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Health Canada Releases Final Guidance on Subsequent Entry Biologics

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Health Canada has released the final version of its guidance document *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)* (Final Guidance), which is an update of the draft guidance released by Health Canada on January 30, 2008 and March 27, 2009 and applies to all pending and future drug submissions for SEBs in Canada.

Biologics are drug products derived from biological sources and include gene therapies, vaccines, antibodies and other therapeutic products derived through biotechnology. An SEB is defined by Health Canada as “a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug.” SEB manufacturers may make reference to the information contained in an innovator’s biologic drug submission – that is, the reference biologic drug submission – in order to reduce the amount of clinical data required to obtain marketing approval for its product.

In their new drug submission, manufacturers are required to clearly identify the product that an SEB is subsequent to. As in the draft guidance, the Final Guidance indicates that the reference biologic drug should be marketed in Canada. However, a manufacturer may be permitted to use a non-Canadian reference biologic drug for comparative studies if the manufacturer can show that the foreign product is a suitable proxy for the version that is approved in Canada. The Canadian and non-Canadian versions of the reference biologic drug must be marketed by the same innovator company in the same dosage form, and the non-Canadian reference product must be from a jurisdiction with an established relationship with Health Canada. Data are required to demonstrate the safety of a non-Canadian reference biologic drug that is to be used in clinical studies in Canada.

SEB manufacturers may apply for one or more of the indications for use granted to the reference biologic drug. In some cases, additional indications may be granted to the SEB in the absence of clinical data if extrapolation to other uses is justified and persuasive. In designing clinical trials, manufacturers should note that equivalence trials are generally preferred, but non-inferiority trials may be permissible in certain cases. If trials reveal superior efficacy to a reference biologic drug product, or an increase in adverse reactions, the product would not be considered an SEB. Demonstration of non-inferiority between an SEB and its reference biologic drug product would not necessarily permit extrapolation of approval of the SEB for all indications, especially if the indications include different dosages from those tested in the trial.

To discuss these issues, please contact the authors.

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Unlike generic drug products, SEB manufacturers will not be able to use the entire product monograph of the reference product as its own. Product monographs must explicitly state that the drug is an SEB. No claims are to be made in the monograph that the SEB and the reference product are bioequivalent or are clinically equivalent. Sponsors are required to develop a risk management plan prior to market authorization.

The Final Guidance document has been published concurrently with amendments to the Health Canada Guidance for the Data Protection provisions of the *Food and Drug Regulations* and *PM(NOC) Regulations*. The Data Protection guidance has been amended to expressly capture new drug submissions for SEBs that are based on a comparison to a Canadian or non-Canadian reference product, if the Canadian reference product is on the list of innovative drug products. Excluded are new drug submissions that include independent clinical trials and are not based on such a comparison. An SEB will not be regarded as an innovative drug (i.e., SEBs will not be eligible for data protection). The guidance on the *PM(NOC) Regulations* has been amended to expressly capture new drug submissions and supplemental new drug submissions for SEBs that demonstrate similarity to a Canadian or non-Canadian reference product. Such submissions are stated as being subject to the *PM(NOC) Regulations*. If the Office of Patented Medicines and Liaison is uncertain whether the new drug submission is for a biologic or an SEB, it is directed to consult the relevant bureau within Health Canada.

For further information as well as the amended guidance documents on Data Protection and the *PM(NOC) Regulations*, access the [Final Guidance](#). 