

provide confirmatory evidence to the regulating authority that the old and new products produced the same clinical effect. This approach of comparability in support of manufacturing changes is analogous to the principles used in the development of biosimilars and the clinical trials required to confirm analytical similarity when developing a biosimilar to an existing reference product.

7.2 CLINICAL TRIALS ARE LESS SENSITIVE THAN ANALYTICS TO DOCUMENT DIFFERENCES

Development of a biosimilar, just like that of an originator biologic, proceeds in a stepwise manner with the clinical trial(s) being the last step. However, for a biosimilar, those studies do not establish safety and efficacy; rather, they confirm the “sameness” of the biosimilar to the reference product, the “sameness” having been established analytically before any clinical studies are undertaken. This stepwise process provides a methodology for confirming that the active biological substance of the biosimilar is essentially the same as the reference product, and through having addressed any “residual uncertainty” (FDA, 2015a) prior to studies in humans. The extensive state-of-the-art analytical data are able to document that the amino acid sequence and protein structure of the biosimilar are identical to the reference product and that the biosimilar has indistinguishable binding characteristics and biological function compared to the reference product. Such data provide reassurance that the biosimilar will produce the same clinical effects as the reference product. Hence, at initiation of the clinical trial, limited residual uncertainty remains. Therefore, the clinical trial is designed to confirm the findings of analytical “sameness” generated in prior steps in developing the biosimilar. Clinical trials are substantially less sensitive in picking differences between the two products (proposed biosimilar and reference product) than analytical methods. In fact, analytical methodologies are able to document many differences between batches of reference product or between products undergoing manufacturing changes that have no clinical relevance (Schiestl et al., 2011). This is an essential point for all biologics. It is not that biologics don’t have differences, whether different batches of the reference product or a biosimilar of that reference product. Indeed they do. However, those differences cannot have clinical relevance.

7.2.1 CASE STUDY

An example is the difference in glycosylation patterns from Enbrel’s pre- and post-manufacturing change (Schiestl et al., 2011). Schiestl et al. documented a 20% change in enrichment of the G2F glycosylation species after the manufacturing change of this anti-tumor necrosis factor biologic, decreasing from over 50% enrichment to 30% enrichment (see Figure 7.1).

This G2F glycosylation does not have an impact on pharmacokinetics or pharmacodynamics (Goetze et al., 2011), does not impact binding, and is not associated with increased immunogenicity. Therefore, this analytical difference, though statistically different, would not be expected to have any meaningful clinical effect. Indeed,