1992 Revisions to the FDA's Bioavailability/Bioequivalence Regulations

In 1992, the FDA revised the *Bioavailability and Bioequivalence Requirements* of 21 CFR Part 320 to implement the Hatch–Waxman Amendments.[16] In its present form, 21 CFR Part 320 consists of Subpart A: *General Provisions* and Subpart B: *Procedures for Determining the Bioavailability and Bioequivalence of Drug Products.* Subpart A describes general provisions including definitions of bioavailability and bioequivalence. Subpart B states the basis for demonstrating in vivo bioavailability or bioequivalence and lists types of evidence to establish bioavailability or bioequivalence, in descending order of accuracy, sensitivity, and reproducibility. Subpart B also provides guidelines for the conduct and design of an in vivo bioavailability study and lists criteria for waiving evidence of in vivo bioequivalence.

As per the FDA's current *Bioavailability and Bioequivalence* regulations, statistical evaluation of bioequivalence studies of systemically active drugs is based on the analysis of drug concentrations in blood or plasma/serum. The rate of drug absorption is based on peak drug concentrations (C_{max}). The extent of drug absorption is based on the area under the drug concentration versus time profile (AUC). Generally, both AUC determined until the last measurable sampling time (AUC_{0-t}) and AUC extrapolated to infinity (AUC_{∞}) are evaluated.

Early Days of the FDA's Bioequivalence Review Process

Criteria for approval of generic drugs have evolved since the 1970s.[17] In the early 1970s, approval was based on mean data. Mean AUC and C_{max} values for the generic product had to be within ±20% of those of the brand-name product. In addition, plasma concentration-time profiles for immediate-release products had to be reasonably superimposable. Beginning in the late 1970s, the 75/75 (or 75/75–125) rule was added to the criteria. According to the 75/75 rule, the test/reference ratios of AUC and C_{max} had to be within 0.75 to 1.25 for at least 75% of the subjects. This was an attempt to consider individual variability in rate and extent of absorption. In the early 1980s, the power approach was applied to AUC and C_{max} parameters in conjunction with the 75/75 rule. The power approach consisted of two statistical tests: (1) a test of the null hypothesis of no difference between formulations using the F test and (2) the evaluation of the power of a test to detect a 20% mean difference in treatments.

Statistically, the power approach and the 75/75 rule have poor performance, and the FDA discontinued the use of these methods in 1986. The problems with both the 75/75 rule and power approach methods arose from the fact that they were based on the conventional null hypothesis test of no difference. Conventional hypothesis testing does not assess the evidence in favor of the conclusion that the test and reference means are equivalent but rather assesses the evidence in favor of a conclusion that the test and reference means are different, which is not the question of interest in bioequivalence analysis.[18–20] That is, the objective of bioequivalence analysis is to establish whether the test and reference means are equivalent—in other words, is the difference between the two means an acceptable difference?