that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" (*FDA Guidance for Industry Quality Considerations in Demonstrating Biosimilarity to Reference Protein Product*, 2012).

A 351(k) application in the United States and similar applications in Europe and other developed countries must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based on data derived from analytical studies, animal studies, and a clinical study or studies, unless the FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application. The goal of a biosimilar development program is thus to demonstrate that the proposed product is biosimilar to the reference product. The overall plan for developing a case of biosimilarity involves the following:

- Stage 1: Analytical and functional similarity: A large number of tests are currently available, and many more are appearing in the literature that can be used to demonstrate the level of similarity. The goal of the biosimilar product development is to create a battery of orthogonal tests that qualifies the product for the category fingerprint-like similarity, wherein the need for any additional testing such as trials in patients is obviated.
- Stage 2: Preclinical or nonclinical safety: Once an acceptable level of analytical and functional similarity has been established, the sponsor should consult with the agencies on the need for this testing and the extent of testing. There is a new consensus developing in the regulatory agencies that purports to avoid any animal testing unless it provides any useful safety information. The nonclinical study must be conducted in species that show safety signals similar or proportional to humans; therefore, it is possible that for some drugs like mAbs, no animal species may be suitable. When a new drug is developed, several animal species are used as the MOA and the safety profile is not known, but for biosimilar products, the comparison with reference product requires species capable of showing an adverse response. This distinction is important to avoid initiating studies similar to what the originator had conducted. The species must be meaningful, and this requires a discussion with regulatory agencies before starting these studies. For example, while rats constitute an excellent species to demonstrate the safety of filgrastim, for adalimumab, only PK studies in a couple of monkeys may be required if the biosimilar product is not structurally and functionally highly similar.
- Stage 3: Clinical pharmacology: The routine PK/PD studies in healthy subjects or where necessary, in patients, is required by all agencies. There is, however, sufficient room for negotiating the size of these trials that may include selecting only the doses within a linear range, avoiding multiple-dose studies and using