FY 77

NATIONAL CENTER FOR DRUG ANALYSIS
Bureau of Drugs, U.S. Food and Drug Administration
1114 Market Street
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Executive Summary of Accomplishments: Fiscal Year 1977

1. Authorized Staff Level: 45 persons

2. Dissemination of Methodology

Methods developed at the Center were reported via a paper in a scientific journal (1) and in-house publications (2-9). About 75% of these papers relate to Drug Quality Assurance and 25% to Biopharmaceutics. Advances reported in these papers include an AOAC collaborative study of a semi-automated method for the analysis of prednisolone or prednisone in tablets, semiautomated methods for analysis of steroid estrogens, of phenytoin, and of digitoxin (in dissolution medium), and manual analysis of conjugated or esterified estrogens by gas-liquid chromatography.

3. Dissolution Testing.

Repeat analyses of the dissolution profiles of 12 samples of digitoxin tablets studied in vivo by Dr. John Wood, Medical College of Virginia, Virginia Commonwealth University, were obtained to aid in the in vitro/in vivo correlation work. In addition, dissolution profiles of about 14 lots of digitoxin tablets were obtained and reported to aid in the selection of new samples for in vivo study.

The Center participated in a collaborative study of dissolution techniques, sponsored by the American Pharmaceutical Association (APhA). Four products (salicylic acid disks, 5- and 18-mg prednisone tablets, and nitrofurantoin capsules) were studied in three apparatuses (rotating basket, paddle, and spinning filter) at various agitation speeds. The data were reported to the APhA Committee on Dissolution Methodology. The Center also collaborated in a smaller study of dissolution techniques sponsored by the Executive Director for Regional Operations, Food and Drug Administration, and the United States Pharmacopeia (USP).

Dissolution analyses were performed on approximately 140 batches of prednisone tablets, prednisolone tablets, and methylprednisolone tablets. About 36 batches of prednisone tablets gave results that were significantly below the newly accepted USP dissolution requirements.

Several factors that cause variation in results when prednisone tablets are analyzed for dissolution characteristics by the NCDA paddle method were identified and corrected. Tools were designed and fabricated to facilitate the alignment of the dissolution apparatus. An intralaboratory collaborative study demonstrated that the use of these techniques and tools significantly reduces the variability of results obtained from this dissolution procedure. Dissolution guidelines for conducting tests of drugs in both the rotating-basket and rotating-paddle apparatuses were written.

The Center obtained dissolution results on 19 batches of chlorothiazide tablets to support headquarters' planning and decisions on future investigations of this drug product.

4. Surveillance/Regulatory Analyses.

In addition to the projects reported in Item 2, the Center developed new automated methods for the analysis of phenothiazine major tranquilizers (chlorpromazine hydrochloride, etc.), of ergot alkaloids (methysergide maleate, etc.), of xanthines (aminophylline, etc.), and of diethylstilbestrol. The official method of analysis for diethylstilbestrol tablets was found to give erroneously low results when applied to low-dosage, enteric-coated tablets, and a revised procedure was devised.

An improved, validated set of monographs for pseudoephedrine hydrochloride drug substance, syrup, and tablets, which includes a semiautomated procedure for measurement of content uniformity, was developed and submitted to the USP for consideration.

A semiautomated method of analysis of ferrous sulfate tablets was subjected to a collaborative study by the Association of Official Analytical Chemists (AOAC) and was accepted as official, first action by the Association.

Ten Drug Quality-Assurance studies were completed in FY 77 (see Table 1).

5. Development of New Technology.

A long-term effort to mechanize the sample preparation of solid-dosage drugs was initiated. A working model of a system that automatically collects and stores slurries of tablets or capsules was built; the system uses a Technicon SOLIDprep Sampler II to blend each individual tablet or capsule in an appropriate solvent, and the system then transfers the prepared slurries to glass vials for later analysis. The apparatus can be operated at rates up to 60 tablets or capsules per hour. Specifications for a more advanced sample-preparation system were written.

Deficiencies in the mechanical design of commercial dissolution apparatuses were studied, and specifications for two benchmark dissolution apparatuses, one using a magnetic drive and the other a direct, dc-motor drive, were prepared. These new designs incorporate feedback and control techniques to stabilize the rotation speed and high-quality drive components to reduce vibration levels.

The Center acquired an additional line printer and installed it in the laboratory area. All analytical worksheets and other computer output can be printed on this device. A cathode-ray terminal (CRT), installed next to the printer, allows analysts to enter data in the on-line mode and to receive immediate printouts of the information they request.

A second CRT has been installed in the Data-Entry Section, and newly developed software allows on-line entry to the computer through this terminal of master-file records, such as sample number, manufacturer, and generic code, for incoming samples.

Several improvements were made in the Center's computerized management-information system. Reports of samples in process at NCDA are now sent on a regular basis to the appropriate district offices. A weekly list of the numbers and types of samples that were received or completed that week is now produced for use by the Center's managers.

6. Other Activities.

The Center participated in one AOAC collaborative study initiated by another government laboratory and conducted one AOAC collaborative study of its own (see Table 2).

References

(1) Brower, J. F. (1977) J. Assoc. Off. Anal. Chem. 60, 27-31. Collaborative Study of a Semiautomated Method for the Analysis of Prednisolone and Prednisone Tablets.

(2) Cox, D. C. (1976) Lab. Info. Bull. 1928. Semiautomated Method for Determination of Digitoxin in Dissolution Medium.

Kolinski, R. E. (1977) Lab. Info. Bull. 1957. Semiautomated Method for Analysis of Certain Steroid Estrogens.

Furman, W. B. & Page, D. P. (1977) Lab. Info. Bull. 1962. Drug Autoanalysis Manual: Requirements for Acceptance of Methods.

Brown, R. L. (1976) Lab. Info. Bull. 1972. Precise Temperature and Voltage Control of Heating Baths for Automated Systems.

Cox, D. C., Myrick, J. W., Kolinski, R. E., Black, J. C., Wells, C. E., Kerner, F. W. & Furman, W. B. (1976) Lab. Info. Bull. 1981. Evaluation of Technicon Model I UV-Visible Spectrophotometer.

(7) Thornton, L. K., Moore, T. W. & Joachims, G. L. (1977) Lab. Info. Bull. 1987. Comparison of USP and GLC Methods in the Assays of Conjugated or Esterified Estrogens.

Myrick, J. W. (1977) Lab. Info. Bull. 2028. Sensitive Automated Determination of Phenytoin.

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Table 1. Drug Quality-Assurance Studies Completed at NCDA in FY 77.

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	Batches out of Compliance with Specifications, %[a]
Conjugated and Esterified Estrogens	99	11.0
CNS Stimulants	54	13.0
Ephedrine and Pseudoephedrine	103	7.8
Steroid Estrogens	58	0.0
596 Thiazide Diuretics	113	0.9
598 Tricyclic Antidepressants	95	1.1
Ergot Alkaloids	34	17.6
Sulfonamides	101	1.0
Adrenergics	126	4.0
Trisulfapyrimidines	47 807	0.0
Digitoxin) Continuous	53	22.6
) Certification		
Digoxin) Studies	23	4.3
	883	53

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

Table 2. AOAC Collaborative Studies Completed at NCDA in FY 77.

Study Title	Originating Laboratory
Gas-Chromatographic Determination of Chlorpheniramine Maleate and Pyrilamine Maleate	Cincinnati District
Semiautomated Determination of Ferrous Sulfate Tablets	National Center for Drug Analysis