

FY 80

NATIONAL CENTER FOR DRUG ANALYSIS
Bureau of Drugs, U.S. Food and Drug Administration
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Executive Summary of Accomplishments: Fiscal Year 1980

1. Staff Level: 44 person years
Allocation: 8 person years: Biopharmaceutics Projects
30 person years: Drug Quality-Assurance Projects
6 person years: Generic Drug Standards Projects

2. Dissemination of Methodology.

Papers written at the Center appeared as journal articles (1-9) and in-house publications (10-19). Reported were semiautomated methods for analysis of chlorpheniramine maleate, nitroglycerin, aspirin, salicylic acid, diethylstilbestrol, reserpine, hydrochlorothiazide, hydroflumethiazide, chlorothiazide, benzthiazide, trichlormethiazide, cyclothiazide, methyclothiazide, polythiazide, cyanocobalamin, amphetamine sulfate, ephedrine sulfate, and methamphetamine hydrochloride; manual methods of analysis for salicylic acid, salicylsalicylic acid, acetylsalicylsalicylic acid, and acetylsalicylic anhydride in aspirin products, and phenobarbital in elixirs; and thin-layer chromatographic (TLC) identification tests for thiazide diuretics, adrenergics, methenamine, methenamine mandelate, methenamine sulfosalicylate, methenamine hippurate, propoxyphene hydrochloride, propoxyphene napsylate, caffeine, phenacetin, aspirin, acetaminophen, salicylic acid, and amphetamine-type drugs. The decomposition of aminophylline in suppository formulations was detailed, and a laboratory sampling protocol, used to assure reliable results in dissolution testing of prednisone tablets, was described.

3. Dissolution Testing.

The Center continued to study the factors that cause variation in results when prednisone tablets are tested for dissolution by the paddle method (USP Apparatus 2). A collaborative study of the USP method was started: ten FDA laboratories are participating.

Extensive comparisons of glass and plastic vessels showed that the latter are preferable: glass vessels cannot at present be manufactured uniformly enough to prevent surface imperfections, and small bumps or other irregularities cause substantial errors in dissolution results with certain formulations.

The videotape presentation "Guidelines for Dissolution Testing, July 1977," prepared by NCDA, was loaned to one university, and the slide/

tape presentation "Guidelines for Dissolution Testing, July 1978," also developed by NCDA, was loaned to 16 firms and three universities to assist in training their laboratory personnel. In addition, an expanded and updated version of the latter presentation was prepared and submitted to headquarters for review, prior to being reproduced for public sale by the National Audiovisual Center.

4. Surveillance/Regulatory Analyses.

The American Society of Hospital Pharmacists, the United States Pharmacopeial Convention, and FDA engaged in a pilot program to study the stability of drugs under actual market conditions. Samples were mailed directly from participating pharmacies to the USPC, who then transmitted the samples to FDA for examination at the Center. The product studied in the pilot program was digoxin tablets. Ninety-two samples of digoxin tablets representing three manufacturers were analyzed for content uniformity, strength, dissolution, and related impurities. A total of 3935 surveillance assays were conducted. Seven samples failed to meet the USP XIX dissolution requirements. These batches were manufactured prior to July 1975, at which time the dissolution requirement was changed from 55 to 65% dissolution; the samples met the requirements of the USP XVIII. Four batches of tablets that were analyzed during this program had been previously analyzed three to four years ago under the digoxin certification program. These batches showed essentially no change in content uniformity, strength, and dissolution. The USP XX assay method was modified to analyze for related impurities. Levels of digoxigenin bisdigitoxoside were found to range from less than 1 to about 5% of declared digoxin. The study provided very useful information, and several additional studies are being planned for FY 81.

Eleven Drug Quality-Assurance studies were completed in FY 80 (see Table 1). Laboratory results from the Center's national survey of the dissolution of aspirin products and levels of impurities were published.

5. Compendial Monograph Evaluation and Development.

The currently official USP monographs for digoxin, digitoxin, nitrofurantoin, and prednisolone are undergoing evaluation to determine their suitability to serve as public standards and to assure they contain appropriate regulatory methods.

6. Development of New Technology.

The Center continued its long-term effort to mechanize sample-preparation processes for tablets and capsules. A new apparatus, which will

grind five tablets or capsules simultaneously, was designed for construction by the Winchester Engineering and Analytical Center. A prototype of a custom-built liquid sampler, constructed at the Center, is being redesigned to allow its use in the laboratory.

Improved programs to acquire and smooth data from continuous-flow analyzers were written and tested with a microprocessor system. A redesigned analog-to-digital converter is being constructed and tested; it will feature improved shielding against interference from radio or television signals, and two additional input voltage ranges that will permit operation of the microprocessor with most of the spectrophotometers and fluorometers currently used by the Center to monitor the output flow streams from continuous-flow analyzers.

7. Other Activities.

Installation of the Hewlett-Packard 1000 Computing System was completed in 1980, permitting improvement of the Center's management information system.

The Center obtained dissolution profiles of 11 commercial samples of aminophylline tablets, in an attempt to find samples suitable for use in a collaborative study of our proposed dissolution methods for this drug.

Reference-standard materials were obtained or synthesized for use in analysis of human serum samples for thioridazine and several of its metabolites. Analytical methodology is being tested in preparation for an in vitro/in vivo correlation study of thioridazine planned for FY 81.

Methodology for the analysis of salicylic acid in urine and aspirin in serum was completed. The in vivo study on aspirin tablets will be conducted in FY 81, using samples of aspirin tablets that were analyzed for dissolution properties during FY 80.

The Center analyzed a sample, presumed to be digitalis tablets, received from the State of Idaho. The identification was confirmed by TLC, mass spectrometry, and photomicrography, with comparison to an authentic sample of digitalis; many court exhibits were prepared and forwarded to Idaho officials.

The 1980 AOAC Spring Workshop, held in St. Louis, was extensively supported by Center personnel, who planned and cochaired the Workshop, organized a session on automated drug analysis, presented two papers, managed the exposition area, supervised catering and other local arrangements, and provided audio-visual equipment operators.

The Center organized and conducted its first formal review and appraisal of its research activities. A committee of four FDA science advisors, chaired by Dr. Neil Castagnoli, University of California, San Francisco, visited the Center, heard presentations on all major research and development areas, and prepared a critique. The critique will be a basis for consideration of improvements in the Center's operation.

8. Other Services.

The Center filled several requests for copies of FDA's Drug AutoAnalysis Manual and NCDA's Good Laboratory Practices Manual and Quality-Control Program.

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Table 1. Drug Quality-Assurance Studies Completed at NCD A in FY 80.

This table presents results of laboratory findings and includes the percentage of all types of defects observed. These percentages do not necessarily reflect the quality of all the drugs on the market since the studies are conducted on drug categories in which high defect rates are suspected.

Study No. and Name	Batches Analyzed	Defective Batches, % ^a
78-33 Barbiturates	328	2.1 7
79-03 Thiazides	126	2.4 3
79-22 Oral Contraceptives	84	1.2 1
79-24 Diethylstilbestrol	22	4.5 1
79-25 Nitrofurantoin	44	4.5 2
79-26 Aspirin (Enteric-coated tablets and suppositories)	68	4.4 3
79-30 Propoxyphene Hydrochloride	94	0 0
79-31 Vitamin Injections	69	1.4 1
79-32 Ephedrine Hydrochloride	39	0 0
79-33 CNS Stimulants	44	6.8 3
79-34 Conjugated Estrogens	58	0 0
ASHP-USP-FDA Special Digoxin Mail-In Study	92	7.6 7
	1068	28 2.6%
566 Digitoxin Continuous	2	0 0
567 Digoxin) Certification	3	33.3 1
78-17 Prednisone) Programs	66	15.2 10

^aPercent of batches not meeting compendial or FDA-imposed requirements.

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3.4%