how changes in attributes over the shelf life will be incorporated into the determination of the similarity acceptance criteria.
- *Multiple testing results*—When there are multiple testing results for the same lot with a given quality attribute or assay, the biosimilar applicant should prespecify which results will be selected for analytical similarity assessment.
- *Assay performance*—The assay methodologies and assay designs used in the analytical similarity assessment should be carefully considered and optimized, as needed. Poor assay performance, including high assay variability, should not be used to justify selection of either a particular evaluation tier or an inappropriately broad similarity acceptance criterion.
- *Differences in attributes that will be considered acceptable*—It may be known in advance that a difference less than or equal to a certain amount for a particular quality attribute would not be expected to have a clinical impact. In this situation, supporting information and an adequate justification for the allowable differences should be provided in the application.

The FDA recommends that the analytical similarity assessment plan be developed in four stages, corresponding to the following activities:

- Development of the risk ranking of the reference product's quality attributes based on the potential impact on the clinical performance categories (i.e., the product's activity as well as pharmacokinetic/pharmacodynamic [PK/PD], safety, and immunogenicity profiles)
- Determination of the statistical methods to be used for evaluating each quality attribute based on the risk ranking and on other factors
- Development of the statistical analysis plan
- Finalization of the analytical similarity assessment plan

These four stages are described in more detail in the following subsections.

9.3.1.1 Development of risk ranking of attributes

The FDA recommends that biosimilar sponsors develop a risk assessment tool to evaluate and rank the reference product quality attributes in terms of potential clinical impact. (Certain quality evaluations of the reference product—e.g., its degradation rates, which are determined from stability or forced degradation studies—generally would not be included in the risk ranking. However, these evaluations will still factor into the assessment of the analytical similarity of the proposed biosimilar and reference product.) The risk assessment tool should be developed considering, at a minimum, the following two factors:

- *Potential impact of an attribute on clinical performance*—Specifically, the FDA recommends that sponsors consider the impact of an attribute on activity as well as on PK/PD, safety,