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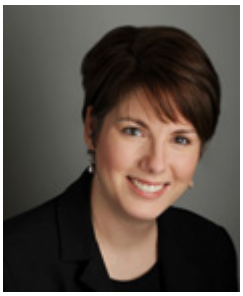

Regulation of Subsequent Entry Biologics in Canada

Tanya Weston

Health Canada released, for public comment only, a revised version of the Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics ("SEBs") on March 27, 2009.[1] The revised version is in respect of a proposed regulatory approval process for SEB's and reflects comments received from stakeholders during a public consultation held in June 2008. The revised version was released in conjunction with Proposed Revisions to Guidance Document: Data Protection under C.08.004.1 of the *Food and Drug Regulations* and Proposed Additions to Guidance Document: *Patented Medicines (Notice of Compliance) Regulations ("PM(NOC) Regulations").*[2]

As described by Health Canada, 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 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.

Key elements of the revised version of the draft guidance document are briefly described below:

- **Proposed Regulatory Framework for SEB's**: It is apparent from the revised version of the draft guidance document and the public consultation held in June 2008 that Health Canada proposes to regulate SEB's through guidance documentation and without amendments to the *Food and Drug Regulations* or the *PM(NOC) Regulations*. More particularly, 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. Health

[1] http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/consultation/2009-03-seb-pbu-notice-avis-eng.pdf

[2] 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_pmnoc_mbac_2009-eng.php.

Canada has also indicated that it will undertake regulatory review of SEB submissions prior to finalizing the guidance documentation.

- **Similarity**: 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. 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 and that the non-clinical and clinical data in respect of the reference product is relevant to the SEB.
- **Reference Product**: The reference product should be an approved biologic product marketed in Canada with "a suitable 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." The Minister of Health may consider an approved reference product from another jurisdiction ("foreign reference product") upon request. Where a foreign reference product is used to demonstrate similarity to an authorized biologic product, the submission must provide a link between the foreign reference product and the product authorized for sale in Canada. More particularly, the SEB submission must document that the foreign reference product is either "marketed by the same innovator company or corporate entity which is approved to market the medicinal ingredient in the same dosage form in Canada, or is marketed through a licensing arrangement with the innovator company or corporate entity which currently markets the version of the product approved in Canada." It is important to note that 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.
- **Differences in Manufacturing Process**: Health Canada will not approve an SEB whose manufacturing process clearly differs from that of the chosen reference product (e.g., use of transgenic organisms versus cell cultures). The impact of any process differences will be assessed taking into consideration factors such as the specific process, the product, the extent of the manufacturer's knowledge of and experience with the process and the development data generated.
- **Data Protection**: Amendments to data protection under c. 08.004.1 of the *Food and Drug Regulations* are not proposed at this time. Health Canada has proposed revising the guidance document in respect of data protection to specify that a submission for an SEB that makes a direct or indirect comparison to an innovative biologic product cannot be filed until six years after the innovative biologic product in question has been approved.
- ***PM(NOC) Regulations***: Amendments to the *PM(NOC) Regulations* are not proposed at this time. Health Canada has proposed revising the guidance document in respect of the *PM(NOC) Regulations* to specify that section 5 of the *PM(NOC) Regulations* will apply to SEB submissions which seek approval based on a direct or indirect comparison to a reference product that has patents listed

on the Patent Register (e.g., the sponsor of the SEB submission must address each patent listed on the Patent Register in respect of the reference product before regulatory approval will be granted). In the case of foreign reference products, if the Canadian version of the reference product has patents listed on the Patent Register, section 5 will also apply to the SEB submission.

For a discussion regarding the implications of the proposed regulatory framework for intellectual property protection of biologics in Canada, please contact Tanya Weston (tweston@mbm.com).

For a discussion of the original draft guidance document, please refer to http://www.mbm.com/News/Quarterly%20e-Newletter/Articles/HTML/Jun%202008%20Articles/Biologics.html dated June 2008.