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 1990

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STAFF LEVEL

The Division of Drug Analysis operated with 61.75 full-time person equivalents.

PUBLICATIONS

In a letter to members, the President of the AOAC discussed the role of the AOAC as an educator of young chemists, particularly in the areas of precise and accurate measurements, evaluation of method ruggedness, and validation of methods through interlaboratory tests. Such education is accomplished by a study of the AOAC's review processes, including its statistical procedures to evaluate analytical methods, by review of new methods by more seasoned analysts, and by watching how a newly published method fares in the "real world." Also reviewed was the overall process used by the AOAC to study and adopt new methods (1).

SUMMARIES OF CURRENT PROJECTS

Abbreviated New-Drug Applications; Analysis of Bulk Drugs

Two hundred seventy-four ANDA bulk drug samples were evaluated in FY 90; about 40 evaluations were performed by field laboratories and the remainder by DDA staff. Four samples were found out of limits (1.46%). These samples represent ANDA submissions from 79 generic drug applicants for 114 drug substances and 105 bulk drug manufacturers.

Biopharmaceutics

Carbamazepine Bulk Drug and Final Dosage Forms

We evaluated innovator and generic bulk drugs and tablets by dissolution and by x-ray powder diffraction to determine the

effect of humidity and temperature on the tablets' release rate and carbamazepine crystal structure. We noted differences among the dissolution profiles but found no direct correlation with crystallinity. We confirmed that the carbamazepine bulk drugs from the innovator and the generic sources were the α polymorph and of comparable particle size. Further, the x-ray diffraction spectra of the innovator and generic tablet products indicated some of the carbamazepine in the tablets was present in the β-polymorphic form (ca 20%).

Megestrol Acetate Dissolution

At the request of the Division of Biopharmaceutics we obtained dissolution profiles on six samples of megestrol acetate tablets. These samples were from the innovator and a generic manufacturer.

Triamterene/Hydrochlorothiazide

This work was performed at the request of FDA's New York Regional Laboratory as a follow-up to their investigations; the work was coordinated with the Division of Biopharmaceutics. We evaluated 21 batches of two formulations from generic manufacturers for compliance with content-uniformity requirements and with several dissolution procedures and their corresponding requirements.

Drug Quality Assurance

Aminophylline Compliance Survey

We evaluated 150 aminophylline products, including a variety of dosage forms and bulk-drug substances, for compliance with compendial specifications. We performed content-uniformity and dissolution studies on final dosage forms as appropriate. We found several samples of aminophylline solutions to be out of limits for pH. The district's inspection follow-up confirmed the

appropriate preservative was not included in these lots, and the product was recalled.

Cefadroxil: Residual Solvents

At the request of Compliance Branch we analyzed three bulk-drug samples of cefadroxil for the presence of dimethylformamide (DMF). We developed and validated a gas-chromatographic procedure for this study. Our analysis of the samples indicated the presence of a volatile component in all samples. However, gas chromatography-mass spectrometry showed that, although the retention times were the same, the volatile component in one sample was not DMF but acetone.

Chlorzoxazone Tablets

We conducted dissolution tests on three samples for New York Regional and Philadelphia District Laboratories. The USP monograph requires use of specialized equipment (2-liter vessels) for this product.

Clonidine Hydrochloride Compliance Survey

We evaluated 75 clonidine hydrochloride products, including a variety of dosage forms and bulk drug substance, for compliance with compendial specifications. We performed content-uniformity and dissolution studies on final dosage forms as appropriate. All samples complied with appropriate compendial specifications.

Compound Q

In March 1990 three samples of injections were collected by San Francisco District from a "buyers club" that had imported the product from China for the treatment of AIDS. We were asked to test the product for strength and impurities. Genelabs, who hold a valid investigational new-drug application for this material,

provided their methodology and reference standards. From tests by size-exclusion high-pressure liquid chromatography, ultraviolet spectrophotometry, electrophoresis, amino acid analysis, and amino acid sequencing, we concluded two of the three samples matched the Genelabs reference materials and the third sample was much more dilute than labeled.

Digoxin Certification

We evaluated thirteen digoxin samples from three generic firms and the innovator company for compendial and CFR compliance for content uniformity and dissolution.

Dissolution

We provided advice on conducting the test and detailed procedures for deaeration of dissolution media to Seattle and San Juan District Offices.

Heparin Sodium Injections

Several lots of this product were implicated in patient comas in a hospital in Bridgeport, CT. Headquarters laboratories found the heparin assay satisfactory. We examined these lots as well as other similar lots for the presence of heavy metals (none found) and by ^{13}C nuclear magnetic resonance spectrometry, ultraviolet spectrophotometry, and size-exclusion high-pressure liquid chromatography. Other than traces of benzaldehyde, the oxidation product of the preservative benzyl alcohol, no significant impurities were found in the suspect lots.

Nitroglycerin Sustained-Release Formulations

At the request of Minneapolis District Office, we ran dissolution tests on six samples of sustained-release nitroglycerin

tablets by the rotating-bottle method. All samples were in compliance.

Purina Mills Inspection

A Division chemist who specializes in computer software and hardware accompanied an FDA investigator on an in-depth inspection of Purina Mills, a large manufacturer of medicated feeds in the St. Louis area. The chemist wrote a detailed report of his observations and recommendations which contributed significantly to the overall findings of the investigation.

Theophylline

We evaluated 150 theophylline products, including a variety of dosage forms and bulk drugs, for compliance with compendial requirements. We performed content uniformity and dissolution studies on the final dosage forms as appropriate. All samples were found to be in compliance.

Generic Drug Standards

Clorazepate Dipotassium Tablets

FDA received reports that clorazepate dipotassium tablets became "fuzzy" on aging. We evaluated samples from six manufacturers in an three-month accelerated-decomposition study at three humidities and two temperatures. We assayed the samples periodically for clorazepate dipotassium and related decomposition products, and photographically documented the physical stability of these uncoated compressed tablets.

Generic Drug Fraud

In the Generic Drug Screening Program the Division dealt with 1,352 samples representing 20 types of dosage forms; the vast

majority of samples were capsules and tablets. We examined 149 different drug products from 73 generic drug companies.

We examined three types of samples: Applicant's Bioequivalence Lot (product) (APL-BIO), Innovator's Bioequivalence Lot (product) (INO-BIO), and Applicant's Current Lot (product) (APL-CUR). The samples were obtained from bioequivalence testing laboratories -- Pharmakinetics (787) and Biodecisions (156) -- and directly from the generic drug company reserve samples (409). Of the samples 623 were APL-BIO, 583 were INO-BIO (paired with APL-BIO samples), and 146 were APL-CUR.

Formulation validation comparisons were performed between the APL-BIO and INO-BIO and APL-BIO and APL-CUR samples for continuity with the approved formulation for the drug product. In addition, all APL-CUR samples were evaluated for compliance with compendial requirements, i.e., content uniformity and dissolution as appropriate.

At the request of the New York Regional Laboratory, we evaluated 32 generic drug samples from the same firm for compliance to compendial specifications. The samples included 12 final dosage products, the majority being combination formulations. Content uniformity and dissolution studies were performed, and all samples satisfied the appropriate product specific requirements.

Because of the potential for criminal prosecutions, we instituted several precautions for all fraud samples. We created a separate, highly controlled storage area for these samples. We instituted testing protocols which required that no analyst have in his/her possession more than one uncharacterized sample at one time; although these protocols slowed our analytical throughput, we reduced the potential for sample mix-up essentially to zero. In addition, we tightened our review procedures and required each "no action" decision to be reviewed and signed off by at least three persons.

All of these samples were logged into our information systems, physically characterized, and processed through our screening procedures: Fourier-transform infrared spectrometry and thermal gravimetric analysis. Based on these screening procedures we were

able to distinguish over 90% of the samples as different, i.e., not requiring further analysis. Approximately 200 of the unresolved pairs were submitted to x-ray powder diffraction analysis to determine if this technique could be used to resolve them; unfortunately, in these instances it could not. There remain approximately 60 unresolved samples; these are being examined by high-pressure liquid chromatography with diode-array detectors to determine if this technique can differentiate them.

From our inventories, we supplied over 70 primary and secondary reference standards to the field laboratories involved in drug fraud investigations.

As a result of this laboratory work, there have been three recalls and numerous follow-up investigations. As an outgrowth of this effort to use physical chemical measurement data to determine whether samples are the same or different, we have established a common data format for several instrumental techniques (see Expert Systems and Spectral Searches, later.)

Surgical Scrubs

We continued development of methods (gas chromatography with electron-capture detection and high-pressure liquid chromatography with electrochemical detection) capable of analysis at the level of nanograms per milliliter or lower. We synthesized highly pure reference standards of certain antimicrobial compounds and metabolites. We identified eight major impurities in a commercial antimicrobial solution and synthesized small amounts of most of these impurities. We also carried out decomposition studies by subjecting solutions of an antimicrobial to light and heat.

We expect to contract for preparation of radiolabeled isomers of an antimicrobial compound and have developed simple laboratory tests to verify the position of ^{14}C in the isomers.

United States Pharmacopoeia Reference Standards

We evaluated 42 USP Reference Standard candidate samples in FY 90; of these, 33 were examined by the Division and nine by FDA District Laboratories (Table 1). Twenty-three of the candidates are new USP drugs and, in addition to evaluating the suitability of the candidate samples, we validated the proposed USP monograph methods.

We developed and submitted a set of improved monograph tests for nandrolone decanoate bulk drug. Included were improved normal-phase high-pressure liquid chromatographic methods (assay, impurities) and thin-layer chromatographic methods (impurities). We are currently evaluating a high-pressure liquid chromatographic procedure proposed by the USPC in Pharmacopoeial Forum.

We reviewed and commented on eight comments or proposals for monograph changes. We made approximately 15 suggestions for changes or improvements in existing monographs, based on our analytical findings.

New-Drug Evaluation

New-Drug Application methods were evaluated for 31 new molecular entities, new esters and/or salts, or unique combination products. Of these, five evaluations were completed by the field (three at Philadelphia District Laboratory and two at Baltimore District Laboratory) and the remainder at the Division. Five evaluations were supplemental method validations in the above product categories.

There were sixteen products composed of new molecular entities, four AIDS-related drugs products, and three proteins and/or peptides. Several of the products involved unique delivery systems, including aerosols and sustained-release implant products.

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

S-Adenosyl-L-Methionine Sulfate

This product is formulated as the p-toluenesulfonate salt in tablets. The material exists as epimers, one of which is much more potent than the other. An NDA Review Chemist asked Division staff to examine several lots of tablets; some of the tablets were badly discolored.

We used an improved version of a published high-performance liquid chromatographic method and a new nuclear magnetic resonance procedure codeveloped with a faculty member at Washington University, St. Louis. Both methods gave closely agreeing estimates of the amount of active epimer present. The nuclear magnetic resonance method gave the definitive results and allowed use of an easily purified, commercially available external standard, a definite advantage over the HPLC method.

Another high-pressure liquid chromatographic procedure, developed at the Division, was used to measure impurities due to hydrolytic decomposition. Results ranged from excellent through badly decomposed, depending on storage conditions and age of samples.

Ioversol Bulk Drug and Final Dosage Form

We analyzed 52 lots of ioversol bulk drug and 12 final dosage forms for residual solvent and volatile decomposition material. These included ethylene glycol, dimethylsulfoxide, chloroform, and dimethyldisulfide. Gas-chromatographic and liquid-chromatographic methods proposed by the innovator were modified and validated for the study.

Lampit Product Evaluation

At the request of the Centers for Disease Control, and coordinated through the Office of New Drug Evaluation, we evaluated two samples of Lampit, an INV drug product, for possible impurities. Since no reference material was available, we isolated and

purified the active drug substance from samples of the tablets. We developed and validated high-performance liquid-chromatographic methods to separate decomposition products; we prepared reference decomposition materials by chemically decomposing our purified reference material. Our analysis of the Lampit tablets showed no significant impurities related to the active drug substance.

Thalidomide

We continued to provide analytical support to the Division of Anti-Infective Drug Products by coordinating analysis of samples of thalidomide tablets from prospective suppliers in Mexico and capsules filled with bulk drug commercially synthesized in the U.S.A. Routinely, the New Orleans District Laboratory performs assay, content uniformity, identity, and purity, while the Division of Drug Analysis performs dissolution. Due to a heavy workload at New Orleans District, DDA performed all monograph tests for one lot of thalidomide capsules in September 1990.

We synthesized additional quantities of highly pure D- and L-thalidomide. 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 revised the monograph dissolution test by addition of a surfactant to the medium. We certified the second lot of thalidomide reference standard (FDA RS, Lot B); Lot A has been consumed.

Other Activities

Awards

A DDA chemist received a $1,500 cash award in recognition of continuing extraordinary efforts on behalf of DDA and FDA in support of various programs for training of visiting scientists from foreign countries.

Another DDA chemist received a $500 cash award in recognition of continuing efforts in representing FDA at various Career Days and Career Fairs sponsored by local schools and the local ACS chapter.

An employee at the Division received recognition for 40 years of government service.

The St. Louis Metropolitan Federal Women's Program Council presented a Division employee with a Federal Women's Program certificate of recognition in the Supervisor Award category, and presented the Division with a Federal Women's Program certificate of recognition in the Agency Award category.

Community Service

Two DDA chemists continued to discuss their work at "career days" and high-school participation programs, a service they have performed for many years.

Computer Activities

Mainframe. We initiated and completed a systems-analysis study of DDA's purchasing and receiving procedures. We began to design an Oracle-based application to integrate purchasing, receiving, and inventory control. We developed FORTRAN programs to aid in tracking our employee's time and attendance. We completed development and testing of a bar-coded personal-property inventory system. A VAX Model 6310 computer was ordered to replace our Hewlett-Packard 1000 and Wang VS 65 computers.

Small Systems. We worked closely with Philadelphia District staff in their evaluation of the Division's electronic drug collection report. We developed, in Oracle, an application that runs on a personal computer to control the Division's microcomputer resources.

Cincinnati Data Acquisition and Report System. The overall goal is to provide Cincinnati District Laboratory with a personal-computer system to acquire data from continuous-flow analyzers and produce laboratory worksheets. It is part of a larger project to develop computerized laboratory databases (collection reports, worksheets, etc.) throughout FDA.

We received LabPro hardware and software designed to acquire and store data from multiple Hewlett-Packard 3396A integrators and have written custom software to acquire data from continuous-flow analyzers through the integrators and to produce summary worksheets (continuation pages) in the format requested by Cincinnati District Laboratory. We expect to make use of these systems in our own laboratories when our Hewlett-Packard 1000 minicomputer is replaced.

Expert Systems and Spectral Searches. The goal is to develop computerized systems to help chemists examine instrumental data on drug formulations -- the active and inactive ingredients of tablets, capsules, etc. We developed programs to translate digitized infrared spectra from Perkin-Elmer and Nicolet spectrometers and thermogravimetric data from DuPont analyzers into standardized computer databases; we are also coding programs to search and match sample data against reference-standard data or data from other samples. Evaluation of three commercially available software packages for spectral searches was completed; although suitable for infrared spectra, none can handle thermal gravimetric data. When this work is finished, we hope to develop "expert systems" to help chemists identify similarities or differences among thousands of different commercial drug formulations.

Dexfenfluramine

Division staff previously supplied samples of dextro and levo enantiomers of fenfluramine to the NIDA Addiction Research Center, Baltimore, for use in their research work (2). The staff at the

NIDA Addiction Research Center prepared a paper for publication regarding the relative biological activity of the enantiomers, and we contributed a write-up of the resolution of racemic fenfluramine to this paper.

Laboratory Planning

The Division of Drug Analysis will leave its current facilities sometime within the next one to three years. We spent a significant amount of time planning for the move; we designed space and layout, and developed facility requirements. We consulted with a National Institutes of Health expert on laboratory design to assist in the development of specifications for our new facility.

Presentations

We presented a poster on a portion of the Surgical Scrubs project at the national ACS Meeting in St. Louis, November 1-3, 1989.

Training Conducted By Division Staff

FDA Drug Forensics Course. Three DDA staff members presented material at the FDA Field-sponsored course on forensic methods in drug analysis. We gave five presentations detailing the procedures developed and utilized for the screening of approximately 1,350 drug-fraud samples.

Saudi Arabian Medicinal Program. A DDA chemist was detailed to Saudi Arabia for six months to support the Saudi Arabia medicinal program. While there, the chemist traveled to each of the three laboratories and provided advanced training in medicinal-product analyses, sample collection, and the maintenance and repair of laboratory instruments.

STAT Program. Four FDA field chemists were detailed to DDA for one month of extensive hands-on training in analytical methods for biotechnology drug products. We gave more than 30 hours of formal presentations on the theory, principles, and applications of chromatographic and electrophoretic techniques. We utilized the remaining time for hands-on laboratory evaluation of these methods with authentic recombinant DNA-derived proteinaceous drug products.

Training Modules. We completed a series of training modules to introduce or refresh analysts on how to perform various analytical techniques (high-pressure liquid chromatography, gas chromatography, ultraviolet/visible spectrophotometry, etc.) at the level routinely required for USP testing. The preparation of these modules was funded in part by the U.S.-Saudi Arabian Joint Economic Commission for use in FDA and in training programs at King Saud University in Saudi Arabia. Currently, these packages are in use in the Mid-Atlantic Region and DDA.

Visitors and Guest Workers. We hosted the following visitors among others, during FY 90:

Yisheng Chen November 1988-January 1990	WHO People's Republic of China
Soo On Woo October 1989	National Blood Center, Singapore
Zhu Ji Guang accompanied by Su Ling Yang Ji Can Zeng Keng Fu Jun Yi Zhao Li Li October 1989	General Secretary, Commission of the Chinese Pharmacopoeia People's Republic of China

Dr. Takeda October - November 1989	National Institute of Hygienic Sciences, Tokyo, Japan
Dr. Mitsuru Uchiyama December 1989	National Institute of Hygienic Sciences, Tokyo, Japan
Erick Tsi Tee Suen Ting-Guang Shyu Ber-Lin Chang Chung-Hwei Lin June 1990	National Laboratories for Foods and Drugs Taipei, Taiwan Republic of China
Ada Bello	FDA Philadelphia District Office
Franklin Russell	FDA Atlanta Regional Laboratory
James Stewart Sylvia Yetts July-August 1990	FDA Dallas District Office FDA Dallas District Office
Gerald Mossinghoff August 1990	Pharmaceutical Manufacturer's Association
William Grosse Louise Henry George Mattox Robert Sieck Gerald Wallace August 1990	Eli Lilly
Irene Maningas September-November 1990	Bureau of Foods and Drugs Manila, Philippines

REFERENCES

(1) Layloff, T. P. (1990) Referee 14(1), 2. Letter from the president.

(2) Division of Drug Analysis, Executive Summary of Accomplishments, Fiscal Year 1989, p. 6.

Table 1. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 90.

Albuterol	Homatropine Methylbromide[b]
Albuterol Sulfate	9-Hydroxypropantheline Bromide
Alprazolam[a]	Hydroxystilbamidine Isethionate
Benzonatate[b]	Levobunolol Hydrochloride
2-(4-Biphenylyl)propionic Acid	Malathion
Butabarbital	Mefenamic Acid
Butoconazole Nitrate	Meperidine Hydrochloride
Carbomer Copolymer	Miconazole Nitrate[c]
Chlordiazepoxide	Norfloxacin
Cisplatin	Phensuximide[b]
Desacetyl Diltiazem Hydrochloride	Pimozide
Deslanoside	Terfenadine (two candidates)
Dihydrocodeine Bitartrate	Thimerosal[a]
Diltiazem Hydrochloride	Transplatin
Diltiazem Hydrochloride[b]	Tretinoin
Disodium Guanylate	Triazolam[a]
Enalapril Maleate	Trientine Hydrochloride
Ethchlorvynol	3-(3,4,6-Trihydroxyphenyl)-alanine
Famotidine	Tubocurarine Chloride[c]
Flurbiprofen	Vitamin A
Flurbiprofen Sodium	

[a]Analyzed by the FDA Philadelphia District Office

[b]Analyzed by the FDA Cincinnati District Office

[c]Analyzed by the FDA Baltimore District Office.