

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 10675

under an extramural contract with the Food and Drug Administration, had just completed a pharmacokinetic evaluation of digitoxin when the agency learned of the results of the Lindenbaum study. Dr. Wagner then proceeded to study the bioequivalence of digoxin tablets. In addition to conducting a bioavailability study on digoxin tablets made by two different manufacturers, Dr. Wagner developed a reproducible in vitro dissolution test which showed significant correlation with in vivo bioavailability test results. The results of the Wagner study were published in The Journal of the American Medical Association in April, 1973 (Wagner, J. G., et al., "Equivalence Lack in Digoxin Plasma Levels," Journal of the American Medical Association, 224:199-204, 1973).

In the meantime, sufficient tablets of the second batch of digoxin tablets which gave low serum digoxin levels in the Lindenbaum study were located for chemical analysis. The Food and Drug Administration's analysis showed that the tablets met the compendial specifications for content uniformity. It was therefore apparent that the problem identified originally by Lindenbaum and his colleagues was attributable to bioavailability and not to potency (Skelly, J. and Knapp, G., "Biologic Availability of Digoxin Tablets," Journal of the American Medical Association, 224:243, 1973).

The Food and Drug Administration recognized that very few well controlled digoxin bioavailability studies had been performed and was aware of data which indicated that even the possibility of batch-to-batch bioavailability inconsistency could not be discounted. The agency continued to implement studies to determine the dimension of the problem and to provide the basis for a systematic regulatory approach to assure the