in the final product. However, such changes in the manufacturing process cannot be allowed to create clinically meaningful differences, and approval is required for each such change by each regulatory authority for every jurisdiction in which the product is made available (Schiestl et al., 2011). This regulatory approval is required prior to the manufacturing change being made. Consequently, the "new" biological product is introduced to the marketplace after the regulatory authority has agreed to the manufacturing change.

The goal of the regulatory approval is to ensure that all prescribers and patients have confidence that the product produced with the newly amended, likely expanded, manufacturing process is "highly similar" to the original biologic and produces the same clinical response as the original product (ICH, 2004). The regulatory process involved with evaluating a manufacturing change focuses on confirming that the postmanufacturing change product is "highly similar" to the premanufacturing change product. The "highly similar" terminology was established as it is impossible to produce an "identical" biological product even from batch to batch, much less with a manufacturing change, such as scale-up or transfer to a different site, or even change in cell line (ICH, 2004). Regulators' review and approval of these technical transfers or manufacturing changes are not revealed to the public in the United States, as the product label does not change and there is no requirement for publication of a summary basis of approval (SBA) for these manufacturing changes.

In Europe, however, the regulatory process involved in the review and approval of manufacturing changes is often published in European Public Assessment Reports (EPARs). In reviewing these EPARs, it is clear that clinical trials are rarely used to justify that these manufacturing changes do not confer a clinically meaningful difference (Vezer, 2016). This is reasonable given the extensive knowledge accumulated over the past three decades on the clinical impact of specific glycosylation patterns and other posttranslational modifications. It is only when glycosylation or posttranslational modifications are introduced by the new process that have not been seen before, or where insufficient data exist to conclude that no clinically meaningful difference is expected, that clinical trials may be an appropriate requirement for regulatory approval (Woodcock, 2007). Reviewing an example can help illustrate the evolution of the clinical trial requirements for manufacturing changes; this is important as the same principles apply to the development of a biosimilar.

7.1.1 Case Study

Amgen changed its manufacturing process for Aranesp (darbepoetin alfa) from a roller bottle process to a more modern high-throughput process to enable an increase in manufacturing capacity. This change required the establishment of a new master cell bank and the use of different media components (EMA, 2008). The glycosylation changes seen from different batches of Aranesp purchased from the market are documented by Schiestl et al. (2011). In order for the EMA to conclude that this manufacturing change resulted in a product that would not produce a clinically meaningful difference (i.e., that the pre- and postmanufacturing process change products were "highly similar"), multiple human clinical trials were required. These trials were not designed to reestablish the safety and efficacy of Aranesp, but to