Dose selection is also important. For instance, some mAbs are thought to inhibit antibody formation when administered at high doses; therefore, studies have to be conducted with low dose (Brinks, 2013). Immunogenicity testing of the biosimilar and the RBD should be conducted within the biosimilar comparability exercise using the same assay format and sampling schedule. The assay used to detect antibodies is an important consideration during the clinical development of a biosimilar and should meet all current standards. Comparison of data obtained for the biosimilar with historical data obtained for the RBD is generally not considered appropriate (Giezen and Schneider, 2014). This is because RBDs may have historical immunogenicity data based on out-of-date assays, which, by today's standards, would be considered to have inadequate sensitivity. Thus, any comparison of immunogenicity needs a side-by-side test of the biosimilar and its RBD to ensure valid comparison. Without a side-by-side comparison, sensitive immunogenicity assays used currently may show higher antibody positive results with the biosimilar.

9.3.5 Extrapolation of Indications

Extrapolation of data is already an established scientific and regulatory principle for biosimilars, which has been exercised, by regulatory agencies, since the first biosimilar approvals. Extrapolation guidance exists in the biosimilar guidelines prepared by the Canada, EMA, US (Health Canada, 2010; EMA, 2015; FDA, 2015), and many other countries. In Canada, biosimilar sponsors are permitted to apply for one or more clinical indications granted to the Canadian RBD. The biosimilar sponsor is not required to submit complete clinical data for every requested indication as long as clinical data and/or scientific rationales are provided that can address the principles that Health Canada uses to determine whether extrapolation is appropriate. Based on the totality of evidence obtained from detailed and comprehensive comparative structural and functional characterizations, nonclinical studies, human PK/PD studies, and pivotal clinical trials, extrapolation of indications could be justified based on: mechanism(s) of action that play(s) a role in each of the indicated conditions for which a sponsor applies; pathophysiological mechanism(s) of the indicated diseases, which is an important determinant in the extrapolation assessment as some mAbs hold indications for the treatment of diseases that bear little resemblance to each other; a safety profile in the respective conditions and/or populations; and clinical experience with the reference biologic drug. In each case, a detailed scientific rationale that appropriately addresses the benefits and risks of such a proposal should be provided to adequately support the data extrapolation (Health Canada, 2010).

It is noted that if the mechanism of action of the drug substance and the target receptor(s) involved in the tested and in the extrapolated indication(s) are the same, extrapolation of indications is usually not problematic. However, when the mode of action is complex and involves multiple receptors or binding sites, the contribution may differ between indications or may not be well known (Weise et al., 2014). Thus, additional data are necessary to provide further reassurance that the biosimilar and the RBD will behave alike, and also in the extrapolated indications. The regulatory flexibility of current regulations in Canada, particularly those for new drug products such as biosimilars and expressed as "the information to be provided on