

DIVISION OF DRUG ANALYSIS

U.S. Food and Drug Administration  
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Executive Summary of Accomplishments: Fiscal Year 1991

## TABLE OF CONTENTS

I. STAFF LEVEL .....	1
II. PUBLICATIONS .....	1
III. SUMMARIES OF CURRENT PROJECTS .....	2
Abbreviated New-Drug Applications;	
Analysis of Bulk Drugs .....	2
Biopharmaceutics .....	3
Digoxin .....	3
Drug Quality Assurance .....	3
Albuterol Sulfate .....	3
Cefadroxil .....	3
Conjugated Estrogens .....	3
Cross-Contamination .....	3
Desert Storm .....	4
Chloroquine tablets .....	4
Diazepam autoinjectors .....	4
Digoxin .....	4
Fenoprofen Calcium .....	4
Nitrofurantoin .....	5
Pancrelipase .....	5
Generic Drug Standards .....	5
Conjugated Estrogens Tablets .....	5
Dyazide .....	5
Fingerprinting .....	6
Generic Drug Bioequivalence Fraud Investigation .....	6
Metered-Dose Inhalers (MDIs) .....	6
Nandrolone Decanoate .....	7
Nortriptyline Hydrochloride .....	7
Prochlorperazine .....	7
L-Tryptophan .....	7
USP Reference-Standard Candidates .....	8

III. SUMMARIES OF CURRENT PROJECTS (continued)

New-Drug Evaluation .....	8
Ioversol .....	8
Niacin .....	9
Pentamidine .....	9
Surgical Scrubs .....	9
Thalidomide .....	10
IV. OTHER ACTIVITIES .....	11
Awards.....	11
Career Days .....	11
Computer Activities: Mainframe .....	11
Computer Activities: Small Systems .....	12
Cincinnati Data Acquisition and Report System .....	12
Expert Systems for Formulation Fingerprinting .....	12
DDA-NCTR Program .....	13
Fourier-Transform Infrared Spectral Library of USP Reference Standards .....	13
Glyburide .....	14
Hirudin .....	14
Laboratory Planning .....	14
Presentations .....	15
AOAC International Meeting .....	15
Bioconference on Analytical Methods Validation .....	15
International Pharmaceutical Federation .....	15
Sigma Xi .....	15
Thermal-Analysis Libraries .....	16
Training Conducted By Division Staff .....	16
Biotechnology .....	16
Saudi Arabians .....	16
STAT biotechnology methods .....	17
Visitors and guest workers .....	17

IV. OTHER ACTIVITIES (continued)	
Training Received By Division Staff .....	18
FDA Law Course .....	18
Inspections .....	18
International Industrial Pharmaceutical	
Research Conference .....	19
Interpersonal Skills Workshops .....	19
Spectra-Physics .....	19
Thermal Analysis .....	19
V. REFERENCES .....	20
Table 1. Candidate USP Reference Standards Examined	
by the Division of Drug Analysis in FY 91 .....	21

## STAFF LEVEL

The Division of Drug Analysis operated with 60.35 full-time person equivalents.

## PUBLICATIONS

The Immediate Past President of the AOAC discussed the need for "quality" measurements in the analytical sciences. Although matters of space, equipment, reagents, standards, and record keeping have been addressed, few standards exist for analytical chemists themselves. Basic requirements in core curriculum, on-the-job training, and experience in development of peer-reviewed methods of analysis are elements in the development of an individual's competency (1).

In a second article the Immediate Past President of the AOAC explored the relationship between the cost of developing and validating an AOAC method and the resultant savings to government and industry laboratories. AOAC methods are recognized in the U.S. Code of Federal Regulations and by U.S. state, Canadian federal and provincial, and other national governments. Because of this acceptance and uniformity, AOAC methods result in considerable savings for regulated industries and commerce. Time, personnel, and laboratory-support requirements for AOAC method validation and approval were also reviewed (2).

The future of the AOAC and its impact on expanding international markets were summarized by the Association's Immediate Past President. Major future challenges for the AOAC include continued method development with emphasis on the needs of the global economy, assurance of quality measurements through analyst training and education, and supply of reference standards and "check samples" (3).

The concept of "fingerprinting" pharmaceutical products through such instrumentation as high-pressure liquid chromatography, Fourier-transform infrared spectrophotometry, x-ray powder diffraction spectroscopy, and thermal gravimetric analysis was outlined. This approach should prove much more efficient than traditional methods of analysis in answering questions of fraudulent manufacturing practices, "sameness" or "differences" of formulations, drift or sudden (unapproved) changes in formulations, and subtle appearances of new impurities or degradation products (4).

The Division's bar code inventory system was described. Bar code labels are prepared and placed on all DDA inventory items. A portable bar code scanner, interfaced with a minicomputer, is used for the yearly "personal property" inventory (5).

A procedure for identification of stearic acid in pharmaceutical products by gas chromatography was presented; the Division uses this method as one way to distinguish formulations in fraud and verification programs (6). Other aspects of these programs include thermal analysis (7), Fourier-transform infrared spectrophotometry (8), physical characteristics of final dosage forms (9), analysis by x-ray powder diffraction (10), and specific chemical tests (11).

#### SUMMARIES OF CURRENT PROJECTS

##### Abbreviated New-Drug Applications; Analysis of Bulk Drugs

Fifty-eight ANDA bulk drug samples were evaluated in FY 91, eight by field laboratories and the remainder by DDA staff. Only two samples failed to satisfy the required compliance criteria (3.5%). This project has been terminated.

BiopharmaceuticsDigoxin

From a survey study (91-05) eight products have been analyzed and selected for use in bioequivalence testing at a later date.

Drug Quality AssuranceAlbuterol Sulfate

This survey study (91-06) was initiated on February 1, 1991, and 24 samples (tablets, injections, and inhalers) have been received to date.

Cefadroxil

Division personnel evaluated bulk cefadroxil product from the innovator and a potential generic supplier. The generic supplier produced cefadroxil of a different crystalline form that was consistent with cefadroxil hemihydrate, whereas the innovator product was consistent with the crystalline structure of cefadroxil monohydrate.

Conjugated Estrogens

The Division performed check analysis on three samples of conjugated estrogens tablets and confirmed that all were out of limits for dissolution as originally found by Cincinnati District Laboratory.

Cross-Contamination

This study consisted of 13 samples of various bulk drug materials collected during an inspection which found possible cross-contamination of the materials during production. Each

sample had to be tested for possible contamination with about 20 different drugs at the lowest possible detection levels. These determinations were accomplished by using two different HPLC methods with multiwavelength UV detection. Although no cross-contaminants were detected, one drug substance was found to contain unacceptably high levels of a related impurity; compliance activities have been initiated.

### Desert Storm

Chloroquine tablets. DDA chemists did dissolution testing on tablets needed for Desert Storm. We were asked to complete the work as rapidly as possible, and two analysts and a shop technician worked during one weekend, completing analysis of all samples in four days.

Diazepam autoinjectors. A DDA chemist evaluated the NDA methodology for a diazepam autoinjection system. This project was given the highest priority since the injectors were intended for self-administration by troops in Desert Storm. In addition to evaluating test methods for the bulk drug and the injection, we were asked to check the volume ejected by the autoinjector and the time required for ejection.

### Digoxin

This survey study (91-05) was initiated on February 1, 1991, and 22 samples were received in FY 91. All samples met compliance specifications.

### Fenoprofen Calcium

Check analysis of these samples for Seattle District confirmed they were outside limits for dissolution. The samples were sent to DDA because the analysis required use of 10-mesh baskets, which were not available at Seattle District.



Nitrofurantoin

Eight samples have been received from San Juan District Investigation Branch for dissolution testing and analysis of magnesium stearate content. This work is in progress.

Pancrelipase

Twelve determinations for lipase activity were made on one sample. Disintegration in gastric fluid was done to determine any loss of lipase activity for these enteric-coated pellets inside the capsules. No significant losses were observed.

Generic Drug StandardsConjugated Estrogens Tablets

Division staff examined an HPLC method proposed to the USP by the Upjohn Company. The procedure uses estropipate, equilin piperazine sulfate, and 17 $\alpha$ -dihydroequilin piperazine sulfate as standards; the latter two standards were submitted by Upjohn. We tested the method on one sample from each of three different firms; we also ran these samples by the official USP method and compared the results obtained from the two methods.

Additional investigations are underway to determine if impurities may be coeluting with other components. A Division organic chemist is attempting to synthesize piperazine sulfate salts of several known impurities for tests in the HPLC procedure. Division analytical chemists have analyzed several potassium and piperazine salts of estrone and equilin to aid in this synthesis.

Dyazide

Two DDA chemists traveled to Puerto Rico for one week to participate in the inspection of a pharmaceutical manufacturing plant and laboratory. They scrutinized manufacturing and

quality-assurance records, and observed dissolution testing being performed. They participated in discussions with the firm's management, and identified numerous problem areas which were made part of the inspection report. Samples collected before and during this inspection were examined for changes in particle size of the bulk drug substances.

### Fingerprinting

A collaborative study has been developed and is nearing implementation. The objective of the collaborative study is to validate the generic drug screening protocol which utilizes physical description, Fourier-transform infrared spectrometry, thermogravimetric analysis, and x-ray powder diffraction to characterize final drug dosage forms. This fingerprinting protocol has been adopted as part of the approval process for generic and new drugs. We are currently developing a national database of fingerprint data to support compliance activities for approved drug formulations.

### Generic Drug Bioequivalence Fraud Investigation

The Division completed the remainder of the 1,400 generic drug fraud samples in FY 91. An additional 81 samples from a follow-up inspection were received, and all of these were also evaluated. About ten samples for forensic screening were completed for the ANDA Bioequivalence Laboratory Audit program. Also, 120 ANDA Pre-Approval Forensic screen samples were received, and about 30 of these had been evaluated at the end of FY 91.

### Metered-Dose Inhalers (MDIs)

Division staff have initiated this work in conjunction with Office of Generic Drugs staff and have prepared protocols for the manufacture and testing of aerosol samples of albuterol sulfate at

the normal dosage and at 4 times the normal dosage; the metered-dose deliveries of these samples will be determined.

#### Nandrolone Decanoate

We isolated and identified two major impurities (hydroperoxides) in decomposed nandrolone decanoate; these compounds are very similar to cholestene hydroperoxides known to cause cancer. Isolation was very difficult due to the instability of the hydroperoxides. We installed a semipreparative column on a high-pressure liquid chromatography system which allows isolation of milligram amounts of impurities. We wrote a critique of a proposed USP high-pressure liquid chromatographic method for the analysis of nandrolone decanoate.

#### Nortriptyline Hydrochloride

Two samples of 75-mg nortriptyline hydrochloride capsules were found by Division chemists to be manufactured not of the same materials.

#### Prochlorperazine

A Division chemist used traditional manual techniques and a new polarizing microscope (with a photographic attachment) to show evidence of "recoating" of tablets.

#### L-Tryptophan

A DDA chemist has been assigned to study impurity profiles in L-tryptophan bulk drug and finished dosage forms. A literature search has been conducted, and the evaluation of an HPLC method for analysis is under way. One objective for this project is to identify a "fingerprint" of impurities which would characterize each material as to its manufacturing source. The identification of the source of the material has been demonstrated by staff at

the Center for Food Safety and Applied Nutrition and their coworkers. This project, which is being conducted jointly with the Center for Food Safety and Applied Nutrition, is to develop chemometric procedures to allow machine "fingerprint" matching and to investigate interlaboratory and intralaboratory variances.

#### USP Reference-Standard Candidates

Ninety-two USP reference-standard candidates were evaluated in FY 91 (Table 1). Of these, 21 samples were new-drug substances for the USP. In addition to evaluating the candidate drug substance, all proposed USP monograph methods for these new USP drug substances were validated. FDA's Baltimore and Philadelphia District Laboratories completed 25 and 8 candidates, respectively; the remainder were examined at the Division.

#### New-Drug Evaluation

Division staff completed 58 New-Drug Application method-evaluation packages (several with multiple methods) in FY 91. The majority of the evaluated methods were for new molecular entities and unique combination formulations. Seven were for AIDS-related drug products, two were for Desert Storm formulations, and four were for proteinaceous drug materials. An additional 25 NDA method evaluations are currently scheduled. Of these, samples have been received for ten evaluations and all ten are currently assigned for validation.

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

#### Ioversol

The Division analyzed about 50 lots of ioversol for four different residual solvents: formaldehyde, dimethylsulfoxide, ethylene glycol, and dimethyldisulfide. These solvents were not considered in the original NDA, and consumer complaints had been

received. Some modifications of the firm's methods had to be made to analyze for these compounds.

### Niacin

The Division has initiated a project to determine the toxicity of regular and sustained-release niacin tablets. A nation-wide survey of niacin tablets for dissolution rates, content uniformity, and impurities is anticipated.

### Pentamidine

The Division performed additional particle-size testing on this NDA, following validation of other methods in the package. The finished product is an aerosol with a specially constructed inhaler. Particle-size testing is becoming increasingly important in the evaluation and approval of many drug products, and DDA has recently acquired apparatus to perform this testing.

### Surgical Scrubs

A collaborative program was established between DDA and the National Center for Toxicological Research to evaluate the potential toxic risk of chronic exposure to topical antimicrobials.

We isolated and identified about ten impurities in a commercial solution of a common antimicrobial compound. We synthesized and purified all but one of these impurities and supplied them to Dr. Chris Long, St. Louis University, for toxicology studies; he finished the short-term (acute) studies; long-term studies are under way. We developed a gradient HPLC procedure to resolve these impurities and determined limits of sensitivity (ultraviolet spectrophotometry and electrochemistry) in preparation for development of more advanced chromatographic methods.

We purchased two milliCuries each of three  $^{14}\text{C}$ -labeled isomers of a commonly used antimicrobial compound. One milliCurie of each isomer was shipped to the Center for Food Safety and Applied Nutrition, Division of Toxicology. The staff there are studying the transport of this compound across the skin and measuring any metabolism by the skin. Working thus far only with one of the  $^{14}\text{C}$ -labeled isomers, they report strong adsorption of the compound onto the experimental apparatus, an experimental difficulty they may not be able to overcome. Taking this adsorption into account, the amounts of the compound passing through and retained by the skin are quite low but are about two orders of magnitude higher than reported by the industry.

We developed a solid-phase extraction procedure to purify and separate another common antimicrobial compound and its major metabolites from body fluids. We synthesized a deuterated isomer of the compound in preparation to synthesize the corresponding tritiated isomer for planned cell-metabolism studies. We continued analytical method development for this compound and its metabolites.

### Thalidomide

We continued to provide analytical support to the Division of Anti-Infective Drug Products by coordinating analysis of samples of thalidomide tablets and capsules from prospective suppliers. Routinely, the New Orleans District Laboratory performs assay, content uniformity, identity, and purity, while the Division of Drug Analysis performs dissolution and occasionally content uniformity.

We supplied thalidomide-related compounds and advice on our monograph tests to workers in other laboratories, and provided our monographs and methods for synthesis of DL-, D-, and L-thalidomide to several individuals and firms having interest in this drug. We also supplied information and advice to a chemist in Baltimore District Laboratory who was part of a team conducting an

establishment inspection on a U.S.A. manufacturer of thalidomide products.

### Other Activities

#### Awards

Thirty-five Division personnel were named in an FDA Group Recognition Award presented to the Generic Fraud Analysis Group for sustained outstanding performance in the development of screening procedures, analysis, and documentation of a large number of drug samples where fraud was suspected.

#### Career Days

A DDA analyst gave talks and demonstrations at several Career Fairs, presenting the idea of a career with FDA to high-school and middle-school science students.

#### Computer Activities: Mainframe

A Digital Equipment Corporation VAX 6310 computer system was acquired in December 1990. The hardware was in place and checked out by Digital Equipment Corporation engineers by the end of December 1990, and the software was installed by Greg Brolund and Mike Buster, Division of Information Systems Design, by January 8, 1991.

Selected Division personnel underwent training during January and February 1991, and a training plan for our general users was devised and implemented over the months of April, May, and June 1991. By July 1991 all DDA users were trained and using the ALL-IN-1 system. DDA personnel also received training in the 20/20 spreadsheet application.

At the end of FY 91, only the Good Laboratory Practices Manual subsystem remained on the Division's old Wang VS system. All other applications had been successfully transferred to the VAX by

DDA personnel. It is expected that the Wang VS computer system will be shut down this fall, and the Division's old Hewlett-Packard computing system will be shut down by the second quarter of FY 92.

Division staff have transferred the following applications from previously used programming languages to our new standard database language (ORACLE): paperless purchase-requisition system; database for USP Reference Standards Candidates; two databases for abbreviated new-drug substances; chemical-inventory system; HPLC column-inventory system; and GLC column-inventory system. Other applications, such as the Division's Drug Electronic Collection Report system and calibration programs used by shop personnel, were modified to make them run in our VAX environment. Division staff were successful in getting our three computer systems to "talk" with one another, making it easier to move information from the Wang and Hewlett-Packard systems to the VAX.

All of these installation activities were accomplished without shutting down the production computers while the new VAX system was being brought up -- a major accomplishment.

#### Computer Activities: Small Systems

Cincinnati Data Acquisition and Report System. A Division chemist finished development of PC-based data-acquisition hardware and software for the Cincinnati District laboratory. The system acquires data from up to four continuous-flow analyzers, processes the data into analytical results, and writes reports as continuation worksheets. After another Division chemist completed bench tests and evaluation, we delivered the system to Cincinnati District Laboratory in March 1991.

Expert Systems for Formulation Fingerprinting. We completed the program modules that allow collection of data from Perkin-Elmer and Nicolet Fourier-transform infrared spectrometers into a common PC database, thus allowing search/match operations



independent of instrument manufacturer; we prepared a comprehensive user's manual for these transfers.

We are evaluating the use of neural networks for pattern recognition of data from drug formulations. We are training a commercial PC-based program to recognize and draw conclusions from patterns in data from Fourier-transform infrared spectrophotometers and thermogravimetric analyzers. The infrared database may also be searched conventionally for the best spectral matches.

We have recommended purchase of multiple samples of several prescription drugs to allow us to gather data on lot-to-lot variability; this information will help us calibrate the sensitivity of our pattern-recognition systems to changes in drug formulations.

#### DDA-NCTR Program

A collaborative research program was established between DDA and the National Center for Toxicological Research which will combine the expertise of DDA in analytical and synthetic chemistry with that of NCTR in biochemical and molecular toxicology to investigate the metabolic profiles, toxic potential, and mutagenesis of selected pharmaceuticals of interest. This program will initially focus on the topical antimicrobials used in surgical-scrub solutions. This program is intended to provide an Agency capability for coupling advanced analytical separation and identification techniques with state-of-science metabolism and toxicology studies to provide information that is specifically relevant to the human case.

#### Fourier-Transform Infrared Spectral Library of USP Reference Standards

Students under the guidance of a DDA chemist have been preparing Fourier-transform infrared spectra of USP Reference Standard materials. Using an approved protocol, a KBr disc is

prepared with the standard material, identity of each material is confirmed, and the spectra are stored on computer disc. The library thus created may be searched using a computer program which selects the best matches with the spectrum of an unknown material. Additional information is stored in a searchable computerized database.

### Glyburide

A DDA analyst participated in a World Health Organization collaborative study of a dissolution method for glyburide (glibenclamide) tablets, an antidiabetic drug. Dissolution profiles were run on six tablets from each of five samples, one sent to us by the World Health Organization and the other four, purchased locally, representing the two products approved in the United States.

### Hirudin

A DDA chemist participated in a collaborative study of a method for hirudin, an anticoagulant protein from leeches produced by recombinant DNA techniques. The method was based on the thrombin-inhibiting activity of the hirudin, and required the use of a microtiter plate and plate reader. We made arrangements to use this equipment at St. Louis University Medical School.

### Laboratory Planning

The General Services Administration has requested that DDA vacate its present laboratory and office areas at 1114 Market Street, St. Louis. Division staff continued to review proposals for construction of our new laboratories. We have been working with GSA and with a GSA-contracted engineering firm to prepare a Solicitation For Offers for a new (leased) laboratory and office facility. DDA staff members prepared the initial space, service, and mechanical specifications. These requirements were given to

the GSA contractor, who prepared a first-draft Solicitation For Offers. This first draft and one subsequent revision have been reviewed by Division staff members, by an FDA specialist in laboratory design, and by a staff member of the National Institutes of Health, Division of Engineering. We will continue to review the plans in future.

### Presentations

AOAC International Meeting. At the 105th annual meeting, Phoenix AZ, August 1991, a Division chemist organized and chaired a symposium on Risk Management in the Laboratory Through Data Quality, and presented a paper on Selectivity Requirements and Capabilities in the Separation and Measurement of Isomeric Compounds in GC and HPLC.

Bioconference on Analytical Methods Validation. At this FDA conference, held on December 3-5, 1990, in Washington, DC, a Division chemist served on a panel charged with determining the minimum information required for method validation in the analysis of body fluids.

International Pharmaceutical Federation. At the 51st Congress of Pharmaceutical Sciences, Washington, DC, September 3-5, 1991, Division chemists presented posters on Physicochemical Requirements for Selective Separations of Isomeric Drugs, the Division's USP Reference Standard Collaborative Testing Program, and the Division's Generic Drug Fraud Screening Procedures.

Sigma Xi. At the annual FDA Sigma Xi Conference, Washington, DC, April 2-3, 1991, Division chemists presented papers on these topics: development and use of DDA's screening procedures for generic fraud samples; the bulk-drug approval process used for abbreviated new-drug applications; the USP Reference Standard collaborative-testing program; information handling for validation of drug formulations; analysis of S-adenosyl-L-methionine tablets

for isomeric purity and presence of decomposition products; determination of p-chloro-m-xyleneol and its major metabolites by high-pressure liquid chromatography with electrochemical detection; and identification of impurities in nandrolone decanoate (co-authored by a faculty member of Washington University, St. Louis).

#### Thermal-Analysis Libraries

Division staff continued to organize and maintain libraries of thermal-analysis data on USP Reference Standards. During FY 91, we added to our libraries thermal-gravimetric data for 115 standards (total is now approximately 230) and differential scanning calorimetry data for 125 standards (total is now approximately 190).

#### Training Conducted By Division Staff

Biotechnology. A one-week training program in analytical methods for biotechnology drug products was presented by a Division chemist at the Baltimore District Laboratory. In another presentation, "Bioanalytical Methods and the FDA," presented at FDA Philadelphia Biotechnology Training Program, a Division chemist discussed problems concerning assay, potency, purity, etc. for recombinant DNA protein drug products; specific methodology and case studies were also presented.

Saudi Arabians. Two groups of analysts from Saudi Arabia were at DDA for three-month training sessions on techniques of pharmaceutical analysis. Included were about two weeks of training in maintenance and repair of laboratory equipment (high-pressure liquid chromatography).

A senior DDA chemist assisted in the formulation of seven basic training modules for a project in Saudi Arabia as well as for newly hired chemists in FDA. The training modules supplement commercially available self-instruction packages. In the modules,

trainees conduct specific applications of analytical techniques (spectrophotometry, chromatography, etc.) to pharmaceutical samples in a regulatory context. The training modules have been utilized by several FDA field laboratories in their training programs for new chemists.

STAT biotechnology methods. A four-week course on techniques for the analysis of "biotechnology" drugs was presented at DDA. The course was attended by four analysts from FDA field laboratories, and included both lectures and "hands-on" training sessions in methods for the evaluation of biotechnology recombinant DNA drug products. Two DDA analysts assisted with the laboratory portions of the training and attended the lectures.

Visitors and guest workers. We hosted the following visitors, among others, during FY 91:

Alexandra Vardaluki October 1990	Ministry of Health, Madrid
Irene E. Maningas September-November 1990	BFAD, Manila, Philippines
Husain Al-Shaikh Muaid Al-Zahrani December 1990	MOC, Saudi Arabia
Fred Lofsvold March 1991	Eugene, Oregon
Paula Slate Wilson DeCamp Thomas Doyle March 1991	FDA
Claire O'Keefe Mary Hall Brenda Rice April 1991	FDA
C. L. Huang April 1991	NFLD, Taiwan

M. Kried April 1991	State of Missouri
Yasushi Takeda April 1991	MHW, Japan
Vijay Vashi May 1991	University of Tennessee, Memphis
Dr. C. H. Siregar May 1991	Indonesia
Dr. V. Das Gupta May 1991	Professor, University of Houston
Diane Smith Margaret Bell May 1991	FDA, Center for Drug Evaluation and Research
Abdulaziz Al-Jerayed Mohammed Sultan May-August 1991	MOC, Saudi Arabia
Syang Yi Su July 1991	FDA
Khoat Pham July 1991	WCG
D. J. Winters Craig Tucker Jim Casey Allen Goldberg Joseph Brucciani July 1991	FDA FDA, Atlanta District FDA, Southeastern Region FDA FDA
Marukh Khan September 1991	FDA, St. Louis Inspection Branch

### Training Received By Division Staff

FDA Law Course. Most of the Division staff attended a three-day seminar on Food and Drug law, conducted by Fred Lofsvold, a retired FDA legal expert.

Inspections. In one-week tours of duty, a Division supervisor and two senior Division chemists assisted Newark District investigators in separate establishment inspections at

Hoechst-Rousell Pharmaceutical Company, Somerville, NJ, Chase Pharmaceutical Company, Newark, NJ, Knoll Pharmaceuticals, Whippany, NJ, and Ciba-Geigy, Summit, NJ.

International Industrial Pharmaceutical Research Conference.

Two Division chemists attended the 33rd Annual International Industrial Pharmaceutical Research Conference: "Considerations in the Measurement and Control of Particles in Pharmaceuticals," Merrimac, WI, sponsored by the University of Wisconsin School of Pharmacy.

Interpersonal Skills Workshops. Five Division managers and supervisors attended these workshops in FY 91.

Spectra-Physics. The Division's two shop technicians received three days of intensive training on the maintenance and repair of Spectra-Physics high-pressure liquid chromatography equipment; as a result, our technicians are now certified by Spectra-Physics to service the Division's Spectra-Physics equipment under our five-year warranty agreement.

Thermal analysis. A DDA chemist spent three days in New Castle, DE, receiving advanced training in thermal-analysis techniques from the equipment manufacturer. Thermal analysis is an important part of our screening protocol for preapproval ANDA samples.

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Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 91.

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Alclometasone Dipropionate a	Flunisolide a)
2-Amino-5-chlorobenzophenone	Fluocinonide (b)
Amoxapine	Fluoroquinolonic Acid
Apraclonidine Hydrochloride	Folic Acid (three candidates)
3-tert-Butyl-4-hydroxyanisole	Glycopyrrolate
Caffeine Melting Point Standard	Guaiacol
Carbidopa (b)	Haloperidol (b)
Ciprofloxacin Ethylenediamine Analog	Idoxuridine (b)
Ciprofloxacin Hydrochloride	Indapamide
Clioquinol	Iodoquinol two candidates (a)
Clomiphene Citrate (b)	Isoniazid (b)
Clomiphene Citrate Related Compound A	Isotretinoin
Codeine Phosphate	Ketoprofen
Cromolyn Sodium	Lactulose
Deferoxamine Mesylate (b)	L-Leucine
Dextromethorphan (b)	Levodopa (b)
Diatrizoic Acid (b)	Levothyroxine a
Disopyramide Phosphate (b)	Lidocaine
Dobutamine Hydrochloride	Lisinopril
Econazole Nitrate	Loxapine Succinate
Enalaprilat	L-Lysine Hydrochloride
Ephedrine Sulfate	Mannitol
Ethinyl Estradiol (b)	Medroxyprogesterone Acetate (b)
Ethionamide	Mesoridazine Besylate
	[(Methylbenzoyl)-3-phenyl]-2-propionic Acid

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 91 (continued).

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Methyprylon a	Ribavirin
Miconazole Nitrate	L-Serine (b)
Mitoxantrone Hydrochloride	Sodium Fluoride
Mitoxantrone Related Compound A	Spironolactone (b)
Mitoxantrone Related Compound B	Sulfanilamide (two candidates)
Neostigmine Bromide (a)	Sulfasalazine
Nitrofurazone	Sulfathiazole
Nonoxynol 9	Suprofen
Norethindrone (b)	Terfenadine Related Compound A
Oxazepam	Thiamylal
Phenytoin (b)	Thioridazine
Physostigmine Salicylate (b)	Thiotepa
Phytonadione (a)	Tolmetin Sodium
Piroxicam	Trifluoperazine Hydrochloride (b)
Polyethylene Oxide	3-(3,4,6-Trihydroxyphenyl)- alanine
Prednisolone Hemisuccinate	
L-Proline (b)	Trimethobenzamide Hydrochloride (b)
Proparacaine Hydrochloride (b)	Tripelennamine Citrate
Pseudoephedrine Hydrochloride (b)	L-Tryptophan
Quinidine Sulfate (b)	L-Tyrosine (b)

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a Analyzed by the FDA Philadelphia District Office.

(b) Analyzed by the FDA Baltimore District Office.