7.4.6 Extrapolation

A unique aspect of biosimilar development and the resulting approval is the concept of extrapolation. As presented throughout this chapter, the goal of biosimilar development is to provide a stepwise set of data that can be interpreted within a "totality of the evidence" approach to enable a regulatory determination that the proposed biosimilar is "highly similar" or "essentially the same" as the reference product (EMA, 2012).

The clinical trial is the final stage of this stepwise approach, and it is designed to confirm the similarity of the biosimilar to the reference product. The trials are not designed to establish safety and efficacy, neither a priori nor in every indication of the reference product. Physicians are often unfamiliar with this unique biosimilar regulatory pathway where it is not required to conduct multiple clinical trials when the reference product is approved in multiple indications. The anti-TNF biologics are approved in multiple indications, with some having a far greater number of indications (such as infliximab) than others (such as etanercept). Since many physicians have direct experience with drugs that may work in one indication and not another, they struggle without seeing data in the specific indication for which they would use the biosimilar. However, once they understand the unique scientific approach used for development and approval of a biosimilar, and its one-to-one relationship with its originator reference product in addition to the fact that the data generated by the sponsor provides evidence that the biosimilar is essentially the same biological substance as the reference product, extrapolation becomes not only feasible but inevitable. If the biological substances are essentially the same (the biosimilar is essentially the same as the reference product), then they must have the same clinical effect in the same indications as the reference product. To the health care provider and patient, using a biosimilar is clinically just like using another batch of the reference product. It is just that in the case of the biosimilar the sponsor is different. If such a complete dataset is acceptable by regulators as proving the sameness of the biosimilar, then it is inappropriate, and indeed unethical, to perform clinical trials of the biosimilar in all additional indications of the reference product.

7.4.7 Interchangeability

There is one final unique aspect of biosimilar clinical trial design if the sponsor is intending to obtain an interchangeability designation in the US. The approach currently envisaged includes switching patients from one treatment (either the biosimilar or the reference product) to the opposite product multiple times. Such switching is usually performed after reaching the primary endpoint for the efficacy analysis. This can be after 12 weeks of treatment for psoriasis (Sandoz, 2015b), 24 weeks of treatment for rheumatoid arthritis (Amgen, 2015c), or after the first course of chemotherapy in breast cancer patients treated with TAC chemotherapy (Blackwell et al., 2015). Such a switching protocol must allow for statistical evaluation of equivalent efficacy of the switching group with a nonswitched group. In addition, immunogenicity is evaluated between the switched group versus the nonswitched group. This makes the clinical trial design somewhat complicated as patients treated with the biosimilar must initially be compared with patients treated with the reference