FY 86

DIVISION OF DRUG ANALYSIS

U.S. Food and Drug Administration
1114 Market Street, Room 1002
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Executive Summary of Accomplishments: Fiscal Year 1986

Staff Level

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

Publications

Papers written or coauthored by Division of Drug Analysis personnel appeared as journal articles (1-9) and an FDA publication (10).

Pharmacy "Mail-In" Program

Through a voluntary program, pharmacists submit samples from their shelf stock for stability testing at the Division. Results from six such studies were published in FY 86.

Betamethasone Sodium Phosphate Injection, Hydrocortisone Sodium Phosphate Injection, and Prednisolone Sodium Phosphate Injection. Fifty-eight samples (two manufacturers) were analyzed for strength, identification, pH, and related impurities. All of the hydrocortisone sodium phosphate injections and prednisolone sodium phosphate injections met USP requirements for strength and pH. Assays of the betamethasone sodium phosphate injections yielded results that were in compliance with the manufacturer's strength and pH limits; there are no USP requirements for betamethasone sodium phosphate injection. All samples were within USP limits for related free steroids. All of these types of injection appear to be stable after storage under actual marketplace conditions (7).

Epinephrine Injection. Two hundred and fifty four samples (ten manufacturers) were analyzed for strength, identification, d-isomer content, related impurities, pH, total acidity, and physical condition. Twenty-three samples did not meet USP requirements for epinephrine strength. Four of these samples were still within their expiration dates and seven had no expiration dates, indicating they were manufactured before 1975. An additional 19 samples did not meet USP requirements for total acidity. Some samples were found to be racemic; it appears that the racemic mixture originates from using d,l-epinephrine as the starting material rather than from racemization during shelf life. Epinephrine injections generally appear to be stable within their expiration dates (6).

Lidocaine Hydrochloride and Epinephrine Injection. Two hundred and twenty samples (four manufacturers) were analyzed for strength, identification, pH, and physical condition. Six samples failed to meet USP requirements for strength of epinephrine, but all six had passed the expiration dates. Of the 62 samples that were analyzed for d-epinephrine, approximately 95% had less than 5% d-isomer present. Only one sample had greater than 10% d-isomer present, and this sample had a low epinephrine content (26%) and had passed the expiration date. In general, such injections appear to be stable after storage under actual marketplace conditions (5).

Pilocarpine Hydrochloride and Pilocarpine Nitrate Ophthalmic Solutions. Two hundred and fifty-two samples (11 manufacturers) were analyzed for strength, identification, pH, and isopilocarpine and pilocarpic acid impurities. All samples of pilocarpine nitrate met USP requirements. Eight samples of pilocarpine hydrochloride had units that exceeded the USP upper limit for strength. All of these samples were in 1- and 2-mL bottles. The amount of isopilocarpine found ranged from 1 to 6.4% and the amount of pilocarpic acid from 1.5 to 10.1%. Although pilocarpine salts in ophthalmic solution decompose into isopilocarpine and pilocarpic acid under various conditions of storage, an amount of pilocarpine is maintained that is within the compendial limits. However, there is a problem of evaporation from some of the 1- and 2-mL containers in which this product is supplied (8).

Prednisone Tablets. One hundred and seventeen samples (18 manufacturers) were analyzed for content uniformity, strength, identification, dissolution, and the presence of other steroids. All samples met USP requirements for content uniformity and strength. Four samples failed to meet USP requirements for dissolution. Prednisone tablets appear to be stable when stored under actual marketplace conditions (3).

Reserpine Injections and Tablets. Ninety-three samples of reserpine injections (three manufacturers) were subjected to tests for identification, pH, presence of other alkaloids, presence of 3,4-dehydroreserpine, and strength; 51 samples of reserpine tablets (12 manufacturers) were examined for identification, presence of other alkaloids, presence of 3,4-dehydroreserpine, strength, and content uniformity. All samples of reserpine injections met USP requirements. Two samples of reserpine tablets representing one lot each from two manufacturers failed to meet USP requirements for content uniformity. Reserpine injections and tablets appear to be stable under actual marketplace conditions (1).

Vitamin E Injection

In 1984 a new type of aqueous Vitamin E injection was introduced into commerce. The product was designed for intravenous injection and contained high levels of surfactants (ca 90 mg of Polysorbate 80 and ca 10 mg of Polysorbate 20 per mL) to hold ca 25 mg of Vitamin E per mL in solution. (Older formulations for intramuscular injection use oil for this purpose.) The Division of Drug Analysis and the Elemental Analysis Research Center (Cincinnati) analyzed the aqueous injection for extraneous materials. Separations by distillation and chromatography, and analyses by ultraviolet spectrophotometry, mass spectometry, and inductively coupled plasma spectrometry revealed the presence of isopropyl alcohol, dibutylamine, N,N-dimethylcyclohexylamine, 2-mercaptobenzothiazole, and zinc, all but the first arising from the rubber stoppers used in the product containers (9).

Estradiol, Estradiol Valerate, and Estrone

Division staff published a high-pressure liquid chromatographic method for the analysis of these three estrogens (10).

Summaries of Current Projects

Abbreviated New Drug Applications -- Analysis of Bulk Drug Substances

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

New Drug Applications -- Method Validation

Forty-three method-validation packages were completed by the Division in FY 86.

Generic Drug Standards

Seventy-nine candidates for USP Reference Standards were examined at the Division in FY 86 (Table 2).

Reports on the evaluation and development of compendial monographs for digoxin and digitoxin were published in the Pharmacopeial Forum (2, 4).

Quality Assurance

Three Drug Product Surveillance studies were completed in FY 86 (Table 3).

The "mail-in" program is designed to study the stability of drugs under actual market conditions; it was continued in FY 86 in cooperation with the American Society of Hospital Pharmacists. Table 3 shows the number of samples analyzed and the percentages of defective batches for the drug studies that were completed in FY 86.

An unusually large defect rate was found for samples of prochlorperazine edisylate (23.8%). All of the defective samples were from two of the three surveyed manufacturers and were subpotent. A review of the analytical data revealed that the subpotency was due to photolytic degradation by ambient light in the pharmacies, which occurs when the pharmacist opens the multiunit package, removes whatever is needed at the time, and then places the remaining units on a shelf in the pharmacy without replacing the protective covering. The manufacturer who had no failing samples distributed the product only in individual light-protected units. All of the original packages of the subpotent products carried warnings about the light sensitivity of the product. By comparison, no defective products were found in the intact multiunit packages. The manufacturers were notified of this pharmacy-handling problem and were urged to change their packaging to reduce its occurrence.

The Division of Drug Analysis performed over 14,930 analyses on 1,365 batches of drugs in FY 86. Thirty-one batches (2.3%) failed to meet the compendial or FDA-imposed requirements for the products. The number of defective batches in each of the program areas and the reasons for the classification as defective are shown in Table 1.

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

Diatrizoate Meglumine and Diatrizoate Sodium Injection. FDA received consumer complaints of unusually high incidence of allergic reactions and a fatality during use of certain lots of these products. Samples of one lot from each of two manufacturers were sent to the Division to be examined for impurities. Our examination of the products by high-pressure liquid chromatography (HPLC) with ultraviolet detection showed the presence of small amounts of 5-acetamido-3-amino-2,4,6-triiodobenzoic acid, a known impurity expected from hydrolysis of diatrizoic acid; no other significant aromatic impurities were seen. Our examination of both products by thin-layer chromatography showed

no other impurities at significant levels. We conducted decomposition studies -- hydrolytic (aqueous reflux) and photolytic (ultraviolet irradiation) -- on one of the products. Three impurities were formed, but none of them were found in either of the untreated products.

Phenothiazine Sulfoxides. Division staff extended their previously published method for the synthesis of thioridazine sulfoxide to permit the preparation of reference standards of the sulfoxides of chlorpromazine, perphenazine, prochlorperazine, and promethazine. These standards allowed the use of HPLC to identify and measure impurities in samples of tranquilizers received in Drug Product Surveillance studies.

Thalidomide. In early 1986 the Division was asked to prepare monographs containing quality-assurance tests for thalidomide bulk drug and tablets, and to synthesize and purify sufficient thalidomide for use as a reference standard. The monographs and reference standard are needed to control the quality of thalidomide tablets purchased for use at the Hansen's Disease Center, Carville, Louisiana, and in other Investigational New Drug projects.

Tolazamide. The Division began research on this drug in the summer of 1985. At first we concentrated on a sample of bulk drug, received under the Abbreviated New Drug Application program, which failed the USP XXI ultraviolet (UV) absorptivity requirement. After extensive testing, we concluded that the USP test was adequate and in fact had revealed an impurity in the bulk drug.

Of greater interest, high-pressure liquid chromatograms revealed that ethanol solutions of initially pure standard tolazamide decomposed over several weeks to give rather high levels (ca 3%) of the N-nitrosamine decomposition product (N-nitrosohexamethyleneimine, NHMI), a known carcinogen. Shortly thereafter, we were asked to develop methods of analysis for NHMI at the parts-per-billion level in bulk drug, and later, in tablets.

In the fall of 1985, experiments demonstrated that the NHMI could arise through decomposition of tolazamide itself. A series of studies through the winter and spring of 1986 showed that the decomposition could arise through a series of solution equilibria, and thus that analyses of tolazamide (bulk drug or tablets) at the parts-per-billion level could only be approximations because formation of such small amounts could rapidly occur in solutions of initially pure drug.

Other significant research during this time included installation and optimization of a Thermedics Model 610 Thermal Energy Analyzer detector for gas chromatography (this detector features a highly specific "nitrosamines" mode); preparation of reference standards of the N-nitrosamines of homopiperidine, 2,2,6,6-tetramethylpiperidine, and morpholine, as well as ca 15 g of NHMI itself; stability studies on these standards in various solvents and storage conditions; an extensive study of the stability of tolazamide in aqueous ammonia, a solvent contemplated for use in sample cleanup but subsequently abandoned (three of the decomposition products were identified); and analysis of bulk tolazamide from five manufacturers for the relatively nontoxic impurity p-toluenesulfonamide (results ranged from less than 0.1 to 1.3 parts per thousand).

In the summer of 1986, Division staff prepared and presented to headquarters staff a seminar on the analysis and decomposition of tolazamide. From this group discussion, the decision was made to continue research on methods of analysis for nitrosamine in tolazamide bulk drug and tablets at the parts-per-billion level. This work initially included HPLC with UV detection and gas-liquid chromatography with detection via thermal energy analysis; the latter technique is now preferred for analysis of tablets.

DDA chemists reviewed several methods for measuring the amount of NHMI in tolazamide bulk drug and selected and validated a procedure that used a hexane extraction followed by an HPLC determination. This method, along with the FDA-imposed limit for NHMI, was sent to all applicants as an approved procedure for monitoring this impurity. All current production of the drug substance is being tested for the nitrosamine with a limit of 100 parts per billion.

Biopharmaceutics

The Division conducted no work under this topic during FY 86.

Other Activities

Automatic sample preparation. The Division received a second Automatic Sample Preparer (ASP II) from the Winchester Engineering and Analytical Center. The ASP II automatically prepares solutions of tablets or capsules suitable for introduction to an automatic analyzer with the Division's Robotic Liquid Sampler (RLS). Division staff made several electrical and mechanical modifications to the ASP II to increase its reliability, and it is now in routine use. A second RLS was fabricated and placed in the laboratory. These devices have significantly reduced the amount of manual labor needed to prepare samples for analysis.

Computer Activities. Division staff wrote a new computer program for general inventory and location of laboratory equipment and chemicals. To date, on-line search capability has been accomplished for the Division's USP reference standards, excipient standards, gas chromatographic columns, high-pressure liquid chromatographic columns, and liquid reagents and solvents. Data entry for the Division's secondary drug standards is now in progress.

The installation of programs and interfaces for on-line acquisition and processing of data from Waters high-pressure liquid chromatographs was completed; worksheets may now be generated automatically by the computer, with minimal manual data entry. Eight additional Waters Data Transfer Modules were received and are being converted for use with the new programs.

A menu-driven, computerized management-information system was developed for administrative managers, line supervisors, and laboratory team leaders. Information on the status of samples is now available in a more timely manner without the need of special programs for every ad hoc request. Work is continuing on the use of bar-code labels for sample control and property inventory. An in-house course on the use of the Hewlett-Packard Command Interpreter file-management system was conducted for the benefit of all users of the System 1000. Experiments in intersystem communications were continued, and we are now able to transfer data files between the Hewlett-Packard 150 personal computer and the Hewlett-Packard 1000 computer, and between the Hewlett-Packard 150 personal computer and the Wang OIS system.

Software For Small Computer Systems. Division staff wrote programs to allow data transfer from a voltammetric analyzer (Princeton Applied Research Corporation, Model 384B) and a Hewlett-Packard Model 85 personal computer. The software also allows control of the model 384B by the Model 85, and off-line processing of voltammetric data.

Further programming has provided an automatic titration system for use primarily for the analysis of samples received under the ANDA and New Drug Application programs. The system is comprised of a standard combination electrode and pH meter for obtaining the potentiometric data and a Brinkman Metrohm Dosimat for titrant delivery. These units are controlled by an Apple II-E personal computer, which provides system integration, data reduction and storage, and documented reports. Analysis by automatic or dead-stop endpoint detection is possible, and routines are provided for the standardization of titrant and determination of bulk drug and composited tablet samples.

Transfer of Surplus Equipment. In the fall of 1985, the Division of Drug Analysis received several dozen assorted laboratory instruments from another government laboratory. Over the next few months, shop personnel inspected, repaired, and installed these instruments in laboratory areas, a major and successful accomplishment.

Presentations. Division staff presented two papers at the AOAC Spring Workshop in Seattle. One described the Division's Robotic Liquid Sampler and its application in automatic sample preparation and analysis; the other outlined the programs developed to accept data from a Waters HPLC system and convert them to worksheets under computer control.

Two Division chemists participated in the 1986 Food and Drug Administration chemist courses given at the Illinois Institute of Technology in Chicago, Illinois. Their topics covered the Division's Robotic Liquid Sampler and the use of the Hewlett-Packard 1040A HPLC detector in method development and identification of impurities in drug samples. Both devices were demonstrated in the laboratory.

References

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(8) Kreienbaum, M. A.; Page, D. P. (1986) Amer. J. Hosp. Pharm. 43, 109-117. Stability of pilocarpine hydrochloride and pilocarpine nitrate ophthalmic solutions submitted by U.S. hospitals.

(9) Wells, C. E.; Juenge, E. C.; Wolnik, K. (1986) J. Pharm. Sci. 75, 724-725. Contaminants leached from rubber stoppers into a water soluble vitamin E intravenous injectable product.

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Table 1. Defective Batches Found in Each of the Program Areas at the Division of Drug Analysis in FY 86.

Defect	Program Area	
	Drug Product Surveillance	ANDA
Strength	0	16
Content Uniformity	0	
Dissolution	0	
Other[a]	0	15
Totals	0	31

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

Table 2. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 86.

Acetaminophen

Acetohydroxamic Acid

N-(Aminocarbonyl)-*N*-[([5-nitro-2-furanyl]-methylene)-amino]-glycine

alpha-Aminopropiophenone HCl

Amitriptyline HCl

Betaine HCl

Betamethasone Sodium Phosphate

Biotin

4,4-Bis(4-(*p*-chlorophenyl)-4-(hydroxypiperadino))-butyrophenone

Brompheniramine Maleate

Bumetanide (and related substances)

- Butyl 3-(butylamino)-4-phenoxy-5-sulfamoyl-benzoate
- 3-Nitro-4-phenoxy-5-sulfamylbenzoic acid

Butorphanol Tartrate

Carisoprodol

Cholecalciferol

Clorazepate Dipotassium

Codeine N-Oxide

Codeine Sulfate

Crotamiton

Cyclophosphamide

Dexbrompheniramine Maleate

Diazepam (and related substances)

- 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzo-diazepin-2-one (limit test)
- 2-Methylamino-5-chloro-benzophenone (limit test)

Digoxin

Dihydrotachysterol

3,3-Di-3-pyridyl-2-butanone

Docusate Sodium

Dried Aluminum Hydroxide

Dried Aluminum Hydroxide Gel

Ergonovine Maleate

Ergotaminine

Estradiol Valerate

Ethosuximide

Fluocinolone Acetonide

Table 2. Candidate USP Reference Standards Examined by the Division of Drug Analysis in FY 86 (continued).

Fluocinonide

Gentisic Acid Ethanolamide

Glycine

Guaiacol

Hydroxypropyl Cellulose

Imidurea

Indomethacin

Isosorbide Concentrate, Lot H

Leucovorin Calcium, Candidates A and B

Levothyroxine

Malic Acid (racemic)

Mazindol

Medroxyprogesterone Acetate

Methyldopate HCl

Nalorphine Hydrochloride

Nandrolone Phenpropionate

Naproxen

Nifedipine (and related substances)

Dimethyl 4-(2-nitrophenyl)-2,6-dimethyl-pyridine-3,5-dicarboxylate (limit test)

Dimethyl 4-(2-nitroso-phenyl)-2,6-dimethyl-pyridine-3,5-dicarboxylate (limit test)

Nitroglycerin

Oxycodone HCl

Padimate O, Candidate B

Phenacetin, Lot G-5

Phosphatidylcholine

Pindolol

Polydimethylsiloxane

Prednisolone Triethylammonium Phosphate

Primaquine Phosphate, Candidate B

Procainamide HCl

Quinine Sulfate

Quininone

Salicylic Acid

Sulfanilamide (melting-point standard)

Sulfasalazine

Tocainide Hydrochloride

Trihexyphenidyl Hydrochloride

Trioxsalen

Trimethobenzamide HCl

Triprolidine HCl Z-isomer

L-Tyrosine

Vitamin A

Table 3. Drug Product Surveillance Studies Completed at the Division of Drug Analysis in FY 86.

This table presents results of laboratory findings and includes the percentage of all types of defects observed. These percentages do not necessarily reflect the quality of all the drugs on the market since some of the studies are conducted on drug categories in which high defect rates are suspected.

Study No. and Name	Batches Analyzed	Defective Batches, %[a]
84-58 Adrenocorticosteroids	458	0.2
85-02 Chlorpheniramine	115	6.1
85-51 Theophylline	115	0
ASHP-FDA Mail-In Program:		
Fluphenazine Hydrochloride	33	0
Prochlorperazine Edisylate	63	23.8
Quinidine Sulfate	45	0
Thiopental Sodium	31	0
Trifluoperazine Hydrochloride	37	0
Triflupromazine Hydrochloride	7	0

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