FY 79

NATIONAL CENTER FOR DRUG ANALYSIS
Bureau of Drugs, U.S. Food and Drug Administration
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Executive Summary of Accomplishments: Fiscal Year 1979

1. Staff Level: 47 person years
   Allocation: 7 person years: Biopharmaceutics Projects
   40 person years: Drug Quality-Assurance Projects

2. Dissemination of Methodology.

Methods developed at the Center were reported in journal articles (1-6) and through in-house publications (7-17). About 20% of these papers concern Biopharmaceutics projects and about 80% deal with Drug Quality Assurance projects. Advances reported in these papers include manual methods of analysis for methylergonovine maleate, ergonovine maleate, salicylic acid, prochlorperazine, and epimeric 17-ketone oxidation impurities in dexamethasone sodium phosphate; thin-layer chromatographic (TLC) procedures for identification of steroids and major tranquilizers, and TLC limit tests for related foreign steroids, p-aminophenol, and p-chloroacetanilide; semiautomated methods of analysis for ergot alkaloids, phenytoin, chlorpheniramine maleate, brompheniramine maleate, aspirin, salicylic acid, codeine phosphate, levodopa, methyldopa, and ethylenediamine; an automated sampling/readout device for analysis of drugs in dissolution media; and guidelines for maintenance of dissolution equipment.

3. Dissolution Testing.

The Center continued to study the factors that cause variation in results when prednisone tablets are analyzed for dissolution characteristics by the paddle method (USP, Apparatus 2). Extensive tests were conducted to compare the results obtained from glass vessels with those from plastic vessels.

The Center conducted Regional Dissolution Workshops at St. Louis, New York City, and Los Angeles for a total of 180 participants from industry and FDA laboratories. In addition the slide/tape presentation "Guidelines For Dissolution Testing" was loaned to 36 firms to assist in training their laboratory personnel.

The Center obtained a large supply of prednisone tablets that are very useful in indicating misalignment of dissolution equipment and poor technique of the operator. These tablets were made available to other FDA laboratories as a quality-control aid.

Twenty-four batches of prednisolone tablets were tested for compliance with the USP XIX monograph, and additional dissolution data were taken using the paddle and round-bottom kettle. This work was done in support of Division of Biopharmaceutics efforts to establish dissolution requirements for prednisolone tablets.

4 Surveillance/Regulatory Analyses.

Through combined techniques of HPLC, TLC, ultraviolet and infrared spectrophotometry, mass spectrometry, and organic syntheses, the Center demonstrated that parabens, commonly used as preservatives, had in fact reacted with components of a commercial theophylline monoethanolamine enema solution; reaction between the parabens and the amine decreased the amount of pure drug and cause the appearance of two impurities, 4-hydroxybenzoic acid and N-(2-hydroxyethyl)-4-hydroxybenzamide. Through similar techniques the Center elucidated the reaction between aminophylline in suppositories and Wecobee, an ingredient of the suppository base; the reaction led to formation of amide impurities, decreased the amount of pure drug, and caused the suppositories to harden.

Seven Drug Quality-Assurance studies were completed in FY 1979 (see Table 1).

5. Development of New Technology.

The Center's long-term effort to mechanize the sample preparation of tablets and capsules was continued. A more advanced model of a system that automatically prepares, collects, and stores slurries of tablets or capsules was completed. The prototype of an automatic sampler, which sequentially samples the tablet or capsule solutions and passes them to a continuous-flow analyzer, was constructed.

In 1979 the Center installed a new Hewlett-Packard 1000 Computing System with 256,000 bytes of main memory. The system is operational, and most of the main programs are already installed in the new system. Plans for further expansion call for increasing the amount of main memory to 512,000 bytes and installing seven more remote terminals by September 30, 1980. Data-base management systems are also being proposed.

Programs to acquire and smooth data from continuous-flow analyzers were written for use by a microprocessor system. The interface between the microprocessor and an AutoAnalyzer Colorimeter II was completed.

A "benchmark" dissolution apparatus, designed by NCDA and constructed by the Winchester Engineering and Analytical Center, was received and is being used in dissolution research. The apparatus is controlled by a microprocessor and utilizes magnetic couplers to minimize shaft vibration.

6. Other Activities.

The Center obtained dissolution profiles of three samples of timed-release theophylline products in support of bioavailability studies conducted by Dr. Sidney Riegelman, University of California at San Francisco.

An in vivo study on aspirin tablets is planned for the second quarter of 1980. Samples for this study were selected from those analyzed during the FY 1979 QASMD survey.

Four drug monographs were assigned to NCDA for evaluation under the Compendial Monograph Evaluation and Development program. These are: digoxin, digitoxin, nitrofurantoin, and prednisolone.

References

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Table 1. Drug Quality-Assurance Studies Completed at NCDA in FY 79.

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]
78-06 Methyldopa and Levadopa	51	15.7 8
78-14 Aspirin Tablets, Compressed and Buffered	204	11.8 32
78-31 Anticoagulants	37	0 0
79-02 Reserpine	68	4.4 3
79-04 Reserpine/Thiazide	32	0 0
79-10 Antimalarials	65 457	0 0 43 9.4%
566 Digitoxin) Continuous	10	0 0
567 Digoxin) Certification	34	14.7 5
78-17 Prednisone) Programs	84	4.8 4
	585	52 8.9%

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