Symposium on Chemical Information Utilization by FDA Bureau of Drugs Chemists

Introductory Remarks†

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This symposium was organized to acquaint the scientific community with the manner in which Bureau of Drugs chemists utilize available chemical information as it pertains to the various areas in which they are involved.

The Food and Drug Administration bears the prime responsibility for regulation of drugs in this country. The authority for FDA's activities is derived from the Federal Food, Drug, and Cosmetic Act. As enacted in 1938, the Act required premarket clearance of new drugs (via New Drug Applications (NDA)) based primarily on safety. In 1941 the requirement for batch certification of insulin was added. Two years later Congress amended the Act to require the batch certification of penicillin products. With the passage of the Kefauver–Harris amendments of 1962 the requirement for showing both safety and effectiveness of a new drug was made mandatory. The 1962 amendments for the first time also required the submission of a Notice of Claimed Investigational Exemption for a New Drug (IND) when human studies are first undertaken. Prior to this amendment an IND was not required to be submitted to the FDA when a new drug was investigated in humans. In regard to antibiotics, all human antibiotics became subject to batch testing and certification.

Chemists have a very responsible role in the review of applications, laboratory testing, and providing chemical information. The important role played by chemists, as well as other professionals, helps assure that drugs of highest quality are available to the public. The review and evaluation of chemical information and data, within a time constraint, requires the ready availability of adequate chemical information, usually from different sources, utilizing different retrieval systems. The Act requires that an evaluation and response be made to an applicant submitting an NDA within 180 days. This includes, in general, the review of the document, laboratory validation of methods, and inspection of the facilities involved in manufacturing the drug. In some instances decisions must be made based on data that do not *absolutely* ensure the validity of such decisions. Therefore, the more substantial data that are available to the chemist concerning the characteristics of a drug, the greater will be the assurance that an appropriate decision will be reached.

The symposium papers are from two viewpoints: the users of chemical information and the suppliers of chemical information. In the first paper, John Richman, Chemist, Division of Anti-Infective Drug Products, discusses the role of chemical information sources from a reviewing chemist's position. This reviewing function primarily is concerned with IND's and NDA's. The second is by Walter Benson, Acting Director, Division of Drug Chemistry, who discusses the role of laboratory chemists along with some other groups and the importance of chemical information utilization. M. L. Andrews, Assistant Branch Chief, Antibiotic Chemistry Branch, then discusses the role of laboratory chemists as it pertains to antibiotics and the certification procedures. The final paper by R. Solkot, Technical Information Specialist, Bureau of Drugs Medical Library, discusses the role of the Bureau of Drugs Library in supplying chemical information from outside sources.

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Chemical Information Sources: Aids in the Review of Drug Applications†

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Applications of computerized databases to the "Chemist's Review" of drug applications are presented with emphasis on the critical topics addressed in the controls review process and the time limitations imposed thereon.

The sustaining force of the drug industry lies in the research and development of novel compounds which demonstrate pharmaceutical activity and have market potential. The principal concern of the Food and Drug Administration is the demonstration of the safety and effectiveness of these new drugs.

A "new drug" is defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act as any drug whose composition is such that it is not yet generally recognized, among qualified

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Table I. Applications and Submissions in the Review Process

type	submitted during fiscal year 1976	1977	total no. in files
INDs	840	960	14 000
NDAs	360	320	18 000
ANDAs[a]	490	580	4 500
DMFs[a]	230	280	3 000
SUPPLEMENTS TO NDAs	2900	3900	N.A.[b]
F.O.I.s[a]	1077	2304	N.A.

[a] Abbreviated NDAs, Drug Master Files, Freedom of Information Requests. [b] Not available.

experts, as safe and effective for use under the conditions prescribed. I have taken the liberty to paraphrase this definition for the sake of brevity. Generally, a new drug comes before the Administration for review as the subject of a "Notice of Claimed Investigational Exemption for a New Drug", commonly referred to as an IND. The IND is submitted under the provision of Section 505(i) of the Act and Paragraph 312.1 of Title 21 of the Code of Federal Regulations. The IND provides for the initiation of clinical investigations which progress through three phases. The initial phase may not begin for 30 days following its submission. During this time interval, the reviewing disciplines must determine whether the available information supports safety of the clinical studies as described in the protocol. If not, the sponsor is then notified to withhold the initiation of studies pending the submission of additional information regarding the safety of the drug. This initial stage of investigation in humans is termed Phase I wherein clinical pharmacology studies begin when the drug is first introduced. Up to this stage only animal and in vitro data are available for determining the basic parameters of the drug. Phase 2 may overlap with Phase I in that it covers the initial efficacy trials on a limited number of patients. Expansion of the investigation into Phase 3 clinical trials provides the assessment of the drug's safety, effectiveness, and optimum dosage schedules in large numbers of patients, using the final dosage form of the new drug product. As the clinical trials progress to this Phase 3 stage, the sponsor should consider submitting a New Drug Application (NDA) under Section 505(b) of the Act and Paragraph 314.1 of Title 21 of the Code of Federal Regulations. By this time the controls portions of the IND regarding composition, manufacturing, and processing operations of the drug should have been adequately and satisfactorily described and revised to the point where an NDA would be an expansion of the information contained in the related IND augmented by any additional information requested by the reviewing chemist.

To present a synopsis of the numbers and types of submissions requiring review by the chemist, Table I lists the types of submissions, the total number carried in the files, and the number submitted during the fiscal years 1976 and 1977. The figures have been rounded off for simplicity.

In addition to the time limit of 30 days imposed for the initial review of an IND with regard to safety, a 60-day deadline for the completed in-depth chemist's review has been imposed through internal policy. No time limits are imposed after the completion of the initial in-depth review of an IND. Once an NDA has been submitted, Section 505(c) of the Act imposes a time limitation of 180 days after receipt of the NDA for a decision on whether the application may be approved or not. Supplements to approved NDAs also fall under this same limitation. Couple these time limitations with other time-consuming factors of the review process, such as document handling time, the necessity for analytical methods validation, establishment inspections, as well as amendments to the NDA, and the necessity for prompt, efficient, and accurate information retrieval systems becomes obvious.

The "Chemist's Review" format for INDs and NDAs is roughly the same; however, the NDA requires more detailed and expanded coverage of the controls portion of the application. Some of the critical topics addressed by the chemist in the review process are commented upon here to give an idea of the types of information required to complete an in-depth, accurate, and comprehensive review.

The information which appears on the front page of the "Chemist's Review" deals with the identification of the product by name, dosage form, route of administration, pharmacological activity, principal indication, structural formula, and chemical name followed by the chronological listing of the date of the initial submission and any amendments thereto. In addition to this information, documents are listed which support the submission, and related documents previously filed are also listed for reference purposes. The remaining topics of concern to the reviewing chemist constitute the "Review Notes" section of the review wherein the following topics are commented upon in detail:

Components of the drug, source of the new drug substance raw material
Composition of the drug and any reasonable variations
Synthesis of the new drug substance raw material
Raw material controls for the new drug substance and other ingredients
Other firms involved in the manufacturing and processing operations
Manufacturing, processing, and labeling procedures
Container and closure system for the finished dosage form dosage form
Specifications and tests imposed on the finished dosage form
Stability of the finished dosage form
Controls content of the labeling
Environmental impact analysis statement

It is the responsibility of the reviewing chemist to evaluate the application with regard to these topics within the required time frame and make recommendations based on his conclusions regarding the standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

In many cases the drugs are novel in structure and have not appeared on the pharmaceutical market. Although the chemist relies on his expertise in the field of medicinal chemistry, the preponderance of information entering the literature makes it impossible to remain currently informed by the classical manual search techniques. Add to this problem the fact that a lot of information does not reach the literature, and it becomes clear that automated data systems are essential to the chemist in reviewing drug applications within the imposed time limitations. "An information system will tend not to be used whenever it is more painful and troublesome for the customer to have the information than for him not to have it" (Mooers law). With this in mind, the ASTRO data retrieval system and the Bureau of Drugs Library search systems have been carefully designed to be as painless and trouble-free as possible. In addition, the systems are revised and augmented from time to time to increase the efficiency and speed the flow of information to the reviewing chemists.

The ASTRO automatic data processing system is maintained and operated in-house by the Drug Review Support Branch and consists of data which have been abstracted from INDs and NDAs. This system also maintains a chronological record of actions regarding the legal status of the submission as well as chemical control information. This system serves as a two-way street in that data can be abstracted directly from the application by the staff of the Drug Review Support

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†

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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

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