4.2.22 Human PK and PD study considerations

- Study design
  - Study population: Study population is an adequately sensitive population to detect any differences, should they exist
  - PD end point: PD end point reflects the biological effects of the drug, they may (or may not) be on mechanistic path of MOA or disease process
  - Route of administration: All routes versus a single route
- Data analysis plan
  - Acceptance range: 80%–125% (90% confidence interval [CI] for PK and PD), scientifically justify use of other ranges
  - Choice of primary end points (e.g., PK—AUC, C_{max}; PD—area under the effect curve [AUEC])
- Others
  - Incidence of immunogenicity

4.2.23 Comparative clinical study considerations

- A comparative clinical study of a biosimilar development program should be designed to investigate whether there are clinically meaningful differences between the proposed product and the reference product.
- Consider the adequacy of the population, sample size, and study duration to detect differences, should they exist.
- The goal of the study is to support a demonstration of no clinically meaningful differences.
- Typically, an equivalence design with symmetric inferiority and superiority margins would be used, but other designs may be justified depending on product-specific and program-specific considerations.

4.2.24 Totality of the evidence

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 PK and PD, safety and tolerability, and immunogenicity studies. Purity includes all CQAs during manufacturing process. Potency is referred to as efficacy studies. In the 2015 FDA draft guidance on scientific considerations, the FDA recommends that a stepwise approach be considered for providing the totality of the evidence to demonstrating biosimilarity of a proposed biosimilar product as compared to a reference product.

The stepwise approach starts with analytical studies for structural and functional characterizations (Figure 4.2). The stepwise approach continues with animal studies for toxicity and clinical pharmacology studies