and potency. Based on the definition of the BPCI Act, biosimilarity requires that there are no *clinically meaningful differences* in terms of *safety, purity* and *potency*. Safety could include pharmacokinetics and pharmacodynamics (PK/PD), safety and tolerability, and immunogenicity studies. Purity includes all CQAs during the manufacturing process. Potency is referred to as efficacy studies. As indicated earlier, in the 2012 FDA draft guidance on scientific considerations, the FDA recommends that a stepwise approach be considered for providing the totality of the evidence to demonstrate the biosimilarity of a proposed biosimilar product as compared to a reference product (FDA, 2015a).

The stepwise approach is briefly summarized by a pyramid illustrated in Figure 3.1. The process starts with analytical studies for structural and functional characterization. The stepwise approach continues with animal studies for toxicity, clinical pharmacology studies such as PK/PD studies, followed by investigations of immunogenicity and clinical studies for safety/tolerability and efficacy.

The sponsors are encouraged to consult with medical/statistical reviewers of the FDA with the proposed plan or strategy of the stepwise approach for regulatory agreement and acceptance. This is to make sure that the information provided is sufficient to fulfill the FDA's requirement for providing totality of the evidence for the demonstration of biosimilarity of the proposed biosimilar product as compared to the reference product. As an example, more specifically, the analytical studies are to assess similarity in CQAs at various stages of the manufacturing process of the biosimilar product as compared to those of the reference product. To assist the sponsors to fulfill the regulatory requirement for providing totality of the evidence of analytical similarity, the FDA suggests several approaches depending on the criticality of the identified quality attributes relevant to the clinical outcomes.

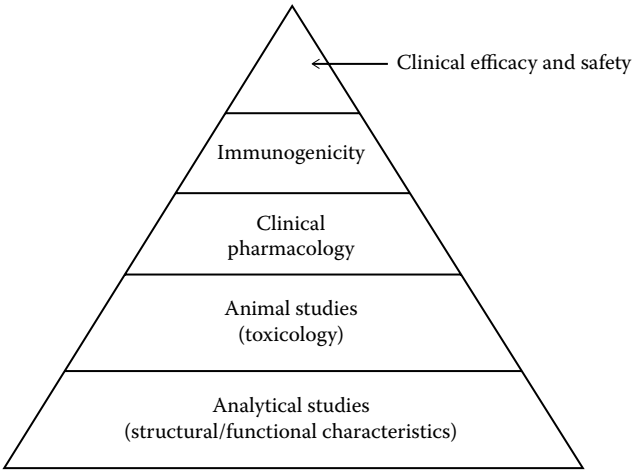

FIGURE 3.1 A stepwise approach to demonstrate biosimilarity.