FY 82

NATIONAL CENTER FOR DRUG ANALYSIS

U.S. Food and Drug Administration
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Executive Summary of Accomplishments: Fiscal Year 1982

1. Staff Level: 44 person years.

2. Dissemination of Methodology.

Papers written or coauthored by Center personnel appeared as journal articles (1-6) and FDA publications (7-11). A method for measuring aspirin and impurities in enteric-coated tablets and suppositories, and a method for dissolution testing of enteric-coated aspirin tablets were published (6). Identification of the cypionate and enanthate esters of testosterone by high-pressure liquid chromatography was described (8).

A continuous-flow semiautomated method of analysis for atropine sulfate, alone or in combination with phenobarbital, was detailed (10), and thin-layer chromatographic identification procedures were provided for androgenic hormones (8) and sulfonamides (9).

A goal-programming decision model, suitable for setting objectives, meeting budgetary and operational constraints, planning personnel utilization, and evaluating different proposals for allocating laboratory personnel to implement FDA's Good Laboratory Practice regulations, was published (2).

3. Dissolution Testing.

The Center continued its study of the factors that cause variation in results when prednisone tablets are tested for dissolution by the paddle method (USP Apparatus 2). Papers were published on three aspects of the research: the effects of deviations in dissolution vessel curvature from the spherical shape required by the USP (3), the effects of improper physical alignment of the components of the dissolution apparatus (4), and the effects of the sampling probes that are used to withdraw solution from the dissolution vessels by automatic sampling equipment (5). The last paper was coauthored with a chemist in Los Angeles District.

Seventy-four sets of the Center's slide-audiotape presentation "Guidelines for Dissolution Testing" have been sold to the public by the National Audiovisual Center.

4. Surveillance/Regulatory Analyses.

Eleven Drug Quality-Assurance studies were completed in FY 82 (Table 1). The results of a study of the stability of digoxin tablets in hospital pharmacies, conducted in 1980 with the cooperation of the American Society of Hospital Pharmacists (ASHP) and the United States Pharmacopeial Convention (USPC), were published (1).

The mail-in program, conducted by FDA in cooperation with ASHP and USPC to study the stability of drugs under actual market conditions, was continued in FY 82. Dexamethasone acetate injection, dexamethasone sodium phosphate injection, nitroglycerin tablets and ointment, and digitoxin tablets were included in the program. The number of samples analyzed and the percentages of defective batches are shown in Table 1.

The six digitoxin tablet samples that failed to meet requirements did not have expiration dates, which indicated that they were probably manufactured before 1975. These findings prompted FDA to issue a reminder to pharmacists concerning the requirement of expiration dating (13).

The findings in the dexamethasone sodium phosphate portion of the program prompted follow-up inspections and sample analyses that are now in progress.

5. Compendial Monograph Evaluation and Development.

The currently official USP monographs for digoxin, digitoxin, nitrofurantoin, prednisolone, sodium levothyroxine, sodium liothyronine, thyroglobulin, and thyroid are undergoing evaluation to determine their suitability to serve as public standards and to assure they contain appropriate regulatory methods. A high-pressure liquid chromatographic method, proposed by Health and Welfare Canada for collaborative study by the Association of Official Analytical Chemists, is being evaluated for four major tranquilizers (phenothiazine derivatives) that are especially prone to decomposition in liquid dosage forms. The USP monographs for these drugs are also being reviewed.

The Center provided comprehensive method-evaluation data (12) to the USPC for their use in revision of the official assay of Dexamethasone Sodium Phosphate Injection. The new high-pressure liquid chromatographic method, proposed by the USPC, was used successfully by Center personnel in the assay of 114 products from 12 manufacturers during the mail-in program.

6. Development of New Technology.

The Center continued its long-term effort to mechanize the sample preparation of tablets and capsules. The sample-preparation apparatus, designed for construction by the Winchester Engineering and Analytical Center, was extensively evaluated with many types of tablet and capsule samples. Our evaluation of the apparatus, which is very promising, was discussed with WEAC personnel, who are planning to construct an improved version. The Center's prototype XY Liquid Sampler, designed to be compatible with the sample-preparation apparatus, is being fitted with new, improved electric valves that will be tested for leakage and resistance to solvents. Technical methods for control of such valves by a microcomputer were developed and published (11).

Improved programs to acquire and process data from segmented-flow analyzers were written and tested with a microcomputer system. The system's data were compared for several months with the data obtained by the Center's Hewlett-Packard System 1000 minicomputer, and satisfactory agreement was found. Methods to interface the microcomputer system with the minicomputer are being explored.

7. Other Activities

At the request of FDA's Division of Drug Product Quality, Center personnel examined several samples of guaifenesin bulk drug powder that had been used to manufacture guaifenesin syrup offered for sale to the Department of Defense. A minor impurity, observed as a small peak in a high-pressure liquid chromatogram, was isolated and identified as the beta isomer of guaifenesin. Synthesis of the beta isomer was accomplished by Center staff to confirm the identification and to allow quantitative analysis of the impurity in the bulk drug.

The Center obtained content-uniformity data and dissolution profiles from 11 commercial samples of theophylline timed-release tablets; the dissolution data were obtained with a microprocessor-controlled system that sampled the dissolution vessels. This work was performed to aid the Division of Biopharmaceutics in their investigation of a reported possible clinical failure of this product. The microprocessor-controlled system was also used to obtain dissolution profiles from seven batches of controlled-release quinidine gluconate tablets and quinidine sulfate tablets for the Division of Biopharmaceutics.

The Center acquired an additional 256K words of memory for its Hewlett-Packard System 1000 minicomputer, raising the total memory size to 640K words; a 120-megabyte disc and an 8-channel multiplexer for input/output devices were also obtained. The operating system software was upgraded to RTE-6/VM, and the high-level language FORTRAN 77 was added.

Renovation of 3500 square feet of the Center's tenth-floor laboratories was completed; modern laboratory services, benches, fume hoods, and flooring were installed. Twenty-five hundred square feet of laboratories on the ninth floor, previously used by another government agency, were reassigned to the Center's use; equipment, computer lines, and computer terminal/printer facilities were installed to allow full occupancy and use by Center staff.

8. Other Services.

The Center filled many requests for material describing maintenance and alignment of dissolution apparatus, and degassing of dissolution media.

References

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Table 1. Drug Quality-Assurance Studies Completed at NCDA in FY 82.

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 some of the studies are conducted on drug categories in which high defect rates are suspected.

Study No. and Name	Batches Analyzed	Defective Batches, %[a]
81-43 Phendimetrazine Tartrate	51	0
81-49 Theophylline	168	0
81-52 Meprobamate	122	0
81-56 Nitroglycerin	108	0
81-57 Atropine Sulfate	98	0
81-58 Methscopolamine	24	4.2
82-01 Levodopa, Methyldopa	71	0
82-02 Acetaminophen with Codeine	94	0
82-03 Acetaminophen	195	3.1
82-04 Aspirin with Codeine	30	0
82-23 Sulfonamides	66	0
ASHP-USPC-FDA Mail-In Program:		
Dexamethasone Acetate Injection	21	0
Dexamethasone Sodium Phosphate Injection	114	9.6
Nitroglycerin Tablets and Ointment	174	0
Digitoxin Tablets	24	25.0
Continuous Certification Programs:		
566 Digitoxin	0	0
567 Digoxin	2	50.0
78-17 Prednisone	29	10.3

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[a]Percent of batches not meeting compendial or FDA-imposed requirements.