Note that this statement can be interpreted to mean that the confidence interval for the ratio of geometric means is between 80% and 125%. An alternative would be to show that the tolerance intervals (or a distribution-free model) overlap sufficiently.

To protect the exclusivity of a brand-name drug product, the sponsors of the innovator drug products will make every attempt to prevent generic drug products from being approved by regulatory agencies such as the FDA. One strategy used in the United States is to challenge the Fundamental Bioequivalence Assumption by filing a c*itizen petition* with scientific/clinical justification. Upon receipt of a citizen petition, the FDA has the legal obligation to respond within 180 days. It should be noted, however, that the FDA will not suspend the review/approval process of a generic submission of a given brand-name drug even if a citizen petition is under review within the FDA.

In spite of the Fundamental Bioequivalence Assumption, one of the controversial issues that has arisen is that bioequivalence may not necessarily imply therapeutic equivalence and therapeutic equivalence does not guarantee bioequivalence either. One criticism lodged in the assessment of average bioequivalence for generic approval is that it is based on legal/political considerations rather than scientific arguments. In the past several decades, many sponsors/researchers have attempted to challenge this assumption but without success.

In practice, verification of the Fundamental Bioequivalence Assumption is often difficult, if not impossible, without conducting clinical trials. Notably, the Fundamental Bioequivalence Assumption applies to drug products with identical active ingredient(s). Whether the Fundamental Bioequivalence Assumption is applicable to drug products with similar but different active ingredient(s), as in the case of biosimilars, becomes an interesting but controversial question.

Similar to the Fundamental Bioequivalence Assumption described above, it has been suggested that a Fundamental Biosimilarity Assumption be developed. The following statement could be considered:

> When a follow-on biological product is claimed to be biosimilar to an innovator product in some well-defined study endpoints, it is assumed that they will reach similar therapeutic effect or they are therapeutically equivalent.

Some well-defined study endpoints are those from different functional areas such as certain physicochemical characteristics, biological activities, pharmacokinetics/pharmacodynamics (PK/PD), and immunogenicity.

1.3 SCIENTIFIC FACTORS AND PRACTICAL ISSUES

1.3.1 Criteria for Biosimilarity

For the comparison between drug products, some criteria for the assessment of bioequivalence, similarity (e.g., comparison of dissolution profiles), and consistency (e.g., comparisons between manufacturing processes) are available in either regulatory guidelines/guidances and/or the literature. These criteria, however, can be classified as (1) absolute change versus relative change, (2) aggregated versus disaggregated, or (3) moment-based versus probability-based. In this section, we briefly review different categories of criteria.