of innovative products in Canada—the *Patented Medicines (Notice of Compliance) Regulations* (the Linkage Regulations) and Section C.08.004.1 of the *Food and Drug Regulations* (the Data Protection Regulations). Of primary concern was that the January 2008 guidance did not address how Health Canada would apply these two important protections, merely stating that all intellectual property protections would be applied. In response to the concerns, draft amendments to the two existing guidances



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for these regulations were released for comment concurrently with the SEB draft guidance.<sup>2</sup>

Under these amendments, the guidances attempt to clarify how Health Canada intends to apply these rules to sponsors of SEBs.

By way of background, the Linkage Regulations (Canada's version of the Hatch-Waxman system) require patents listed on the Patent Register (similar to the *Orange Book*) to be addressed wherever there is a "direct or indirect" comparison or reference to a product with listed patents. As set out in the current draft SEB guidance, "By definition, an SEB relies on prior information from the reference biologic drug and an approval could be granted based on a reduced amount of clinical information tailored to each class of products and/or case." The draft SEB guidance goes on to state, "An SEB would only be authorized for sale based on a submission that makes a *direct or indirect comparison* to an innovator biologic product for the purposes of demonstrating similarity." The proposed amendments to both the Linkage Regulations guidance and Data Protection Guidance contain similar comments, implying that in all cases—given that an SEB by its nature will be comparative—the regulations will be applied by Health Canada. In doing so, the draft guidances attempt to

track the regulatory language of both sets of regulations, supporting Health Canada's position that SEBs shall be subject to the Linkage Regulations and the Data Protection Regulations.

Biologic patents are listable on the Patent Register in Canada provided they meet the requirements of subject matter, timing and relevance to the marketed product. In accordance with the draft guidances, an SEB manufacturer should need to "address" relevant patents listed on the Patent Register, either by agreeing to await patent expiry, or by sending a "notice of allegation" to the patentee, alleging either non-infringement or invalidity.

However, while Health Canada's intended practice, as set out in the draft guidances, supports the application of the Linkage Regulations whenever an SEB uses an innovative biologic as a reference product, it is likely to be challenged. Guidelines are not regulations and it is the regulatory language that will govern. Without new and clear regulations, it is expected there will be litigation relating to the scope of the guidances and their consistency with the regulations. Health Canada's position is that current and ongoing initiatives under the legislative and regulatory renewal at the Ministry will provide a better forum for developing a specific regulatory pathway for SEBs. However, the lack

of regulations is concerning to the innovative industry.

## Interchangeability Concerns

Similarly, the issue of whether an SEB should be interchangeable with its innovative counterpart has been hotly debated in Canada.

Health Canada's initial draft guidance had correctly pointed out that approval through the SEB pathway does not necessarily mean the product can be substituted with the reference product used by the SEB to obtain approval. This reference raised speculation that Health Canada, as the federal regulator, may play a role in attempting to make determinations of interchangeability. The view of many stakeholders, however, is that Health Canada, as the body that determines safety and efficacy, should play no such role. This would be consistent with the practice in many European countries which prevents interchangeability, except under a physician's express direction.

There is no reference to interchangeability or substitutability concepts in the current draft guidance; it merely states that, "Authorization of an SEB is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic drug." While this statement does not necessarily preclude Health Canada from becoming involved in such determinations in future, it should ensure, as a starting point, that approvals of SEBs will contain no statements of equivalence. Indeed, in the OMNITROPE product monograph (PM), there is no statement of equivalence with the reference product GENOTROPE.

**These issues will no doubt continue to be the subject of much debate, particularly as SEB versions of newer biologics begin to appear.**

## Product Monograph/ Labeling Requirements

The draft guidance provides few specifics on the nature of statements permitted in an SEB's labeling/Product Monograph (PM). The current draft guidance states that the SEB will not be able to utilize the PM of the reference biologic drug in its entirety as its own, and that the PM should be developed in a manner that is consistent with the existing guidance at Health Canada. The guidance states further, "there should be no claims for bioequivalence between the SEB and reference biologic drug" and "there should be no claims for clinical equivalence between the SEB and the reference biologic drug." While these restrictions are commendable, for clarity's sake there should be a requirement that the PM include a statement specifically stating non-equivalence with the reference product used to obtain approval, consistent with Health Canada's position in the draft guidance.

## Potential Use of Foreign Reference Products

Another significant issue arising from the draft guidance is the ability of an SEB manufacturer to use a non-Canadian reference product to obtain approval. While the March 2009 guidance was somewhat clearer on this point than the initial draft guidance, the circumstances in which a foreign reference product can be used as the product to which an SEB is compared are yet to be fully defined.

The initial draft guidance raised concerns that an SEB manufacturer could compare its product to a foreign product that had never before

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been approved in Canada in order to obtain approval. The March 2009 draft guidance indicated that, while it will be possible to use a foreign version of a product, the product must have been approved in Canada. However, the product need not have been actually marketed in Canada.

The draft guidance now states that, where a foreign reference product is used, the SEB submission must include sufficient information to explicitly explain the link between the foreign reference biologic drug used in any comparative studies to the version of the innovator product that is approved in Canada. The proposed guidance further specifies that, in order to sufficiently explain the link between the non-Canadian reference biologic drug and the version of the product authorized for use in Canada, the submission must contain documentation that the non-Canadian reference biologic drug is marketed by the same innovator company or corporate entity that is approved to market the medicinal ingredient in the same dosage form in Canada, or that it is marketed through a licensing arrangement with the innovator company or corporate entity that currently markets the version of the product approved in Canada.

While these statements clarify the earlier draft guidance, many questions remain on how this policy

will play out, from both a safety perspective and an intellectual property perspective. For example, it is unknown how Health Canada will be able to satisfy itself as to the safety and efficacy of the product without having a track record in the Canadian population. While documents released with the most recent guidance from Health Canada indicate that the department will not require that reference biologic drugs be approved and marketed in Canada, and that "there are alternative means of obtaining credible and valid information about a reference product," there is no indication of what those "alternative means" may be. Also, while the March 2009 draft guidances imply that the use of a foreign reference product will still engage the Linkage Regulations and the Data Protection Regulations, there is concern that these will not, at the end of the day, be found to apply.

These issues will no doubt continue to be the subject of much debate, particularly as SEB versions of newer biologics begin to appear. ▲

- 1 The most recent guidance can be found at: <http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/2009-03-seb-pbu-eng.php>.
- 2 These draft amendments can be found at: [http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/notice\\_avis\\_pmnoc\\_mbac\\_2009-eng.php](http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/notice_avis_pmnoc_mbac_2009-eng.php); and [http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/notice\\_avis\\_2009\\_dp\\_pd-eng.php](http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/notice_avis_2009_dp_pd-eng.php).