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NATIONAL CENTER FOR DRUG ANALYSIS
Bureau of Drugs, U.S. Food and Drug Administration
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Executive Summary of Accomplishments: Fiscal Year 1981

1. Staff Level: 44 person years.

2. Dissemination of Methodology

Papers written at the Center appeared as journal articles (1-5) and FDA publications (6-18). A high-pressure liquid-chromatographic assay for aspirin and salicylic acid in bulk drug and tablets was published. The Center identified contaminants in dexamethasone sodium phosphate injections and in theophylline olamine enemas, and published the results. Also reported was a method of assaying individual pentaerythritol tetranitrate tablets by differential pulse polarography. The procedures used by the Center for maintenance and calibration of its scientific apparatus were described at a symposium and published.

Continuous-flow semiautomated methods of analysis were reported for betamethasone, chlordiazepoxide, chlordiazepoxide hydrochloride, cortisone acetate, diazepam, fenoprofen, hydrocortisone, hydrocortisone acetate, hydrocortisone sodium succinate, indomethacin, lorazepam, naproxen, paramethasone acetate, prazepam, tolmetin, butabarbital sodium, and nitrofurantoin; the methods for the last two drugs utilize the relatively new technique of flow-injection analysis.

Thin-layer chromatographic identification procedures were provided for aspirin and nonaspirin salicylate, barbiturates, erythritol tetranitrate, fenoprofen, indomethacin, isosorbide dinitrate, mannitol hexanitrate, naproxen, pentaerythritol tetranitrate, tolmetin, and tricyclic antidepressants.

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). A collaborative study of five samples of prednisone tablets in 11 FDA laboratories was conducted by the Center. The results show that comparable results can be obtained among laboratories if the Center's procedures for equipment alignment and degassing of media are followed.

The Center compared the official USP calibrator tablets with NCDA's "Performance Standard No. 2," a sample of prednisone tablets used by the Center and several other FDA laboratories to check dissolution equipment. The ability of the USP calibrators and Performance Standard No. 2 to respond to incorrect adjustment of equipment and to excess gas in dissolution media was carefully measured. The official calibrators do not respond as markedly as Performance Standard No. 2 to procedural errors.

Dissolution results may also be changed if one uses a "probe" (a tube or filter cartridge) to take aliquots from the dissolution medium for automated analysis. The effects of several types of probes, both commercially available units and a special low-volume probe designed at the Center, were published.

An expanded and updated version of the Center's slide-tape presentation "Guidelines for Dissolution Testing" was put into production for public sale by the National Audiovisual Center.

4. Surveillance/Regulatory Analyses.

Fifteen Drug Quality-Assurance studies were completed in FY 81 (see Table 1). Laboratory results from the Center's national survey of the dissolution of commercial prednisone tablets were published (6).

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. Review of several monographs for major tranquilizers (phenothiazine derivatives) in liquid dosage forms has just started.

6. Development of New Technology.

The Center continued its long-term effort to mechanize the sample preparation of tablets and capsules. A new apparatus, designed for construction by the Winchester Engineering and Analytical Center, was completed and delivered to NCDA, where it is now undergoing evaluation. The apparatus grinds five tablets or capsules simultaneously and processes them in groups of 30 in a sample holder that is compatible with the Center's prototype XY Liquid Sampler. The design of the latter is complete except that the electric valves show excessive leakage; other valves will be obtained and tested.

Improved programs to acquire and process data from segmented-flow analyzers were written and tested with a microprocessor system. Programs that store the intermediate absorbance data on cassette tape were finished. The system's data were compared for several days with the data obtained by the Center's Hewlett-Packard System 1000 minicomputer. The test revealed that the results from the minicomputer showed somewhat better precision than those from the microcomputer, and software improvements for the latter will be continued.

7. Other Activities.

The Center conducted a collaborative study of its method for dissolution of aminophylline tablets with Dallas District Laboratory. The results were acceptable. The method and data were forwarded to EDRO for consideration.

Analytical methods were finished and validated for the assay of thioridazine and its major metabolites in human serum. Reference standards of several of the metabolites were synthesized and characterized. Several postmortem blood samples provided by the St. Louis County Medical Examiner's office were analyzed for thioridazine and its major metabolites.

In May 1981 the Center conducted a Dissolution Workshop for EDRO and headquarters chemists. Lectures and laboratory experiments were designed to demonstrate correct technique, emphasize potential pitfalls, and transmit the latest results of the Center's and several EDRO chemists' dissolution research programs.

The Center acquired another 128K words of main memory, raising the total storage capacity of the Hewlett-Packard System 1000's central processing unit to 384K words. A larger disk is on order. Other hardware improvements were the installation of a terminal and printer in the laboratory area on the ninth floor. Software upgrades included PASCAL, FORTRAN 4X, IMAGE/1000, and RTE IVB with Session Monitor and file-security systems.

8. Other Services.

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

FY81

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Table 1. Drug Quality-Assurance Studies Completed at NCDA in FY 81.

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]	
79-34 Conjugated Estrogens	58	0	0
80-24 Anti-Inflamatory Agents	32	0	0
80-29 Major Tranquilizers	231	0.4	1
80-30 Steroid Estrogens	40	0	0
80-31 Psychostimulants	217	0	0
80-41 Coronary Vasodilators	51	3.9	2
80-55 Adrenocorticosteroids	584	1.9	11
80-56 Terpin Hydrate	43	0	0
80-60 Adrenergics	116	8.6	10
80-61 Local Anesthetics	207	0.5	1
80-62 Cardiac Glycosides--Liquid	15	0	0
81-12 Butabarbital Sodium	38	7.9	3
81-27 Reserpine with Hydrochlorothiazide and Hydralazine	24	12.5	3
81-40 Sulfisoxazole	65	0	0
81-41 Testosterone	35 1721	0	0 31 1.8%
566 Digitoxin) Continuous		0	
567 Digoxin) Certification		7.7	
78-17 Prednisone) Programs		11.7	
	1818		39 2.1%

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