to establish the safety and efficacy of each new product identical in active ingredient and dosage form with a drug product previously approved as safe and effective. However, many of the DESI notices included, as a requirement for approval of the duplicate drug application, presentation of evidence that the "biological availability" of the test product was similar to that of the innovator's product.

Development of the FDA's Bioavailability/Bioequivalence Regulations

Introduction in the late 1960s and early 1970s of sophisticated bioanalytical techniques made possible measurements of drugs and metabolites in biological fluids at concentrations as low as a few nanograms per milliliter. Because these techniques were applied to investigate the relative bioavailability of various marketed drug products, it became apparent that many generic formulations were more bioavailable than the innovator products, whereas others were less bioavailable.

In the late 1960s and early 1970s, many published studies documented differences in the bioavailability of chemically equivalent drug products, notably chloramphenicol,[6] tetracycline,[7] phenylbutazone,[8] and oxytetracycline.[9] In addition, a number of cases of therapeutic failure occurred in patients taking digoxin. These patients required unusually high maintenance doses and were subsequently found to have low plasma digoxin concentrations.[10] A crossover study conducted on four digoxin formulations available in the same hospital at the same time revealed striking differences in bioavailability. The peak plasma concentrations, after a single dose, varied by as much as sevenfold among the four formulations. These findings caused considerable concern because the margin of safety for digoxin is sufficiently narrow that serious toxicity or even lethality can result if the systemically available dose is as little as twice that needed to achieve the therapeutic effect.

Creation of an Office of Technology Assessment (OTA)

To address this problem of bioinequivalence among duplicate drug products, the U.S. Congress in 1974 created a special OTA to provide advice on scientific issues, among which was the bioequivalence of drug products. The OTA formed the Drug Bioequivalence Study Panel. The basic charge to the panel was to examine the relationships between chemical and therapeutic equivalence of drug products and to assess whether existing technological capability could assure that drug products with the same physical and chemical composition would produce comparable therapeutic effects. After an extensive investigation of the issues, the panel published its findings to the US Congress in a report, dated July 15, 1974, entitled Drug Bioequivalence.[11,12] The panel concluded that variations in drug bioavailability were responsible for some instances of therapeutic failures and that analytical methodology was available for conducting bioavailability studies in man. Several recommendations pertained to in vivo bioequivalence evaluation. The panel recommended that efforts should be made to identify classes of drugs for which evidence of bioequivalence is critical, that current law requiring manufacturers to make bioavailability information available to the FDA should be strengthened, and that additional research aimed at improving the assessment and prediction of bioequivalence was needed.