

Torys on Food and Drug Regulatory

F&D 2008-2
February 15, 2008

Draft Guidelines on Subsequent Entry Biologics

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Health Canada has released a draft guidance document titled “Information and Submission Requirements for Subsequent Entry Biologics (SEBs).” The document outlines the regulatory review process that Health Canada will use for a biologic that is similar to an approved innovator biologic. Comments on the draft may be submitted until March 15, 2008.

Definition of Subsequent Entry Biologics

Biologics are drug products derived from biological sources that are listed on Schedule D of the *Food and Drugs Act*. The list includes blood products, cells and tissues, gene therapies, vaccines, radiopharmaceuticals and therapeutic products derived through biotechnology. R&D costs for biologics are generally considerably greater than for conventional pharmaceutical drugs because biologics are structurally complex and difficult to manufacture.

An SEB is defined by Health Canada as “a biologic product that would enter the market subsequent to, and similar to, an approved innovator biologic, which would rely in part, on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to a reference biologic product.” Health Canada does not endorse the use of the term “generic” biologic to describe SEBs because this description incorrectly implies that the same approval process and marketed use for conventional generic drugs will apply to SEBs.

A reference biologic is one that has received marketing approval from Health Canada on the basis of a complete quality, safety and efficacy assessment, including clinical trial data. A manufacturer can demonstrate that a new biologic is “similar” to an approved reference product through comparative studies, relying on data that have previously been generated for an innovator manufacturer. If the manufacturer so demonstrates, the approval process for an SEB may be considerably streamlined compared with that of an innovative biologic.

Regulatory Framework for Biologics and SEBs

Like conventional pharmaceutical drugs, biologics are approved for sale in Canada through the new drug submission (NDS) process outlined in Division 8 of the *Food and Drug Regulations*. The draft guidance document on SEBs indicates that the existing framework for biologic, pharmaceutical and generic drugs will provide the regulatory framework for SEBs and, if appropriate, the practices for regulating generic drugs will be applied to SEBs.

To discuss these issues, please contact the authors. For media calls, please contact [Stuart Wood](#), Director, Marketing & Business Development, 416.865.8205.

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To be approved through the SEB pathway, a product must demonstrate “similarity” to an appropriate reference product, which would normally be a product approved in Canada, through an extensive comparison between the products. An appropriate reference product is one that has been on the market for a sufficient period of time to generate a substantial amount of safety and efficacy data. The determination of similarity is based upon analytical testing, biological assays, clinical data and non-clinical data as outlined in detail in the draft guidance document. Even if they contain similar active ingredients, a product made by a manufacturing process different from that of its reference biologic will not be eligible for the SEB regulatory pathway.

Unlike for generic drugs, the manufacturer of an SEB cannot use the product monograph of the reference biologic, so is required to develop its own monograph in accordance with Health Canada policies.

A Notice of Compliance on an SEB will not automatically be granted for all the indications of its reference product. The indications for a particular SEB will be based upon the data submitted during the NDS process and will be subject to considerations such as the level of reliance on the reference product, the demonstrated level of similarity and the availability of post-market information.

Patent Register and Data Exclusivity

Biologics are subject to the same provisions of the *Patented Medicines (Notice of Compliance) Regulations (PM (NOC) Regulations)* and the *Food and Drug Regulations (Data Protection)* as traditional pharmaceutical drugs. Specifically, biologics that meet the definition of an “innovative drug” under the *Food and Drug Regulations* may be eligible for an eight-year term of data protection (with an extra six months for pediatric indications). During this time, any data submitted to Health Canada relating to the innovative drug may not be used by competitors seeking marketing approval of an SEB. Patents that claim the medicinal ingredient, formulation or dosage form of a biologic, or an indication for the biologic, for which drug regulatory approval is sought may be listed on the Patent Register and therefore subject to the protection of the *PM (NOC) Regulations*.

Proposed Amendments to the Food and Drug Regulations

The guidance document indicates that the *Food and Drug Regulations* will be amended to provide a comprehensive legal basis for the regulatory framework of SEBs. The amendments will include changes to the NDS pathway that are specific to SEBs with demonstrated similarity to a reference biologic. Health Canada intends to harmonize the approval process for SEBs, to the extent possible, with international organizations such as the World Health Organization and the International Conference of Harmonization.

Several Canadian patents covering biologics have either recently expired or will expire shortly. It is therefore expected that the number of NDS filings on SEBs will increase over the coming years. Health Canada states that the regulatory framework for SEBs is “not intended to be a disincentive for innovation nor [to] become unduly burdensome for SEB sponsors.” Further guidance from Health Canada will be necessary to ensure that the approval process for all biologics is fair and efficient.

In light of the current and future interest in SEB products, innovator biologic manufacturers should carefully consider their regulatory strategy to ensure that inventive products are protected to the full extent permitted under the *PM (NOC) Regulations* and the *Food and Drug Regulations (Data Protection)*. Such a regulatory strategy should include an assessment of whether a biologic is an “innovative product,” and particular attention should be paid to the claim language in all patents relating to the product. 