FY 78

NATIONAL CENTER FOR DRUG ANALYSIS

Bureau of Drugs, U.S. Food and Drug Administration
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Executive Summary of Accomplishments: Fiscal Year 1978

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 via papers in journals (1, 2) and in-house publications (3-6). Half of these papers relate to Drug Quality Assurance and half to Biopharmaceutics. Advances reported in these papers include an AOAC collaborative study of a semiautomated method for the analysis of ferrous sulfate in drugs, a gas-liquid chromatography procedure for the determination of estrone or estradiol in oil-base injections and aqueous suspensions, a semiautomated method for analysis of major tranquilizers in drugs, and a comprehensive set of guidelines for dissolution testing.

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). For example, the influence of aeration versus deaeration of the dissolution medium was measured on over 60 samples of prednisone tablets; the Center recommended deaeration of dissolution media to the USP, and the recommendation was accepted.

Recommended practises for dissolution testing were published as guidelines in April 1978. In July 1978 the Center conducted workshops to familiarize employees of over 50 pharmaceutical firms with critical factors in dissolution testing. Audiovisual presentations (videotapes and slide/cassette demonstrations) were prepared and have been loaned to 37 firms to assist their laboratories in training their personnel. In addition, copies of the videotape presentation were given to eight FDA field laboratories, and copies of the slide/cassette demonstration were given to 16 FDA field laboratories, Biopharmaceutics Laboratory, National Center for Antibiotics Analysis, and the USP.

The Center identified two samples of prednisone tablets that show promise as potential "calibrators" for the paddle method. These samples and the calibrator sample proposed by the Pharmaceutical

Manufacturers Association were extensively studied to evaluate their ability to indicate misalignment of equipment and poor technique of the operator.

4. Surveillance/Regulatory Analyses.

Development of modern, sensitive methods for the analysis of aspirin products was started. A high-performance liquid chromatography (HPLC) method was validated and is being used to measure and identify trace impurities, such as O-salicylsalicylic acid, as well as the more common decomposition product, salicylic acid.

Through combined techniques of HPLC, thin-layer chromatography, ultraviolet and infrared spectroscopy, and organic syntheses, the Center identified a white precipitate found in a commercial dexamethasone sodium phosphate solution for injection as being an oxidation product of dexamethasone, specifically a mixture of 16α- and 16β-methyl epimers of 9-fluoro-11β-hydroxy-16-methylandrosta-1,4-diene-3,17-dione.

Twelve Drug Quality-Assurance studies were completed in FY 78 (see Table 1).

5. Development of New Technology.

A Harrick rapid-scan ultraviolet-visible spectrophotometer was received and installed. A microprocessor system, which will control the spectrophotometer and acquire data from it, is now being developed.

Programs to acquire and smooth data from AutoAnalyzers were written for use by a microprocessor system. The interface between the microprocessor and the AutoAnalyzer Colorimeter II is being developed.

A microprocessor-controlled apparatus, which automatically samples and analyzes dissolution medium from six vessels, was designed and completed. The apparatus integrates components of a Technicon AutoAnalyzer, an ultraviolet spectrophotometer, and a KIM-1 microprocessor.

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 collects and stores slurries of tablets or capsules was built. Sensors to detect mechanical movement and microprocessor programs for control of the apparatus are being developed.

"Benchmark" dissolution apparatuses, which use direct-drive motors or magnetic couplers to reduce vibration, are being constructed at Winchester Engineering and Analytical Center in collaboration with NCDA.

The Center installed a graphic terminal through which we are now able to conduct remote operations with the Parklawn Computer Center (PCC). The terminal is being used to access PCC's graphic and high-language software, and to obtain faster processing of the Center's financial accounting procedures and reports. In the near future the Center will install an HP 1000 computing system which will give us improved data-acquisition and control features, faster computing speed, data-base management, and the use of Real Time Basic programming. The acquisition of this larger machine will enable us to service the Center's laboratory and management personnel much more efficiently and with more varied data systems.

6. Other Activities

The Center participated in two collaborative studies, conducted by the USP: a gas-chromatographic analysis of barbiturates and an HPLC method for analysis of triamcinolone acetonide cream.

The Center obtained content-uniformity data for 17 samples of aminophylline, oxtriphylline, and theophylline (alone and in combination with sodium glycinate) in tablets, capsules, and suppositories and provided the data to Dr. Sidney Riegelman, University of California at San Francisco, who has studied these products in vivo.

References

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(3) Kolinski, R. E., Cox, D. C., Brower, J. F. & Wells, C. E. (1977) Lab. Info. Bull. 1982. The Determination of Estrone or Estradiol in Sesame-Oil-Base Injections and Aqueous Suspensions Using Gas-Liquid Chromatography.

(4) Wells, C. E., Moore, T. W. & Juhl, W. E. (1978) Lab. Info. Bull. 2024. Automated Sampling/Readout Devices for Dissolution Media. Discrete Sample-Collection System.

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(6) Anon. (1978) Lab. Info. Bull. 2146. Guidelines for Dissolution Testing.

Table 1. Drug Quality-Assurance Studies Completed at NCDA in FY 78.

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]
592	Adrenocorticosteroids		690	3.2 22
612	Antiarrhythmics		120	0.8 1
617	Major Tranquilizers		290	0.7 20
626	Androgenic Hormones		125	0.8 1
627	Progestins		55	1.8 1
628	Xanthine Derivatives		271	3.7 10
629	Nitroglycerin		41	0 0
637	Chlorpheniramine Maleate and Brompheniramine Maleate		93	3.2 3
643	Digoxin (Preparations other than tablets)		17	0 0
644	Acetaminophen and combinations with codeine and sodium butabarbital		287	1.0 3
645	Sodium Butabarbital and combinations with other barbiturates		64	7.8 5
78-1	Meprobamate		110 2163	0 0 66 3%
566	Digitoxin	Continuous	31	29.0 9
567	Digoxin	Certification	14	0 0
78-17	Prednisone	Programs	186	22.6 42
			2394	117 4.9%

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