DIVISION OF DRUG ANALYSIS

U.S. Food and Drug Administration
1114 Market Street, Room 1002
St. Louis, MO 63101

Executive Summary of Accomplishments: Fiscal Year 1989

Staff Level

The Division of Drug Analysis operated with 57.5 full-time person equivalents.

Publications

In cooperation with the St. Louis Police Laboratory and the St. Louis County Medical Examiner, Division staff developed and published (1) a procedure for synthesis of gram quantities of phenothiazine sulfoxides by aqueous nitrous acid oxidation of phenothiazines at room temperature. The chiral levomepromazine gave rise to diastereoisomeric products analogous to those previously reported for thioridazine sulfoxidation. Phenothiazine sulfoxides are commonly found as impurities in drug samples and as components in the blood of persons who have died from overdoses; thus, a procedure to produce reference standards of the sulfoxides is of general interest.

In many areas of the world, there is a need to estimate the quality of drug preparations using a minimum of laboratory resources. Division staff published a procedure for the analysis of theophylline tablets by simple thin-layer chromatographic methods (2). Easily built equipment, designed to allow the test to be run in the field, was employed to assay the drug content of a single tablet or to determine its dissolution or disintegration characteristics without the use of any instrumentation. It is expected that the techniques can be extended to many other drugs.

Summaries of Current Projects

Abbreviated New-Drug Applications; Analysis of Bulk Drugs

Under the ANDA bulk-drug approval program, the Division receives about 50 to 60 ANDA approval requests per month, representing over 300 drug substances from about 200 applicant companies and nearly 300 bulk-drug manufacturers. In FY 89, 618 ANDA bulk-drug samples were received and analyzed. An additional 250 ANDA applications were approved based on cross-reference to previous laboratory analyses. This brings the total ANDA bulk-drug application approvals to 868 for FY 89. Of the samples ana-

lyzed, nine failed to meet compendial and/or ANDA requirements (1.5% failure rate).

New-Drug Evaluation

Method Validation. In FY 89 the Division received 46 NDA Method-Validation Packages (MVPs) and completed 43. The majority of the MVPs (36) required validation of multiple procedures for bulk-drug substances and final dosage forms. Seven of the MVPs were "supplemental approval" requests involving minor changes in methodology.

In addition the Division worked on the following projects requested by NDE Review Chemists:

Thalidomide. Division staff continued to provide analytical support to the Division of Anti-Infective Drug Products and analyzed samples of thalidomide tablets from prospective suppliers in Mexico and capsules filled with bulk drug commercially synthesized in the U.S.A. The examinations include assay, content uniformity, dissolution, identity, and purity. In mid-1989 all quality-assurance analytical work, except for dissolution and heavy metals, was successfully transferred from the Division of Drug Analysis to the FDA New Orleans District Laboratory.

Division staff synthesized highly pure D-thalidomide and more L-thalidomide. At the direction of the headquarters review chemist, we supplied D- and L-thalidomide to Allen S. Goldman, M.D., Director, Center for Craniofacial Anomalies, University of Illinois College of Medicine at Chicago, Georgia B. Vogelsang, M.D., Johns Hopkins Hospital, Baltimore, and James V. Silverton, Ph.D., National Institutes of Health. Our methods for synthesis of D- and L-thalidomide were provided to several individuals and firms having interest in the isomers of this drug.

We also discussed our cleanup of impure racemic thalidomide with Melvyn Morales, Gillis W. Long Hansen's Disease Center, Carville, LA; as a result, the Hansen's Disease Center modified their contract with a commercial supplier of bulk thalidomide, and subsequent batches were provided in much higher purity.

Generic Drug Standards

One hundred and twenty-four candidates for USP Reference Standards were examined at the Division in FY 89; of these, 86 were analyzed by the Division and 38 by FDA District Laboratories (Table 1).

In addition, the Division worked on the following projects:

Surgical Scrubs. Doctors and nurses may scrub with antimicrobial soap solution before surgery as often as fifteen times a day. What is the fate of the antimicrobial compounds p-chloro-m-xylenol (PCMX) and chlorhexidine digluconate (CHG) in humans? What are typical blood and urine levels of these compounds, their metabolites, and their degradation products in surgeons and nurses? What are the target organs in humans who use these products?

To help answer these questions, Division staff continued development of methods (gas chromatography with electron-capture detection and high-pressure liquid chromatography (HPLC) with electrochemical detection) capable of analyzing at the level of nanograms per milliliter or lower. We developed a protocol for safe handling of biological fluids. A preliminary study on rabbits was carried out with the cooperation of Joseph P. Hanig, Ph.D., Division of Research and Testing; Division of Drug Analysis staff analyzed extracts of rabbit blood and urine and used these extracts to evaluate preliminary methods of extraction for metabolites. Division staff also synthesized reference standards of the two major metabolites of PCMX -- its sulfate and its glucuronide.

Quality Assurance

Eight Drug Product Surveillance studies were completed in FY 89 (Table 2).

Division of Drug Analysis staff also participated in the following specific areas of drug quality assurance.

Clorazepate Dipotassium Stability Study. Eight formulations of generic clorazepate dipotassium tablets were stressed under conditions of high temperature and humidity to determine the physical and chemical stability of the tablets. Both physical and chemical instability were observed at 40°C and 93% relative humidity, leading to a considerably reduced shelf life.

Department of Defense Extended Shelf-Life Study. Samples of vincristine sulfate were tested for stability as part of a continuing extended shelf-life study for the Department of Defense.

Dextran Sulfate. In 1989, this compound enjoyed brief interest as a possible AIDS drug. The Division was asked to develop methods to assure the quality of the drug, which is manufactured primarily in Japan. Division staff attempted method development with HPLC (reverse phase and gel permeation), cyclic voltam-

metry, and isotachophoresis; we also consulted with university experts in the techniques of nuclear magnetic resonance spectrometry and mass spectrometry (conventional and fast-atom bombardment). None of these techniques was successful. The project was cancelled when the medical community decided that dextran sulfate, taken orally, is ineffective in the treatment of AIDS.

Diatrizoate Meglumine and Diatrizoate Sodium Injection. Division staff continued to develop high-pressure liquid chromatographic methods of analysis for impurities in this product, which has been associated with patient deaths (3). Two reference standards were prepared for use in method development; 3,5-diacetamido-2,6-diiodobenzoic acid was synthesized by literature procedures, and 3,5-diacetamido-2,4-diiodobenzoic acid was isolated from a mixture prepared by gentle reduction of diatrizoic acid.

Drug Quality Assurance in Other Nations. Planning and coordination continued on simple, low-cost analytical methods of drug control designed to test tablets or capsules in the field with minimal laboratory equipment (4). A Division chemist visited Warsaw, Poland, in June 1989 to review the project with Polish officials and select drugs to be studied. An official of the Institute for Drug Control, Warsaw, visited the Division in September 1989 to report on progress and continue coordination activities.

Insulin. We were asked by Division of Drug Quality Evaluation to investigate why certain batches of insulin injection nearing expiry date gave different assays by reverse-phase HPLC and by rabbit bioassay. Division staff studied samples from the batches in question, fresh samples of insulin injection, and an aged, purposefully decomposed sample. We concluded that different commercial brands of HPLC columns had differing abilities to separate insulin from its impurities; those columns that gave good separation gave lower, more correct results than those that gave poor or no separation.

Residual Solvents in Cefadroxil Formulation. Five lots of generic cefadroxil formulations were tested for the residual solvent acetonitrile and compared to this residual solvent in the innovator product. An appropriate validated method was developed, and the presence of the acetonitrile was verified by gas chromatography with mass-spectral detection.

Screen of Generic Products for Dissolution Compliance. Five production lots of tablets were tested for compliance with USP requirements for dissolution: chlorthalidone (25 mg), hydrochlorothiazide (100 mg), methyclothiazide/deserpidine (5 mg/0.5 mg), pentaerythritol tetranitrate (80 mg, sustained-release),

and procainamide HCl (1,000 mg, sustained-release). All samples were found in compliance with the USP specifications

Biopharmaceutics

No activity in FY89.

Other Activities

AOAC International Convention. The Association of Official Analytical Chemists held their international convention in St. Louis in September 1989. The Division supplied personnel to assist in convention activities and hosted four tours of our facilities.

Awards. Two Division chemists received an FDA Group Recognition Award for their work as part of the American Red Cross Voluntary Agreement Group, as noted in letters from Dr. Frank E. Young, Commissioner of FDA, June 5, 1989. These chemists participated in extensive inspections of blood banks at the American Red Cross, St. Louis, and Travenol (Baxter Health Care Laboratories), Round Lake, IL.

Community Service. Two Division chemists discussed their work at four "career day" and high-school participation programs. These chemists have been involved in this type of community service for several years.

A chemist received an award from the Internal Revenue Service for faithful service in support of their Black History programs and a letter of thanks from St. Louis Community College at Forest Park for his work with that group.

Computer Activities (Mainframe). DDA personnel processed 119 Sample Analysis Reports in one week, a first ever for the Division. One thousand two hundred forty-nine generic fraud samples were received and logged in. Division staff implemented new review procedures that significantly improved the quality of information generated in computerized reports and introduced new policies that dramatically reduced downtime due to application and software problems. We refined our computerized ANDA database and created a similar database for generic ANDAs. A bar-code system for controlling FDA personal property was designed and installed. The file system on the Hewlett-Packard 1000 computer was converted from File Manager to Command Interpreter. Software that emulates a DEC VT220 protocol was installed on our Wang VS computer system and was used to tap into the VAX systems in Parklawn Computer Center.

Lack of a service contract forced DDA staff to troubleshoot and repair the Division's aging Hewlett-Packard 1000 minicomputer; problems with multiplexer drivers and a bar-code reader, and with the system's analog-to-digital converter board were diagnosed and repaired.

Division staff continued to improve the electronic purchase-request system by installing a more advanced password-protection system at the supervisory-approval level. About 1,000 purchase requests are processed yearly by this system.

Computer Activities (Small Systems). Division staff developed the "front end" of our system to create, print, and transmit electronic drug-collection reports, a project with FDA-wide potential.

The Division developed several useful "macro" routines for our Hewlett-Packard ChemStations, which are personal computers that control and process data from Hewlett-Packard HPLC systems. The routines were installed on both ChemStations and allow analysts to calculate conveniently such critical HPLC parameters as peak resolution and symmetry.

Division staff began the "Cincinnati Data Acquisition and Report System" project. The overall goal is to provide Cincinnati District Laboratory with a personal-computer system to acquire data from continuous-flow analyzers and produce laboratory worksheets. It is part of a larger project to develop computerized laboratory databases (collection reports, worksheets, etc.) throughout FDA. We confirmed literature reports that a Hewlett-Packard 3396A integrator could serve as a collector and preprocessor of data from a continuous-flow analyzer. Division personnel wrote the overall Project Definition and coded programs to allow an analyst to enter necessary identification data -- sample number, manufacturer, drug name, dosage form, etc. We are now researching multichannel operation, in which up to four continuous-flow analyzers and their individual integrators could be serviced by one personal computer. We expect to make use of these systems in our own laboratories when our Hewlett-Packard 1000 minicomputer is replaced.

Dexfenfluramine. At the request of Dr. Dr. Errol De Souza, NIDA Addiction Research Center, Baltimore, Division staff synthesized highly pure dexfenfluramine. In the U.S.A. this drug is supplied to patients as the racemate but in Europe as the more expensive dextro isomer. Dr. De Souza wanted a portion of pure dextro isomer for his research into the relative pharmacological activities of the dextro isomer and the racemate.

Expert Systems and Spectral Searches. The goal is to develop computerized systems to help chemists examine instrumental data

on drug formulations -- the active and inactive ingredients of tablets, capsules, etc. Division staff are now writing programs to translate digitized infrared and x-ray spectra and thermogravimetric and differential scanning calorimetric thermograms from diverse instruments into standardized computer databases; we are also coding programs to search and match sample data against reference-standard data or data from other samples. Evaluation of three commercially available software packages for spectral searches is underway. When this work is finished, we hope to develop "expert systems" to help chemists identify similarities or differences among thousands of different commercial drug formulations.

Foreign Visitors and Guest Workers. The Division hosted the following visitors, among others, during FY 89:

Delwin Johnson August-December 1988	Forest Park Community College, St. Louis
Dr. Ahmed Geneidi October 1988	Cairo, Egypt
Stephen Shark October 1988	Division of Generic Drugs FDA
Bimal Kanta Mohanty October-November 1988	WHO Orissa State, India
Ragupathy Naidu Chiang Loo November 1988	Ministry of Health Malaysia
Wendy Nelson November 1988	Epidemiology Branch FDA
Chen Yisheng November 1988-January 1990	WHO People's Republic of China
Sulaiman Fraihidi December 1988	Saudi Arabia
Robert Linhardt December 1988	University of Iowa
Huang Chyn-Liang May 1989	Center for Development of Science and Technology Republic of China

Mahammad Dada Albahlai Ahdulayiz August 1989	Saudi Arabia
Pauline Lacrony Alice M. An September 1989	Health & Welfare Canada
Witold Wieniawski September-October 1989	Institute of Drug Control Warsaw, Poland

High-Pressure Liquid Chromatographic Columns -- Quality Assurance. Division staff programmed a personal computer to allow automated data acquisition from an HPLC column and automated calculations of the column's quality attributes, such as symmetry, efficiency, and resolution. The system has been installed in the laboratory and has been used to evaluate over 300 columns, thus improving quality control of the Division's laboratory results.

Training Conducted By Division Staff. In the summer of 1989, four DDA staff traveled to Saudi Arabia to continue the training that was begun in 1987 and continued into 1988. The four-member team provided two months of "hands-on" training for the Saudi Arabian, Ministry of Commerce (MOC) medicinal-analysis program. The training focused on high-performance liquid-chromatographic analytical procedures. The training was given primarily to the six medicinal analysts and to various members of the Ministry staff and managers at the three laboratory sites: Jeddah, Dammam, and Riyadh. A fifth DDA chemist joined the training team and continued the training program for an additional six months. He provided, on a rotational basis, training and expert assistance to each of the medicinal-analysis laboratories.

Training was also extended to foreign visitors and Review Chemists from FDA's Division of Generic Drugs and Offices of New Drug Evaluation I and II.

References

(1) Owens, M. L., Juenge, E. C., and Poklis, A. (1989) J. Pharm. Sci. 78, 334-336. Convenient oxidation of phenothiazine salts to their sulfoxides with aqueous nitrous acid.

(2) Flinn, P. E., Juhl, Y. H., and Layloff, T. P. (1989) Bull. WHO 67, 555-559. A simple, inexpensive thin-layer chromatography method for the analysis of theophylline tablets.

(3) Division of Drug Analysis, Executive Summary of Accomplishments, Fiscal Year 1988, p. 2.

(4) Division of Drug Analysis, Executive Summary of Accomplishments, Fiscal Year 1988, p. 3.

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 89.

Acyclovir

Albuterol

Aminosalicylic Acid

3-Anilino-2-(3,4,5-trimethoxybenzyl)acrylonitrile

Aspartame

Baclofen

Benzonatate[b]

Benztropine Mesylate[b]

Benzyl Benzoate[b]

Betamethasone[b]

Betamethasone Acetate[c]

Betamethasone Sodium Phosphate

Biotin

Bisacodyl

N,N-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide

Butorphanol Tartrate[b]

3-tert-Butyl-4-hydroxyanisole

Butylparaben

Calcium Lactobionate

Captopril

Cellulose Acetate Phthalate

p-Chlorobenzhydrylpiperazine

2-Chloro-3,5-dimethylphenol

(o-Chlorophenyl)diphenylmethanol

Chloroxylenol

Chlorpheniramine Maleate[a]

Cholestyramine Resin[a]

Cimetidine[b]

Clemastine Fumarate

Clotrimazole

L-Cysteine Hydrochloride

Cytarabine

Deslanoside[b]

Desoxycorticosterone Acetate[c]

Diethyltoluamide

α-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride

Dipyridamole

Docusate Calcium[c]

Docusate Sodium[c]

Dyphylline[c]

Edetate Disodium

Epinephrine Bitartrate[c]

Estriol

Estrone

Fluorometholone

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 89 (continued).

Fluphenazine Enanthate Dihydrochloride[b]

4-Formylbenzenesulfonamide

Galactose

Gemfibrozil

Hydrocodone Bitartrate

Hydrocortisone Butyrate[b]

Hydromorphone Hydrochloride

Hydroxyzine Hydrochloride

Imidazole[b]

Imidurea[a]

Iminodibenzyl

Indigotindisulfonate Sodium[b]

Iopamidol

Isopropyl Palmitate[b]

Isosorbide Dinitrate, Diluted

Leucovorin Calcium

Levocarnitine

Levodopa[a]

Mannitol

Maprotiline Hydrochloride[c]

Menthol

Mepivacaine Hydrochloride

Mercaptopurine

Methazolamide

Methazolamide[b]

Methenamine[b]

Methyldopa

3-O-Methylmethyldopa

Methylphenidate Hydrochloride

Metocurine Iodide (two candidates)

Minoxidil

Morphine Monohydrate

Morphine Sulfate (Pentahydrate)

Nalorphine Hydrochloride

Naphazoline Hydrochloride[a]

Naproxen Sodium[c]

Nifedipine Nitrophenylpyridine Analog

Nifedipine Nitrosophenylpyridine Analog

Nitrofurantoin

Norethindrone Acetate

Norgestrel

Noroxymorphone Hydrochloride

Oxymetazoline Hydrochloride

Oxyquinoline Sulfate

Palmitic Acid

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 89 (continued).

Paramethadione	Testosterone
Phenolsulfonphthalein[b]	Testosterone Cypionate[b]
Pilocarpine Hydrochloride	Testosterone Enanthate
Pindolol[c]	Testosterone Propionate[b]
Potassium Guaiacolsulfonate	α-Tocopherol
Prochlorperazine Maleate	α-Tocopheryl Acetate
Promethazine Hydrochloride[c]	Tolbutamide
Propoxyphene Napsylate	Triamcinolone Acetonide
Quinethazone	Trimethoprim
Ranitidine Hydrochloride	Triprolidine Hydrochloride[b]
Sodium Nitroprusside[c]	Tyloxapol[c]
Sodium Propionate[b]	Uracil Arabinoside
Squalane[c]	Vanillin
Sulfamethoxazole	Verapamil Related Compound A
Sulfisoxazole Acetyl	Verapamil Related Compound B
Sulindac	Vinblastine Sulfate
Terbutaline Sulfate[b]	

[a]Analyzed by the FDA Philadelphia District Office

[b]Analyzed by the FDA Baltimore District Office.

[c]Analyzed by the FDA Cincinnati District Office.

Table 2. Drug Product Surveillance Studies Completed at the Division of Drug Analysis in FY 89.

Study No. and Name	Batches Analyzed	Defective Batches, %[a]
Completed in FY 89		
835 Hydroxyzine HCl	202	0
836 Indomethacin	117	0
837 Conjugated Estrogens	8	12.5
899 Amitriptyline	170	0
Initiated and Completed in FY 89		
934 Aminophylline	153	0
935 Isosorbide Dinitrate	160	0
936 Theophylline	198	0
937 Clonidine HCl	71	0
Totals:	1079	0

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

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