(iv) route to detect potential PK differences. It is also expected that the sc route is more immunogenic than the iv route (FDA, 2014a), which makes the sc route more appropriate for investigating immunogenicity differences between the biosimilar and the RBD. Immunogenicity is a major issue that triggers concern and debate for developing not only biosimilars, but all biologics. For example, the EMA has authorized at least two biosimilar epoetins for the treatment of renal anemia and chemotherapy-induced anemia. However, one of these epoetins was only studied using the iv route of administration. Thus, it was not authorized by EMA for subcutaneous use since the subcutaneous route of administration had previously been associated with increased immunogenicity leading to the development of antibodies that cross-react with endogenous protein and, subsequently, pure red cell aplasia (PRCA) (EMA, 2008).

When seeking authorization of a biosimilar in Canada, sponsors should consider the principles of study design, statistical methods, and criteria of acceptance as outlined in Health Canada's Guideline *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* as a general guidance for conducting comparative PK studies (Health Canada, 2012). It should be noted that comparative bioavailability criteria differ between the various regulatory agencies, for example, 90% CI of C_{max} is not applicable; AUCt is used; and potency correction may be required for all key parameters by Health Canada (Pen et al., 2015). According to Health Canada's guidance document for PK studies, the 90% CI of AUCt, as well as of the relative mean C_{max} of the biosimilar to the reference product, should be within 80%–125%. At the same time, the FDA recommends that sponsors provide the geometric means, arithmetic means, geometric mean ratios, and 90% CI for AUCt, AUCi, and C_{max} (FDA, 2014b).

It is important to recognize that, unlike generics, biosimilars are not considered to be identical to their respective RBDs. A comparable PK profile between the biosimilar and the RBD does not guarantee that a biosimilar has effects on the body that are comparable to those of the RBD. Therefore, comparative human PD data are desirable and can help to reduce residual uncertainty and support extrapolation of indications. A comparative human PD study can be combined with a PK study to characterize PK/PD relationships. The PD parameters used in comparative studies should be clinically validated and considered as surrogate markers of clinical outcomes, for example, absolute neutrophil count for a biosimilar G-CSF. The PD surrogate should be sensitive enough to detect potential changes induced by the biosimilar and the RBD. Importantly, a therapeutic dose for patients may induce a ceiling PD response in healthy volunteers, thus masking potential differences (dosing sensitivity) between products. In such cases, a lower dose in the steep part of the dose-response curve should be considered (assay sensitivity), and a separate human PD study may be needed. A patient PD study demonstrating similar effects on a clinically relevant PD surrogate could strengthen the claim of biosimilarity. Relevance of the PD surrogate to the mechanism(s) of action of the product is essential in supporting the extrapolation of indications. If pivotal evidence for extrapolation is based on PD parameters and, for the claimed indications, different mechanisms of action are pertinent, then sponsors should provide additional data, either PD or clinical data to cover all claimed clinical indications.