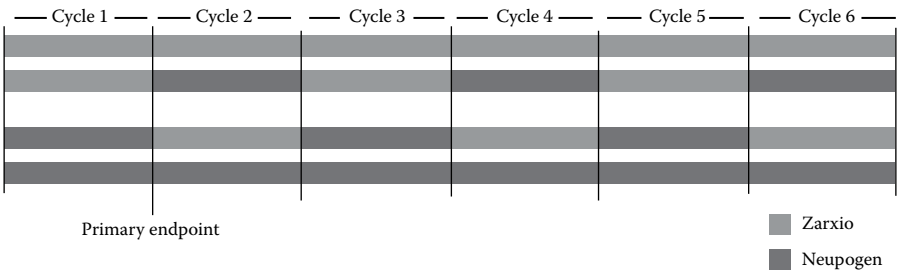

FIGURE 7.4 **(See color insert.)** Clinical trial design of the Zarxio biosimilar confirmatory clinical trial presented at the January 7, 2015, Oncologic Drug Advisory Board (Sandoz, 2015c). The upper and lower groups were treated continuously with either the biosimilar (light gray) or the reference product (dark gray). The inner groups were switched back and forth five times between the initial product assigned and the other product (biosimilar or reference product). Initial statistical comparison at the primary endpoint time point was between the two groups treated with the biosimilar compared with the two groups treated with the reference product. Thereafter, efficacy or immunogenicity could be compared between the groups treated continuously versus the groups switched back and forth between products.

product at the time of the primary endpoint evaluation. After the primary endpoint time point is reached, subjects must be randomized thereafter into a switched treatment group or a nonswitched group (that is, a portion of the patients continue consistent treatment throughout the entire protocol).

Sandoz's approach to accomplish this design is to start with four groups upon initiation to include two groups being treated with the reference product and two groups being treated with the biosimilar, all in a blinded fashion. Upon reaching the primary endpoint, one group being treated with the biosimilar and one group being treated with the reference product enters a switching period where all subjects assigned to that group are switched back and forth multiple times between the reference product and the biosimilar (Blackwell et al., 2015; Figure 7.4).

7.5 SUMMARY

Clinical trial designs to support the approval of biosimilars in the highly regulated markets are quite different from those used for the approval of novel drugs. There is a paradigm shift required in approaching biosimilar clinical trials wherein the focus is on confirming the similarity of the structure and function of the biosimilar molecule to that of the reference product (Woodcock, 2012).

This is performed in a stepwise fashion beginning with well-established and proven analytical and functional comparison methods that can sensitively pick up very minor differences between the molecules, some of which may well have no clinical relevance. Since the focus is on comparing the molecules and not challenging the safety and efficacy of the reference molecule, the clinical design uses different approaches to minimize clinical variability and using endpoints that take into consideration the biologic function of the molecule. Equivalence designs are often required, although noninferiority designs are justified. The designs and methodologies used