Branch or from the "Chemist's Review", a copy of which is routinely distributed to them. The ASTRO data system, in Mark IV language, contains approximately 40 pieces of data covering the topics appearing on the first page of the "Chemist's Review" along with additional information regarding drug composition, legal status, investigators, contraindications, and distributors. These data are being updated constantly and serve as essential tools in the review process. An important and useful facet of the ASTRO data system lies in the Chemical Compound Substructure Search System (SSS) and was developed as a computerized retrieval system for searching by way of chemical substructure in assembly language. A fragment search acts as a filter to reduce the search file and offers an atom-by-atom comparison of compounds which have passed the fragment screens. A chemical search through the SSS locates any FDA submissions which contain the compound of interest.

Although I have touched on the aspects of the ASTRO search system only briefly, I emphasize its utility to the reviewing chemist. Unfortunately, I have been describing what is analogous to a delicious cake and now must tell you that you cannot have any of it unless you are on the staff of the Food and Drug Administration since the databases contain confidential information.

Additional support in the "Chemist's Review" process is available through the Bureau of Drugs automated literature services. There are many databases available through the library and I shall restrict my comments to a brief summary of the major systems.

MEDLARS (computerized literature retrieval services of the National Library of Medicine) contains the following databases available through the on-line network:

Medline	1 900 000 references
Toxline	380 000 references
Toxback	200 000 references
Chemline	385 000 names for structures of 200 000 unique compounds
Catline	175 000 references to books and serials
Serline	about 18 000 serial publications

Avline, Cancerlit, Cancerpor, and Epilepsyline are also included in this system.

The BRS (Bibliographic Retrieval Services, Inc.) system contains 16 databases which include *CA Condensates* and MEDLARS. This system has proved valuable in aiding the chemist to search information relating to syntheses and drug activity.

The SDC (Systems Development Corporation) system covers 26 databases on various topics some of which also appear in the systems which I have already described.

The Lockheed Information Systems, a most recent acquisition by the Bureau of Drugs Library, contains 87 databases and should prove essential in aiding the chemist in the review process. One of the outstanding databases in this system is the CA Patent Concordance which contains 113 000 patents at the present time.

A third major category relates to spectral information which we have termed miscellaneous despite its importance to the reviewing chemist. A brief description of these spectral databases demonstrates the advancements in automated data-handling systems which aid the chemist.

Walter Reed Hospital Databases: X-ray powder diffraction files.

NIH–EPA Chemical Information System (CIS): mass spectra, about 26 000; carbon-13 NMR spectra, about 7000; X-ray diffraction data (Cambridge Crystal File), about 17 000.

SIRCH-III (ASTM/DOW Infrared Spectral Files): includes Sadtler standard and commercial spectral data. Access to this system is through the FDA Parklawn Computer Center and consists of two disks covering more than 100 000 entries.

The most recent proposals under consideration are the establishment of an ultraviolet spectral database for prescription drugs and excipients and the entering of all approved new drug application analytical methodology into a database. Implementation of this latter proposal by the Executive Director of Regional Operations (EDRO) may begin this year.

In conclusion, we can say that despite the ever increasing number of drug submissions requiring in-depth reviews within the imposed time frames, the reviewing chemist is assured aid by the increasing numbers and sophistication of the databases available at his request.

Chemical Data: An Essential Tool in the Regulation of Drugs†

WALTER R. BENSON* and WILLIAM W. WRIGHT

Division of Drug Chemistry and Pharmaceutical Research and Testing, Bureau of Drugs, Food and Drug Administration, Washington, D.C. 20204

Received September 12, 1978

How the Bureau of Drugs laboratories and offices obtain chemical data from the scientific literature, from user complaints and product defect reporting systems, from the drug manufacturers, from analyses of drug samples collected from the market, and from analytical research are described. The chemical data thus educed have been used successfully in developing new analytical methods, in establishing better specifications of drug quality, in removing adulterated drugs from the marketplace, in successfully prosecuting purveyors of substandard drugs, and in general assuring that consumers are provided with safe and effective drugs of high quality.

The Food and Drug Administration (FDA) uses chemical data in most of its programs that are intended to ensure that the Nation has a safe and effective drug supply.[1,2] It is the purpose of this paper to describe the way in which FDA's Bureau of Drugs (BD) uses chemical data from industry, universities, and government, particularly intramural research. The programs that will be covered include: Drug Quality Assurance, Biopharmaceutics, Drug Abuse, Over-the-Counter Drugs, Poison Control, Drug Listing, NDA Analytical Method

† Presented before the Division of Chemical Information, 175th National Meeting of the American Chemical Society, Anaheim, Calif., March 15, 1978.

This article not subject to U.S. Copyright. Published 1979 by the American Chemical Society

Validation, National Center for Drug Analysis, and Bioresearch Monitoring.

1. DRUG QUALITY ASSURANCE (DQA)

FDA has the responsibility for monitoring the quality of drugs on the market and to take all necessary measures to assure that the manufacturing, processing, packing, and holding of drugs result in marketed products of the highest feasible quality. At various times FDA has determined that certain marketed drugs are not of adequate quality; i.e., they are subpotent or superpotent, contaminated or mislabeled. As a result of these deficiencies, serious injuries and deaths have sometimes occurred. Chemical data used in the DQA project are generated in part as a result of (a) complaints, (b) projects to improve official methods, and (c) research to determine the scientific basis of analytical methods.

A. Complaints. Some of the research problems investigated by the Division of Drug Chemistry arise through complaints. For example, a medicated aerosol, sold over the counter (OTC) which had been implicated in the deaths of 18 persons, was received for analysis without any official analytical methodology, although accurate knowledge of the nature of its components was urgently needed. The information on deaths had been gathered by the NEISS system of the Consumer Product Safety Commission (CPSC). Since there was no official method of analysis for the product, it was qualitatively analyzed by combined gas chromatography–mass spectrometry. The data were collected and processed by a minicomputer. Ten of the 11 separated peaks were identified[3] with the assistance of the mass spectral search system of the National Institutes of Health, Division of Computer Research and Technology, Chemical Information System. This service is now available through Cyphernetics.[4] The propellants were also analyzed by infrared spectrophotometry, using a gas cell.[3] Of all the components identified, the one which appeared to be responsible for the deaths was 1,1,1-trichloroethane. It was not declared on the label. This misused product was removed from the market through the actions of FDA's compliance program. Companies with five similar products which contained that same component were required to remove it from future formulations.

Another series of complaints, which arose from the industry, concerned the OTC drug Ipecac syrup, which was not effective for its claimed use as an emetic. FDA's district laboratories found that the Ipecac syrup met the compendial specifications (USP XVIII, 1970), in spite of the complaints. The drug was potentially dangerous for two reasons: (1) the poisonous alkaloids emetine and cephaeline were present, and (2) the poison the drug was expected to remove from the patient's stomach was not being removed.

The samples were forwarded to the Division of Drug Chemistry (DDC) in Washington, D.C., for further analyses. When the complaint samples were subjected to column partition chromatography, an additional compound was found which had not been reported previously in Ipecac preparations. This compound was determined by normal identification procedures (GLC, GC/MS, IR, NMR, UV, TLC, etc.) to be ephedrine.[5] The method developed is now the official method in the USP XIX monograph for Ipecac. The chemical data used in taking regulatory action were in the form of official worksheets prepared by analytical chemists. References to these data are discussed, in general, in ref 1.

Complaints can be organized. For example, scientific groups wishing to cooperate with the FDA in reporting drugs which are defective and/or give adverse reactions can participate in a system in which the reports are transmitted to the FDA through the U.S. Pharmacopeia. Similar arrangements have been made with the American Society of Hospital Pharmacists and the Society of Nuclear Medicine.[6] Evaluation of these chemical data usually leads to further sample collections and analyses by FDA laboratories. The chance that FDA will find drugs which do not meet specifications is greater with these samples than with samples collected randomly. The deficiencies found included clumping, wrong calculations, adverse drug reactions, a label change, a change needed in the USP monograph, and others.

When medical claims are made for a drug product, the manufacturer is required to furnish the FDA with data as prescribed in the Federal Food, Drug, and Cosmetic Act. Such was the case with Laetrile® among many others. FDA received reports that Laetrile was on the market and that it was not effective for its claimed purposes. In order to protect consumers from this product and to comply with requirements of the law, the FDA determined what was in the product,[7] how much was present,[8] and whether it was mutagenic.[7] FDA Commissioner Donald Kennedy had the history of this product reviewed.[8] Mandelonitrile β-glucuronide, the compound patented as Laetrile, was synthesized[7] and characterized. Analytical methods were also developed to distinguish Laetrile, amygdalin, and neoamygdalin.[7] Mandelonitrile β-glucuronide was not found in several commercial Laetrile preparations. These samples did, however, contain amygdalin, in some cases neoamygdalin, and sometimes other compounds. In some cases solutions were found to be nonsterile. Using a modified Ames test, mandelonitrile β-glucuronide, mandelonitrile, and a mixture of amygdalin and neoamygdalin were each found to be mutagenic.[8] The FDA issued posters to warn consumers of the danger to their health in using these nonapproved drug products. Scientific journals, the *FDA Drug Bulletin*, and the *FDA Consumer* are playing important roles in distributing the results of the use of chemical data and the data themselves.

The FDA received a report that quinidine was contaminated with a number of new compounds while it was being processed and handled. Reference standard materials were prepared and a method of analysis was developed for examining commercial samples.[10] It was found that commercial samples of quinidine routinely contained from 3 to 22.1% of 10,11-dihydroquinidine. After quinidine and dihydroquinidine were obtained in a relatively pure state, it was finally possible to establish the absolute configuration of quinidine by single-crystal X-ray crystallography.[11] The separate physiological effects[12] of each compound were determined.

As a result of complaints about the official content uniformity test for radioactive drugs in capsule form, DDC developed an improved method[13] which uses intact individual capsules. The method is rapid, precise, and specific, while *not* destroying the sample.

B. Compendial Method Improvement. Although the complaint mechanism is useful to FDA, we also try to improve compendial methods even when no complaint has been received.

Improving compendial methods requires analytical insight, sometimes new analytical instrumentation, and research. The resulting chemical data constitute proof of new methods by which DDC helps to maintain and improve the quality of the U.S. drug supply. For example, the USP method for dienestrol was so nonspecific that almost any reducing substance would interfere. Two methods were developed[14] and one was made official. The official method depended on separation, nitrosation, and polarographic determination. The other more specific method depended on separation and photolysis to a yellow product. An even better method[15] for dienestrol, which is directly applicable to creams and individual tablets, involves a rapid, quantitative acid-induced isomerization. This method[15] was adopted as official first action by the Association of Official Analytical Chemists.

Thyroid preparations have long caused problems to the analyst for many reasons. Dry natural protein containing thyroid hormones yielded to a UV method using I_2.[16] However, this useful but nonspecific and relatively insensitive method could not be used for single tablet assay and was tedious. A new method, depending on the conversion of all iodine atoms to I_3, was developed for the analyses of sodium levothyroxine (T_4) and sodium liothyronine (T_3).[17]

In a continuing effort to analyze individual thyroid tablets, a method was developed which was dependent on ignition in oxygen.[18] This method was rapid enough for content uniformity but could not be used in all cases for T_3 and T_4, since combustion in some formulations was incomplete. Research is underway to combine the HPLC analysis of reference standards[19] with some of the existing clean-up procedures[16-18] to achieve a method that is not only specific but also sensitive to all compounds present. The analyses will probably involve the use of a Spectraphysics 8000 HPLC computer system.

In order to have a single method to analyze for all important gaseous impurities in medicinal gases, an infrared (IR) spectrophotometric method of analysis for trace impurities was developed.[20] This method, which involves the use of a 10-m gas cell, will detect most organic and inorganic compounds present in trace quantities in medicinal gases where USP specifications require that none be present. Methane was found at low levels in some samples, and four common inorganic gases were detectable below their USP limits. Three inorganic gases were not measurable at the USP limits (NO, NO_2, and H_2S). The ASTM First-1 Fast IR Search system is used when unknowns are submitted for analysis.[20] This system is currently available throughout the FDA where APL programs[21] make it easy to use.

In an effort to bring more specific and rapid qualitative and quantitative methods into the official compendia and to see how well proton magnetic resonance chemical data could be reproduced from laboratory to laboratory, a collaborative study of a ^1H NMR method for disulfiram (NF XIV) was completed.[22] Fourier transform NMR was extremely useful in speeding up this process. The average percent recovery by 18 laboratories using this rapid, specific method was 99.7 ± 1.4%.

Three simple, specific colorimetric methods for oral contraceptives[23-25] were developed, one of which has been adopted by the USP XIX as the official method of assay.[25]

When the melting point identification data of a derivative of propantheline bromide USP XIX failed to be useful in our laboratory and in the USP laboratory, thin layer chromatography and infrared spectrophotometry were used successfully for the identification of the intact active moiety in six marketed products and in the bulk drug.[26] A method to identify drugs by mass spectrometry, now under development,[27] does not involve a computer in contrast to other systems[4] and is not dependent upon the instrument used.

C. Why Do Methods Work? In an effort to understand the fundamental basis of certain analytical methods, chemical data are obtained to optimize the method and to extend it. The USP method for diethylstilbestrol (DES) depends on a quantitative photolysis procedure in which a bright yellow product is formed from *cis*- and *trans*-DES. The structure of this product proved to be a model system for trapping the elusive dihydrophenanthrene derivative believed to have been formed by the photolysis of a *trans*- or *cis*-stilbene[28] but not recognized until then. A similar mechanism[29] and yellow product were found[14] for dienestrol. Since both DES and dienestrol pass through unstable *cis*-stilbenediols, these intermediates were synthesized for a number of *cis*-stilbenediols free of trans isomers via a Diels–Alder reaction to determine if this type of intermediate would actually photolyze faster or at all. The hypothesis was correct.[30]

As described in a recent review[31] on column partition chromatography (CPC), work in DDC is typically a blend of theory and practice. Usually specific, practical goals are set or questions are asked. These questions are answered or goals are achieved by first studying some of the chemistry of the drug. For example, a detailed theoretical study was made of the partition of tolbutamide as ion pairs with tetraalkylammonium cations. This resulted in a basic contribution to CPC, which is also a method for the assay of tolbutamide in tablets.[32] In another example, parabens in syrups interfered with the assay for barbiturates. A study of the alkaline hydrolysis of parabens involving rate constants at various temperatures, pH's, and viscosities resulted in a general study and a specific optimized assay for barbiturates.[33] These ion-pairing studies require the use of computers in the rapid, automatically calculated and coded separations of mixtures of drugs,[31] called distribution maps or contour maps.

Finally, the stereochemical properties of amphetamine have been studied extensively for years, but such studies have never achieved a practical method for the assay of the dosage form. In a derivative approach, amphetamine was given enhanced optical rotation which resulted in a practical assay for amphetamine in a single tablet.[34]

2. BIOPHARMACEUTICS

The FDA established the biopharmaceutics program to cover both bioavailability and bioequivalency of drugs. The bioavailability of a drug refers to the amount of active drug substance which becomes systemically available to achieve its therapeutic action. Studies have documented that some drug products with identical active ingredients may not produce the same systemic levels; i.e., they are not bioequivalent. FDA has developed necessary methodology involving such techniques as dissolution testing, assays for drugs in biological fluids, and animal model testing for establishing biopharmaceutic performance specifications and for determining bioequivalence. In-house laboratory activities include basic research on formulations and the testing of products that might be subject to bioavailability problems.

Some collaborative research has been accomplished on such subjects as establishing the bioequivalence of 5-mg prednisone and prednisolone tablets.[35] Similar papers on digitoxin,[36] tetracycline,[37] and dihydroergotoxin have been prepared. Contracts administered by the biopharmaceutics program involve, for example, the generation of pharmacokinetic data on tetracycline hydrochloride, digoxin, digotoxin, prednisolone, prednisone, quinidine sulfate, acetazolamide, oral coronary vasodilators, and sulfisoxazole. Field ionization mass spectrometry is being studied as a potential analytical technique for imipramine[38] and other drugs. Mass spectrometry is a powerful tool for determining small quantities of drugs in biological fluids with great specificity. In order to take advantage of instrumentation already available in the FDA, deuterated reference standards are being synthesized and used in developing techniques for the quantitation of drugs. As an example, tolbutamide-d_7 was prepared and used for direct probe samples of reference standards, with encouraging results.[39] Work using this capability has also been started on propoxyphene. These techniques require special dedicated computers to handle the large amount of data generated[3,27] or to simplify an analysis through a selection process or in single and multiple ion monitoring.

Prednisolone is being used as a model drug, since chemical data on its bioavailability are needed. DDC has attempted to analyze it by means of spin immunoassay.[40] However, as with the radioimmunoassay there are serious crossover reactions. Work is underway to correct this. In addition, an HPLC method which separates and quantitates the predni-

solone and other interfering related substances has achieved some success at the nanogram level with reference standards and plasma.[41] All HPLC and GLC instruments are connected to a minicomputer for easy data manipulation.

3. DRUG ABUSE TREATMENT MONITORING

As a part of Drug Abuse Treatment Monitoring, it is proposed that a federally approved and selected laboratory test be developed for opiates, barbiturates, amphetamines, cocaine, and other drugs, as appropriate, in the patient's urine under a special schedule. These chemical data are to be used as a clinical tool for diagnosis and as one technique in overall program evaluation by monitoring the patient's drug-using patterns before and after treatment.[42]

4. OTC PROJECT

In 1962, Congress passed the Kefauver–Harris Drug Amendments to the Food, Drug, and Cosmetic Act to require that all new drugs, including over-the-counter (OTC) drugs, be approved for efficacy as well as safety before marketing. In 1972 after a partial evaluation, FDA began its over-the-counter evaluation project. FDA has established 27 therapeutic categories of OTC drugs through the publication of final monographs. Each monograph will include testing procedures. On the basis of instructions issued by the Bureau of Drugs, the field laboratories will assure that drugs which failed to comply with the specifications of the final monographs are removed from the market. Field compliance follow-up efforts on approximately 8000 antacid products began early in 1977 after the first monograph was released. The medicated OTC aerosol cited earlier[3] was involved in the OTC project, the Drug Listing Project, the Poison Control Project, and several other projects in the Bureau of Drugs.

The amount of chemical data which is now being generated and used for compliance programs for OTC drugs will certainly increase sharply after monographs by classes have been provided for all 27 categories and after the surveillance programs are in progress.

5. POISON CONTROL PROJECT

This project, among other things, maintains surveillance by continually enlarging the information base through the compilation of reports of poisoning and through research on the mechanism and prevention of poisoning. Data on injuries due to ingestion of drugs are supplied to support necessary compliance action when a problem is noticed. Data are also supplied upon request to the OTC drug review panels. CPSC is performing most of the computer support (Medical Oriented Data System; MODS) for this and the NEISS project. The Ipecac[5] and the medicated night-time aerosol spray[3] problems were identified by this system and also by FDA's field districts, which alerted headquarters.

6. DRUG LISTING PROJECT (DL)

The Drug Listing Act of 1972 requires that all drug establishments register not only their name and address but all their commercially marketed drug products with the FDA. The list of drugs, biologics, veterinary drugs, and medicated feed premixes must also contain the chemical composition together with names of active ingredients, dosage form, and concentration of bulk drugs. This project locates and assigns the Chemical Abstracts Service (CAS) Registry Number for each chemical entity, or assigns an FDA number when the CAS number is not available or not possible. Homeopathic drugs (ground daisies and animal extracts are two examples) need a number, even though they are not pure.

Each company submits its own number to the FDA for each drug product. These numbers are used by the FDA to publish the National Drug Code Directory. The Directory provides a consistent source of information for planning FDA prescription drug regulation and compliance efforts and serves as a reference for all public and private organizations that buy prescription drugs. A new system which will file searches based on Boolean logic will be available by the summer of 1978.[43] A Human OTC Drug Directory and a Veterinary Drug Directory are also planned.

When a request was received for the names of all drugs containing $CHCl_3$, nearly 3000 such drug products were identified. The present Drug Listing system identified 2500 drugs and a Federal Register Announcement identified the remainder. The system should become even more important when and if a drug monograph is required for every drug on the market.

7. METHOD VALIDATION PROCESS

As a part of their New Drug Applications, drug manufacturers are required to submit laboratory methods to ensure the identity, purity, and potency both of the new drug substance and of all its dosage forms. Before 1965 these methods were generally subjected only to a paper review; they were accepted if they appeared reasonable and if the manufacturer's results (including chemical data) from using these methods appeared adequate. However, experience showed that when regulatory laboratories attempted to use these same reasonable methods to analyze marketed drugs, many of them proved to be unsatisfactory. It was therefore found necessary to submit these methods to laboratory testing before their validity could be judged. DDC has engaged in such validation studies for the past 12 years.

It is the responsibility of the NDA review chemist to decide whether the method should be validated. When validation is deemed necessary, the method and samples are submitted to both DDC and one of FDA's field laboratories. It is then DDC's responsibility to determine, from the chemical data generated in the two laboratories, if the method is suitable for regulatory analysis or for use by the manufacturer in controlling the product's quality.

Requirements for a regulatory method are generally more restrictive than those for a manufacturing control method. For example, although the methods submitted for a methyl methacrylate monomer and copolymer drug could be repeated, the methods were not specific enough. Therefore an NMR method was developed in the DDC laboratory to determine the starting material rapidly and specifically.[44] These materials had to be mixed for the surgeon just prior to use. NMR proved to be a useful technique to determine that 21% monomer was being given to the patient at the time of insertion (4 min after mixing), far in excess of the 1.9 to 3.5% present after 1 hour. These data were not found in the NDA.

If materials not available to the regulatory laboratory are needed to perform the method or to interpret the results, the method is not acceptable for regulatory use. In fiscal year 1977, methodology contained in 64 NDA's was submitted for validation. Of the 64 methods submitted, 12 (or 19%) were found not acceptable and had to be either modified or replaced by an entirely new approach. This took place only after each firm with a problem method had been invited to demonstrate it in the FDA laboratory.

A similar situation exists among radioactive drugs except that more than 19% of the NDA methods are revised or dropped. The chemical data collected under NDA validation studies, under the SNM/USP/FDA reporting system[6] (among others) and from the surveillance programs, all aid Bureau

Table I. Drug Quality Assurance Studies Completed at NCDA in FY 76 and Interim Quarter

study no. and name	batches analyzed	defective batches, %[a]
538 progestins	42	2.4
539 androgenic hormones	72	1.4
540 sedatives	282	5.0
547 antithyroids	15	6.7
548 antimalarials	37	5.4
556 papaverine	48	6.2
557 phenazopyridine	13	0
562 nitrofurantoin	37	8.1
564 ferrous sulfate	83	2.4
565 oral contraceptives	69	0
566 digitoxin } continuous certification	69	10.1
567 digoxin } studies	52	9.6
568 local anesthetics	218	0.9
573 nitrate coronary vasodilators	165	3.7
579 reserpine	133	6.0

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

of Drugs in its attempts to regulate this drug supply. Since technetium-containing drugs constitute nearly 83% of the radioactive drug market, the FDA initiated research programs to try to understand its chemistry,[45] although the other radioactive drugs are not being neglected.[13,46] In addition, computerized reporting systems were developed for use in these complicated analyses.[47]

8. NATIONAL CENTER FOR DRUG ANALYSIS

The National Center for Drug Analysis (NCDA), located in St. Louis, Mo., is another division of the Bureau of Drugs. The Center acquires data by chemical analyses, stability studies, identity tests, uniformity assays, and, in many instances, the dissolution rates of marketed drug products.[48]

Drug samples collected in nationwide surveys under the Quality Assurance of Marketed Drugs Program are analyzed to determine if they are in compliance with the legal standards of identity, strength, quality, and purity. These samples are analyzed primarily by automated analytical systems which are interfaced directly to an analog-to-digital converter on a Hewlett-Packard 2116C minicomputer system. The minicomputer performs the necessary calculations and produces a worksheet which presents the results of analysis. Together, the automated systems and minicomputer afford the Center a highly efficient means of performing tens of thousands of assays on a variety of pharmaceutical products, statistically analyzing these results and reporting them to the proper decision points, and collecting the historical data necessary for the planning of future programs. Tables I and II list the categories of drug products surveyed in fiscal years 1976 and 1977, respectively. These tables present results of laborabory findings and include the percentage of all types of defects observed. The percentages do not necessarily reflect the quality of all drugs on the market, since the studies were conducted on drug categories where high defect rates were suspected.

Rates of dissolution of drug products are obtained to support FDA research efforts in determining bioavailability and bioequivalence of drug products. Sources of variability in performing the dissolution test have been reduced as a result of these studies.

Some idea as to the diversity of NCDA's activities can be seen from the subjects of a few of the numerous reports generated by this group and published between 1975 and 1977: reserpine in tablets,[49] papaverine in tablets and capsules,[50] digoxin,[51] and conjugated or esterified estrogens.[52]

Table II. Drug Quality-Assurance Studies Completed at NCDA in FY 77

study no. and name	batches analyzed	defective batches, %[a]
580 conjugated and esterified estrogens	99	11.0
583 CNS stimulants	54	13.0
585 ephedrine and pseudoephedrine	103	7.8
589 steroid estrogens	58	0.0
596 thiazide diuretics	113	0.9
598 tricyclic antidepressants	95	1.1
600 ergot alkaloids	34	17.6
604 sulfonamides	101	1.0
613 adrenergics	126	4.0
622 trisulfapyrimidines	47	0.0
566 digitoxin } continuous certification	53	22.6
567 digoxin } studies	23	4.3

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

9. BIORESEARCH MONITORING OF HUMAN DRUGS

In evaluating the safety and effectiveness of new drugs, the FDA must review data obtained by the sponsor. Nonclinical and clinical studies must be properly designed to prevent human subjects from being exposed to unnecessary risks and at the same time to obtain valid data. Chemical data are a small part of the total data collected, but if the study is poorly done, the remaining clinical data would be of little use. These chemical data will not be discussed because they are no different from the same data reported under the Drug Quality Assurance program.[53]

ACKNOWLEDGMENT

We wish to thank the following for their cooperation in assembling the material in this report which reflects some of the expertise and the problems they face in FDA: The DDC Branch Chiefs, T. Doyle, L. Ford, J. Graham, R. Stark, and Dr. T. Layloff of NCDA; all BD's PMS managers, W. Cobb (Drug Listing), R.H. Carpenter (Drug Quality Assurance), W.E. Gilbertson (OTC Drug Evaluation), J.J. Crotty (Poison Control), B.F. Stonecipher (Drug Abuse Treatment Monitoring), and G. Knapp (Biopharmaceutics).

REFERENCES AND NOTES

(1) S. Bellman et al., *J. Chem. Inf. Comput. Sci.*, **17**, 94–109 (1977).
(2) H. Reynolds, H. P. Eiduson, J. P. Weatherwax, and D. D. Dechert, *Anal. Chem.*, **44**, 22A (1972).
(3) E. B. Sheinin, W. R. Benson, W. L. Brannon, and G. Schwartzman, *J. Assoc. Off. Anal. Chem.*, **58**, 530–540 (1975).
(4) G. W. A. Milne and S. R. Heller, *Am. Lab.* **9**(9), 43–54 (1976).
(5) J. Levine, E. Smith, et al., FDA, private communication, 1973.
(6) L. A. Ford, A. Shroff, W. R. Benson, H. Atkins, and B. A. Rhodes, *J. Nucl. Med.*, **39**, 116–117 (1978).
(7) C. Fenselau, S. Pallante, R. P. Batzinger, W. R. Benson, R. P. Barron, E. B. Sheinin, and M. Maienthal, *Science*, **198**, 625–627 (1977).
(8) T. Cairns, J. E. Froberg, S. Gonzales, W. S. Langham, J. J. Stamp, J. K. Howie, and D. T. Sawyer, *Anal. Chem.*, **50**, 317–322 (1978).
(9) D. F. Kennedy, *Fed. Regis.*, **42** (151), 39768 (Aug. 5, 1977).
(10) E. Smith, S. Barkan, B. Ross, M. Maienthal, and J. Levine, *J. Pharm. Sci.*, **62**, 1151–1155 (1973).
(11) R. Doherty, W. R. Benson, M. Maienthal, and J. McD. Stewart, *J. Pharm. Sci.*, **67**, 1698–1700 (1978).
(12) T. Balazs, E. Herman, and J. Atkinson, *J. Pharm. Sci.*, **67**, 1355–1357 (1978).
(13) L. A. Ford and M. Jaffee, *Int. J. Appl. Radiat. Isot.*, **26**, 21–23 (1975).
(14) A. F. Summa and J. H. Graham, *J. Pharm. Sci.*, **54**, 612 (1955).
(15) J. H. Graham, D. Banes, and J. B. Proctor, *J. Assoc. Off. Anal. Chem.*, **55**, 190–193 (1972).
(16) J. E. Moody, Jr., J. R. Hohmann, and G. B. Kaplan, *J. Pharm. Sci.*, **57**, 634–639 (1968).
(17) J. H. Graham, D. Banes, M. E. Biesemeyer, and A. Nadkarni, *J. Pharm. Sci.*, **63**, 763–766 (1974).

(18) J. H. Graham, *J. Pharm. Sci.*, **64**, 1393–1396 (1975).
(19) D. Smith and J. Graham, *J. Assoc. Off. Anal. Chem.*, in press.
(20) W. L. Brannon, W. R. Benson, and G. Schwartzman, *J. Assoc. Off. Anal. Chem.*, **59**, 1404–1408 (1976).
(21) R. Venable, Laboratory Information Bulletin 1918A, Food and Drug Administration, Washington, D.C., 1977.
(22) E. B. Sheinin and W. R. Benson, *J. Assoc. Off. Anal. Chem.*, **61**, 55–59 (1978).
(23) J. Y. P. Wu, *J. Assoc. Off. Anal. Chem.*, **53**, 831–833 (1970).
(24) J. Y. P. Wu, *J. Assoc. Off. Anal. Chem.*, **57**, 747–751 (1974).
(25) J. Y. P. Wu, *J. Assoc. Off. Anal. Chem.*, **58**, 75–79 (1975).
(26) W. L. Brannon, W. R. Benson, and M. M. Smith, Jr., *J. Assoc. Off. Anal. Chem.*, in press.
(27) R. P. Barron, W. R. Benson, and J. Roach, *J. Assoc. Off. Anal. Chem.*, **60**, 635–641 (1977).
(28) T. D. Doyle, W. R. Benson, and N. Filipescu, *J. Am. Chem. Soc.*, **98**, 3262–3267 (1976).
(29) T. D. Doyle, W. R. Benson, and N. Filipescu, *Photochem. Photobiol.*, **27**, 3–8 (1978).
(30) M. Maienthal, W. R. Benson, E. B. Sheinin, T. D. Doyle, and N. Filipescu, *J. Org. Chem.*, **43**, 972–975 (1978).
(31) T. D. Doyle and J. Levine, *J. Assoc. Off. Anal. Chem.*, **61**, 172–191 (1978).
(32) T. D. Doyle and S. Barkan, *J. Assoc. Off. Anal. Chem.*, **59**, 1170–1174 (1976).
(33) S. Barkan and T. D. Doyle, *J. Assoc. Off. Anal. Chem.*, **60**, 1022–1029 (1977).
(34) J. D. Weber, *J. Pharm. Sci.*, **65**, 105–108 (1976).
(35) V. K. Prasad, J. P. Hunt, and B. E. Cabana, presented at the National Meeting of the American Pharmaceutical Association, New York, N.Y., 1977.
(36) V. K. Prasad, B. E. Cabana, J. Hunt, W. Furman, D. Cox, C. Wells, and J. Wood, in ref 35.
(37) V. K. Prasad, T. C. Alston, V. P. Shah, K. M. Campbell, B. E. Cabana, D. Masterson, and R. Schwartz, in ref 35.
(38) Stanford Research Institute (Dr. Anbar); see Second Annual Report, SRI Project 4276, Aug 1977, by Dr. Henry Heck et al., Contract 223-75-3006.
(39) R. Barron, W. Benson, M. Maienthal, E. Sheinin, and W. Brannon, FDA, private communication, 1978.
(40) W. R. Benson, M. Maienthal, G. Yang, E. B. Sheinin, and C. W. Chung, *J. Med. Chem.*, **20**, 1308–1312 (1977).
(41) E. Smith, FDA, private communication, 1978.
(42) D. F. Kennedy, *Fed. Regis.*, **42**(208), 56896 (Oct 28, 1977).
(43) W. Cobb, FDA, private communication, 1978.
(44) E. B. Sheinin, W. R. Benson, and W. L. Brannon, *J. Pharm. Sci.*, **65**, 280–283 (1976).
(45) W. R. Benson, G. Yang, M. W. Heitzmann, and L. A. Ford, *J. Labelled Compd. Radiopharm.*, **15**, 343–352 (1978).
(46) M. W. Heitzmann and L. A. Ford, *J. Assoc. Off. Anal. Chem.*, **58**, 995–997 (1975).
(47) L. A. Ford and M. W. Heitzmann, Proceedings of the Symposium on Computers in Nuclear Medicine, 1977.
(48) T. Layloff, NCDA, FDA, private communication.
(49) M. A. Kreienbaum, *J. Assoc. Off. Anal. Chem.*, **58**, 289-292 (1976).
(50) B. J. Westerberger, Method 65 in "Drug Autoanalysis Manual", Richard F. Heuermann, Ed., Food and Drug Administration, Washington, D.C., 1976.
(51) R. D. Kirchhoefer, Laboratory Information Bulletin 1941, Food and Drug Administration, Washington, D.C., 1976.
(52) L. K. Thornton, T. W. Moore, and G. L. Joachims, Laboratory Information Bulletin 1987, Food and Drug Administration, Washington, D.C., 1977.
(53) For further reading on the application of chemical data in medicine, read "Chemistry in Medicine", American Chemical Society, Special Issues Sales, Washington, D.C. 20036, 1977, p 138.

Sources of Chemical Information Used in Antibiotic Certification†

MARY LOU ANDREW* and LOLA G. WAYLAND
Food and Drug Administration, Washington, D.C. 20204

Received September 12, 1978

Because of a legislative mandate requiring the predistribution testing and certification of each batch of antibiotics produced for human use in the U.S.A., the National Center for Antibiotics Analysis (NCAA) must utilize a wide variety of techniques for establishing its official methods. Methods adapted from material submitted by the manufacturers in Forms 5 and 6, as well as from other sources, such as literature searches, the NCAA reprint collection, and cross reference file are described.

The Federal Food and Drug Act requires the use of analytical methods for enforcement. Analyses are directed toward answering the question of whether the product meets the requirements of the Act. Certain restrictions on the methods used are due to the fact that we are a regulatory agency, not merely a laboratory performing analytical procedures.

The law requires that drugs must meet the specifications of the official compendia. For most drugs, this is usually the USP/NF. However, for antibiotics, official specifications and methodology are established by incorporating them into the regulations. The Antibiotic Regulations are published in the Code of Federal Regulations, Title 21, Parts 430–460 for drugs for human use, and Parts 536–555 for the certifiable veterinary antibiotic products. Insulin is covered by Part 429. The CFR is available as an annual update from the Government Printing Office. Between annual editions, announcements for new regulations, changes, and deletions are available in the "Federal Register", the government newspaper which appears every workday. It, too, is available from the Government Printing Office by subscription. More than 500 pages of the CFR are devoted to tests and methods of assay for antibiotics, including sterility, biological tests, microbiological and chemical assays, general and specific chemical tests, and tests on specific dosage forms. Also included are specifications, interpretations, and special tests for each certifiable antibiotic preparation. Therefore, the methods in the CFR are conclusive, even if other more modern methods may be available. The methods must be accurate and precise, enabling us to reproduce our own results, and other laboratories also must be able to use these methods satisfactorily.

Methods of antibiotic certification must be specific, sensitive, precise, and accurate, as well as practical. This paper discusses various sources of analytical methods, and ways in which they have been established.

FORMS 5 AND 6 VALIDATION PROCESS

The CFR defines Form 5[1] as a request to provide for certification of a new antibiotic product. A Form 6 provides data to accompany or precede every initial request for certification of a batch of a "me-too" drug.

The arrival of a Form 5 application is generally not our first indication of the existence of a given new antibiotic entity. The National Center for Antibiotics Analysis (NCAA) subscribes to a number of scientific and trade journals which are reviewed every month, and copies of any pertinent articles are retained

† Presented before the Division of Chemical Information, 175th National Meeting of the American Chemical Society, Anaheim, Calif., March 15, 1978.

* Address correspondence to author at FDA, 200 C St., S.W., Washington, D.C.

This article not subject to U.S. Copyright. Published 1979 by the American Chemical Society