FY 85

DIVISION OF DRUG ANALYSIS

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

Executive Summary of Accomplishments: Fiscal Year 1985

Staff Level

The Division of Drug Analysis operated with 50 full-time person equivalents.

Publications

Papers written or coauthored by Division of Drug Analysis personnel appeared as journal articles (1-6) and FDA publications (7, 8).

A computer model that simulates laboratory operations and production scheduling at the Division of Drug Analysis was described (4). The model was based on established empirical relationships between laboratory personnel, the number of laboratory samples awaiting analysis, and the number of samples that will be completed during ensuing time periods. Scheduling heuristics determined allocation of resources to laboratory activities.

Division personnel developed procedures for the determination of total epinephrine, the ratio of d- to l-epinephrine, and decomposition products in lidocaine-epinephrine local anesthetics (1, 6). In the measurement of the d/l enantiomeric ratio, a derivative of epinephrine with a chiral reagent permitted separation of the isomers on reverse-phase, high-pressure liquid chromatographic columns. The methods were devised to determine whether epinephrine, initially formulated as the more active l-isomer in local anesthetics, racemized upon storage to the less active dl mixture. Analysis of about 70 samples showed that, even after the expiration date had passed, most contained 5% or less of the d-epinephine isomer.

During a survey of nitrofurantoin products, a previously unidentified impurity was noticed in the high-pressure liquid chromatogram of an oral suspension. Division personnel identified the impurity as 3-(5-nitrofurfurylideneamino)hydantoic acid and discovered that it was generated by the presence of citric acid, an excipient in the oral suspension (5). The concentration of the impurity ranged from 20 to 300 µg/mL in several lots of commercial oral suspension. An efficient synthesis of the hydantoic acid impurity was achieved by treatment of nitrofurantoin with citrate buffer; selective hydantoin ring cleavage was accomplished in preference to the generally observed cleavage at the azomethine linkage. The hydantoic acid was identified by an independent method of synthesis and by NMR, IR, TLC, and elemental analyses.

As a part of our long-term effort to mechanize the sample preparation of tablets and capsules, Division personnel published a case history of the development of a continuous-flow analyzer equipped with a robotic arm and electronically controlled valves for sample introduction (2). A microprocessor subsystem controlled the arm, and the valves were controlled by the main microprocessor system. A serial (RS 232) interface provided control information to the robotic module for movements and timing. The FORTH computer language was used to obtain adequate program execution speed, maximum reprogramming capability, and minimum debugging effort. The low-cost robotic module provided the critical timing and sequence of solution introduction required for successful operation of a continuous-flow analyzer.

The source of optical artifacts in circularly polarized luminescence was examined by application of the method of Mueller matrices. Expressions developed for the circularly polarized luminescence intensity illustrated that the artifact in most cases was due to the small inherent birefringence in the photoelastic modulator employed in the experimental measurements (3)[a].

Division personnel also provided high-pressure liquid chromatographic methods for the analysis of erythrityl tetranitrate, isosorbide dinitrate, and pentaerythritol tetranitrate (7), and for the assay of individual probenecid tablets (8).

Summaries of Current Projects

Abbreviated New Drug Applications -- Analysis of Bulk Drug Substances

One hundred sixty-two batches of active drug substances were analyzed in support of the Division of Generic Drugs review of Abbreviated New Drug Applications (ANDAs; see Table 1).

Drug Quality Assurance

Seven Drug Product Surveillance studies were completed in FY 85 (Table 2). Additional samples were analyzed in support of the Government Wide Quality Assurance Program (GWQAP) and the Process Validation Program.

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[a]This work was performed while Mr. Timper was a graduate student and before his employment at the Division of Drug Analysis.

The "mail-in" program is designed to study the stability of drugs under actual market conditions; it was continued in FY 85 in cooperation with the American Society of Hospital Pharmacists. Table 2 shows the number of samples analyzed and the percentages of defective batches for the drug products whose analyses were completed in FY 85. The following products are currently being studied: quinidine sulfate tablets, capsules, and injections, thiopental sodium injections, and liquid dosage forms of chlorpromazine hydrochloride, perphenazine, prochlorperazine edisylate, promethazine hydrochloride, and trifluoperazine hydrochloride.

The Division of Drug Analysis performed over 70,000 analyses on 2,010 batches of drugs in FY 85. Eighty-five batches (4.2%) 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 1.

At the request of the Center for Drugs and Biologics, the Division received for analysis a water-soluble Vitamin E product, intended for intravenous injection and labelled to contain 25 mg of α-tocopherol acetate, 90 mg of Polysorbate 80, and 10 mg of Polysorbate 20 per mL; Division personnel collaborated with FDA's Elemental Analysis Research Center, Cincinnati, in the examination of the product for contaminants by gas-liquid chromatography, gas chromatography/mass spectrometry, high-performance liquid chromatography, and inductively coupled plasma emission spectroscopy. The contaminants identified were isopropyl alcohol, dibutylamine, N,N-dimethylcyclohexylamine, 2-mercaptobenzothiazole, and zinc, all but the first arising from the rubber stoppers used in the product containers. This work has been submitted for publication.

The Division of Drug Analysis continued its long-term effort to mechanize the sample preparation of tablets and capsules. Division personnel consulted with engineers at the Winchester Engineering and Analytical Center on the design of the second version of an automatic sample preparer, which will put the active drug ingredient into solution from 30 individual tablets or capsules loaded in vials placed in a rectangular sample tray. The Division's new Robotic Liquid Sampler was tested under routine laboratory conditions, and a revised operator's manual and extensive documentation of the FORTH programs were completed.

Division personnel extended their previously published procedures to allow synthesis of reference standards of the sulfoxides of chlorpromazine, perphenazine, and proclorperazine; the sulfoxides of these major tranquilizers are often seen as impurities during the analysis of commercial dosage forms.

A new thermal energy analyzer detector was installed on one of the Division's gas chromatographs; this detector, which is highly specific for nitroso, nitro, or nitrogen compounds depending on the operating temperature selected, will be of great use in the analysis of drugs for nitrosamines.

Biopharmaceutics

The Division of Drug Analysis obtained dissolution profiles on three sustained-release theophylline products in four media. Portions of these samples were sent to the university contracted to do the in-vivo study. This work was done to aid the Division of Biopharmaceutics address the problem of dose dumping of theophylline taken with meals.

Other Activities

Several multiplexer (MUX) interface panels were installed throughout the Division's laboratory and office space; these panels allow up to eight serial (RS 232) devices to communicate over a single, multiplexed channel with the Division's central minicomputer. During installation several difficult problems had to be diagnosed and corrected by the Division's computer specialists and consultants.

The Division has acquired two Hewlett-Packard 1040A diode-array, uv-visible detectors for high-pressure liquid chromatography systems. As supplied by the manufacturer, only qualitative information (spectra, retention times, chromatograms, etc.) may be generated. Division personnel wrote complex programs to cause the 1040A to emulate a Hewlett-Packard 3390 integrator; this custom software permits integration of peak areas after the chromatographic data have been obtained and stored on disk. Division personnel also prepared a set of slides and an accompanying script that demonstrate the qualitative capability of the 1040A detector; this material was provided to twelve FDA District Laboratories.

Although the Division makes heavy use of high-pressure liquid chromatography, there is, as yet, no implemented automatic transfer of data from the analytical systems to the central computer. Thus, much manual data entry takes place. In 1984, the Division instituted a high-priority, long-term research program to provide direct, automatic data transfer between Waters liquid chromatographs and the Hewlett-Packard System 1000 computer. The Waters Data Transfer Module was designed to intercept useful data flowing through the digital circuits of a Waters high-pressure liquid chromatograph, store the data, and transmit them after the run is completed to another computer for data reduction and report writing. As supplied by the manufacturer, the Data Tranfer Module transmits short blocks of data, which "lock up" the Hewlett-Packard System 1000 computer and prevent it from processing other necessary timed-shared operations. Thus, as supplied, the

Waters Data Transfer Module was of limited use in the Division's laboratories. Division personnel and consultants modified the factory-supplied programs, resident in the Data Transfer Module's memory chips (EPROMs), to allow transfer of large blocks of data; wrote routines in FORTRAN on the Hewlett-Packard System 1000 minicomputer to accept data simultaneously from eight Data Transfer Modules at an extremely high transmission rate (9600 baud) without loss of data; worked out the protocols and set-up procedures required to use the Hewlett-Packard MUX interface; and programmed the Hewlett-Packard System 1000 computer to manipulate the data, provide a user interface, and allow worksheets to be written by the computer from data received on-line from Waters high-pressure liquid chromatographs. Only a short final test is required before the system may be installed in our laboratories.

Another complex program was written to allow the Hewlett-Packard System 1000 computer to accept and manipulate data from Hewlett-Packard 3390 series integrators; this program is a start toward networking gas and high-pressure liquid chromatographs with the Division's central minicomputer; the eventual goal is to produce on-line worksheets automatically from any chromatographic instrument.

The master programs for the graphics workstation, which operates on a time-shared basis with the Hewlett-Packard System 1000 computer, were improved by Division personnel and consultants; the programs allow various Hewlett-Packard subroutines to be used easily by laboratory staff to prepare slides for lectures, posters for presentation of papers at scientific meetings, electrical schematics, and attachments to analytical reports.

Division personnel interfaced an Intermec bar-code reader with the Hewlett-Packard System 1000 minicomputer. The bar-code reader is being used to log in samples received under the Mail-In Program. The bar-code labels are printed at the Division and mailed to Product Surveillance Branch, who sends them to the submitting pharmacies.

An on-line data-retention system was designed and installed by Division personnel. All data calculated by the System 1000 computer are now captured and stored on disc. District offices are currently receiving, by electronic mail, monthly summaries of the results of within-limits samples.

The use of forms-driven menus is increasing at the Division, and a menu-driven laboratory management information system is being planned.

References

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Table 1. Defective Batches Found in Each of the Program Areas at the Division of Drug Analysis in FY 85.

Defect	Program Area			
	Drug Product Surveillance	Mail-In	Process Validation	ANDA
Strength	4	20		
Content Uniformity	10	21		
Dissolution	6		1	
Other[a]	16	3	1	3
Totals	36	44	2	3

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

Table 2. Drug Quality Assurance Studies Completed at the Division of Drug Analysis in FY 85.

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]
84-01 Nitroglycerin Transdermals	43	2.3
84-02 Coronary Vasodilators	182	3.3
84-54 Adrenergics	39	4.3
84-55 Reserpine with Hydralazine and Hydrochlorothiazide	23	17.4
84-56 Conjugated Estrogens	49	18.4
85-01 Steroid Estrogens	49	0
85-03 Phendimetrazine	38	0
Process Validation:	142	2.1
ASHP-FDA Mail-In Program:		
Aminophylline Tablets, Capsules, and Injections	163	1.2
Levothyroxine Sodium Tablets and Injections	208	6.7[b]
Liothyronine Sodium Tablets	9	77.8[b]
Liotrix Tablets	35	31.4[b]
Nitrofurantoin Tablets, Capsules, and Injections	47	6.4
Theophylline Tablets and Capsules	158	0

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

[b]Samples analyzed by new, specific methodology presented in USP XXI. These products were manufacturered and distributed before the new compendial standard(s) became official.