creative statistical models to design trials to reduce the number of the subject required. The clinical pharmacology studies also serve the purpose of evaluating safety and immunogenicity; the adverse events recorded in these studies are of high value in establishing biosimilarity. Monitoring antibodies in these studies further supports immunogenicity comparisons.

- Stage 4: Clinical trials in patients: These may be required in two instances, first, when the regulatory agencies are not convinced of the similarity of the product, leaving sufficient residual uncertainty, and second, where PD studies are not meaningful in healthy subjects and these are linked to the safety of the product. Even when conducted, these clinical studies in patients are limited to a single indication and in the easiest population to recruit, reducing the burden of cost and time for the biosimilar product developer; however, it requires a lot of scientific finesse on the part of the sponsor to secure concessions from the regulatory agencies on their clinical trial protocols.
- Stage 5: Postmarket surveillance: Postmarket surveillance is required in EU, but the FDA is flexible, and it may not be necessary; under risk evaluation and mitigation strategies, the FDA will declare what, if any, surveillance studies are needed. The developer may, however, want to conduct open-label studies postapproval to support its marketing plans. Once it is approved, the biosimilar product need not revert to the reference product for any similarity studies, except where it is desired for marketing purposes.

4.5 Levels of similarity

Until the FDA took a giant step in 2014 to define various levels of similarity leading to biosimilarity, the standard of biosimilarity needed for approval was somewhat vague. Figure 4.5 shows a tier-based definition

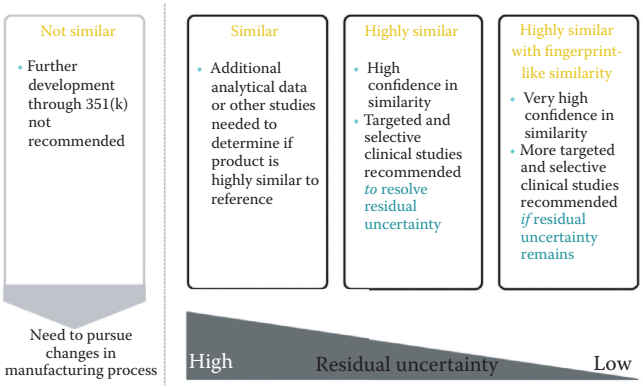

Figure 4.5 Confidence-based levels of biosimilarity.