employed. Since substantially greater variability is expected in any clinical trial, especially considering patient factors, it is critical to try to limit the variability in the conduct of the clinical trial to enable a signal from differences between the biosimilar and the reference product to be seen. This means that the patient population should be selected to minimize variability of clinical response. By way of contrast, during the development of a novel biological drug the sponsor must demonstrate the clinical effect of the product in a variety of populations that vary by gender, race, age, and weight. However, for a biosimilar it minimizes these sources of variability allowing for focus on the key question as to whether the biosimilar produces the same biological response as the reference product in a head-to-head study. Once again, this requires a paradigm shift in thought and strategy for clinical trials for biosimilar development.

7.4.1 Case Study

One example of patient factors contributing to variability is with pegylated proteins (proteins wherein a single long chain of polyethylene glycol is added covalently to the protein to eliminate renal clearance). Pegfilgrastim (Neulasta which is a longer acting neutrophil stimulator for patients given chemotherapy) was developed to produce a longer residence time of the product in the blood so that a single dose could be used with each course of chemotherapy (Amgen, 2015d). The product was initially dosed in a weight-based approach with pharmacokinetic studies, but the phase III investigation was undertaken using a fixed dose of 6 mg. The variability of the initial studies produced a coefficient of variation of approximately 35%; however, when larger fixed-dose pharmacokinetic studies were performed the variation was approximately 85%, complicating the demonstration of pharmacokinetic bioequivalence (Yang et al., 2015). With such high intersubject variability, "noise" may mask the differences between a proposed biosimilar and the reference product. To improve the sensitivity of a pharmacokinetic study of pegylated protein products, it is necessary to limit subject factors such as gender and weight. With pegfilgrastim it is also critical to limit the variation of baseline neutrophil counts because the clearance of this drug is determined by receptor-mediated uptake (receptors on neutrophils bind and initiate clearance). These factors are far more variable than any analytical difference between pegfilgrastim products.

7.4.2 Pharmacokinetics

Pharmacokinetic studies are often called "phase I" studies in the development of a novel compound. This terminology is not appropriate for the development of a biosimilar because the pharmacokinetic study is pivotal to confirming the similarity of the biosimilar to the originator. Therefore, biosimilar sponsors also refer to the pharmacokinetic study as a pivotal study for demonstrating biosimilarity. Indeed, only a pharmacokinetic/pharmacodynamic study may be required to confirm biosimilarity to the reference product, and no additional efficacy study may be needed. This possible approach is allowed by several regulators (EMA, 2014; FDA, 2014) when justified.