F184

DIVISION OF DRUG ANALYSIS*

U.S. Food and Drug Administration
1114 Market Street
St. Louis, MO 63101

Executive Summary of Accomplishments: Fiscal Year 1984

Staff Level

The Division of Drug Analysis operated with 49 full-time person equivalents.

Publications

Papers written or coauthored by Division of Drug Analysis personnel appeared as journal articles (1-11) and FDA publications (12-19).

Drug Quality Assurance

In cooperation with the American Society of Hospital Pharmacists (ASHP), the Division of Drug Analysis continued the "mail-in" program, designed to study the stability of drugs under actual market conditions. Analytical results were published for the following types of drug samples received from U.S. pharmacies: dexamethasone acetate suspensions and dexamethasone sodium phosphate injections (2), digitoxin tablets (1), and nitroglycerin tablets (3).

All 21 samples (two manufacturers) of dexamethasone acetate suspension met United States Pharmacopeia (USP) requirements. Of 114 samples of dexamethasone sodium phosphate injection (11 manufacturers), 11 samples (three manufacturers) failed USP assay requirements for strength and showed evidence of degradation by oxidation.

Of 25 samples of digitoxin tablets (19 lots, seven manufacturers), two lots failed USP requirements for strength, content uniformity, and dissolution, and four lots failed USP requirements for dissolution only. All six defective lots showed no expiration date, which indicated that they were manufacturered before 1975.

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*The reorganization that merged the Bureau of Drugs and Bureau of Biologics into the Center for Drugs and Biologics has resulted in several organizational title changes. As of September 25, 1984, the Division of Drug Analysis is the organizational title of the St. Louis facility previously designated as the National Center for Drug Analysis or the Center for Drug Analysis.

For nitroglycerin tablets, all 167 samples (three manufacturers) met USP requirements for content uniformity, strength, and disintegration. Six samples that showed unusual disintegration characteristics also dissolved slowly by one or more alternate methods (dissolution in a syringe, in USP Apparatus 2, or in USP Apparatus 3); however, other samples that disintegrated normally also showed slow dissolution. The study thus revealed that the USP disintegration test will not distinguish between rapidly and slowly dissolving nitroglycerin tablets.

In 1982, an impurity, discovered in a sample of digoxin injectable solution commercially packaged in a syringe for single-dose delivery, was found to originate from the rubber closure of the syringe and was identified as 2-mercaptobenzothiazole (2-MCBT), a common accelerator for rubber vulcanization. Several similarly packaged injectable solutions of a variety of drugs from various manufacturers were examined, and over half contained 2-MCBT. The compound was identified by ultraviolet (UV) spectrophotometry (including a pH-dependent shift in its absorbance maximum), by mass spectrometry, and by comparison with standard 2-MCBT using silica gel and reversed-phase high-performance liquid chromatography (HPLC). The presence of this impurity in injectable solutions may have implications with regard to toxicity and may interfere with the assay of digoxin injectable solution by HPLC (6).

In support of other Drug Quality Assurance studies, HPLC methods were developed for dexamethasone sodium phosphate in ophthalmic ointment (17) and sodium levothyroxine in bulk, tablet, and injection formulations (9). Semiautomated continuous-flow methods were reported for aminophylline or dyphylline in injections and tablets (19), folic acid in tablets (16), oxtriphylline in tablets (19), phenylpropanolamine hydrochloride alone or in combination with caffeine in sustained-release capsules and tablets (14), quinidine gluconate in injections and tablets (18), quinidine polygalacturonate in tablets (18), quinidine sulfate in capsules, injections, and tablets (18), theophylline in capsules and tablets (19), theophylline sodium glycinate in tablets (19), and tridihexethyl chloride in combination with meprobamate in tablets (5). Thin-layer chromatographic identification procedures were provided for folic acid (15), phendimetrazine (13), and steroid estrogens (12).

Biopharmaceutics

The Division of Drug Analysis continued to study the factors that cause variation in results when prednisone tablets are tested for dissolution by the paddle method (USP Apparatus 2). Two additional papers in the series were published. One describes the interaction between tablets and glass or plastic vessels. Even when both types of vessel pass USP specifications for dimensions, certain products may give significantly different results when tested in glass or plastic vessels, and thus the type of vessel employed should be recorded (8). The second paper reports a collaborative study by 11 laboratories of the USP dissolution test for prednisone tablets with Apparatus 2. To

our knowledge, this was the first successful collaborative study of the paddle dissolution method. The low standard deviations, both within laboratories and among laboratories, were ascribed to tight control of equipment setup via leveling and centering adjustments and a final check with Division of Drug Analysis' Performance Standard No. 2 test tablets (7). In addition, a history of the development of the paddle dissolution procedure was published. Early difficulties with the original apparatus, early lack of agreement among laboratories, studies and refinements of the apparatus, and the final successful collaborative study were reviewed (10).

In 1978, Division of Drug Analysis personnel published "Guidelines for Dissolution Testing," a detailed account of our setup and test procedures for the USP basket and paddle methods. These guidelines have had considerable impact in the regulated industry, as evidenced by numerous citations in the literature and by discussions with other scientists at conferences. In 1984, Division of Drug Analysis scientists published an addendum to these guidelines, which addresses improvements in the apparatus and techniques accrued in the intervening six years (11).

Generic Drug Standards

An HPLC method for determination of prednisolone in tablets and bulk drugs (16 samples) was collaboratively studied by six laboratories, and was recommended as an alternative to the official Association of Official Analytical Chemists (AOAC) and USP XX colorimetric methods (4).

Summaries of Current Projects

Drug Quality Assurance

Twelve Drug Product Surveillance studies were completed in FY 84 (Table 1). The mail-in program is designed to study the stability of drugs under actual market conditions; it was continued in FY 84 in cooperation with the ASHP. Epinephrine hydrochloride injections, epinephrine hydrochloride/lidocaine hydrochloride injections, betamethasone sodium phosphate injections, prednisolone sodium phosphate injections, hydrocortisone sodium phosphate injections, nitrofurantoin tablets and oral suspensions, theophylline tablets and capsules, aminophylline tablets, injections, and suppositories, levothyroxine sodium tablets and injections, liothyronine sodium tablets, and liotrix tablets were included. The number of samples analyzed and the percentages of defective batches are shown in Table 1. Additional samples were analyzed in support of the Government Wide Quality Assurance Program (GWQAP) and the Process Validation Program.

The Division of Drug Analysis performed over 63,000 analyses on 2,184 batches of drugs in FY 84. One hundred and ten batches failed to meet the compendial or FDA-imposed requirements for the products. The

number of defective batches in each of the program areas and the reasons for the classification as defective are shown in Table 2.

The Division of Drug Analysis continued its long-term effort to mechanize the sample preparation of tablets and capsules. A new sampler system, comprised of a robotic arm and valves controlled by a microcomputer, was programmed and tested. The robotic liquid sampler selects sample or standard solutions sequentially and feeds them into a conventional continuous-flow analyzer. The samples are taken from sample trays designed by the Winchester Engineering and Analytical Center for use with the second, improved version of their automatic sample preparer (ASP II). Our current research is aimed at manual use of the sample trays for preparation of samples for the robotic liquid sampler while we await delivery of the ASP II.

Two research projects concerning analysis of aspirin products are underway. The first centers on preparation of samples for analysis by HPLC. Solvent systems are being tested for their ability to suppress sample decomposition while the sample solutions await analysis. In addition, recoveries of aspirin decomposition products are being measured. The second project involves development of efficient syntheses of certain aspirin decomposition products (linear oligomers of salicylic acid) and their purification for use as reference standards in future surveys of aspirin products and for allergenic tests by headquarters personnel.

Division of Drug Analysis personnel prepared pure reference standards of the 16α- and 16β-methyl-17-ketone decomposition products of dexamethasone for use by New York District Laboratory staff in their drug analysis and research projects.

Biopharmaceutics

p-Chloronitrobenzene (p-CNB), a suspected carcinogen, is a starting material in a common synthesis of acetaminophen. At the request of the PMS manager for Biopharmaceutics, Division of Drug Analysis staff developed an HPLC method for detection and measurement of p-CNB in acetaminophen products. The method, which utilized a rapid-scan, UV spectrophotometer as the detector, could detect as little as 5 ppm of p-CNB. No p-CNB was found in any of the four samples available for analysis (two samples of bulk drug and one sample each of capsules and tablets).

The Division of Drug Analysis obtained dissolution profiles of eight commercial samples of oral, sustained-release theophylline products, in various media and apparatus conditions, to aid the Division of Biopharmaceutics address the problem of dose dumping of theophylline taken with meals.

Also at the request of the Division of Biopharmaceutics, Division of Drug Analysis personnel measured the dissolution rate of several samples of sustained-release phenylpropanolamine products, and oral suspensions of ampicillin, amoxicillin, sulfamethoxazone, and trimethoprin.

Generic Drug Standards

Division of Drug Analysis staff participated in an AOAC collaborative study, conducted by Health and Welfare Canada, of a new HPLC method for several drug classes, including phenothiazine tranquilizers. This method had previously been used successfully in a Drug Quality Assurance study of major tranquilizers at the Division of Drug Analysis.

Other Activities

Division of Drug Analysis personnel developed interfaces between the Division's Hewlett-Packard System 1000 computer and several scientific instrument systems: (a) a Hewlett-Packard automatic, spectrophotometric dissolution analyzer, which allows computer generation of worksheets for dissolution analyses without manual re-entry of data; (b) several Hewlett-Packard integrators, which permit direct transmission of gas and liquid chromatographic data to the computer; and (c) several Waters Associates "Data Transfer Modules," which allow direct transmission of liquid chromatographic data to the computer. Software to generate on-line worksheets from chromatographic analyses (systems b and c) is now being written. All of these interfaces were accomplished through Hewlett-Packard multiplex (MUX) cards, each of which accepts up to eight RS232 inputs; the study and implementation of control software for these complex multiplexers has required considerable effort but will pay handsome dividends through the eventual elimination of manual data entry by chemists and technicians.

Division of Drug Analysis staff also wrote custom software to allow special treatment of chromatographic data produced by Hewlett-Packard 1040A detectors. These detectors are rapid-scan, UV-visible spectrophotometers that generate large amounts of chromatographic and spectra data stored on diskettes. Although the factory-supplied control programs work well for routine analyses, it is sometimes impossible to retrieve and compute analytical results from unforeseen components that absorb at unexpected wavelengths. The Division of Drug Analysis custom software allows such data retrieval and computations after the chromatographic data have been obtained.

A computer-aided "graphics workstation" was installed and programmed. The workstation allows easy preparation of high-quality, multicolor drawings or text for use in scientific presentations, preparation of figures for journal articles, slides for lectures, schematics for documentation of custom electronic circuitry, and so forth. Although this system has only recently become operational, it has gained ac-

ceptance by laboratory staff and will save many hours of personnel time by elimination of tedious manual preparation of graphics material.

Programs were completed to allow direct transfer of collection information for "mail in" samples from the Wang OIS word processor to the Hewlett-Packard System 1000 minicomputer for entry into the Division of Drug Analysis sample-inventory system. A cardless data-entry system was installed to process information on samples submitted by field offices. The system is "menu driven," and it uses easy-to-fill-in forms for data entry from terminals. Data-entry programs used by analysts were also converted to this "forms" mode. A project to develop an on-line data-retention system was conceived and started; it is expected to be operational by the end of 1984. A Hewlett-Packard 150 personal computer and two graphics printers were added to the minicomputer system. The number of programmers supported by the system increased from four to eight.

A Wang PC system, including a 10-megabyte hard disk and a graphic printer, were added to the upgraded Wang OIS 115 system. The PC addition included a number of software packages that expanded the total Wang system's capability for asynchronous communications, data entry, and information processing.

Division of Drug Analysis staff developed a gradient-elution HPLC method for analysis of aspirin impurities in aspirin products to be used in a future survey. In addition, a packet of material designed to demonstrate the analytical capabilities of the Hewlett-Packard 1040A HPLC detector was prepared for several other scientific laboratories. The analysis of aspirin decomposition products was the subject of the demonstration.

A chemist at the Division of Drug Analysis served as a reviewer of proposals, submitted in response to a request for bids, for the construction of a robotic cleaner for animal cages in headquarters laboratories.

Many copies of the Division of Drug Analysis Good Laboratory Practices Manual were distributed through Freedom of Information requests or by sale from the National Technical Information Service.

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Table 1. Drug Quality Assurance Studies Completed at Division of Drug Analysis in FY 84.

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]
82-45 Phenothiazine Tranquilizers	217	3.2
83-05 Phenylpropanolamine	59	27.7
83-14 Reserpine with Thiazides	36	0
83-15 Thiazide Diuretics	189	0
83-27 Barbiturates	255	11.0
83-28 Barbiturate Mixtures	5	0
83-29 Corticosteroid Phosphates	65	0
83-30 Antiarrhythmics	138	0
83-31 Xanthine Derivatives	140	4.3
84-03 Digoxin, Digitoxin	74	1.4
84-25 Nitrofurantoin	25	0
84-39 Thyroxine, Liothyronine	107	2.8
ASHP-FDA Mail-In Program:		
Betamethasone Sodium Phosphate Injections	9	0
Epinephrine Injections	255	16.5
Hydrocortisone Sodium Phosphate Injections	14	0
Lidocaine and Epinephrine Injections	220	2.7
Prednisolone Sodium Phosphate Injections	35	0

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

Table 2. Defective Batches Found in Each of the Program Areas

Defect	Program Area			
	Drug Product Surveillance	Mail-In	Process Validation	GWQAP
Strength	3	40		
Content Uniformity	7			
Dissolution	22			7
Other[a]	8	21	2	
Totals	40	61	2	7

[a]Alcohol, limit tests, impurities, etc.