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Pharma in brief - Canada

Health Canada releases revised guidance document on approval pathway for biosimilars (formerly "subsequent-entry biologics")

Guidance document: Information and Submission Requirements for Biosimilar Biologic Drugs [***Biosimilars Guidance Document***]
Date: revised November 14, 2016; released December 2, 2016
Related enactments: *Food and Drugs Act*, RSC 1985, c F-27
Food and Drug Regulations, CRC, c 870 [***Food and Drug Regulations***]

Summary

Health Canada has revised its guidance document on the approval pathway for biosimilar biologic drugs (**biosimilars**). The headline change is in the name: Health Canada has retired the "subsequent-entry biologics" moniker. The revised *Biosimilars Guidance Document* also contains overhauled guidelines for selecting reference biologics, satisfying the scientific review requirements of the Biologics and Genetic Therapies Directorate (**BGTD**), labelling, and post-market considerations.

The *Biosimilars Guidance Document* replaces the March 2010 *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)* as Health Canada's primary resource on approval of biosimilars. Several of the changes were previewed in a draft revision that was published for consultation and comments in December 2015. Others were introduced in the revised guidance document following these consultations, which were completed in February 2016.

Background

The *Biosimilars Guidance Document* continues Health Canada's policy of *sui generis* regulatory treatment for biosimilars. A biosimilar is not a "generic" biologic drug and unlike a generic pharmaceutical, cannot be approved by way of an abbreviated new drug submission. Instead, sponsors seeking approval for a biosimilar must file a new drug submission (**NDS**) and comply with the requirements in the *Biosimilars Guidance Document*.

The NDS pathway for biosimilars differs from that for pharmaceuticals because it can be completed with a reduced clinical and non-clinical package based upon demonstrated similarity to a previously approved biologic drug (but not another biosimilar). Although this is similar in principle to the comparisons made for generic drugs, authorization of a biosimilar is not a declaration of pharmaceutical equivalence, bioequivalence, or clinical equivalence to the reference biologic drug.

Biosimilars are regulated as new drugs and are subject to the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, as well as the data-protection provisions in section C.08.004.1 of the *Food and Drug Regulations*.

Highlights

The revised *Biosimilars Guidance Document* clarifies a number of existing processes and requirements. It also introduces changes intended to streamline the preparation and review of biosimilar submissions. Here are the highlights:

- **New options for reference biologic drugs.** As before, a biosimilar must clearly identify and be subsequent to a biologic drug authorized in Canada. While it remains preferable that the same reference biologic drug is used throughout development of the biosimilar, the *Biosimilars Guidance Document* now permits the use of multiple reference biologic drugs under some circumstances. It also provides simplified requirements for supporting the selection of non-Canadian reference biologic drugs.

- **"Similar," not "comparable."** In most cases, biosimilars are no longer described as being "comparable" to the reference biologic drug; instead, they are referred to as being "similar."

- **Clarified basis for determination of similarity.** The *Biosimilars Guidance Document* clarifies that as a matter of policy, all relevant data will be taken into account when making a final determination of similarity. It also adjusts the emphasis of the data required to demonstrate similarity, providing that "…the weight of evidence should be provided by the structural and functional studies. The degree of similarity at the quality level will determine the scope and the breadth of the required non-clinical and clinical data. The non-clinical and clinical programmes should be designed to complement the structural and functional studies and address potential areas of residual uncertainty."

- **Broader acceptance of alternative means of manufacture.** Biosimilars employing clearly different approaches to manufacture than the reference biologic drug may be eligible for approval under the *Biosimilars Guidance Document*. This is a departure from the previous policy that such products may not be suitable for authorization as biosimilars. In these cases, sponsors are cautioned to carefully consider expression-system differences that may present challenges to demonstrating similarity to the reference biologic drug.

- **Changes to information requirements for clinical trial applications (CTAs).** *In vivo* animal studies may no longer be necessary to support a clinical trial application, provided the comparative structural, functional and non-clinical *in vitro* studies are considered satisfactory and no issues are identified that would preclude administration into humans. Sponsors are encouraged to request both scientific advice meetings (**SAMs**, discussed below) and pre-CTA consultation meetings to ensure compliance with BGTD requirements.

- **Changes to the non-clinical and clinical information required.**

    - **Non-clinical studies.** The requirements for *in vivo* non-clinical studies have been simplified and reduced. These studies may not be necessary where similarity is well-established by structural and functional studies, and where extensive *in vitro* mechanistic studies are indicative of similarity. The former list of recommended studies has been deleted from this section; sponsors are encouraged to provide a scientific justification for their approach and consult with the BGTD.

    - **Clinical studies.** A preamble has been added to the section on clinical studies clarifying the purpose of the clinical programme: to show that there are no clinically meaningful differences between the biosimilar and the reference biologic drug. This is followed by detailed revisions to the guidelines for pharmacokinetic, pharmacodynamic, and clinical efficacy trials, the latter of which may not be required in all circumstances. These revisions are complemented by a new section outlining the requirements for comparative immunogenicity studies. The *Biosimilars Guidance Document* also clarifies that if clinical studies reveal differences between the biosimilar and the reference biologic drug, including statistical superiority of the biosimilar, it may be ineligible to proceed as a biosimilar.

- **More flexibility on indications.** The *Biosimilars Guidance Document* now contains a clear policy statement that a biosimilar sponsor is eligible to apply for the indication(s) and condition(s) of use that are held by the reference biologic drug authorized in Canada. Clinical studies are not required to support approval in each indication, provided similarity has been established and a detailed scientific justification has been provided. A sponsor may also seek approval for indications beyond those for which the reference biologic drug is authorized, but these situations are outside the scope of the *Biosimilars Guidance Document*.

- **Revised labelling requirements.** The product monograph guidelines have been amended to include additional detail regarding the comparisons and basis upon which the biosimilar was approved. In addition, the biosimilar product monograph should now include safety and efficacy information from the product monograph of the reference biologic drug.

- **Risk-management plans.** Additional guidance is provided regarding the considerations that should be addressed in a risk-management plan, as well as a new reference to Health Canada's *Guidance Document — Submission of Risk Management Plans and Follow-up Commitments*.

- **Post-market requirements.** The section in post-market requirements has been restructured. The sections on adverse drug reaction reporting and periodic safety update reports have been consolidated and the section on suspension or revocation of NOCs has been removed. A new section on post-NOC changes has also been added. This section reinforces that biosimilars are subject to the same regulatory requirements as other new drugs, including compliance with Health Canada's guidance documents on post-NOC changes. This section also recognises that Health Canada will consider supplemental new drug submissions seeking post-NOC approval for new indications held by the reference biologic drug on a case-by-case basis.

- **Consultation & SAM pilot programme.** Sponsors are encouraged to consult with the BGTD early and throughout the approval process. Sponsors are also invited to participate in the three-year pilot of a "stepwise" review approach that was introduced in September 2015. Under the pilot programme, a sponsor provides the BGTD with the data it will rely upon to demonstrate similarity between a biosimilar and its reference biologic drug early in the development process. The BGTD will hold a SAM with the sponsor and, following that meeting, issue one of three recommendations:

  - to continue as a biosimilar;
  - to continue as a conventional drug; or
  - to provide additional comparability data, following which a recommendation will be made either to continue as a biosimilar or to further consult with the BGTD.

Links:

Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs (November 14, 2016)
Previous documents: Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (March 5, 2010)
Draft – Revised Guidance Document: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (December 7, 2015)
Pilot programme: Notice – Subsequent Entry Biologics Scientific Advice Meeting Pilot
Related enactments: *Food and Drugs Act,* RSC 1985, c F-27
Food and Drug Regulations, CRC, c 870

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