

CENTER FOR DRUG ANALYSIS

U.S. Food and Drug Administration
1114 Market Street
St. Louis, MO 63101

Executive Summary of Accomplishments: Fiscal Year 1983

Staff Level

The Center operated with 43 full-time personnel.

Publications

Papers written or coauthored by Center personnel appeared as journal articles (1-11) and FDA publications (12-18).

Drug Quality Assurance

In a recent survey of aspirin tablets, Center personnel found several unknown impurities (in addition to the common decomposition product, salicylic acid). The discovery of these previously unreported impurities led to a study of the thermal decomposition of aspirin. When pure aspirin, alone or mixed with common tablet excipients, was heated in the dry state, it formed decomposition products whose properties matched those of the impurities found in certain samples of aspirin tablets. The identities of the impurities (linear oligomeric salicylate esters) were confirmed by high-pressure liquid chromatography (HPLC), ultraviolet, infrared, and nuclear-magnetic-resonance spectra, and elemental analyses (4).

In preparation for the current study of epinephrine injections, Center personnel prepared and purified reference standards of adrenochrome and adrenolutin, which are colored oxidation products of epinephrine. To separate, identify, and measure the purity of these compounds, new HPLC and thin-layer chromatography (TLC) techniques were developed (3).

In support of other Drug Quality-Assurance studies, HPLC methods were developed for acetaminophen in combination with codeine phosphate in tablets and elixirs (15) and for mixtures of guaifenesin, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, brompheniramine maleate, and codeine phosphate in elixirs (16). Semiautomated continuous-flow methods were reported for conjugated estrogens or esterified estrogens in tablets (12) and for phendimetrazine tartrate in capsules or tablets (14). A TLC identification procedure was provided for local anesthetics (13).

Biopharmaceutics

The Center continued to study the factors that cause variation in results when prednisone tablets are tested for dissolution by the paddle method (United States Pharmacopeia (USP) Apparatus 2). Two additional papers in the series were published. One describes the poor performance of the USP disintegrating and nondisintegrating calibrator tablets, the failure of the USP suitability test to measure actual equipment suitability, and the desirable characteristics of tablets intended for use as "calibrators" or performance standards (7). The second paper details the effect of air dissolved in the dissolution medium, gives methods to evaluate the magnitude of the effect on a given tablet product, and describes several preferred techniques for deaeration of dissolution media (8).

In 1979, the Center was assigned the task of developing methods of analysis for thioridazine and its major metabolites in human blood plasma. At that time, an in vivo bioavailability study was planned in which personnel at a medical university were to administer the solutions, tablets, or capsules and draw blood samples, and Center personnel were to perform the analyses of the blood samples.

Thioridazine is rapidly metabolized to several major components in the blood stream. To provide a clear picture of the drug's bioavailability, it was necessary to assay the blood samples for three of the major metabolites plus thioridazine itself. Only one of the metabolites was commercially available in high purity. Reference standards for the other two metabolites had to be synthesized; this was particularly difficult because one of the metabolites, the ring sulfoxide, existed as previously unreported stereoisomers. Center personnel developed a method of synthesis that gave gram quantities of highly pure reference standards (5).

A very sensitive method was needed for analysis of the blood samples because single tablets or capsules were to be administered to the volunteers. Center personnel extended previously published methods to give the needed sensitivity. In the procedure, HPLC was used to separate thioridazine and its metabolites; after automated post-column oxidation, the compounds were measured fluorometrically (6).

As a sidelight, the new methods and standards have been used in forensic laboratories to study toxic or fatal human overdoses of thioridazine. In cooperation with the St. Louis County Coroner's Office, Center personnel performed analyses of post-mortem blood samples for thioridazine and its major metabolites; the results confirmed the presence of the newly discovered metabolites (the stereoisomeric ring sulfoxides) (2). The reference standards and methods were given to the St. Louis County Coroner's laboratory, whose personnel are now conducting further toxicology studies.

In cooperation with several United States Public Health Service hospitals, FDA conducted a study at the Center to answer this question: When tablets are stored in automatic counting machines commonly used in hospital pharmacies, the tablets are exposed to the ambient pharmacy temperature and humidity; what effect, if any, does such exposure have on the tablets' dissolution rates? Five tableted products (amitriptyline hydrochloride, digoxin, prednisone, hydrochlorothiazide, and tolbutamide) were studied. When exposed and nonexposed tablets were tested for dissolution rate and content uniformity, no noticeable differences were found (1).

Several years ago the Center began to study the dissolution rates of selected timed-release products. In these studies many aliquots of dissolution medium must be taken and analyzed at several time intervals during an 8- to 24-hour test. In some cases, analysis of the dissolution medium requires chemical reaction to form a colored or fluorescent species. Center personnel devised microcomputer-controlled aggregates of commercially available equipment to allow such tests to be conducted overnight unattended (18).

Generic Drug Standards

As part of the Compendial Methods Evaluation and Development (CMED) program the Center is analyzing samples of all types of thyroid products and evaluating the current official methods. Center personnel recommended HPLC methods for the official assay and uniformity of dosage units for levothyroxine sodium (9) and liothyronine sodium (10).

Center personnel also recommended an HPLC method for the analysis of prednisolone drug substance and tablets (11).

Other Activities

In 1982 Center personnel participated in a training program for supervisors, sponsored by the Executive Director of Regional Operations. One of the Center's presentations, an overview of computers for field laboratory personnel, was later published (17).

Summaries of Major Projects

Drug Quality Assurance

Twelve Drug Quality-Assurance studies were completed in FY 83 (Table 1). The mail-in program is designed to study the stability of drugs under actual market conditions; it was continued in FY 83 in cooperation with the American Society of Hospital Pharmacists (ASHP). Prednisone tablets, reserpine tablets and injections, and pilocarpine ophthalmic solutions were included. The number of samples analyzed and the percentages of defective batches are shown in Table 1.

The Center received and installed a new Hewlett-Packard automatic spectrophotometric dissolution analyzer. Center personnel modified the factory-supplied programs to yield data and charts better suited to the needs of CDA and modified the programs and apparatus to permit specialized tests, such as dissolution profiles of barbiturate capsules and tablets.

High-pressure liquid chromatography has increased the detection of impurities in drugs. It revealed the presence of an unknown foreign substance in samples of nitrofurantoin oral suspension. Center chemists identified the substance as 3-(5-nitrofurfurylideneamino)hydantonic acid and developed a method of synthesis to make a highly pure reference standard. For use in a survey of reserpine products, Center personnel synthesized and purified reference standards of two commercially unavailable impurities, isoreserpine and 3,4-didehydroreserpine.

The Center continued its long-term effort to mechanize the sample preparation of tablets and capsules. The Automatic Sample Preparer (ASP), designed for construction by the Winchester Engineering and Analytical Center, was extensively evaluated with many types of tablets and capsules. Our current research is aimed at the design of improved sample trays and solvent seals. The Center's prototype XY Liquid Sampler, designed to be compatible with the ASP, was fitted with improved electric valves, and revised microcomputer programs for control of the valves and the sampler were developed.

Biopharmaceutics

The USP dissolution requirement for chlorpromazine hydrochloride tablets caused certain manufacturers to reformulate their products to produce faster dissolution. There have been reports of toxic reactions when patients were switched from one brand of these tablets to another. To see whether there were important differences in dissolution rates between "old" and "new" formulations, the Center conducted content-uniformity tests and dissolution profiles on 41 samples of chlorpromazine hydrochloride tablets.

The Center obtained content-uniformity data and dissolution profiles from seven commercial samples of promethazine tablets and nine commercial samples of methyltestosterone tablets. This work was done to aid the Division of Biopharmaceutics in the selection of samples to be used in an in vivo study at the University of Georgia.

Also at the request of the Division of Biopharmaceutics, Center personnel measured the dissolution rates of several commercial samples of timed-release phenylpropanolamine hydrochloride capsules and cortisone acetate tablets.

To facilitate collection and analysis of aliquots of dissolution medium for profile tests, the Center acquired and programmed an improved microcomputer timer (MicroMaster). It will be substituted for

previously used microcomputer timers that are no longer commercially available. The new timer is much easier to program and can be used by laboratory personnel untrained in assembly-language programming.

The Center filled several requests for material describing maintenance and alignment of dissolution apparatus, and degassing of dissolution media.

The Center's slide-audiotape presentation "Guidelines for Dissolution Testing" continues to be sold to the public by the National Audiovisual Center.

Generic Drug Standards

Phenothiazines are very potent tranquilizers. Some of them are easily decomposed by heat or light. Most of the official USP XX methods do not measure the stability of these drugs. As a part of the CMED program, Center personnel are developing stability-indicating methods for phenothiazines in liquid dosage forms.

Eleven of the 13 phenothiazine drugs listed in USP XX were exposed to heat or ultraviolet light. All the drugs decomposed, some much more than others. The four that decomposed the most were studied further.

An HPLC method, developed by scientists at Health and Welfare Canada, Ottawa, was extended to separate the decomposition products formed in the heat and light experiments. The method was validated and used for sample analysis in a recent study of major tranquilizers.

Other Activities

Center personnel interfaced the Center's Hewlett-Packard System 1000 minicomputer and the Center's Wang 105 OIS word processor. This direct communication link permits documents to be revised, edited, or transformed by glossary subprograms before entry into the minicomputer. One specific application permits sending and receiving of data on pharmacy mail-in samples from word processors at headquarters to the Center's word processor. In turn, these data are relayed to the minicomputer. The system eliminates tedious, error-prone manual re-entry of sample data.

Every operating computer program underwent revision or modification due to the installation of the new RTE-6/VM operating system on the Center's Hewlett-Packard System 1000 minicomputer. Documentation of existing programs was greatly improved, and all user manuals were updated.

New input/output (I/O) technology was needed to connect additional units to the System 1000 computer; this problem was solved by the installation of a Hewlett-Packard multiplexer card in one of the computer's I/O slots. At present, several terminals and a printer are

attached to this card, and we plan to interface several scientific instruments to it in the near future.

A major reorganization of disc allocation provided each of the Center's operational groups with its own storage space and provided individual users with private spaces.

Center personnel responded to a special request from the Divisions of Biometrics and Drug Quality Evaluation by designing a new format for magnetic-tape files of completed studies. These tapes will be processed by Division of Biometrics to generate profiles of drug manufacturers.

In February 1983 two chemists from the Center accompanied personnel from the St. Louis Inspection Station on an inspection of KV Pharmaceuticals, one of the country's largest manufacturers of timed-release formulations. The purpose of the inspection was to become familiar with current industry practice in production and laboratory testing of sustained-action drugs.

Many copies of the Center's Good Laboratory Practices Manual were distributed through Freedom of Information requests or by sale from the National Technical Information Service.

References

- (1) Knapp, G. G. and Page, D. P. (1983) *Amer. J. Hosp. Pharm.* 40, 623-625. Effect on Dissolution of Tablet Storage in Counting Machines.
- Poklis, A, Wells, C. E., and Juenge, E. C. (1982) *J. Anal. Toxicol.* 6, 250-252. Thioridazine and Its Metabolites in Post Mortem Blood, Including Two Stereoisomeric Ring Sulfoxides.
- Juenge, E. C., Flinn, P. E., and Furman, W. B. (1982) *J. Chromatogr.* 248, 297-302. Liquid Chromatographic Separation and Detection of Epinephrine and Its Oxidation Products, Adrenochrome and Adrenolutin.
- Reepmeyer, J. C. (1983) *J. Pharm. Sci.* 72, 322-323. Thermal Decomposition of Aspirin: Formation of Linear Oligomeric Salicylate Esters.
- Juenge, E. C., Wells, C. E., Green, D. E., Forrest, I. S., and Shoolery, J. N. (1983) *J. Pharm. Sci.* 72, 617-621. Synthesis, Isolation, and Characterization of Two Stereoisomeric Ring Sulfoxides of Thioridazine.
- (6) Wells, C. E., Juenge, E. C., and Furman, W. B. (1983) *J. Pharm. Sci.* 72, 622-625. Simultaneous Assay of Thioridazine and Its Major Metabolites in Plasma at Single Dosage Levels with a Novel Report of Two Ring Sulfoxides of Thioridazine.

- (7) Cox, D. C., Furman, W. B., Thornton, L. K., Moore, T. W., and Jefferson, E. H. (1983) J. Pharm. Sci. 72, 910-913. Systematic Error Associated with Apparatus 2 of the USP Dissolution Test III: Limitations of Calibrators and the USP Suitability Test.
- (8) Cox, D. C., Furman, W. B., and Page, D. P. (1983) J. Pharm. Sci. 72, 1061-1064. Systematic Error Associated with Apparatus 2 of the USP Dissolution Test IV: Effect of Air Dissolved in the Dissolution Medium.
- Anon. (1982) Pharmacopeial Forum 8, 2327-2329. In-Process Revision. Levothyroxine Sodium and Levothyroxine Sodium Tablets. (This report was prepared and submitted by CMED Project Leader J. F. Brower.)
- Anon. (1983) Pharmacopeial Forum 9, 2733-2735. In-Process Revision. Liothyronine Sodium and Liothyronine Sodium Tablets. (This report was prepared and submitted by CMED Project Leader J. F. Brower.)
- Brower, J. F. (1983) Pharmacopeial Forum 9, 3566-3570. Stimuli to the Revision Process. Compendial Monograph Evaluation and Development -- Prednisolone. Report of Findings and Recommendations on the Monographs for Prednisolone and Tablets.
- 12) Thornton, L. K. and Jefferson, E. H. (1981) Lab. Info. Bull. 2391F. Semiautomated Method for Analysis of Conjugated and Esterified Estrogens Tablets.
- 13) Flinn, P. E. (1983) Lab. Info. Bull. 2391M. TLC Identification of Local Anesthetics in Semi-Solid and Liquid Dosage Preparations.
- McCullen, P. A. (1981) Lab. Info. Bull. 2391R. Semiautomated Analysis of Phendimetrazine Tartrate.
- Thornton, L. K. (1982) Lab. Info. Bull. 2391W. Determination of Acetaminophen and Codeine Phosphate in Tablets and Elixirs by HPLC.
- Allgire, J. F. and Wells, C. E. (1983) Lab. Info. Bull. 2391X. Determination of Guaifenesin, Phenylephrine HCl, Phenylpropanolamine HCl, Brompheniramine Maleate, and Codeine Phosphate in Elixirs by HPLC.
- Kerner, F. W. (1983) Lab. Info. Bull. 2690. An Overview of Computers for Field Laboratory Personnel.
- (18) Wells, C. E., Black, J. C., and Moore, T. W. (1983) Lab. Info. Bull. 2700. Microcomputer Controller for Automated Sampling/Readout Device for Dissolution Media.

Table 1. Drug Quality-Assurance Studies Completed at CDA in FY 83.

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
82-19 Chlorpheniramine Mixtures	171	2.3
82-21 Thyroid Products	95	1.1
82-22 Ergot Alkaloids	41	7.3
82-36 Progestins	30	0
82-37 Anticoagulants	34	0
82-38 Trisulfapyrimidines	15	0
82-39 Pilocarpine	67	0
82-40 Diethylstilbestrol	15	0
82-46 Androgenic Hormones	37	0
83-11 Selected Corticosteroids	159	
83-12 Folic Acid	36	0
83-13 Reserpine	42	
ASHP-FDA Mail-In Program:		
Prednisone Tablets	117	2.6
Reserpine Tablets and Injections	142	1.4
Pilocarpine Ophthalmic Solutions	253	2.0

^aPercent of batches not meeting compendial or FDA-imposed requirements. 1254