

of manufacturing changes on a product. While the comparison of two independent products is clearly outside the scope of this guidance, the aim is similar and many of the principles and approaches are applicable. The Canadian SEB guidance (Health Canada, 2010) provides details regarding expectations for the similarity exercises and the applicability of ICH Q5E.

The similarity demonstrated through the quality similarity exercise between the proposed biosimilar and the RBD should be the primary basis for the decision of whether the biosimilar pathway is appropriate for the biosimilar product. The studies that make up the quality similarity exercise should be comprehensive and appropriately justified. The studies should be performed using reliable analytical methods that have been optimized to detect potentially meaningful differences. These studies should include multiple orthogonal methods to characterize the appropriate physical, chemical, and biological attributes. This should include functional assays to evaluate the range of biological activities.

The Canadian biosimilar guidance states that the goal of the determination of similarity between the two products being compared is that they be *highly similar rather than identical* and that any differences observed in quality attributes should have *no adverse impact on safety and efficacy*. This recognizes that the nature of biological drugs precludes the determination of two products being identical and provides the criteria for the determination of highly similar. This definition of highly similar appropriately links the output of the quality similarity exercises to potential clinical outcomes, thus providing a benchmark to filter the noise (differences due to method variability and minor molecular variation) from the signal (clinically meaningful differences).

In practice, the identification of differences that have “no adverse impact on safety and efficacy” is fraught with uncertainty in that the potential impact of differences in the quality similarity of the products is often unknown and there is often considerable uncertainty regarding the mechanisms of action of the molecule. It is incumbent upon the sponsor of the biosimilar product to provide the demonstration that the differences have no adverse impact. Great care should be taken in the design of the quality similarity studies to ensure that all available information regarding the *critical quality attributes (CQAs) and the quality determinants of the safety and efficacy* of the product has been considered. In addition, the results of the quality similarity studies should be discussed fully within the framework of the potential clinical impact, including *justification of assumptions and qualification of the uncertainty*.

The relationship between the observed differences in the quality similarity exercise and the potential clinical outcomes links the determination of similarity to the mechanisms of action of the molecule in the clinic which becomes the basis of the contribution of the quality similarity exercise to the determination of the extrapolation of indications. Considering the extrapolation of indications in this way has two important consequences. First, there is the potential for the determination that a biosimilar meets the definition of highly similar to the RBD in *some, but not all, indications*, if there is a difference in the mechanism of action across indications. Thus, biosimilarity is contextually based rather than an inherent quality of the molecule. Second, the choice of supporting clinical and nonclinical studies needs to consider the gaps in the quality similarity exercise with respect to potential mechanisms of action in order to