

10674 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

normal human volunteers of 4 batches of commercially marketed digoxin tablets. The study noted marked differences in serum digoxin levels achieved with tablets produced by different manufacturers. Significant variation between different batches prepared by a single manufacturer was also observed. Lindenbaum conducted the study after observing low serum digoxin concentrations in several patients receiving unusually large maintenance doses of digoxin.

The tablets used in the study had not been analyzed for compliance with compendial specifications including potency and content uniformity. Subsequently, the Food and Drug Administration analyzed tablets from batches used in the Lindenbaum study and found that the two batches which gave acceptable serum digoxin levels met these compendial specifications. One batch which had given very low serum digoxin levels did not meet these compendial specifications varying from 76 to 152 percent of labeled potency. At that time sufficient tablets of the other batch which gave low serum digoxin levels could not be found for analysis. On this basis, it was the Food and Drug Administration's view that the problem identified by Lindenbaum may have been one of potency and not bioavailability (Vitti, T. G., Banes, D., Byers, T. E., "Bioavailability of Digoxin", The New England Journal of Medicine, 285:1433, 1971).

Somewhat prior to this, the Food and Drug Administration had begun a systematic investigation of several formulations of the cardiac glycosides. John G. Wagner, Ph.D., Professor of Pharmacy, Upjohn Center for Clinical Pharmacology, University of Michigan, Ann Arbor, Michigan,