FY87

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 1987

Staff Level

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

Publication

Compendial Monograph Evaluation and Development

Division personnel continually review new USP methods and revisions published in the Pharmacopeial Forum. Occasionally, we engage in long-term research to produce substantially improved official methodology for drug analysis. One such study was published in FY 87 (1). The report gave an evaluation of, and recommend revisions for, current USP monographs on nitrofurantoin, nitrofurantoin tablets, and nitrofurantoin oral suspension. It presented a suggested monograph for nitrofurantoin capsules, which article is not currently in the USP. New high-pressure liquid chromatographic methods were recommended to replace polarographic and TLC procedures for identification, assay, and impurity tests. Also reported were the results of a collaborative study of the new methods.

Summaries of Current Projects

Abbreviated New-Drug Applications -- Analysis of Bulk Drug Substances

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

New-Drug Evaluations -- Method Validation

Forty-three method-validation packages were completed by the Division in FY 87.

Thalidomide. Division staff continued refinement of a synthesis for thalidomide to be used as a reference standard and wrote a detailed synthetic procedure. About 2.5 Kg of highly pure thalidomide was prepared. About 1 Kg of this material was shipped to the Hansen's Disease Center, Carville, Louisiana, to serve as an emergency supply of the drug, which is used to treat certain forms of leprosy, while the Hansen's Disease Center searched for an FDA-approvable commercial supplier of the drug.

We continue to provide analytical support to the Division of Anti-Infective Drug Products for this project since no source has yet been approved, and have analyzed samples of thalidomide tablets from prospective suppliers in Brazil and Mexico and bulk drug synthesized at Tulane University. The analyses include assay and tablet content uniformity, and examinations for identity and purity. Reference standards of two common impurities -- phthalylglutamic acid and phthalylglutamine -- were synthesized and purified by Division staff. Monographs containing procedures for the examination of thalidomide tablets and bulk drug were also prepared, and guidelines for the synthesis of pure thalidomide were written.

Two chemists at the Division of Drug Analysis received the 1987 FDA Award of Merit for a portion of this work.

Generic Drug Standards

Eighty-four candidates for USP Reference Standards were examined at the Division in FY 87 (Table 2).

A report on the evaluation and development of compendial monographs for nitrofurantoin was published in the Pharmacopeial Forum (1).

Quality Assurance

Eight Drug Product Surveillance studies were completed in FY 87 (Table 3). Under this program the Division of Drug Analysis performed 23,104 analyses on 533 batches of drugs. Six batches (1.1%) failed to meet the compendial or FDA-imposed requirements for the products. The number of defective batches and the reasons for the classification as defective are shown in Table 1.

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

Hydralazine Hydrochloride Injection. The Division received these samples from Newark District Office in April 1986. The manufacturer had informed FDA that several batches of injection

had decomposed, and that the decomposition appeared to be related to a batch of propylene glycol used in their manufacture. The firm also provided an analytical procedure (high-pressure liquid chromatography) and a list of seven identified decomposition products. Newark District Office asked us to verify the identity of the major decomposition products and to assess whether the firm's proposed decomposition schemes were chemically feasible.

The firm declined to supply reference standards of any of the decomposition products. Of the seven, we purchased two and synthesized three: 1-aminophthalazine, 1,2,4-triazolo[3,4-a]-phthalazine, and 3-methyl-1,2,4-triazolo[3,4-a]phthalazine; the latter two compounds were prepared from hydralazine free base, which itself had to be prepared highly pure and free of oxidation products. The Division's analyses of the injections agreed with those of the manufacturer except for a few of the impurities which were found at somewhat higher levels.

Potassium Chloride Sustained-Release Capsules. Several such samples were analyzed for both potassium and chloride content with the Division's ion chromatograph. Total assays and dissolution rates were obtained. These were special samples of finished dosage forms received under the ANDA program.

Ranitidine Hydrochloride Tablets. In January 1987, the Canadian Health Protectorate informed the FDA that an impurity in ranitidine hydrochloride tablets (generic and innovator) was being detected by TLC. This impurity remained at the origin and was highly colored. The amount of this impurity increased under high temperature (80°C) and humidity (75%). Humidity appeared to be the most critical factor.

In May 1987, the Division of Drug Analysis was asked to do an accelerated stability study on both unit dose and bottle packages of a brand of ranitidine hydrochloride tablets. The samples were of two different lots. The samples were stored in an incubator at 40°C and 75% relative humidity and were tested at 0, 1.5, and 3 months. In addition, some samples were stored in a refrigerator at 3°C.

The results at time 0 for the two lots were 101.8 and 98.8% of label, with only a small amount of one impurity in one lot.

At 1.5 months, the first lot assayed 83.8%, with five impurities (total of 5.2%), and the second lot assayed 97.9%, with one impurity (total of 1.4%).

At 3 months, the first lot assayed 22.5% of label, with seven impurities (total of 27.6%), and the second lot assayed 95.8%, with one impurity (total of 0.34%). The refrigerated samples

assayed an average of 101.4% of label, with one impurity (total of 0.94%).

Biopharmaceutics

The Division conducted no work under this topic during FY 87.

Other Activities

Training Conducted By Division Staff In Foreign Countries. In April 1987 two Division chemists and one electronics technician traveled to Cairo, Egypt, to install the equipment and chemicals required to form a new dissolution laboratory in the Egyptian National Organization for Drug Control and Research and to train Egyptian staff in their use. From January to March the equipment was tested in the Division's laboratories, adapted for use with Egyptian power sources (220 volts and appropriate plugs), recrated, and shipped. This project was conducted under the auspices of the U.S. Agency for International Development as a part of their project to improve drug quality in Egypt.

Also in April 1987 two Division chemists traveled to Riyadh, Saudi Arabia, to consult with the Ministry of Commerce (MOC) and to develop with them a plan for laboratory testing to help improve the quality of drug products distributed there. The developed plan was subsequently adopted for implementation and funding by the MOC and the U.S.-Saudi Arabian Joint Economic Commission. The overall plan provided for the training of counterpart Saudi Arabian laboratory directors, expanding the laboratory staff and equipment resources at three sites, and establishing a training program in drug-analysis procedures. The portions of this plan implemented in FY 87 included the visits of eight Saudi Arabian counterpart laboratory directors and managers to our Division for discussions on laboratory operations, and the procurement, inventory, checkout, recrating, and shipment of equipment and supplies to establish at three sites in Saudi Arabia the laboratory essentials to perform most aspects of drug-quality testing. In addition, the Division's thin-layer chromatography (TLC) expert, a reemployed annuitant, has been assigned to Saudi Arabia for FY 88 at their expense to assist in the development of TLC methods for screening samples of imported drugs. The counterpart training programs for the laboratory operating personnel were developed for implementation in FY 88.

Training Received Off Site By Division Staff. Two DDA chemists visited the FDA/NIH campus for one-month training sessions in advanced methods of analysis of proteinaceous drugs, including electrophoretic and chromatographic procedures. Such techniques

are often encountered in methods submitted to the Division for examination under the New-Drug Evaluation program.

Computer Activities. In December 1986 the Division installed a new computer, a Wang VS 65 that replaces an older Wang OIS 115. Cables were run from the computer room to seven printers and about 20 terminals located throughout the ninth- and tenth-floor areas. The new system is based on Wang's OFFICE software package that allows users to select either the enhanced word-processing software or the new Word Processing Plus. Additionally, OFFICE allows users to send and receive mail, create calendars and schedule meetings, create information cards, sort inter-office mail items into folders, keep track of correspondence, receive and send broadcasts, keep phone logs, and develop and use programming languages (Procedure, BASIC, FORTRAN) under the data-processing features. Although the major use of the system is word processing, several other vital needs are being served: synchronous and asynchronous telecommunications with the Parklawn Computer Center, e.g., transmission of accounting data and electronic mail, and for direct communication link with the Division's Hewlett-Packard 1000 laboratory computer system and with other smaller computers. A program that will allow "paperless" preparation of purchase orders has nearly been finished.

The Division has developed a barcoded Sample Control ("S") Card which, when used in conjunction with barcoded analyst numbers and status statements, allows the facile entry of the sample number and related data into a computerized information system. The information system can then be used more readily to track the status of sample assignments. The barcoded "S" card is also used by the Sample Room staff to prepare inventories of samples scheduled for incineration. Formerly our chemists had to read each sample label and write out the lists of drugs and the amounts of each for the incinerator operators.

The Division continued to implement the computerized laboratory inventory of chemicals and chromatographic columns on its Hewlett-Packard System 1000. Over 95% of the materials have been catalogued in the computer listing. The program allows searches from any laboratory terminal for reference standards, reagents, solvents, or columns, provides their laboratory location, and allows one to "sign out" or "sign in" an item when it is removed from or returned to common storage. The program saves considerable time because it eliminates physical searches throughout the ninth- and tenth-floor areas for supplies and immediately reports whether a desired item is available at the Division. The chemist who wrote the program also gave several training sessions to DDA staff.

Software For Small Computer Systems. A commercially available program ("AUTOSKETCH") was installed on the Division's Leading

Edge personal computer; this program allows facile preparation of posters, announcements, and other text-oriented applications, as well as easy entry of complex chemical structures, which may then be plotted within reports.

Division staff wrote an interface program to allow transmission of word-processing text files from a portable computer (Tandy 600) to the Wang VS 65. This procedure allows one to write reports while on a business trip and later to transfer them electronically to the Wang VS 65 for final editing and printing.

Foreign Visitors and Guest Workers. The Division hosted the following visitors, among others, during FY 87:

Guillermo Rosas November-December 1986	Mexico
S. Chan	Malaysia
W. Suchunwanit	Thailand
J. Alcasabas	Philippines
J. Tang December 1987	Singapore
Alicia Larrinaga February 1987	Argentina
M. A. Johnston March 1987	Australia
Sonia Malka Lizabeth Sanabria April 1987	Venezuela
Osama Kebir May 1987	Egypt
C. Lee	Republic of China
M. Liao	
H. Yen	
H. Shen	
C. Horng	
H. Lin	
Y. Tsai	
S. Lin June 1987	
Samia Shalaby	Egypt
Nadia El Sayed	
Naguib Wassef	
Amal Afifi June-July 1987	

A. Kassim A. Aidaroos A. Gamdi July 1987	Saudi Arabia
Abdulrahman S. Al-Khalifa August 1987	Saudi Arabia
Abdullaly I. Abdullaly Mohammed Somali Ali Omar Moussa Mohammed DeBassi September 1987	Saudi Arabia
Jin Zhizhu September-December 1987	Peoples Republic of China

Reference

(1) Kreienbaum, M. A. (1987) Pharmacopeial Forum 13, 2171-2176. Compendial Monograph Evaluation and Development -- Nitrofurantoin: Report of findings and recommendations on the monographs for nitrofurantoin, nitrofurantoin tablets, and nitrofurantoin oral suspension, and a recommended new monograph for nitrofurantoin capsules.

Table 1. Summary of Analyses Performed At the Division of Drug Analysis in FY 87.

Totals	
Batches Analyzed	1,483
Assays	38,798
Defective Batches	25 (1.7%)

Defective Batches Found in Each of the Program Areas

	Program Area	
Defect	Drug Product Surveillance	ANDA
Strength	2	5
Content Uniformity	0	0
Dissolution	4	2
Other[a]	0	12
Totals	6	19

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

Table 2. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 87.

Acetanilide

α-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane

Allopurinol

3-Amino-4-phenoxy-5-sulfamoylbenzoic acid

α-Aminopropiophenone HCl

Anthralin

Beclomethasone Dipropionate

Biotin

Bromcriptine Mesylate

Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate

Captopril

Captopril Dimer

Carbamazepine

Carbomer Homopolymer

Cephaeline Hydrobromide

Cetylpyridinium Chloride

Clotrimazole

Cocaine HCl

Codeine Sulfate

Desipramine HCl

Dextrose

Dienestrol

Dihydrotachysterol

Dopamine HCl

Doxepin HCl

Equilin

Ergocalciferol

Ergoloid Mesylate

Estropipate

Ethotoin (and related substance) 5-Phenylhydantoin

Folic Acid

Fructose

Gemfibrozil

Glyceryl Behenate

Halazepam

Haloperidol

Histamine Dihydrochloride

Ibuprofen

o-Iodohippuric Acid

Isopropyl Myristate

Leucovorin Calcium

Levorphanol Tartrate

Table 2. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 87 (continued).

Lorazepam (and related substances)

- 2-Amino-2',5-dichlorobenzophenone
- 7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one
- 6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde
- 6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic acid
- 6-Chloro-4-(o-chlorophenyl)-2-quinazoline methanol

Mannitol

Meclofenamate Sodium

Melphalan HCl

3-Mercapto-2-methylpropanoic acid 1,2-diphenylethanolamine

Mesoridazine Besylate

3-Methoxytyrosine

2-Methylamino-5-chlorobenzophenone

Metoprolol Tartrate

Monoglycerides

3-Nitro-4-phenoxy-5-sulfamoylbenzoic acid

Nonoxynol 9

Noroxymorphone HCl

Nortriptyline HCl

Oxybutynin Chloride

Oxymorphone

Perphenazine

Phenylcyclohexylglycolic Acid

Phosphated Riboflavin

Prazosin HCl

Propantheline Bromide

Pseudoephedrine HCl

Quinidine Gluconate

Riboflavin

Rifampin Quinone

Ritodrine HCl

Salicylamide

Sodium Fluoride

Tamoxifen Citrate

Thimerosal

Thiotepa

(E)-Thiothixene

2-[N-(2,2,2-Trifluoroethyl)-amino]-5-chlorobenzophenone

Tolazamide

Valproic Acid

Vincristine Sulfate

Table 3. Drug Product Surveillance Studies Completed at the Division of Drug Analysis in FY 87.

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]
549 Psychostimulants	16	0
551 Theophylline	0	0
552 Anticoagulants	28	0
553 Local Anesthetics	93	0
622 Codeine Phosphate et al.	49	0
623 Acetaminophen with Codeine	143	0
624 Aspirin with Codeine Phosphate	45	0
625 Acetaminophen	159	3.1

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