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 1988

Staff Level

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

Summaries of Current Projects

Abbreviated New-Drug Applications; Analysis of Bulk Drugs

Under the ANDA bulk-drug approval program, the Division receives about 80 to 90 ANDA approval requests per month, representing over 300 drug substances from about 200 applicant companies and nearly 300 bulk-drug manufacturers. In FY 88, 932 ANDA bulk-drug samples were received and analyzed. An additional 388 ANDA applications were approved based on cross-reference to previous laboratory analyses. This brings the total ANDA bulk-drug application approvals to 1320 for FY 88. Of the samples analyzed, 11 failed to meet compendial and/or ANDA requirements (1.2% failure rate).

New-Drug Evaluation

Method Validation. In FY 88 the Division received 42 NDA Method-Validation Packages (MVPs) and completed 36. The majority of the MVPs (25) required validation of multiple procedures for bulk-drug substances and final dosage forms. Eleven 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:

Ciprofloxacin Hydrochloride. Division staff isolated several hundred milligrams of the active ingredient from commercial tablets and supplied the material to a review chemist for further testing.

Potassium Chloride. Two brands of potassium chloride sustained-release capsules were evaluated for dissolution and dispersibility. These studies were conducted in simulated gastric and intestinal dissolution media on 42 capsules. The dispersibility profile on all capsules was monitored photographically during the dissolution sampling interval. Dissolution profiles were obtained through ion-chromatographic methods developed and validated by Division personnel for this study.

Thalidomide. Division staff continued to provide analytical support to the Division of Anti-Infective Drug Products and have analyzed samples of thalidomide tablets from prospective suppliers in Brazil and capsules filled with bulk drug commercially synthesized in the U.S.A. The examinations include assay, content uniformity, dissolution, identity, and purity.

The Division's monographs for thalidomide bulk drug, capsules, and tablets were revised and distributed to co-workers who had previously received them. Our method for synthesis of racemic thalidomide was also provided to several individuals and firms interested in commercial manufacture of this drug.

Racemic thalidomide was provided to Dr. Miles Cloyd, University of Texas, for *in vitro* microbiological tests. Highly pure L-thalidomide was synthesized and used in the validation of optical-rotation purity tests; portions were also provided to Dr. James V. Silverton, National Institutes of Health, for examination by X-ray crystallography.

Generic Drug Standards

Sixty-six candidates for USP Reference Standards were examined at the Division in FY 88 (Table 1).

Quality Assurance

Four Drug Product Surveillance studies were completed in FY 88 (Table 2). Three studies were initiated in FY 88: Conjugated Estrogens, Indomethacin, and Hydroxyzine.

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

Diatrizoate Meglumine and Diatrizoate Sodium Injection. Division staff analyzed an additional sample of this product, which has been associated with patient deaths (1). The sample complied with all USP XXI monograph requirements. Two impurities were tentatively identified, and synthesis of required reference standards is being attempted.

Drug Quality Assurance in Emerging Nations. Planning and coordination were nearly completed to implement simple, low-cost analytical methods of drug control designed to test tablets or capsules in the field with minimal laboratory equipment. The model procedure is based mainly on thin-layer chromatography and includes checks for impurities, a semiquantitative assay for the active ingredient, and an estimate of dissolution time; all tests are carried out with reference to a "standard tablet or capsule" representing a product with known acceptable drug activity and bioavailability. The next phase of the work involves field tests of the methods developed to date and extension of the basic concept to cover other drugs in worldwide use; to accomplish this phase, PHS has funded a joint research project with officials in the Drug Institute in Warsaw to provide Polish laboratory staff and facilities to extend the technique. Division personnel revised the written methods, based on comments received from collaborating laboratories, and negotiated costs and staffing requirements jointly with Polish officials. Visits of DDA staff to Warsaw and implementation of the plan are scheduled for October 1988.

Tetrahydro-9-aminoacridine (THA). In November 1987 the Division received several samples of THA bulk drug and capsules collected from Warner-Lambert, who holds the clinical IND, and from Dr. Summers, California, and Professional Compounding Centers Of America, Inc., Sugarland, Texas. Summers and Professional Compounding Centers Of America were distributing the drug without a valid NDA or IND. Additionally, some patients had suffered liver damage while taking the drug. The Division's assignment was to assay the bulk drug and capsules, and to evaluate the purity of THA in all the samples. Using methods and standards supplied by Warner-Lambert, as well as thin-layer chromatographic tests devised here, Division staff found no impurities in any of the samples. Division staff also used ultraviolet, infrared, and mass spectrometry to identify the drug substance.

Biopharmaceutics

Amitriptyline Hydrochloride. Thirteen batches from three manufacturers representing five dosage levels were evaluated by Division staff for dissolution and content uniformity. All samples were within USP specifications for dissolution and content uniformity.

Other Activities

Training Conducted By Division Staff In Foreign Countries. In the summer and fall of 1987, three DDA staff and two student aides selected, purchased, adapted, and shipped over $400,000 worth of laboratory equipment to Saudi Arabia in support of the Joint Commission on Economic Development. The purchase of the equipment was the first phase in the DDA support of the Medicinal Testing project in Saudi Arabia. During the fall of 1987, three DDA staff traveled to Saudi Arabia to install the equipment and begin the training of Saudi Arabian laboratory personnel on utilization of the equipment for drug screening. Installation and training were conducted at three laboratory sites. Nine Saudi Arabian laboratory personnel were involved in the initial training program.

In a related assignment, DDA staff gave three weeks of intensive training to Abdulaziz Al-Jerayed from Saudi Arabia; the training covered maintenance and repair of infrared and UV-visible spectrophotometers and Waters high-pressure liquid chromatographs, as well as an introduction to thin-layer chromatography.

Training Received By Division Staff. Three DDA chemists attended an eight-week evening course on high-pressure liquid chromatography offered at the University of Missouri-St. Louis.

Several staff members received training on ORACLE, a fourth-generation database-management system widely accepted in FDA. In addition, one person completed a college course on programming in FORTRAN.

American Red Cross Blood-Bank Investigations. In support of this nationwide FDA effort, two Division scientists, one a specialist in automated analysis, the other in computer operations, accompanied an FDA investigator in a large-scale effort to track sample analysis, flow of analytical data, control of sample acceptance and shipment, and computer usage at the St. Louis office of the American Red Cross. Many problems were uncovered in all four phases, and the team produced an extensive list of suggested operational improvements. Later, one of the Division scientists who participated in the St. Louis inspection was detailed for two weeks to assist in a similar inspection of Travenol (Baxter Health Care Laboratories), Round Lake, IL.

Mainframe Computer Activities. Four Waters Associates Data Transfer Modules were installed in DDA laboratories. These interfaces, along with extensive programs written by DDA staff, permit automatic transfer of data from high-pressure liquid chromatographs to the Division's Hewlett-Packard 1000 computer and automatic generation of worksheets. The software was also

revised to handle runs of more than 96 samples at a time (overnight operation).

The operating system for the Hewlett-Packard 1000 minicomputer was converted from "File Manager" to "Command Interpreter," which required recompilation of all existing application software on the system and training of DDA staff in the differences between the two operating systems. The transition was performed smoothly.

The Division continues to make heavy use of the Wang OFFICE program; upgrades were installed and implemented. A Spelling Verifier utility for Wang word processing was purchased and installed.

Automatic-dialing modem facilities were installed and implemented on the Wang VS system to support electronic-mail links to field laboratories and headquarters. Procedures were developed and implemented for direct dial-up and access to Headquarters' computerized payroll facilities and to electronic mail from the Center for Drug Evaluation and Research.

Three workstations were installed on the Wang VS system, including one archiving workstation. With these additions, the input/output capacity of the Wang VS became saturated. Plans were developed to increase the Wang VS capacity through additional memory and greater input/output capability.

Division staff implemented several complex BASIC programs that allow preparation of purchase requests on the Wang VS computer. The system is completely paperless, except for the final printout of the purchase order or of a copy of a phone order for the file. A person wishing to request items selects the manufacturer and enters the description of each desired item. The purchase request is then electronically routed to the employee's supervisor for approval, to the Deputy Director for final approval, and then to the Fiscal Clerk, who checks accuracy of prices, GSA contract numbers, etc., and who runs the final printout of the finished purchase order. Status of requests may be viewed at any Wang terminal. The system also allows electronic "check off" of items received.

Two additional application packages were developed by DDA staff for the Wang VS system. One includes file structure and development plans for an ANDA sample-tracking system. The second consolidates word-processing libraries, thus enhancing disk-space utilization, and runs automatically every evening.

The ANDA worksheet-generation program was modified to include more appropriate data fields. In addition, the worksheet data

entered by a chemist to generate a worksheet are now captured in the ANDA database, thus eliminating data reentry.

The Laboratory Information Management System for the ANDA program was enhanced to permit accessing results via the five-digit ANDA number. Completed results for an ANDA application can now be readily confirmed without knowledge of the assigned three-digit extension code supplied by the Division's ANDA Team Leader.

Small Computer Systems. Division staff completed a comprehensive user manual for the computerized electrochemical system developed last year. Seminars and individual training sessions were given on the operation and applications of the Princeton Applied Research 384 electrochemical system interfaced to a Hewlett-Packard 85 personal computer.

A Hewlett-Packard Vectra personal computer was installed to serve as a workstation for the Hewlett-Packard 1000 mainframe and as a stand-alone processor for development of database-management projects. In addition to terminal-emulation software (VTERM), the system is equipped with FORTRAN, BASIC, and ORACLE. Division staff are now using ORACLE to develop computerized entry of Collection Reports and formation of the corresponding database. The package is being designed in consultation with FDA investigators for eventual use by FDA Districts.

Two hardware systems were installed on the Division's Leading Edge personal computer and evaluated by Division staff: a Wang Local Office Connection card, which allows the Leading Edge to be used as a Wang workstation and permits storing and retrieving Wang documents from 5.25-inch diskettes, and a Philips CD-ROM player, which permits searching and reading information from compact disk, read-only databases.

Foreign Visitors and Guest Workers. The Division hosted the following visitors, among others, during FY 88:

Witold Wieniawski March 1988	Warsaw Poland
Abdulaziz Al-Jerayed April-May 1988	Riyadh Saudi Arabia
Jain-Xing Chen April-September 1988	Shanghai China
William G. Marnane May 1988	Review Chemist FDA Headquarters

Shawky Farag June 1988	Review Chemist FDA Headquarters
Cho Wan Chen June 1988	Review Chemist FDA Headquarters
Kathleen E. Jongedyk June-July 1988	Review Chemist FDA Headquarters
Raj Kishore July-August 1988	Review Chemist FDA Headquarters
Jack Schepman Mary Womack August 1988	FDA Cincinnati District
B. V. Shetty August 1988	Review Chemist FDA Headquarters
Abdul Rehman Al-Khalifa August 1988	Ministry of Commerce Saudi Arabia
Chandra Vijayaraghavan August-September 1988	WHO Madras, India
Delwin Johnson August-December 1988	Forest Park Community College, St. Louis
Brian Foster September 1988	Health & Welfare Canada Ottawa

Community Service. A chemist from the Division participated in the St. Louis Public Schools Role Model Program. This program is directed toward seventh-, eighth-, and ninth-grade students and their teachers. The chemist demonstrated an automatic chemical analyzer that determined ferric sulfate in commercial drugs. The students and teachers enjoyed the demonstration and left the fair with a better understanding of FDA's mission in drug analysis.

Reference

1) Division of Drug Analysis, Executive Summary of Accomplishments, Fiscal Year 1986, pp. 4-5.

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 88.

Albuterol Sulfate

Alclometasone Dipropionate

2-Amino-2',5-dichlorobenzophenone

3-Amino-6-chloro-1-methyl-4-phenylcarbostyril

Beclomethasone Dipropionate

Benzoic Acid

Bromocriptine Mesylate

Bupivacaine Hydrochloride

Calcium Pantothenate

Chlorothiazide

2-Chloro-4N-furfurylamino-5-sulfamoylbenzoic Acid

4-Chloro-5-sulfamoyl-anthranilic Acid

4-(4-Chlorophenyl)-2-pyrrolidinone

6-Chloro-4-(o-chlorophenyl)-2-quinazoline Carboxyaldehyde

6-Chloro-4-(o-chlorophenyl)-2-quinazoline Carboxylic Acid

6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol

7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acetyl-2H-1,4-benzodiazepin-2-one

Chlorzoxazone

Cholestyramine Resin

Clemastine Fumarate

Clofibrate

Colchicine

Cromolyn Sodium (two candidates)

Dexamethasone

Dihydrotachysterol

Docusate Potassium

Doxylamine Succinate

Estrone

Ethyl Maltol

2-Ethylaminopropionphenone Hydrochloride

Ethylcellulose

Fenoprofen Calcium

Fenoprofen Sodium

Guaifenesin

Guanadrel Sulfate

Hydrochlorothiazide

Hydrocortisone

Ibuprofen

Lactulose

Meclizine Hydrochloride

Meclofenamate Sodium

Methylergonovine Maleate

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 88 (continued).

Methylprednisolone	Probucol
Metoclopramide Hydrochloride	Probucol Related Compound A
Mexiletine Hydrochloride	Probucol Related Compound B
Naloxone	Probucol Related Compound C
Niacin	Propoxyphene Hydrochloride
Niacinamide	Sennosides
Phenylpropanolamine Hydrochloride	Sodium Taurocholate
Praziquantel	Tetracaine Hydrochloride
Praziquantel Related Compound A	Thiothixene (two candidates)
Praziquantel Related Compound B	Tolmetin Sodium
Praziquantel Related Compound C	Valproic Acid

Table 2. Drug Product Surveillance Studies Completed at the Division of Drug Analysis in FY 88.

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]
738 Diazepam	31	0
739 Tolazamide	48	0
833 Thyroxine	145	3.4
834 Amitriptyline	170	0

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

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