## INTRODUCTION

No topic seems so simple but stimulates such intense controversy and misunderstanding as the topic of bioequivalence. The apparent simplicity of comparing in vivo performance of two drug products is an illusion that is quickly dispelled when one considers the difficulties and general public misunderstanding of the accepted regulatory methodology. One sometimes hears members of the public and medical experts alike stating various opinions on the unacceptability of approved generic drug products based on misconceptions regarding the determination of therapeutic equivalence of these products to the approved reference. These misconceptions include the belief that the U.S. Food and Drug Administration (FDA) approves generic products that have mean differences from the reference product of 20% to 25% and that generic products can differ from each other by as much as 45%. In addition, some incorrectly assume that bioequivalence testing in normal volunteers does not adequately reflect bioequivalence and therefore therapeutic equivalence in patients. When the current bioequivalence methods and statistical criteria are clearly understood, it becomes apparent that these methods constitute a strict and robust system that provides assurance of therapeutic equivalence. In this chapter, we will discuss the history, rationale, and methods utilized for the demonstration of bioequivalence for regulatory purposes in the United States. In addition, we will touch on the challenges of determining bioequivalence of locally acting oral drug products.

## OBJECTIVES OF BIOEQUIVALENCE STUDIES

The most important concept in the understanding of bioequivalence is that the sole objective is to measure and compare formulation performance between two or more pharmaceutically equivalent drug products. Formulation performance is defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance and eventually leading to one or more pharmacologic effects, both desirable and undesirable. If equivalent formulation performance from two products can be established, then the clinical effects, within the range of normal clinical variability, should also be equivalent. This is the same principle that leads to an equivalent response from different lots of the brand-name product.

Generic drug products must be both pharmaceutically equivalent and bioequivalent to be considered therapeutically equivalent and therefore approvable. Pharmaceutical equivalents must contain the same amount of the same drug substance and be of the same dosage form with the same indications and uses. Thus, an immediate-release tablet would not be considered pharmaceutically equivalent to an oral liquid suspension, capsule, or modified-release tablet. Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the