SEBs in Canada are regulated under the same regimen as any new drug. Once market authorization has been granted to a biosimilar, the product becomes a self-standing, independent product, with one caveat: a biosimilar may not be used as an RBD for another biosimilar. The reasons are the following:

1. Canadian regulations are product-specific.
2. Division 8 of the Canadian Food and Drug Regulations indicates that the package submitted in support of a new drug (new drug product) has to satisfy the Minister in terms of safety, efficacy, and quality. This allows for a fair amount of flexibility. At minimum, it allows for the regulator to use science to tailor the information to the product.
3. Generic drug regulations and intellectual property considerations, in the form of the patent linkage regulations, also have a bearing on how biosimilars are regulated, together with data protection provisions.

This chapter deals extensively with the underlying science that was the basis of the Canadian approach to regulating biosimilars. In particular, the present chapter discusses quality, clinical and statistical aspects of biosimilar development, and their importance for the consideration of extrapolation of indications.

9.2 QUALITY CONSIDERATIONS

9.2.1 Complexity of Biologics

For biologics, changes to the starting materials, manufacturing process, equipment, or facility can result in significant unexpected alterations in the intermediate stage product, drug substance, and/or final product. Herein lies the challenge of demonstrating the similarity of a biosimilar to its RBD. This challenge is compounded by the limitations of the analytical methods available to assess the similarity.

The purpose of the analytical and biological similarity exercises is to establish an evidence-based link between the RBD and the biosimilar in order to *leverage the existing body of knowledge available in the public domain regarding the efficacy and safety of the product*. The strength of this link, or perhaps more appropriately, the *residual uncertainty* in the similarity resulting from a thorough evaluation of the results of the analytical and biological similarity exercises drive the breadth and scope of the clinical and nonclinical similarity exercises. It is essential that the analytical and biological similarity exercises demonstrate that the biosimilar and the RBD are highly similar within the limitations of the current state-of-the-art analytical methods for a candidate molecule to be considered biosimilar.

9.2.2 Demonstrating Quality Similarity

The analytical and biological similarity, termed the *quality similarity* for the purposes of this chapter, is not a foreign concept to the regulation of biologics. ICH Q5E Comparability of Biotechnology/Biological Products Subject of Changes in their Manufacturing Process (ICH Q5E, 2004) provides a basis for evaluating the impact