Publication of the 1977 Bioavailability and Bioequivalence Regulations

In 1977, the FDA published its *Bioavailability and Bioequivalence* regulations under Title 21 of the Code of Federal Regulations (21 CFR). The regulations were divided into Subpart A: *General Provisions*, Subpart B: *Procedures for Determining the Bioavailability of Drug Products*, and Subpart C: *Bioequivalence Requirements*.[13] With the publication of these regulations, a generic firm could file an ANDA that provided demonstration of bioequivalence to an approved drug product in lieu of clinical trials. Subpart B defined bioavailability in terms of rate and extent of drug absorption, described procedures for determining bioavailability of drug products, set forth requirements for submission of in vivo bioavailability data, and provided general guidelines for the conduct of in vivo bioavailability studies. Subpart C set forth requirements for marketing a drug product subject to a bioequivalence requirement. ANDAs were generally still restricted to duplicates of drug products approved before October 10, 1962 and determined to be effective for at least one indication in a DESI notice.

An important feature of the 1977 regulations was the provision for waiver of in vivo bioequivalence study requirements (biowaivers) under certain circumstances. Applicants could file biowaiver requests for oral dosage forms and oral solubilized dosage forms. Waivers could be granted duplicate DESI-effective immediate-release oral drug products with no known bioequivalence problems. Biowaivers could also be granted for drug products in the same dosage form, but a different strength, and proportionally similar in active and inactive ingredients to a drug product from the same manufacturer for which in vivo bioavailability had been demonstrated. Both drug products were required to meet an appropriate in vitro test (generally dissolution) approved by the FDA.

Availability of the Paper NDA Route for Duplicate Drug Products

The FDA did allow some duplicate drug versions of post-1962 drug products to be marketed under a "paper NDA" policy.[14] Under this policy, in lieu of conducting their own tests, manufacturers of such duplicate drug products could submit safety and effectiveness information derived primarily from published reports of well-controlled studies. However, such reports of adequate and well-controlled studies in the literature were limited, and the FDA staff effort involved in reviewing paper NDAs became a substantial and often inefficient use of resources.

1984 Hatch–Waxman Amendments

In 1984, the Drug Price Competition and Patent Term Restoration Act (the Hatch–Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act by creating Section 505(j) of the Act (21 USC 355(j)), which established the present ANDA approval process.[15] Section 505(j) extended the ANDA process to duplicate versions of post-1962 drugs but also required that an ANDA for any new generic drug product shall contain information to show that the generic product is bioequivalent to the reference listed drug product. Evidence of bioequivalence was now required for all dosage forms.