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 1993

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

I. STAFF LEVEL

The Division of Drug Analysis operated with 57 full-time equivalent positions in FY-93. The Division has 49 full-time permanent employees and throughout FY-93 has employed 20 part-time student aides from six local universities, and several guest workers including consultants and high school teachers through an intern program.

II. PUBLICATIONS

Synthesis and Stability of Labeled PCMX

PCMX, p-Chloro-m-Xylenol, is utilized in surgical scrub antiseptic formulations as an antibacterial agent. In high amounts, PCMX can be toxic. The synthesis and stability of isotopically-labeled PCMX was studied to support metabolism studies in rodents, primates, and human hepatic cells. Deuterium and tritium labeled PCMX were prepared and the isotope exchange reactions monitored to determine conditions of suitable stability for metabolic studies. This work was performed and published (1) jointly by the Division of Drug Analysis and the FDA National Center for Toxicological Research.

Single-Puff Albuterol MDI Analysis

Metered-dose inhaler (MDI) formulations provide a rapid and efficient means for therapeutic drug delivery. Uniform dosing with MDIs can be problematic given the many factors that can influence the drug delivered from the device and, more critically, the amount of drug substance within the proper particle size range for efficient delivery and retention in the lungs.

The preferred procedure for determining the particle size distribution of delivered drug substance is by cascade impactor methods. Often, however, the small dose of drug delivered in a

single MDI actuation is difficult to determine with precision at each stage of the impactor device. It is further believed that multiple actuations may alter the collection efficiency of the cascade impactor.

In this paper (2), a highly sensitive analytical method employing HPLC with electrochemical detection provides sufficient sensitivity to determine with high precision and accuracy the particle size distribution of MDI delivered albuterol from a single actuation. Further studies are underway to ascertain the effect of repetitive albuterol loading on the impactor plates at each cascade impactor stage relative to drug collection efficiency.

Niacin Dissolution Profiles

Niacin, a vitamin available in over-the-counter tablet and capsule forms, has found considerable popularity as the drug of choice for hypercholesterolemia. Several reports have implicated high dose Niacin sustained-release formulations with liver toxicity.

In this study (3), appropriate conditions for monitoring the dissolution profiles of immediate- and sustained-release Niacin tablets and capsules are presented. This dissolution method has been utilized to survey currently available Niacin formulations. (See National Surveillance Program, Niacin Tablets, below.)

Chlorhexidine Digluconate Impurities

Chlorhexidine Digluconate is an antimicrobial agent utilized in surgical scrub and dental mouth wash formulations. As part of a study on stability of surgical scrubs formulations to the formation of potentially toxic degradation products, chlorhexidine digluconate solutions were subjected to stress decomposition conditions. Eleven related degradation products were identified and

characterized by mass spectrometry, nuclear magnetic resonance spectrometry, and independent synthesis to confirm appropriate structural parameters of the degradants (4). Six of the synthesized impurity materials represent new compounds.

Halogenated Compound Gas Standards

A microgravimetric procedure was previously developed for the preparation of accurate cylinder gas standards for volatile organic compounds at the part-per-billion (ppb) range. The present study (5) evaluates the use of this procedure for preparing such standards at the part-per-trillion (ppt) level. Using gas chromatography with electron capture detection, prepared cylinder gas standards were monitored over a three year period. Results of these studies indicate that the gas standards are stable and provide precise, reproducible results, even at the ppt level, for the volatile halogenated organic compounds investigated.

III. SUMMARIES OF CURRENT PROJECTS

DRUG QUALITY ASSURANCE

ANDA Methods Validation Program

In FY 92, the Division was assigned the responsibility of performing ANDA method validation for products manufactured in Canada, Sweden and Switzerland. Ten ANDA method-validation packages were evaluated in FY-93.

ANDA Pre-Approval Forensic Program

In this program, samples of the generic bioequivalence lot and innovator lot submitted for bioequivalence testing are obtained from the ANDA applicant reserve. These samples are evaluated with the Division's fingerprinting protocol -- Fourier-transform infra-

red spectrometry, thermogravimetric analysis, etc. -- to validate the approved formulation and determine if substitution of formulations may have occurred. A total of 200 samples were evaluated in FY-93. The fingerprinting results are being retained for future validation and for incorporation into a national database of approved drug products.

Samples from domestic generic manufacturers have been transferred to the FDA New York Regional Laboratory and the Philadelphia District Laboratory. Samples obtained from generic manufacturers in Canada, Switzerland and Sweden continue to be processed at this Division.

NDA Pre-Approval Forensic Program

In this program, samples of the innovator clinical and pilot lots are obtained from the NDA applicant reserve. These samples are evaluated with the Division's fingerprinting protocol -- Fourier-transform infrared spectrometry, thermogravimetric analysis, etc. -- to validate the approved formulation and determine if substitution of formulations may have occurred. A total of 75 samples were evaluated in FY-93. The fingerprinting results are being retained for future validation and for incorporation into a national database of approved drug products.

ANDA Bioequivalence Testing Program

In this program, generic and innovator bioequivalence samples are secured from contract bioequivalence laboratories and evaluated with the Division's fingerprinting protocol. The results are compared with fingerprinting results obtained with equivalent samples secured from the applicant's reserve of the bioequivalence lots to confirm proper formulation consistency. A total of 75 samples were evaluated in FY-93.

AOAC Associate Referees

Four Division chemists are AOAC Associate Referees for proposed method-development projects. After the methods have been developed and validated, full interlaboratory collaborative studies will be conducted on the analytical methods. These studies will be published upon completion of the projects.

USP Committee of Revision

The Division Director currently serves on the USP XXII Committee of Revision as a member of the Chemistry II Subcommittee and chairman of the Subcommittee on General Chapters. Committee responsibilities dealing with policy and procedures are generally handled by the Director and Deputy Director along with analysts with knowledge in these particular areas.

National Surveillance Program

The Division continues to be active in the CDER, Office of Compliance drug product survey program. The following surveys were completed.

Niacin Tablets: Orally administered Niacin, available over-the-counter as a vitamin in immediate release and sustained release formulations, is often prescribed in higher dosage for the control of high cholesterol. Incidents of liver toxicity have been reported with some of the sustained release products. The survey samples included fifty five samples from a cross-section of manufacturers and dosage forms. All samples were submitted to full USP compendial testing (i.e., identity, assay, and content uniformity). All samples complied with these USP specifications.

A dissolution method was developed and validated for Niacin oral dosage forms. Considerable variability was observed within both the immediate release and the sustained release formulations.

Some immediate release products had dissolution characteristics similar to sustained released product and vice versa. Methods for determining related impurities were developed but significant related impurities were not observed in the survey samples.

The dissolution procedure with representative laboratory results for the survey samples has been submitted to the USP for consideration as a compendial method for Niacin tablets. Several papers based on these studies have been submitted for publication.

Miconazole: This antibiotic, formulated as an ointment, cream, or suppository, is a defined USP article. All nineteen of the samples secured in this survey have been evaluated utilizing the USP procedures and found to comply with the USP compendial specifications.

Zidovudine (AZT): This drug substance is the first anti-viral product approved by the FDA for AIDS. These products are not defined USP articles. Seven samples received in this study were evaluated utilizing the innovator methods which were validated when the drug substance and products were approved. All samples satisfied the appropriate NDA compliance specifications.

Carbamazepine Collaborative Study

Carbamazepine is a narrow therapeutic range drug product utilized in controlling epileptic seizures. Samples of all U.S. approved products were obtained from the marketplace and subjected to full USP and British Pharmacopeial methods to confirm compliance. Particular emphasis was directed at the dissolution characteristics of these drug products. All samples studied satisfied appropriate USP specifications.

Generic Drug Task Force Project

This project, requested by the CDER Office of Compliance, involved working with a Grand Jury investigation on alleged fraud in a generic company's submissions for drug approval. A total of four drug products were involved in the investigation, which resulted in a three count indictment and conviction.

Other Fraud Investigations

Two additional investigations of alleged fraudulent submissions for drug approval were conducted. Both investigations were triggered by information obtained during drug product pre-approval inspections. One investigation was for a generic product submitted by a foreign applicant and the other investigation was for a domestic New Drug Application.

GENERIC DRUG STANDARDS

Albuterol Metered-Dose Inhalers

The Division of Drug Analysis provided laboratory support for the extensive clinical trial to determine dose-response characteristics for albuterol metered-dose inhaler formulations. The clinical trial is sponsored by the CDER, Office of Generic Drugs.

A variety of dosages of albuterol suspended in a Freon propellant were manufactured under contract for the FDA. Several sizes of metering valves were also included, as were placebo formulations which include only the propellant and propellant with surfactant, oleic acid. After manufacture all batches were shipped to the Division for lot-release testing. All lots of dosage forms were tested for water content, leaks, total albuterol canister assay, albuterol unit-spray assay, and albuterol particle-size distribution. The bulk albuterol and oleic acid were also evaluated. The various albuterol assays utilized a more precise liquid

chromatographic procedure with fluorescence detection that the Division staff developed and validated for this study.

The second phase of this study, stability testing, has been completed. Also in progress is further method-development work aimed at providing superior USP methods for the evaluation of metered-dose inhaler products.

A Division chemist developed an analytical procedure sensitive enough to permit particle-size analysis of a single puff from an albuterol metered-dose inhaler. The procedure uses liquid chromatography with electrochemical detection. The lower sensitivity of previous methods required from five to 40 puffs from the inhaler be delivered into the cascade impactor; multiple puffs may result in erroneous measurements of particle size due to agglomeration effects. The results of this study have been published (2).

Fingerprinting

Collaborative Study: The Division is conducting this study to evaluate the Division fingerprinting protocol and to examine the variance in data obtained among different laboratories. Samples for the collaborative study were sent to five FDA laboratories. All laboratories evaluated the procedures for physical characterization and Fourier-transform infrared analysis.

The results of the physical characterization and Fourier-transform infrared analysis collaboration were very successful. The thermal gravimetric analysis collaborative results indicate difficulties in temperature calibration. Studies are continuing to resolve this difficulty.

USP Reference-Standard Candidates

Ninety eight USP reference standard candidates were evaluated FY 93 (Table 1). Of these, 16 samples (16%) were new-drug

substances for the USP. In addition to the evaluation of the candidate drug substances, all proposed USP monographs for these new USP drug substances were validated. FDA's Baltimore, Cincinnati, and Philadelphia District Laboratories completed 28 (29%), 1 (1%), and 6 (6%) candidates, respectively; the remainder (64%) were examined at the Division.

USP Methodology

While examining candidate USP reference standards, Division staff occasionally identify problems with USP methodology. As time permits, improvements are developed and submitted to the USP for consideration. In some cases, the USP is simply informed of the problem. The following summarizes some of these findings:

Acepromazine Maleate: In the related substances test, the instructions for preparing the test solution were unclear and also missing a ratio amount for a solvent mixture. Appropriate corrections will appear in a future issue of the Pharmacopeial Forum.

Azaperone: The suggested changes in the HPLC assay for the injection monograph, which was previously published in the Pharmacopeial Forum, were adopted in the 8th supplement (6).

Ciprofloxacin: The HPLC assay in this recently adopted monograph is the same procedure that is used in the Ciprofloxacin Hydrochloride monograph with the exception that the column temperature was changed from 30°C to 40°C. This change did not make sense as all other parameters and system suitability requirements were the same in both methods. The Division recommended that the temperature be kept at 30°C for both procedures. The directions for making the standard preparation and assay preparation were not clear and we recommended a change in wording to clarify the directions. These comments will be published for review in a future Pharmacopeial Forum.

Droperidol: The suggested changes in a proposed HPLC assay for the injection monograph, which was previously published in the Pharmacopeial Forum, were adopted in the 8th supplement (7).

Methamphetamine Hydrochloride: Our laboratory suggested that the current HPLC assay procedure used in the methamphetamine tablets monograph be adopted as the method of assay for the pure drug substance to replace the non-specific perchloric acid titration. Supporting data were submitted, and the suggestion was published for review (8).

Miconazole Nitrate: The suggested change in the GC assay of the cream monograph, which was previously published in the Pharmacopeial Forum, was adopted in the 8th supplement (9).

Pindolol: Directions for the preparation of the mobile phase used in the HPLC assay and chromatographic purity tests were unclear. A suggested change was made, which was published for review (10).

Quinidine Gluconate: Our laboratory suggested a change in the resolution factor used in the dihydroquinidine limit test. This change is the same one that has already been adopted for the Quinidine Sulfate monograph and will appear in a future issue of the Pharmacopeial Forum for public comment.

Quinidine Sulfate: The suggested change in the resolution factor used in the HPLC test for the limit of dihydroquinidine sulfate, which was previously published in the Pharmacopeial Forum, was adopted in the 8th supplement (11).

Succinylcholine Chloride: In the chromatographic purity method, we were unable to detect two impurity standards at the level spotted when using the spray reagent cited in the method. Two other spray reagents were also tried with no better results.

This problem has been referred to the USP's laboratory investigation

Thiotepa: We encountered problems with the drying instructions for the reference standard, and found that determination of water content by Karl Fischer titration was a better way to determine total solids than the loss on drying method. USP replied that they received similar comments from the manufacturers and a suggested change in determining the water content was published for review (12).

Valproic Acid: The suggested change in the GC assay of the capsule monograph, which was previously published in the Pharmacopeial Forum, was adopted in the 8th supplement (13).

NEW-DRUG EVALUATION

Method Evaluation

Division staff completed 24 New-Drug Application method validation packages during FY 93. The majority of the evaluations were for new molecular entities and unique combination formulations. Twelve of the formulations were for high-priority, life-threatening diseases; two of these were AIDS therapeutics.

Mebendazole

Mebendazole, a drug for the treatment of intestinal worms, is poorly soluble and exists in several polymorphic forms. Since the drug is not adsorbed, the polymorphic form could drastically alter the therapeutic efficacy of the drug product. The purpose of this project was to develop tests to identify the polymorphic forms. Division staff have synthesized the various polymorphic forms and characterized them by Fourier-transform infrared spectrometry, X-ray powder diffraction, and thermal methods. Dissolution

studies have been conducted to determine relative solubility and dissolution characteristics of these polymorphic species. Further studies to characterize these polymorphs continue.

Thalidomide

Three thalidomide samples from different manufacturers were certified for utilization in Investigational New Drug studies during FY-93. The New Orleans District Laboratory performed the identity, content uniformity, and related impurity tests for these certification samples.

Sucralfate

Sucralfate, a drug substance for the treatment of ulcers, was extensively evaluated to assure therapeutic adequacy. This non-stoichiometric drug substance promotes the healing of ulcers in the digestive tract without being absorbed systemically. A comparison of generic and innovator drug substances was conducted to determine the suitability of generically supplied material. The evaluation included testing all samples by established compendial procedures and additional studies including high resolution Proton, Carbon and Aluminum NMR studies. These studies confirmed that the generic supply of drug substance has essentially identical chemical and physical properties under conditions of use (i.e., in gastric fluid).

Antineoplastin

Antineoplastin, an Investigational New Drug (IND) for cancer, was evaluated in support of compliance with IND regulations. Since the drug substance is not available commercially, the material was prepared by independent synthesis to confirm the molecular structure of the Antineoplastin components. Sufficient drug substance was subsequently isolated from the drug product and

purified to serve as reference standard material. These studies confirmed that the drug product was as it is purported to be in the IND application.

Hetastarch

Hetastarch, a high molecular weight hydroxyethyl starch product, is utilized as a plasma volume expander. Studies were conducted to determine the equivalency of generic drug substance with the innovator material. The various Hetastarch samples and reference standards were evaluated by Gel Permeation Chromatography to confirm the validity of this analytical method and the characterization of the Hetastarch samples. This project was a joint study with the Center for Biologic Evaluation and Research (CBER).

Lomefloxacin

At the request of the Office of Drug Evaluation, samples from several manufacturers of Lomefloxacin, an antibacterial drug substance, were extensively evaluated for assay, impurity and other physical and chemical properties. Testing included High Performance Liquid Chromatography, Thin-Layer Chromatography, Fourier-transform infrared spectrophotometry, thermal methods of analysis, Nuclear Magnetic Resonance spectrometry, and Optical Activity measurements. A Division analyst presented the results of these studies to FDA and manufacturer representatives at headquarters and attended an FDA Drug Advisory Committee meeting related to these studies.

Ibogaine

At the request of the Pilot Drug Evaluation Staff, samples of Ibogaine, an alkaloid, were evaluated for identity, assay and impurities. This drug substance, submitted as an IND for Heroin addiction treatment and highly touted by the AIDS community, was

produced by a semi-synthetic procedure. It was necessary to confirm the molecular structure of the supplied material versus the native material isolated from natural products. Since compendial methods of analysis were not available, procedures were developed and validated. These methods included proton and carbon Nuclear Magnetic Resonance spectrometry, Gas Chromatography with Mass Spectral detection, High Performance Liquid Chromatography, and Optical Activity measurements.

Dyazide

Extensive developmental work on the dissolution procedure for Dyazide, a major hypertensive agent, was performed in support of defining the current USP method for this product. Various dissolution media, including different pH and surfactant additive conditions, were evaluated for the innovator and generic products. The results of this study were reported to the FDA Division of Biopharmaceutics.

Ciclopirox Olamine

In response to a request from the Division of Anti-Infective Drug Products, the thermal properties of Ciclopirox Olamine were evaluated. These studies included Thermal Gravimetric Analysis and Differential Scanning Calorimetry to determine the crystalline nature and information concerning thermal degradation processes of the drug substance.

IV. Other Activities

Thalidomide Research

Activities related to thalidomide continue from previous years. Enantiomerically pure thalidomide has been synthesized for investigational studies of graft-versus-host disease. Additional studies to characterize different polymorphic forms of racemic

thalidomide have been completed. The polymorphic form of crystalline thalidomide could drastically affect the bioavailability of the drug in solid oral dosage formulations.

Analysis of Cosmetic Sample

Analyses were carried out on a cosmetic sample suspected of containing traces of two irritants thought to cause cataract formation. Evaluation by High Performance Liquid Chromatography and Gas Chromatography with Mass Spectral detection against reference standards found neither irritant present at the detection level (i.e., 1 ppm). A report was issued to the assigning unit; Surveillance and Data Processing Branch.

Reference Standards Supply

The Division continues to supply reference standards to other FDA laboratories in support of their research and compliance activities. Over fifteen requests for over twenty five reference materials were processed in FY-93. These requests were from seven FDA laboratory units at headquarters and in the field.

Awards

Several awards were issued to Division staff in FY-93 based on exceptional service to the Division and helpful suggestions to improve Division operations.

A Special Act award was presented for the development and implementation of the Division Occupational Safety and Health and the Chemical Hygiene Plans and manuals. Two awards were presented for exceptional performance during the extended absence of the Division accounting technician and purchasing agent.

Two awards were presented for suggestions that improved operation of the laboratory programs at the Division.

Career Days

Several Division chemists participated in St. Louis area career days and high-school programs in FY-93. Presentations were made at the American Chemical Society (St. Louis Section) Career Day, the St. Louis Public School Career Awareness Fair, Women of Tomorrow Plan Today, sponsored by the St. Louis Public Schools, Career Education Office, Science and Technology Shadowing Role Model Program, and the Science and Technology Executive Council.

Computer Activities: Mainframe

Transfer of all critical operations from the administrative Wang VS and laboratory Hewlett-Packard 1000 computer systems to the Digital Equipment Corporation VAX computer system have been completed.

Division staff have developed several new Oracle-based systems for data storage and report writing. The subsystem for dissolution analysis is now operational. Analysts working at VAX terminals can generate printed dissolution reports on facsimile worksheets from the information stored in the laboratory database. Input forms for general-purpose analytical worksheets or reports have been fully implemented and currently are extensively utilized by laboratory personnel. Users may enter a description of the sample, a summary of analysis, comments, and a description of the reserve sample. Printed reports on facsimile worksheets can be prepared by analysts working at VAX terminals.

Division staff continue to expand the capabilities of integrated ordering, purchasing, accounting, and inventory systems. New user-input screens for the VAX/Oracle accounting subsystem have been implemented for generation of purchase orders, COD payments, and blanket purchase agreements. Unique bar code tags are

generated upon receipt of equipment to facilitate inventory control.

Some Division databases are available on-line for use by other FDA laboratory and headquarters units. These databases allow on-line access to our inventory of chemicals and columns for liquid and gas chromatography, to our instructional videotapes and slide-audiotapes, drug reference standards, and to our electronic index to Laboratory Information Bulletins.

The Oracle sample tracking and accountability system has been substantially updated to include supervisory functions for sample assignment and approval of completed studies. Summary memoranda of completed studies can also be incorporated into the computer records. Computerized generation of proposed sample destruction schedules has also been incorporated into the system. Record and file security procedures have been incorporated in the system to prevent either accidental or deliberate unauthorized data or record alteration.

Presentations

Division chemists also made the following presentations by invitation or at pharmaceutical meetings:

Presentation on Fingerprinting of Pharmaceutical Dosage Forms, G.D. Searle, Skokie, IL, October 1992.

o - Presentation on Fingerprinting of Pharmaceutical Dosage Forms, ODE Review Chemists, Rockville, MD, December 1992.

o - Presentation on Fingerprinting of Pharmaceutical Dosage Forms, Pharmaceutical Manufacturer's Association, Analytical Research and Development Steering Committee, Washington, DC, December 1992.

o - Presentation on Fingerprinting of Pharmaceutical Dosage Forms, Sterling Winthrop Worldwide Analytical Conference, Frazer, PA, April 1993.

o - Presentation on Fingerprinting of Pharmaceutical Dosage Forms, Association of Analytical Chemists, New York - New Jersey Section, New Brunswick, NJ, April 1993.

o - Presentation entitled "Validation of Computerized Liquid Chromatographic Systems", FDA Regulatory Seminars for Review Chemists, Washington, DC, April 1993.

o - Presentation on New Drug Evaluation Methods Validation Problems, American Association of Pharmaceutical Scientists, Chicago, IL, May 1993.

o - Presentation on Fingerprinting of Pharmaceutical Dosage Forms, Long Island University Program, North Brunswick, NJ, May 1993.

o - Presentation on New Drug Evaluation Methods Validation Problems, Applied Analytical Industries Seminar, Wilmington, DE, June 1993.

o - Presentation on New Drug Evaluation Methods Validation Problems, Pharmaceutical Technology Seminar, North Brunswick, NJ, June 1993.

o - Presentation on New Drug Evaluation Methods Validation Problems and Analyst Training Program, Atlanta Regional FDA Laboratory, Atlanta, GA, June 1993.

o - Poster presentation entitled "Capillary Electrophoresis Separation and Measurement of Diatrizoic Acid and Mono- and Di-Iodo Impurities in Radiopaque Solutions", AOAC International Meeting, Washington, DC, July 1993.

o - Poster presentation entitled "HPLC Separation and Measurement of Diatrizoic Acid and Mono- and Di-Iodo Impurities in Radiopaque Solutions", AOAC International Meeting, Washington, DC, July 1993.

o - Presentation entitled "Application of Neural Networks to Trace HPLC Profiles for Discriminating Among Commercial Manufacturers of L-Tryptophan", in "Technology of the Future: Neural Networks/Artificial Intelligence", AOAC International Meeting, Washington, DC, July 1993.

o - Presentation on New Drug Evaluation Methods Validation Problems, Eli Lilly, Indianapolis, IN, July 1993.

o - Presentation on Fingerprinting of Pharmaceutical Dosage Forms and Analyst Training Program,' FDA Office of Regional Affairs Supervisory Training Program, Baltimore, MD, September 1993.

o - Presentation on Analytical Methods for Biotechnology Pharmaceutical Products, FDA Office of Regional Affairs Supervisory Training Program, Baltimore, MD, September 1993.

Training Conducted by Division Staff

Visitors and Guest Workers. The Division hosted the following visitors, among others, during FY 93:

Joan Stapleton and L. Valentin Feyns, United States Pharmacopeia Staff, Rockville, MD, October 1992.

Professor Daniel Armstrong, University of Missouri at Rolla, December 1992.

Mohammed Al-Kefary and K. Al-Zubairi, Saudi Arabia, February 1993.

Bristol-Myer Squibb Company, about 6 people for tour of Division facilities, February 1993.

Khalid Alfhaid, Pharmacist, Saudi Arabia, training on analytical methods and drug law, March 1993

Professor Louis Luzzi, University of Rhode Island, March 1993.

Pfizer, Inc., about 15 people for tour of Division facilities, March 1993.

Ortho Pharmaceuticals, Inc., about 20 people for tour of Division facilities, April 1993.

Professor Claude Lucchesi, Northwestern University, Evanston, IL, April 1993.

Eden S. Robles, Food and Drug Regulations Officer, Manila, Philippines, WHO/PAHO Fellow for training, April through June 1993.

Dr. Eric Richmond and Dr. Barry Garfunkle, Merck and Company, Inc., April 1993.

Professor Glen A. Petrie, Central Missouri State University, Faculty Science Advisor, May through August 1993.

William Anderson, St. Louis University High School, Teacher Intern Program, May through August 1993.

Dot M. Davis, Rockwood South High School, Teacher Intern Program, June through August 1993.

Vaughan Morrill III, Sumner High School, Teacher Intern Program, June through August 1993.

Joseph Freeman, FDA Kansas City District, for training, June 1993.

Professor Steve Dina, Department of Biology, St. Louis University, High School student tours (about ten students each visit), June 25, July 9, and July 23, 1993.

Dr. Roger Alexander, United Kingdom Medicines Control Agency, August 1993.

Dr. Umesh Banakar, St. Louis College of Pharmacy and Dr. Dutd and Dr. Nadkarni, Torrent Pharmaceutical Company, India, August 1993.

Dr. Robert Baum, G.D. Searle and Pharmaceutical Manufacturers Association Representative. Presentation on Light Stability Testing, August 1993.

Other Professional Activities

Seminars presented at the Division during FY 93 appear in Table 2.

Three Division chemists were assigned to one week pharmaceutical inspections at the FDA Newark District. Subsequent to these assignments, two Division analysts returned for two weeks to the Newark District to assist Compliance Branch review of laboratory data secured during inspections.

V. REFERENCES

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George C. Rhoderick, Walter L. Zielinski, and Walter R. Miller, "Gas Standards Containing Halogenated Compounds for Atmospheric Measurements", Environmental Science and Technology, 27 (13), 2849-54 (1993).

"United States Pharmacopeia," 22nd Rev., United States Pharmacopeial Convention, Inc., Rockville, MD, 1990; 8th Suppl., 1992, p. 3221. Azaperone Injection.

(7) "United States Pharmacopeia," 22nd Rev., United States Pharmacopeial Convention, Inc., Rockville, MD, 1990; 8th Suppl., 1992, p. 3249. Droperidol Injection.

(8) Anon. (1992) Pharmacopeial Forum 18, 4294-4295. Methamphetamine Hydrochloride.

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"United States Pharmacopeia," 22nd Rev., United States Pharmacopeial Convention, Inc., Rockville, MD, 1990; 8th Suppl., 1992, p. 3280. Miconazole Nitrate Cream.

(10) Anon. (1993) Pharmacopeial Forum 19, 5722-5723. Pindolol.

(11 "United States Pharmacopeia," 22nd Rev., United States Pharmacopeial Convention, Inc., Rockville, MD, 1990; 8th Suppl., 1992, p. 3301-3302. Quinidine Sulfate.

(12) Anon. (1992) Pharmacopeial Forum 18, 4327. Thiotepa.

"United States Pharmacopeia," 22nd Rev., United States Pharmacopeial Convention, Inc., Rockville, MD, 1990; 8th Suppl., 1992, p. 3318. Valproic Acid Capsules.

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 93.

Acepromazine Maleate (a)	Acetaminophen (a)
Acyclovir (a)	L-Alanine (c)
Amantadine Hydrochloride	Apraclonidine Hydrochloride
Aspirin	Azathioprine (a)
Betamethasone	Betamethasone Acetate
Bupivacaine Hydrochloride	Caffeine
Caffeine Melting Point Standard	Calcium Pantothenate
Chlorzoxazone	Ciprofloxacin
Ciprofloxacin Ethylenediamine	Clavam-2-carboxylate Potassium Analog
Clofazimine (a)	Clorsulon (a)
Alpha Cyclodextrin	Beta Cyclodextrin
Cyclomethicone 4	Cyclomethicone 5
Cyclomethicone 6	Cyproheptadine Hydrochloride
Decoquinate	Desacetyl Diltiazem HCl
Dexbrompheniramine Maleate (a)	Dexchlorpheniramine Maleate (a)
Dexpanthenol (a)	Diacetylfluorescein (a)
Diazepam	Diflunisal (a)
Digoxin	Dihydrotachysterol
Diphenhydramine HCl (c)	Ergoloid Mesylate
Estriol	Ethotoin
Ethylparaben	Ethynodiol Diacetate
Famotidine	Fluorescein (a)
Fluphenazine Decanoate DiHCl (a)	Glipizide (a)
Glipizide Related Compound A (a)	Homatropine Methylbromide, Candidate B
Hydrocortisone (c)	Hyoscyamine Sulfate
Imipramine Hydrochloride	Indomethacin (a)
Isoflurane	L-Isoleucine (c)
Isosorbide Dinitrate, diluted (a)	Ketamine Hydrochloride
L-Leucine	Loperamide Hydrochloride, Candidate B (a)

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 93. (continued)

Malic Acid (racemic)	Maltol (FCC)
Menthol	3-Mercapto-2-methylpropionic Acid
Methocarbamol (a)	Methoxyflurane
Metolazone (b)	Miconazole
Miconazole Nitrate	Molindone Hydrochloride (a)
Naloxone (a)	Naproxen (a)
Naproxen Sodium	Nitrofurantoin (a)
5-Nitro-2-furfuraldazine	Nortriptyline Hydrochloride
Oxyquinoline Sulfate (a)	Phenacetin Melting Point Standard
Phenylbutazone	Phytonadione
Pindolol	Polydimethylsiloxane (a)
Pramoxine Hydrochloride	Praziquantel
Procainamide Hydrochloride (a)	Propylene Glycol
Pyrantel Pamoate	Ranitidine Related Compound A
Ranitidine Related Compound B	Ranitidine Related Compound C
Sodium Lactate, Candidate B	Succinylcholine Chloride (a)
Sulfinpyrazone (a)	Terfenadine
Theophylline	Timolol Maleate (c)
Alpha Tocopheryl Acetate	Trihexyphenidyl Hydrochloride
Tropicamide (c)	Xylometazoline Hydrochloride

(a) Evaluated at FDA Baltimore District Laboratory.
(b) Evaluated at FDA Cincinnati District Laboratory.
(c) Evaluated at FDA Philadelphia District Laboratory.

Table 2. Seminars Presented at the Division of Drug Analysis in FY-93.

Dr. Carl Tenpas, CAChe Scientific: "Prediction and Visualization of Molecular Properties and Reactivity", October 7, 1992.

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Professor Andre d'Avignon, Department of Chemistry, Washington University, St. Louis, MO: "High Resolution 13C-1H Cross-Correlation NMR Characterization of Nandrolone Decanoate and Its Degradation Products", October 22, 1992.

Wangkan Lin, Department of Chemistry, University of Missouri - St. Louis, St. Louis, MO: "Molecular Modeling and Structural Studies of Iron (III) Complexes", October 29, 1992.

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Professor Daniel Armstrong, Head, Bioanalytical Research Institute, University of Missouri - Rolla, Rolla, MO: "Resolution and Determination of Trace Enantiomeric Impurities for Biologically Important Molecules", December 1, 1992.

Thomas Brueggemeyer, FDA National Forensic Chemistry Center, Cincinnati, OH: "Pattern Recognition Techniques and Their Application to Forensic Spectroscopy", December 10, 1992.

A. Richard Long, Director, FDA Animal Drug Research Center, Denver, CO: "Matrix Solid Phase Dispersion", December 11, 1992.

Dr. Apryll Stalcup, Department of Chemistry, University of Hawaii-Manoa, Honolulu, HI: "Control and Enhancement of Chiral Separations in HPLC: Development and Utility of a Derivatized Carbohydrate Stationary Phase", March 5, 1993.

Eric Richmond, Merck and Company, Inc., West Point, PA: "Non-Destructive Spectroscopy of Pharmaceutical Dosage Forms", April 5, 1993.

Table 2. Seminars Presented at the Division of Drug Analysis in FY-93 (continued).

Dr. William Furman, FDA Division of Drug Analysis, St. Louis, MO: "Validation of Computerized Liquid Chromatographic Systems", April 27, 1993.

Dr. Yubing Tang, Department of Chemistry, University of Missouri-Rolla, Rolla, MO: "Basic GC and HPLC Research Studies on Cyclodextrin Phases for Chiral Separations of Racemates", May 12, 1993.

Dr. Thomas O'Shea, Center for Bioanalytical Research, University of Kansas, Lawrence, KS: "Capillary Electrophoresis with Electrochemical Detection as an Analytical Tool", June 3, 1993.