valid study design. On the other hand, the concept of alternating is referred to as either the switch from T to R and then the switch back to T (i.e., T to R to T) or the switch from R to T and then the switch back to R (i.e., R to T to R). Thus, the difference between the switch from T to R then the switch from R to T and the switch from R to T then the switch from T to R needs to be assessed for addressing the concept of alternating.

The experimental design that can be used to demonstrate interchangeability is ideally a standard at least two-sequence, two-period (2 × 2) crossover design; however, it does not work well with drugs with long half-life. In those instances, a parallel group design is generally preferred. Unfortunately, parallel group design does not provide independent estimates of variance components such as intersubject and intrasubject variabilities and variability due to subject–by-product interaction. This creates a major challenge for assessing biosimilarity and interchangeability (in terms of the concepts of switching and alternating) of biosimilar products under parallel group designs. For establishing switchability, a 4 × 2 crossover design (i.e., TT, RR, TR, RT) is suitable. For demonstrating the similarity during alternating, a two-sequence, three-period dual design (i.e., TRT, RTR) may be useful since it allows a back excursion, the switch from T to R and then back to T (i.e., T to R to T) and from R to T and then back to R (i.e., R to T to R). These can be combined to produce designs such as TT, RR, TRT, and RTR.

Given the highly specific nature of responses anticipated in the use of biological drugs and their biosimilar and interchangeable alternates, the sponsor is encouraged to consult with regulatory agencies with justification for the nature of these protocols.

The rewards of obtaining an interchangeable status are many; even though the outcome is legally difficult to grasp, overall, it means exclusivity in the market for a limited time as described in the following (42 U.S.C. 262(k)(6); https://www.law.cornell.edu/uscode/text/42/262):

> (6) Exclusivity for first interchangeable biological product—Upon review of an application submitted under this subsection relying on the same reference product for which a prior biological product has received a determination of interchangeability for any condition of use, the Secretary shall not make a determination … that the second or subsequent biological product is interchangeable for any condition of use until the earlier of—
> (A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable with that reference product.

4.15 Conclusion

The Biosimilars are additionally required to be evaluated for identity, which is the starting step to establishing whether a product qualifies as a biosimilar candidate (Figure 4.15). The assumption is that if the identities