OL. 32, NO. 11 NOVEMBER 1977

Food Drug Cosmetic Law JOURNAL

Priority Setting in the Real World

. . . . . DONALD KENNEDY

Bioavailability / Bioequivalance

. . . . . BERNARD E. CABANA

A COMMERCE CLEARING HOUSE PUBLICATION
PUBLISHED IN ASSOCIATION WITH THE FOOD AND DRUG LAW INSTITUTE, INC.

THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis contributions and comments are invited.

The FOOD DRUG COSMETIC LAW JOURNAL is published monthly by Commerce Clearing House, Inc. Subscription price: 1 year, $40; single copies, $4. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

November, 1977
Volume 32 • Number 11

Second-class postage paid at Chicago, Illinois and at additional mailing offices.

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The equivalency and interchangeability of drugs is the main focus of *James T. Doluisio's* article "A Definition of Bioequivalence/Bioavailability and a Historical Perspective." He discusses the fact that drugs that are deemed bioequivalent are not necessarily interchangeable. Among the other topics discussed are the difference between "drugs" and "drug products" and the FDA regulations concerning interchangeability. Mr. Doluisio is dean of the College of Pharmacy of the University of Texas at Austin. The article begins on page 506.

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A Study of the Drug Laws of the Federal Republic of Germany

By DANIEL F. O'KEEFE, JR. and RAINER G. CZENIEK

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Mr. Czeniek Is an Attorney and a Member of the Parliamentary Research Service of the German Bundestag in the Federal Republic of Germany.

Introduction

THIS PAPER PROVIDES a brief yet comprehensive survey of the major provisions of the recently enacted drug laws of the Federal Republic of Germany. Rather than attempting a point-by-point comparison with American law that might obscure the underlying structure of the German regulatory scheme, this paper considers the German system on its own terms and reserves comparative commentary for the conclusion.

The paper will examine the scope of the revised German drug laws, the process by which drugs must be legally approved for marketing, the guidelines established for the transition to the new regulatory scheme, the specific controls on the distribution, advertising and promotion of drugs, and the enforcement provisions of the new legislation. In addition, we will touch on several major areas which we believe will be of special interest to the reader, including the regulation of drug imports and exports and the legislated boundaries of product liability.

To put the current regulatory scheme into perspective, it may be helpful to summarize first the history of drug regulation in Ger-

many and to indicate the scope and nature of the changes encompassed in the new law.

Scope of German Drug Regulation: Past History and Recent Revisions

The Constitution of the Federal Republic of Germany authorizes the Federal legislature to regulate the manufacture, promotion and distribution of drugs.[1] In 1961 the German Bundestag (the German Federal Legislature) enacted its first comprehensive law on the subject[2] followed in 1965 by a law on the advertising of medicines.[3]

Under the 1961 drug law, only manufacturers of brand name drugs (as opposed to generics) are required to register with the Federal government. There are no provisions in the 1961 law requiring general premarket approval of any drug and no provisions requiring submission of safety and effectiveness data to the Federal government for drugs.[4] Drugs found to be unsafe can be removed from the market, however, by administrative decision of the appropriate state authorities, whose decision is reviewable by a special court. The burden of proof that a drug is unsafe generally is on the government.

On May 6, 1976, the German Bundestag approved a totally revised drug law. Entitled "Bill on the Reform of the Drug Law,"[5] it was the result of one and a half years of intensive discussions and several hearings in various Committees of the German Bundestag. *The new German law will become effective on January 1, 1978.*

The principal committee of the Bundestag which worked on the new law was the "Parliamentary Subcommittee on Reform of the German Drug Law." The work of this Subcommittee, chaired by Prince Wittgenstein, laid the foundations for the Committee Report and the Motion proposed by the Committee for Youth, Family and Welfare to the full assembly of the German Bundestag (hereinafter

[1] Constitution of the Federal Republic of Germany, Article 74, Nos. 19 and 11.

[2] "Law on the Manufacture, Sale and Distribution of Drugs (Drug Law)", *Federal Gazette I*, page 533 (1961). The manufacture and distribution of addicting medicines is controlled by a special law on narcotics.

[3] "Law on Advertising in the Field of Curative Medicine", *Federal Gazette I*, page 604 (1965).

[4] In the case of so-called "drug specialties," that is, drugs "containing substances, the effects of which are not generally known in the field of medical science", a report on pharmacological and clinical trials with respect to drug safety has to be presented by the aplicant. (Sec. 21(1a) as amended on June 23, 1964.) (Emergency amendment —Thalidomide).

[5] *Federal Gazette I*, page 2445 (1976) (hereinafter cited as "German Drug Law").

referred to as "Committee Report") on the background, intent, and meaning of the new law.

The Department of Youth, Family and Health recommended a total revision of the German drug law[6] to the Bundestag. The Committee Report cites the Thalidomide tragedy as an example of the dangers connected with drugs, and stresses the intent of the new law to improve the safety of drugs. The Report also notes that scientific advances in the drug field have taken place rapidly since 1961 and that internationally recognized standards in drug testing and manufacturing practices have not been incorporated into German law.[7] The Bundestag agreed with the Committee's approach and a total revision was enacted instead of making amendments to the old law.

The new law is divided into ten articles. The major articles are:

Article 1—replaces the 1961 law. It is the heart of the new law and controls the manufacture, sale and distribution of drugs.

Article 3—contains transitory provision relating to drugs on the market when the new law becomes effective on January 1, 1978.

Article 4—contains amendments to the laws relating to advertising of medicines.

The major changes which will be effected by new German law will be:

(1) To require manufacturers to prove the safety and effectiveness of each "finished drug product" introduced on the German market after January 1, 1978;

(2) To establish commissions to review all drugs on the market prior to January 1, 1978;

(3) To establish a Federal drug monitoring system to gather data on adverse reactions and other risks associated with the use of marketed drugs;

(4) To establish explicit provisions regarding the testing of drugs on humans, including provisions relating to informed consent;

(5) To establish a system of limited liability and mandatory insurance to compensate persons injured by a drug;

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[6] Draft of a law on the Reform of the Drug Law, Drucksache 7/3060.

[7] Report of the Committee for Youth, Family and Health (13th Committee), Printed Matter (Drucksache) 7/509 (1976) (hereinafter cited as "Committee Report"), II.1. page 5.

(6) To conform German law to that of other European Economic Community (EEC) countries in accordance with 3 Pharmaceutical Directives promulgated by the EEC;[8]

(7) To increase information available to the public; particularly by requiring a package insert for all (including both prescription and non-prescription) "finished drug products," listing contraindications, side effects and interactions with other products;

(8) To require all advertising to state label warnings and other information in considerable detail;

(9) To require manufacturing and marketing permits from the country of manufacture for imported drugs. In the case of non-EEC countries to require the recipient to obtain an importer's license.

The new law will be administered by the Institute for Drugs in the Federal Health Office (FHO) within the Department of Youth, Family and Health. This is roughly equivalent to the U. S. version of the Bureau of Drugs in the Food and Drug Administration of the Department of Health, Education and Welfare.

The FHO will be empowered to decide which drugs will be approved for marketing and which shall be removed from the market, and to supervise the drug safety monitoring program. Plant inspection and drug law enforcement, however, will be the responsibility of the appropriate administrations of the ten "states" within the Federal Republic and of West Berlin. This division of authority is consistent with the general German constitutional principles that the "Federal" government makes decisions only if uniformity is absolutely necessary and that enforcement decisions are "state" matters.[9] In fact, the German system is structured so that the "states" administer all provisions of Federal law, unless the Constitution expressly provides otherwise.[10]

In 1976, the FHO had about 1,250 employees and its budget was approximately $28 million. It is anticipated that by 1978 the Institute of Drugs will increase its present staff of about 170 to about 350 employees, about 65 percent of whom will be involved in the "authorization admission" of drugs.

To assist in the implementation of the new law, the Federal Minister for Youth, Family and Health (hereinafter the Federal

[8] No. 65/65 of January 26, 1965; No. 75/319 of May 20, 1975; No. 75/318 of May 20, 1975.

[9] Constitution of the Federal Republic of Germany, Art. 87, 87a, 87b.

[10] Constitution of the Federal Republic of Germany, Art. 83.

Minister) is in the process of writing regulations. While these regulations are not required to be approved by the Bundestag, it is anticipated that the concerned Committees will be advised prior to final promulgation of the regulations. Also, the Federal Council, composed of 41 representatives of the state governments, must approve most of the regulations implementing the new law.

Provisions of the Reformed German Drug Law

The new German drug law, like its American counterpart, is characterized by a central regulatory scheme intended to prevent the introduction onto the market of potentially dangerous or ineffective drugs through preclearance procedures.

As previously noted, on May 6, 1976 the German Bundestag approved the new drug law for the Federal Republic. Published in the *Federal Gazette* on August 24, 1976, the new law will become effective on January 1, 1978.[11]

Definitions and Scope

The term "drug"[12] is broadly defined to include substances which are intended to cure, relieve, prevent or diagnose illness, injury or symptoms thereof, or to influence a function of the body. The definition also includes items which are "considered" as drugs, including medical devices, which are not treated separately under German law.[13] These latter "drugs" are known as "fictive" drugs and are subject to considerably less regulation than drugs in the first definition. There is also a "catchall" under which the term "drug" includes products admitted or registered as drugs by the government, or exempted by order from such procedures. Food, tobacco, and cosmetics are expressly excluded from the definition.

The term "finished drug products"[14] is defined as "drugs which are manufactured beforehand and then marketed in packages ready for distribution to the consumer." It includes not only brand name drugs, but also generic drugs (a change from the old law).

Prescription drugs are to be defined by the Federal Minister (in agreement with the Minister of Economics and subject to approval of the Federal Council). The Minister may declare prescription status for drugs which can be safely used only under a doctor's supervision or for drugs which can be injurious to health if not used as directed.

[11] German Drug Law, Article 10.
[12] German Drug Law, Article I, Sec. 1, Sec. 2.
[13] German Drug Law, Article I, Sec. 1, Sec. 2(2).
[14] German Drug Law, Article I, Sec. 1, Sec. 4(1).

where such occurs frequently.[15] In addition, drugs "not generally known in the field of medical science" are automatically placed on prescription status for a specified period of time.[16]

Non-prescription drugs are not defined as such, but, in fact, constitute the remainder.

There are also special provisions in the German drug law with regard to animal drugs, radio active drugs, vaccines, test allergens, blood, and homeopathics.

The New Regulatory Scheme

The marketing of "hazardous drugs" is prohibited. "Hazardous drugs" are defined as those "justifiably suspected of having harmful effects that exceed the bounds considered justifiable in the light of knowledge available of medical science" when used as directed.[17]

Under the new law, the Federal Minister has the authority, subject to the approval of the Federal Council,[18] to issue "statutory orders"[19] that prohibit, limit, or require the use of certain substances and/or preparations made from such substances in the manufacture of drugs. In addition, the Federal Minister has the authority to forbid the marketing of drugs that do not comply with these "regulations," if it is deemed necessary for the protection of human or animal health.[20]

The new law also prohibits the marketing of drugs which have false or misleading claims, or have "significantly diminished quality."[21]

After December 31, 1977, every "finished drug product" which is not a "fictive" drug, newly introduced on the German market, must receive a formal "admission authorization" from the Federal Authority prior to marketing.[22] While the definition of "finished drug product" appears rather narrow, the great preponderance of drugs presently marketed in Germany meet the definition and the term includes both over-the-counter (OTC) and prescription drugs. Furthermore, the Federal Minister, with the approval of the Federal Council, may "extend the regulations on the admission authority to

[15] German Drug Law, Article I, Sec. 7, Sec. 48(2)(1).

[16] German Drug Law, Article I, Sec. 7, Sec. 49.

[17] German Drug Law, Article I, Sec. 2, Sec. 5.

[18] The Federal Council is composed of 41 representatives delegated by the 10 state governments in the Federal Republic.

[19] In effect, a regulation implementing the law is legally binding as long as consistent with the law. (Constitution of the Federal Republic of Germany, Article 80(1).)

[20] German Drug Law, Article I, Sec. 2, Sec. 36.

[21] German Drug Law, Article I, Sec. 2, Sec. 38.

[22] German Drug Law, Article I, Sec. 4, Sec. 21.

other drugs . . . to prevent a direct or indirect jeopardy of human or animal health."[23]

There are a few finished drugs for which formal admission is not necessary. Generally, these exceptions are for drugs made in limited quantity in a pharmacy and for drugs used in clinical trials.[24] The Federal Minister also has the authority, subject to the approval of the Federal Council and after consultation with scientific experts, to "release certain drugs or groups of drugs . . . from the obligation to apply for admission authorization" where public health is not endangered.[25]

Application for admission is made by the pharmaceutical enterprise[26] with the Federal Health Authority.[27] The application is to be accompanied by detailed information on the drug including its identity, side effects, contraindications, interactions, the method of manufacture and quality control, and results of analytical trials, pharmacological and toxicological trials and clinical or other tests.[28] Expert opinion is also to be included.[29] The Committee Report indicates that pharmacological, toxicological and clinical tests must be submitted in most cases *only* for "pharmaceutical novelties."[30]

It may be of interest to note that release of trade secret information by government officials would be a violation of the German Criminal Code.[31] Hence it was deemed unnecessary to include a specific provision protecting trade secrets in the new drug law.[32]

In the case of drugs for which the effects and side effects are known, and drugs of comparable composition to already approved drugs ("me-too" drugs), "other scientific documentation" may be substituted for pharmacological-toxicological and clinical test results. The term "other scientific documentation" is defined to include "medi-

[23] German Drug Law, Article I, Sec. 4, Sec. 35(1)2. The Bundestag made it clear by a specific Resolution that bulk drugs are to be included by statutory order where necessary for safety. Resolution No. 1 of the German Bundestag enacted on May 6, 1976, Drucksache 7/5025, page 3.

[24] German Drug Law, Article I, Sec. 4, Sec. 21(2).

[25] German Drug Law, Article I, Sec. 4, Sec. 36 (so-called "standard admission").

[26] Defined as the "party marketing drugs under its own name." German Drug Law, Article I, Sec. 1, Sec. 4(18).

[27] German Drug Law, Article I, Sec. 4, Sec. 21(1).

[28] German Drug Law, Article I, Sec. 4, Sec. 22(1)(2).

[29] German Drug Law, Article I, Sec. 4, Sec. 24.

[30] Committee Report III.1. "Zu Sec. 21," Drucksache 7/5091, page 14.

[31] German Criminal Code, as amended January 2, 1975, *Federal Gazette I*, page 1, Secs. 203-205.

[32] Committee Report III.1 "Zu Sec. 102," page 22. See also Resolution No. 4 of the German Bundestag, Drucksache 7/5025, page 3.

cal experimental documentation prepared in accordance with scientific methods . . . ."[33] This less extensive documentation is also sufficient for the components of a drug that is merely a new combination of known ingredients, and even for the new combination itself, if its safety and effectiveness can be demonstrated logically from current knowledge and evaluation of the known ingredients.[34]

Although the FHO may decline to issue the "admission authorization" (formal approval), it may do so only under certain conditions, including insufficient testing, insufficient substantiation of therapeutic efficacy, or a reasonable suspicion that the drug, when used as directed, has harmful effects exceeding justifiable bounds.[35] While the law does not define safety or effectiveness, the Committee Report notes that there can be no absolute guarantee of safety[36] and that the term "effectiveness" is relative, to be viewed in the context of whether the drug is for use in the treatment of a serious or minor ailment.[37] The Committee Report also makes clear that, while the burden of proof of safety and effectiveness is on the pharmaceutical enterprise applicant, medical experience evidence would be accepted as sufficient support as a substitute for medical—clinical trials, unless a "pharmaceutical novelty" is to be evaluated.[38]

Application for certain drugs (which are new to medical science) are reviewed by an "admission authorization commission". The commission is to be composed of scientific experts.[39] Drugs reviewed by the commission will be available only on prescription, and are those drugs "containing substances the effects of which are not generally known in the field of medical science," or "drugs which are preparations made from substances, the effects of which are generally known, if the effects of these preparations as a whole are not generally known in the field of medical science." The Federal Minister (without the need for approval of the Federal Council) may stipulate such drugs.[40]

Drugs other than defined above (which may be either prescription or OTC) are "admitted" in accordance with standards approved

[33] German Drug Law, Article I, Sec. 4, Sec. 26(2), sentence 2.

[34] German Drug Law, Article I, Sec. 4, Sec. 22(3). Committee Report II.2. page 6. See also Resolution No. 5 of the German Bundestag, Drucksache 7/5025, page 3.

[35] German Drug Law, Article I, Sec. 4, Sec. 25(2).

[36] Committee Report III.1. "Zu Sec. 1," and II.6. Drucksache 7/5091, page 11 and page 9.

[37] Committee Report II.2, Drucksache 7/5091, page 5-7.

[38] Committee Report III.1. "Zu Sec. 21." Drucksache 7/5091, page 14; Resolution No. 5 of the German Bundestag. Drucksache 7/5025, page 3.

[39] German Drug Law, Article I, Sec. 4, Sec. 25(6).

[40] German Drug Law, Article I, Sec. 7, Sec. 49(4).

and published by the FHO after receiving recommendations from "commissions" established by the FHO to review drugs by therapeutic class.[41] The principal objective of these commissions is to prepare the existing documentation so that applicants may refer to the published results of a commission's work when applying for admission of an existing drug, a me-too-drug, or a combination, the safety and effectiveness of which is reasonably apparent.[42]

Wherever the FHO disagrees with a commission's recommendation, it must give its reasons.[43]

Decisions regarding approval or disapproval of an application for "admission authorization" are to be made within four months. This period may be extended by an additional three months. The time period may be suspended to permit applicants to "correct faults" in their application.[44]

The FHO also has the authority to impose conditions on admissions[45] and it may authorize the marketing of a drug of high therapeutic value prior to completion of tests necessary for a comprehensive assessment of the drug.[46]

The pharmaceutical enterprise is also required to notify the FHO of changes in the material submitted in support of its application and, under some conditions, must apply for readmission after acceptance of its original application.[47]

"Admission authorizations" automatically expire five years from the date of issuance (or in two years if no use is made of it). Applications for renewal are to be made three to six months prior to expiration of the authorization. They are renewed for a further five year period if there are no grounds for refusal of an initial application. The FHO may request further information on the drug at time of renewal.[48]

"Admission authorization" may also be withdrawn, revoked or suspended if it is determined that the drug is unsafe or lacks therapeutic efficacy. Notice and a "hearing" are provided to the applicant unless danger is imminent.[49]

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[41] German Drug Law, Article I, Sec. 4, Sec. 25(7).

[42] Committee Report III.1, "Zu Sec. 24," Drucksache 7/5091, page 14-15, *see also* footnote 106.

[43] *Id.*

[44] German Drug Law, Article I, Sec. 4, Sec. 27(2).

[45] German Drug Law, Article I, Sec. 4, Sec. 28(1)(2).

[46] German Drug Law, Article I, Sec. 4, Sec. 28(3).

[47] German Drug Law, Article I, Sec. 4, Sec. 29.

[48] German Drug Law, Article I, Sec. 4, Sec. 31(2).

[49] German Drug Law, Article I, Sec. 4, Sec. 30.

Costs for the "admission authorization" procedure are borne by the applicants.[50]

Decisions regarding authorizations are published in the *Federal Gazette*[51] and the Federal Minister is authorized, subject to approval of the Federal Council, to "settle further details concerning the procedures involved with respect to the admission . . . ."[52]

Regulations for drug testing comprise a separate section of the new law. Under that section, the Federal Minister is authorized, after consultation with experts and with the consent of the Federal Council, to issue "guidelines" (regulations) concerning the obligatory standards and methods for any analytical, pharmacological, toxicological and clinical trial.[53]

Testing on humans is also regulated under the law. The law requires informed consent, medically-supervised, medically justified tests, and prohibits the use of prisoners or those placed in institutions by court or government order. In general, the rules of the Declaration of Helsinki, as amended in Tokyo, are followed.[54]

Transition Regulations

The German law has a highly significant—if temporary—series of "grandfather" clauses.

A "finished drug product" which is on the German market on January 1, 1978 (the effective date of the new law) is "deemed authorized for admission" if:

> (1) it was on the market on August 24, 1976 (the date the new law was published in the *Federal Gazette); or*
>
> (2) if an application with respect to it was filed by August 24, 1976 and if the application as later accepted and the drug entered in the Register of Pharmaceutical Specialties in accordance with the 1961 drug law.[55]

Notification that this clause applies must be given to the FHO within six months after January 1, 1978. The notification must include information on the labeling and ingredients. "Finished drug products" may continue to be marketed only if timely notification is made.[56]

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[50] German Drug Law, Article I, Sec. 4, Sec. 33.

[51] German Drug Law, Article I, Sec. 4, Sec. 34.

[52] German Drug Law, Article I, Sec. 4, Sec. 35(1) No. 1.

[53] German Drug Law, Article I, Sec. 4, Sec. 26(1).

[54] German Drug Law, Article I, Sec. 6, Secs. 40-42.

[55] German Drug Law, Article 3, Sec. 7(1).

[56] German Drug Law, Article 3, Sec. 7(2).

Therefore, in order to have the advantages of the "grandfather" provisions, it is imperative to give proper notification to the FHO no later than June 30, 1978.[57]

Once proper notification is given, "finished drug products" subject to this provision may continue to be marketed for twelve years after January 1, 1978 without further action. Application for renewal should be filed prior to expiration of the twelve years.[58] If "objections" are raised at renewal time, the applicant will have three years to correct any cited deficiencies.[59]

Thus, "finished drug products" currently on the market, in effect, have a fifteen-year "grace" period with respect to the new rules on admission. They are not subject to the new label or package insert provisions (discussed later) until one year after their admission has been renewed.[60] The FHO has authority, however, to "impose conditions for the provision of warning indications . . . in order to prevent a . . . jeopardy of human or animal health . . ." during the "grace" period.[61]

During the twelve-year "grace" period, the Committee Report indicates that the "commissions" are expected to develop monographs which would be used as the scientific basis for determining the safety and effectiveness of existing drugs, when their renewal application is filed.[62]

Distribution, Promotion, Price Control, Labeling, and Advertising.

In Germany, Federal law controls distribution. Drugs generally may be sold only by pharmacies[63] and there is no German counterpart to the status of ethical and proprietary OTCs in the U. S. However, the Federal Minister, after consultation with experts, (and in agreement with the Minister for Economics, subject to the approval of the Federal Council) may permit non-prescription drugs to be sold outside of pharmacies where "jeopardy of human health is not to be feared."[64]

Detail men (who distribute drug samples and supply the medical profession with trade information) are required to have credentials equivalent to a pharmacist ("specialized knowledge") under the Ger-

[57] German Drug Law, Article 3, Sec. 7(2).
[58] German Drug Law, Article 3, Sec. 7(3)(4).
[59] German Drug Law, Article 3, Sec. 7(5).
[60] German Drug Law, Article 3, Sec. 11.
[61] German Drug Law, Article 3, Sec. 12.
[62] Committee Report III.2. "Zu Sec. 7." Drucksache 7/5091, page 22.
[63] German Drug Law, Article I, Sec. 7, Sec. 43(1).
[64] German Drug Law, Article I, Sec. 45.

man Law.[65] These "medical representatives" have an additional obligation to notify employers of any adverse reactions to the company's drugs reported to them in the course of their work.[66]

To some extent, the German Federal law regulates the prices of drugs. It authorizes the Minister of Finance (in agreement with the Federal Minister of Youth, Family and Health and the Minister for Labor and Social Affairs, and subject to approval of Federal Council) to fix retail and wholesale price margins. Prices are to take into account the legitimate interests of the consumer, the pharmacist and the wholesaler.[67] Price control, however, does not extend to manufacturers.

Labels for finished drug products (both prescription and nonprescription) must show the name and address of the manufacturer or distributor, the brand name of the drug, its admission number, its dosage form, its content, the method of application, the name and quantity of its active components and its expiration date if shelf life is less than three years. The FHO may require warning and storage indications.[68]

In addition, package inserts are required for all finished drug products (both prescription and non-prescription). These must include the name and address of the manufacturer or distributor, the brand name of the drug, the name and quantity of its active ingredients, the therapeutic category, the contraindications, the side effects, interactions with other products, dosage instruction and the method of application. The FHO may require warnings and storage instructions.[69] As drugs are generally marketed as finished drug products (packaged drugs) in Germany, the consumer receives the full package insert on both prescription and non-prescription drugs. This is contrary to the procedure in the U. S. where the package insert generally is intended only for the information of the physician and pharmacists.

Advertising of drugs in Germany is governed by the "Law on Advertising in the Field of Curative Medicine."[70] This law too was significantly amended. The amendment requires all advertisements for drugs (not "fictive" drugs) to contain the name and address of the pharmaceutical enterprise, the brand name of the drug, the name and

[65] German Drug Law, Article I, Sec. 14, Sec. 75.
[66] German Drug Law, Article I, Sec. 14, Sec. 76.
[67] German Drug Law, Article I, Sec. 14, Sec. 78.
[68] German Drug Law, Article I, Sec. 2, Sec. 10.
[69] German Drug Law, Article I, Sec. 2, Sec. 11.
[70] *Federal Law Gazette I*, p. 604 (1965).

quantity of its active ingredients, the therapeutic category, contraindications, side effects, and warnings required to be on labels.[71]

Advertisements for prescription drugs may be made only to health professionals. Also, advertisements for drugs which are intended to "eliminate sleep disorders or psychic disturbances in humans or to influence the state of mood" may be displayed only to health professionals.[72]

Advertisements to consumers do not have to include the name and quantity of each active ingredient. Reminder ads need not contain any of the required information.[73] Reminder ads may give only the identity of the drug and its brand name. The new advertising provisions go into effect on January 1, 1978.

Manufacturing Practices and Drug Monitoring

Commercial manufacturers must obtain a permit from the state authority in which the operation is located.[74] "Pharmaceutical enterprises" as well as those engaged in testing, storing, or marketing of drugs must inform the proper state authority before engaging in business.[75]

The Federal Minister is authorized in agreement with the Minister of Economics and subject to approval of the Federal Council to issue regulations covering manufacturing, testing, storage, packaging, marketing, record keeping, personnel and the like.[76] Drugs must also meet the standards of the German Pharmacopoeia.[77]

The new law also established a formal, though voluntary, drug monitoring system. The Federal Minister is to establish regulations detailing methods for recording and analyzing risks associated with drugs.[78] The FHO is to be the central agency receiving and evaluating data. The Committee Report requested the cooperation of industry, the medical profession and others in this effort.[79]

Enforcement and Product Liability

The "state" authorities can enforce the law through administrative injunction and seizure of drugs.[80] Courts of law can inflict criminal

[71] German Drug Law, Article 4. The Committee Report indicates that a strong minority opposed requiring all of this detail in business and advertising. Committee Report III.3. "Zu Nummer 3" Drucksache 7/5091, page 23.

[72] *Id.*

[73] *Id.*

[74] German Drug Law, Article I, Sec. 3, Sec. 13.

[75] German Drug Law, Article I, Sec. 11, Sec. 67.

[76] German Drug Law, Article I, Sec. 8, Sec. 54.

[77] German Drug Law, Article I, Sec. 8, Sec. 55.

[78] German Drug Law, Article I, Sec. 10, Sec. 63.

[79] Committee Report I.3. and III.1. "Zu Sec. 57," pages 7 and 19.

[80] German Drug Law, Article I, Sec. 11, Sec. 69.

penalties.[81] The potential penalties for violation of the law range from a fine to imprisonment up to ten years.

In essence, intentional violation of law or statutory orders where the act is deemed extremely dangerous to health is punishable by imprisonment up to two years or an unlimited fine. The same acts performed negligently rather than intentionally reduce the maximum prison term to one year. In very serious instances, where the health of a large number of persons is jeopardized, imprisonment may be for as much as ten years.

Intentional violation of the law or its regulations not deemed extremely dangerous is punishable by a maximum prison term of one year or an unlimited fine. These offenses would include violation of the admission provision, or violation of misleading claims provisions.[82] Negligent, rather than intentional violation of the "not extremely dangerous" variety, results in a "disciplinary offense" and is punishable by fine.[83]

Intentional or negligent violation of provisions not directly related to health risks (such as marketing after expiration date, failure to notify proper authorities, etc.) is punishable by a maximum fine of $20,000.[84]

The new law also establishes a system of limited liability for injuries caused by drugs. If a person is killed or seriously injured, the manufacturer of the drug must compensate the injured party. Liability exists only if "the drug, under correct stipulated usage has damaging effects, which exceed the bounds considered justifiable in the light of knowledge available of medical science . . . or the damage has occurred as a result of [misbranding] . . . or the instructions for usage do not comply with available knowledge of medical science."[85] Negligence need not be shown.

If the injured party is contributorily negligent, compensation is diminished in proportion to the injured party's negligence.[86]

Damages are limited to the costs of medical treatment plus costs of damage suffered by others dependent on the injured party, to the extent of the normal life expectancy of the injured party and the extent of the dependency. The maximum liability is about $200,000 or a $12,500 annuity. The maximum liability for the manufacturer for any one drug

[81] German Drug Law, Article I, Sec. 17, Secs. 95, 96.
[82] German Drug Law, Article I, Sec. 17, Sec. 96.
[83] German Drug Law, Article I, Sec. 17, Sec. 97(1).
[84] German Drug Law, Article I, Sec. 17, Sec. 97(2).
[85] German Drug Law, Article I, Sec. 16, Sec. 84.
[86] German Drug Law, Article I, Sec. 16, Sec. 85.

is about $83 million or annuity up to about $5 million.[87] If several persons are awarded damages and the total exceeds the maximum, compensation of individuals is reduced.[88] Companies are required to insure.[89]

Imports and Exports

There are no provisions in the new law regarding export of drugs from Germany.

The law with respect to imports has been substantially changed:

In the case of a drug imported for the first time after December 31, 1977 from an EEC country, the drug must be formally admitted as in the case of any other product newly introduced into the German market.[90] When filing the application the pharmaceutical enterprise must show that the drug has the proper manufacturing and marketing permits in the country of manufacture, as well as showing that the drug meets the requirements of German law for admission of a drug.[91] The presentation of a special import license, however, is not required. It is only necessary that the recipient of the imported drug be a pharmaceutical enterprise, wholesaler or owner of a pharmacy.[92]

With respect to drugs imported for the first time after December 31, 1977 from non-EEC countries, in addition to the required admission authorization, and manufacturing and marketing permits from the country of manufacture, the applicant must also show that the recipient of the imported drug is a licensed importer.[93] A licensed importer[94] may only import drugs intended for humans:

(1) If it can be shown that the drugs were manufactured in compliance with the requirements for Good Manufacturing Practice (GMP) of the World Health Organization, a certificate of the proper authority in the manufacturing country is sufficient, if such certificates are mutually acknowledged between Germany and that country.

(2) If certificates are not mutually recognized, then the German state authorities must certify that, after investigation, such GMP standards are met.

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[87] German Drug Law, Article I, Sec. 16, Secs. 86, 87, 88 No. 1 and 2.

[88] German Drug Law, Article I, Sec. 16, Sec. 88.

[89] German Drug Law, Article I, Sec. 16, Sec. 94.

[90] German Drug Law, Article I, Sec. 13, Sec. 73(1).

[91] German Drug Law, Article I, Sec. 4, Secs. 22(5) and (6).

[92] German Drug Law, Article I, Sec. 13, Sec. 73(1) No. 1.

[93] German Drug Law, Article I, Sec. 4, Sec. 22(5) in connection with Section 13, Sec. 73(1) No. 2, Sec. 72(1). The applicant for admission of the imported drug (pharmaceutical enterprise) and the importer (recipient) need not necessarily be identical.

[94] German Drug Law, Sec. 13, Sec. 72(1).

(3) If neither of the above is met, the importer must obtain a statement from the appropriate German state authority that the import is in the interests of the general public.[95]

The Federal Minister is authorized to accept as valid the "admission" issued by another country.[96]

Imported finished drug products already on the German market on January 1, 1978 and otherwise "grandfathered" may continue to be marketed as German produced drugs already on the market with respect to admission and grandfather status. "Grandfathered" drugs, "deemed authorized for admission", need only meet the requirements of the import provisions: Drugs imported from an EEC country need only be received by a pharmaceutical enterprise, wholesaler or owner of a pharmacy.[97]

"Grandfathered" drugs from non-EEC countries must be imported by a licensed importer,[98] who is generally required to prove that the GMP rules were complied with in the manufacturing country, if drugs intended for humans are concerned.[99]

All imported drugs—like their German manufactured counterparts —must meet standards of the German Pharmacopoeia.[100]

Conclusion

The recent reform of the German drug law imposes a comprehensive new regulatory framework on the production and marketing of drugs in the Federal Republic of Germany. As in American drug law, the heart of the system is the requirement that new drugs be approved, based on demonstrated safety and efficacy, before they may be introduced into the market. Although American law does not require such prior approval for most OTCs and other "not new" drugs, "admission authorizations" are mandatory in Germany for practically all finished drug products except fictive drugs. The German approval process for drugs with known effects recognizes significant differences among drugs. It grants substantial latitude to the applicant regarding the extent of documentation required to demonstrate safety and efficacy. This part of the German system is somewhat reminiscent of the abbreviated new drug procedures in the United States. The establishment

[95] German Drug Law, Sec. 13, Sec. 72(2).

[96] German Drug Law, Sec. 4, Sec. 37(1).

[97] German Drug Law, Article I, Sec. 13, Sec. 73(1) No. 1.

[98] German Drug Law, Article I, Sec. 13. Sec. 73(1) No. 2 71(1).

[99] German Drug Law, Article I, Sec. 13. Sec. 72(2).

[100] German Drug Law, Article I, Sec. 8, Sec. 55(3).

of special commissions to review "new" drugs whose effects are beyond general medical knowledge had no direct counterpart in United States law.

Transition provisions are necessarily a major element of any sweeping new system of regulation. The new German law essentially grants a fifteen-year grace period to finished drug products already on the market when the legislation was first officially published. Drugs on the market on August 24, 1976, or drugs on which an application has been filed by that date may be entitled to this "grandfather" protection, provided that they are on the German market on January 1, 1978, when the new law comes into force. However, in order to have that advantage, it is also imperative to give proper notification to the FHO by June 30, 1978.

The plan to have scientific commissions develop monographs in the interim to serve as the basis for evaluating the safety and effectiveness of drugs when renewal applications are filed after the grace period is reminiscent of the OTC review and the National Academy of Sciences-National Research Council drug efficacy study conducted in the United States. In both nations, then, essentially all drugs on the market will eventually have met some safety-efficacy standard.

The German law, like its American counterpart, places substantial controls on the manufacturing, distribution and promotion of drugs that have met the applicable preapproval standards, although the two regulatory systems differ in their strictness with regard to the various steps in the production-marketing process. The statutes of both nations authorize extensive regulation of the manufacturing process itself, although it remains to be seen if German regulations will be as comprehensive as those issued by the FDA. Consistent with its broad categorization of "finished drug products", the German marketing controls tend to treat all drugs similarly, disregarding the American distinction between ethical and proprietary drugs, limiting almost all drugs to sale only in pharmacies, and requiring extensive labeling and package inserts intended for consumers for all drugs, including those sold only on prescription. In addition, the approach to drug advertising and promotion in the new German drug law is quite different from that in the United States. The German requirement that advertising for most OTC drugs contain warnings and contraindications is not required by American law. And the substantial credentials required of detail men in Germany, as well as the potential control over retail and wholesale prices exercised by the Minister of Finance, are elements not found in American law.

The enforcement provisions of the German law resemble the United States statute in authorizing injunctions, seizure of drugs and criminal penalties for violations. The German law, however, makes rather fine distinctions in relating the severity of the penalty to the severity of the offense. The German law also circumscribes civil remedies, again drawing distinctions based on the nature of the offense. The German law further sets forth a concept of limited product liability not found in its American counterpart.

Finally, the German law significantly controls imports of finished drug products while placing no restrictions on exports whatsoever. Drugs coming to Germany from EEC countries must meet the standards of the country in which they are manufactured and the normal admission authorization requirements for any drug product marketed in Germany. Drugs coming to Germany from non-EEC countries, however, face the additional requirement of showing on their application that the intended recipient is a licensed importer. These licensed importers can only trade in drugs manufactured under certain approved conditions. Imported products currently on the market will be allowed to take advantage of the same transitional grace period as German drugs, but they still must meet the special import regulations, including the requirement that only licensed importers handle drug products originating in non-EEC nations.

In short, the recently revised German drug law is responsive to many of the same needs that have motivated drug legislation in this country, particularly the insistence on demonstrated safety and efficacy. As this survey has shown, however, the specific details of drug regulation in the two countries differ significantly. But for the most part, the different specifics are simply a natural reflection of the necessarily different perceptions of the problem, regulatory styles, and legal-political systems of the two nations. **[The End]**

A Definition of Bioequivalence/ Bioavailability and a Historical Perspective

By JAMES T. DOLUISIO, Ph.D.

Dr. Doluisio Is Dean of the College of Pharmacy of the University of Texas at Austin.

THIS CONFERENCE has been planned to aid both scientific and regulatory professionals in the area of bioequivalency and bioavailability. The primary emphasis of the program will be on how the new Food and Drug Administration (FDA) bioequivalency/bioavailability regulations work.

My charge is to set the stage for our discussion through some historical background on the need for bioequivalency/bioavailability regulations. To understand the issues involved in bioequivalency, you must first understand the difference between the terms "drug" and "drug product." In simple terms, a "drug" can be viewed as an active therapeutic moiety and the "drug product" can be viewed as the delivery system containing the therapeutic moiety. The new regulations are not intended to determine whether or not a drug has therapeutic advantages or disadvantages, but rather they are intended to determine whether or not two different delivery systems, for example, drug products from perhaps different manufacturers, are performing in an equivalent manner. Throughout our discussion you should keep in mind that it is not the drug that is in question, but rather its dosage formulation, that is, delivery system.

Expiration of Patents on Leading Drug Products

One reason that the area of bioequivalence is taking on increased importance is that we are in an era when many drug patents are expiring and these drugs can be made available from several different manufacturers. When this occurs, it is incumbent on the newer manufacturer

to demonstrate that his drug product performs in a similar manner to the original drug product on which extensive clinical evidence has been accumulated. In the 1940's, 1950's, and 1960's many new drugs were developed and the prescription market largely consisted of products available from a sole source of manufacture. As late as 1974, only 60 of the top 200 drug products were multi-source. However, for various reasons, many of which we may feel inappropriate, a trend has developed to where, in the near future, for example 1985, there may be a complete reversal of the market situation. It is estimated that in 1985 approximately 139 of the top 200 products will be multi-source, that is, not under patent protection. In the next five years, it has been estimated that 6% of Rx dollars will be coming off patent annually. (Of course these types of estimates contain many assumptions.)

The reasons and economic implications of this change to "multi-source" in the top 200 drug products can be far-ranging and I am certain would be an interesting topic to pursue. However, what is important to recognize for this conference is that if regulations were not developed to insure bioequivalency in the multi-source market, therapeutic inequivalency would cause a medical nightmare as patents expire.

Utilization of Drug Product Interchange as a Method of Drug Cost Containment

Often there are price differentials between the multi-source drug products and hospitals and prescription reimbursement programs, such as in Medicaid, are developing procedures to take advantage of these price differentials as the availability of multi-source products increases. For example, the Department of Health, Education and Welfare (HEW) is developing a maximum allowable cost (MAC) or "ceiling" limit for reimbursement of selected multi-source drugs. The first drug products to be examined for MACs were Ampicillin capsules. IMS survey information indicated that for bottles of 100 of 250 mg capsules of Ampicillin, prices varied among certain manufacturers from at least $6.00 to $18.74. Careful examination of bioequivalence and other quality assurance data indicated that there was no evidence of bioequivalence problems. Later this month there will be a national MAC established of $7.25 for this particular product. If a pharmacist receives a prescription for a brand above the "ceiling" of $7.25, it is intended that he interchange to a product at or below this ceiling since he will not be reimbursed above the ceiling unless the physician indicates that a particular brand is a medical necessity. The establishment of this ceiling of $7.25 is estimated to produce a Medicaid program savings of $345,000 (approximately 32 percent) for reimbursement of 250 mg

Ampicillin capsules. Thus far, six dosage form of two drugs, Ampicillin and Penicillin VK, have been reviewed and the estimated annual MAC savings in the Medicaid program is between $1.58 and $1.97 million (approximately 30 percent).

Changing Responsibilities for Pharmacists and Physicians

The interchange of drug products as intended in the MAC regulations is prevented by many state antisubstitution laws. However, in the past six years some 22 states have revised these laws to allow at least some form of brand interchange by the pharmacist. It is expected that the opportunity for brand interchange will become greater in the next ten years as more of the top 200 drugs became multi-source. In the past when a physician wrote a prescription for a tradename product, he was both specifying the drug that was to be used and the manufacturer's product. Only in the case of a generically written prescription (some 10 percent of prescriptions written) did the pharmacist have the ability to select the manufacturer's product. The intent of the change in drug product selection laws is not to alter the physician's right to specify the drug to be used for the patient but it is intended to alter his ability to select a specific manufacturer of that drug. Again, this topic would be an interesting one to pursue, but it would not be an appropriate diversion from the main topic of this conference. However, it is important to note these changing responsibilities as a part of the historical perspective of bioequivalency and bioavailability. Physicians are concerned that they have a diminished ability to specify a specific drug product in which they have developed a clinical confidence. Physicians are concerned that evidence has shown there are inequivalent drug products in the market and they do not wish their patients' therapy to be compromised by the pharmacist's choice of a less clinically effective product. On the other hand, pharmacists have felt an increased problem in inventory as more products become multi-source and they are required to inventory different brands of what they have regarded as equivalent products. Pharmacists feel that their education is oriented to dosage form technology and that since they are the purchaser of the products from the manufacturer, they are more aware than the physician of the cost differentials among equivalent products.

Examples of Drug Product Inequivalence

That marketed drug products can be inequivalent has been amply demonstrated for digoxin, chloramphinicol, and other drugs. What has been difficult to demonstrate is whether the problem is small or great. Let me review with you one well documented case of drug

product inequivalence. This figure shows the blood levels of four different marketed products of chloramphinicol administered to human subjects. If the blood levels had been superimposable, the drug products would have been bioequivalent, that is, they would have done their job as a delivery system and each product would have caused the same rate and extent of absorption of the active ingredient chloramphinicol. Clearly, the blood levels are not superimposable and the products were not equivalent. *In vitro* laboratory studies demonstrated that even in *in vitro* studies the products had different rates of disintegration and of dissolution.

OTA Report of Bioequivalence

In 1973, HEW Secretary Weinberger appeared before the Health Subcommittee of the Senate and stated that "In absence of demonstrated differences in uniform quality and therapeutic equivalence, there is no reason why the Government should pay more for a drug than the lowest price at which it is widely available."

This statement was quickly challenged. Opponents of this view stated that in terms of quality and therapeutic equivalence, significant differences among drug products have been shown. To resolve the issue, the Office of Technology Assessment (OTA) of the U. S. Congress set up a study commission to determine the scientific aspects of the issue. The study commission was chaired by Dr. Robert Berliner, Dean of Yale Medical School, and consisted of seven physicians, two pharmacists (of which I was one), and a statistician. Some of the conclusions of this 1974 report were:

(1) Current standards and regulatory practices do not insure bioequivalence for drug products.

(2) Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures and it is probable that other failures have escaped recognition.

(3) Most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available.

(4) It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic to toxic concentration in blood, and certain pharmaceutical characteristics.

(5) A system should be organized as rapidly as possible to generate an official list of interchangeable drug products. In the

development of the list, distinctions should be made between two classes of drugs and drug products:

(1) Those for which evidence of bioequivalence is not considered essential and that could be added to the list as soon as standards of pharmaceutical equivalence have been established and satisfied.

(2) Those for which evidence of bioequivalence is critical. Such products should be listed only after they have been shown to be bioequivalent or have satisfied standards of pharmaceutical equivalence that have been shown to insure bioequivalence.

The report offered many opinions and suggested many ways to improve compendial standards and regulatory activities. As a member of this study commission, I was pleased to see that many of our opinions and recommendations were incorporated into the January bioequivalency/bioavailability regulations. The report included the statement: "It is clear from the conclusions we have already stated that we do not believe that all chemical equivalents are, at present, interchangeable. We do believe, however, that the goal of interchangeability is achieveable within most, if not all, classes of oral drug products . . ." This report was issued in July, 1974, and I believe established guidelines for the FDA regulations that were released in January, 1977.

Definition of Terms

To understand the topic there are certain terms which will come up time and time again and even as one who conducts research in the field, I find these terms confusing. We have already discussed an example of the use of blood levels to determine whether or not a drug product is adequately delivering the drug to the body. There are three measurements of blood levels that are often utilized:

(1) Total area under the blood-versus-time curve—the greater the area, the greater the extent of absorption;

(2) The time at which the peak blood level occurs (t_{max}) — t_{max} is related primarily to the rate at which the drug product delivers the drug to the body;

(3) The peak blood level value (c_{max}) — in some cases this value can be related to both rate and extent of absorption.

Let me review the definitions:

Bioavailability means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalent Drug Products—pharmaceutical equivalents or alternatives whose rate and extent of absorption are not significantly different when administered to man at the same molar dose under similar experimental conditions.

Pharmaceutical Equivalents—drug products identical in: (1) amount of active drug ingredient; (2) dosage form; (3) meeting compendial or other standards of identity, strength quality and purity; but may not be identical in terms of inactive ingredients; ex. Erythromycin Stearate Tablets (Brand X), and Erythromycin Stearate Tablets (Brand Y).

Pharmaceutical Alternatives—drug products that contain identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Ex. Erythromycin Stearate *v.* Estolate; Tablets *v.* Capsules.

Bioequivalence requirement means a requirement imposed by the Food and Drug Administration for *in vitro* and/or *in vivo* testing of specified drug products which must be satisfied as a condition of marketing.

Types of bioequivalence requirements:

(1) *in vivo* test in humans;

(2) *in vivo* animal model correlated with human data;

(3) *in vivo* animal model not correlated with human data;

(4) *in vitro* bioequivalence standard correlated with human data;

(5) currently available *in vitro* test not correlated with human data.

In vivo human testing ordinarily required if well documented evidence exists that products intended to be used interchangeably:

(1) do not give comparable therapeutic effects;

(2) are not bioequivalent drug products;

(3) exhibit narrow therapeutic ratio.

Closing Statement

I hope I have provided you with an adequate historical perspective and enough jargon to allow you to understand and participate in this conference. Bioequivalency is a topic that already has great importance and will have increasing importance in the future. As one who is working in the area of biopharmaceutics, I feel strongly that there is a science and a technology to the development of dosage forms that optimize the drug's effectiveness in the patient. **[The End]**

Bioavailability/Bioequivalence

By BERNARD E. CABANA, Ph.D.

Dr. Cabana Is the Director of the Division of Biopharmaceutics of the Bureau of Drugs, Food and Drug Administration.

DESPITE THE POPULARITY of this topic and the many conferences and symposia held over the years to discuss this subject, misinterpretation and controversy continue concerning drug bioavailability and drug interchangeability. While I have serious doubt that I will eliminate a significant amount of the controversy, I hope that today I will be able to remove much of the existing confusion and misunderstanding which I find exists.

In my presentation I will briefly outline and discuss the key provisions of "Bioavailability/Bioequivalence Regulations" which were published as a final order on January 7, 1977, stressing those areas which are being misinterpreted and may raise controversy, particularly in dealing with generic drugs. Also I will briefly include some remarks concerning the issues of drug interchangeability.

Permit me to state at the start that these regulations were purposely divided into two separate regulations; Subpart B "Procedures for Determining the Bioavailability of Drug Products" and Subpart C "Bioequivalence Requirements," in order to separate the majority of elements dealing with bioequivalence issues from those dealing with bioavailability and pharmacokinetic data to support drug labeling. However, in an effort to avoid redundancy, portions of each section were written to apply to the other section, so I would caution the reader that the two regulations cannot be viewed as totally independent.

Bioequivalence Requirements

Summarized in Table 1 are key provisions of the "Bioequivalence Requirement."

Table 1—Key Provisions of Bioequivalence Requirements

A. Defines procedures for establishing a bioequivalence requirement Section 320.51

B. Sets forth criteria to establish a bioequivalence requirement Section 320.52

C. Defines bioequivalence requirements Section 320.53

D. Sets forth requirements for *in vitro* batch testing and certification Section 320.55, 320.56

E. Sets forth requirements for *in vivo* bioequivalence testing Section 320.57

F. Requirements for marketing a drug product subject to a bioequivalence requirement Section 320.58

G. Requirements for *in vivo* testing of a drug product not meeting an *in vitro* bioequivalence standard Section 320.61

Outlined in Table 2 is a brief summary of the criteria to be used to establish a bioequivalence requirement. Time does not permit me to discuss these at length, but it should be noted that drug products meeting any one of the first three criteria (A, B or C) will ordinarily require *in vivo* testing to satisfy the bioequivalence requirement. The obvious exception is where the Agency imposes an *in vitro* bioequivalence standard which is based on *in vitro/in vivo* correlative data.

A key provision of these regulations is the "Petition Mechanism" by which any interested party including the Commissioner may propose to establish a bioequivalence requirement on any given drug if said drug meets certain criteria previously described in Section 320.52. Bioequivalence requirements are to be established through rulemaking procedures by proposal, comment and finalization in the *Federal Register*.

Table 2—Criteria and Evidence to Establish a Bioequivalence Requirement

(A) Documented therapeutic failure

(B) Documented bioinequivalence

(C) Drug product exhibiting a narrow therapeutic ratio

(D) Medical determination of serious adverse effect in the treatment or prevention of a serious disease or condition

(E) Physicochemical evidence:

(1) low solubility

(2) poor dissolution rate

(3) particle size/surface area

(4) physical structural characteristics: for example, polymorphic forms

(5) high ratio of excipients to active drug

(F) Pharmacokinetic evidence:

(1) localized absorption

(2) inherently poor absorption

(3) first-pass metabolism

(4) rapid drug clearance

(5) drug instability in G-1 tract

(6) dose-dependent kinetics

The types of bioequivalence requirements are outlined in Table 3.

Table 3—Bioequivalence Requirements

(1) *In vivo* test in humans

(2) *In vivo* test in animals that has been correlated with human *in vivo* data

(3) *In vivo* test in animals not correlated to human data

(4) *In vitro* bioequivalence standard, that is, correlated with *in vivo* data

(5) *In vitro* test not correlated to human *in vivo* data

Another key provision of the bioequivalence regulations is the general requirement for batch testing and, as necessary, batch to batch certification of a given drug product by the Food and Drug Administration (FDA) (along the lines of the digoxin certification program) to assure that each lot meets an appropriate *in vitro* specification.

When certification procedures are applied to a given drug, a manufacturer is required to submit samples of each batch to the FDA and withhold distribution of the batch until notified by the FDA. Ordinarily, the Commissioner will terminate this requirement for a given manufacturer on a finding that the manufacturer has satisfactorily met the *in vitro* requirement on four consecutive batches. It should be noted, however, that the manufacturer will be required to continue

conducting the *in vitro* test on each batch of the drug to assure batch to batch performance.

Section 320.56 imposes a requirement for *in vitro* testing of each batch of a drug having a bioavailability/bioequivalence requirement. It has been the practice of the Division of Biopharmaceutics for the last 2-3 years to require as a basis of drug approval both *in vivo* and *in vitro* data. Quinidine sulfate is a drug for which all manufacturers met *in vivo* and *in vitro* requirements as a basis of new drug application (NDA) or abbreviated new drug application (ANDA) approval. Such data will be the basis of compendial revisions in the very near future. In certain cases, dissolution rate testing was imposed on a given manufacturer based on the dissolution performance data submitted for his particular product. Under Good Manufacturing Practice (GMP) regulations, they are required to perform such a test on each batch and records of all resulting *in vitro* data. These regulations, as of February 7, 1977, impose these same *in vitro* requirements under the bioequivalence requirements to assure greater uniformity of product performance.

In addition, Section 320.62 imposes a requirement for maintenance of records for inspection of all *in vivo* and *in vitro* tests on any marketed batch of a drug product for a period of 2 years after the expiration date of the product to be submitted to the Agency upon request. The Division of Biopharmaceutics is currently working with the Office of Compliance to establish the survey of such data as a routine element of Current Good Manufacturing Practice inspection.

Section 320.58 deals with specific prerequisites for marketing a drug product subject to a bioequivalence requirement and has been the subject of many inquiries to the Agency. These inquiries have both asked for specific information on the methodology to be applied to a particular drug dosage form as well as general information regarding the overall regulatory status which the product will hold under the bioequivalence regulations.

Because of the wide dissemination of these comments, I will simply highlight the points which are pertinent.

(1) Firms holding approved NDAs or ANDAs are not required to conduct any additional studies until such time as a bioequivalence is established for their drug product.

(2) Approval requirements governing product bioequivalence in effect before January 7, 1977, continue to prevail until July 7, 1977.

(3) To become final, new requirements will go through the process of rulemaking, that is, proposal, comments and finalization.

(4) Firms not holding an approved NDA or ANDA who wish to market a new drug must obtain approval of a full NDA or ANDA, as applicable, before introducing the drug into interstate commerce.

(5) Under Section 320.21 any person submitting a new drug application after July 7, 1977, shall include in the application either: (1) evidence demonstrating *in vivo* bioavailability; or (2) information to permit waiver.

In further response to such inquiries the Division of Biopharmaceutics released a list of current bioavailability/bioequivalence requirements for drug efficacy study implementation (DESI) *effective* drugs (appendix 1). Drug products for which the *in vivo* bioequivalence requirement is deferred because of lack of methodology will continue to be deferred until due notice. It is likely that the current bioavailability/bioequivalence requirements for specific drugs will undergo some changes in the near future. The exact requirement for each class of drugs or individual drugs will be published as a proposal in the *Federal Register* before being finalized.

Bioavailability Regulations

Summarized in Table 4 are the key provisions of the Bioavailability Regulations.

Table 4—Key Provisions of Bioavailability Regulations

(A) Defines "Bioavailability" both in terms of rate and extent of drug absorption (Section 320.1)

(B) Defines procedures for determining the bioavailability of drug products (Section 320.4)

(C) Sets forth requirements for submission of *in vivo* bioavailability (Section 320.21)

(D) Sets forth criteria for waiver of human *in vivo* bioavailability studies (Section 320.22)

(E) Provides general guidelines for conduct of *in vivo* bioavailability studies (Section 320.26)

(F) Imposes a requirement for filing an Investigational New Drugs. (Section 320.31)

The definition of bioavailability which is shown on the next table is occasionally the subject of controversy in dealing with drugs which undergo rapid renal or metabolic clearance or with drugs

whose rate of absorption has been deemed to have no medical consequence. It has been the experience of the Agency in reviewing drug applications that slowly absorbed drugs are often more erratically absorbed resulting in large coefficients of variation in blood level. Emphasis has been placed on the rate of absorption from the dosage forms in order to minimize variance in drug absorption and to establish *in vitro/in vivo* correlation. With drugs which undergo rapid first pass metabolism it is not sufficient to demonstrate total absorption by measurement of urinary metabolites. Rather, one must demonstrate that the active drug reaches the systemic circulation in sufficient quantity to elicit a therapeutic effect. To obtain this type of information the drug in solution is preferred as a reference standard.

Outlined in the next three tables are specific requirements for submission of *in vivo* bioavailability data which took effect July 7, 1977.

Table 5

"Bioavailability" means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.

Tables 6 and 7

Requirement for Submission of *In Vivo* Bioavailability Data

(1) After July 7, 1977, NDA or ANDA shall include either:

(A) *in vivo* bioavailability data; or

(B) Information to permit the FDA to waive *in vivo* requirement.

(2) Supplemental application involving a change in:

(A) manufacturing process;

(B) product formulation or dosage strength;

(C) labeling to provide a new indication or new dosage regimen, such as pediatrics (if clinical studies are required to support new or additional labeling).

(3) The FDA may defer submission of *in vivo* data:

(A) if application is under review as of July 7, 1977;

(B) if application is otherwise approvable;

(C) if applicants to provide within a specified time (1) or (2) above.

(4) Any firm holding an approved NDA if notified that there are data demonstrating that:

(A) the dosage regimen in the labeling is based on incorrect assumptions or facts regarding pharmacokinetics which could result either in subtherapeutic or toxic level; or

(B) batch to batch variability, that is, ± per cent, in drug bioavailability.

A petition was recently sent to the Agency concerning Section 320.21(b)(2) which deals with the requirement for *in vivo* bioavailability testing to support a labeling change which solely provides for a new indication. It is not the intent of the Agency to require *in vivo* bioavailability data unless the new indication requires a dosing regimen not currently specified in the labeling. Therefore, consideration is being given to amending this section and combining it with Section 320.21(b)(3) which set forth requirements for a new dosage regimen.

Section 320.21(f) sets forth a bioavailability requirement to be imposed on any holder of an approved full or abbreviated new drug application where there are data demonstrating that:

(A) The dosage regimen in the labeling is based on incorrect assumptions or facts regarding the pharmacokinetics of the drug which could potentially result in subtherapeutic or toxic levels; or

(B) Batch to batch variability, such as, ± 25 per cent in drug bioavailability.

The Commissioner promulgated this section without going through rulemaking procedures, stating that these requirements represented existing FDA policy under Section 505(j) of the Act; but he did invite comments from affected manufacturers and any interested party.

The Agency has received several petitions submitted to the Hearing Clerk requesting that Section 320.21(f) be proposed through rulemaking procedures because of its potential impact on pharmaceutical manufacturers. Several petitioners objected to the use of the word "assumptions" regarding the pharmacokinetics of the drug, and further requested clarification as to the availability of "data" to the affected manufacturers. Other manufacturers requested clarification concerning the example given, that is, automatically applying the batch to batch requirement where variations of ± 25 per cent bioavailability occurs, stating that considerations should be

given to good manufacturing practice and consonant with the therapeutic ratio of the drug product and the potential adverse effects in the treatment of the diseased state.

Serious consideration is being given to amending this section in order to further clarify the intended approach. However, let me stress that invocation of this section by the Agency would be based on actual data and a summary of such data would be made available to the affected manufacturer(s). Further, considerations of critical nature of the drug and potential adverse effect would be given as spelled out under the bioequivalence procedural regulations.

The use of the word "assumptions" was purposely chosen since in many instances the Agency is dealing with older drugs where pharmacokinetics and bioavailability information is either nonexistent or poorly defined. In certain instances, such considerations as dose proportionality and biologic half life are assumed rather than established by adequate studies or known as a scientific fact. Occasionally, evidence of biopharmaceutic problems are brought to the attention of the FDA by generic manufacturers attempting to obtain ANDA approval. Among other things, their submissions point out that the problem is sufficiently big enough so as to prevent the Agency from using the innovator product as a reference standard.

Waiver of *In Vivo* Bioavailability

The one section of the regulation which has resulted in the largest number of inquiries is Section 320.22 which deals with criteria for waiver of *in vivo* bioavailability. A firm may request the FDA to waive *in vivo* requirements provided that the firm submits the request with the NDA application and documents that the drug meets specified criteria under Section 320.22(B)(C) or (D), which are outlined in Tables 8, 9, 10. Justification for the waiver must be provided by the applicant and concurred upon by the Agency.

Let me briefly discuss these criteria and point out a few facts. Section 320.22(b) permits waiver of an oral or IV solution. It further permits waiver of inhalants. The prerequisite is that the drug must be identical to an already approved drug product subject to a full NDA for which the necessary pharmacokinetic information has presumably been obtained.

Section 320.22(c) (Table 9) permits waiver of DESI effective—solid oral dosage form of drugs (other than enteric coated or controlled release dosage form) not listed in the January 7, 1977, *Federal*

Register publication. The Agency will continue to request *in vitro* data on such drugs. It should be noted that less than effective drugs which are raised to effectiveness in subsequent DESI Notices will be addressed prior to publishing the DESI Notice. Bioavailability/bioequivalence requirements will be included in future DESI Notices where deemed necessary by the Agency.

Section 320.22d (Table 10) permits waiver of an *in vivo* testing for a number of specified conditions. A common thread is the requirement that *in vitro* data, for example, dissolution rate, must be provided by the manufacturer as a basis of drug approval. It is the intent of the Agency to require such *in vitro* testing on each batch of such drugs.

Table 8

Section 320.22(b) Permits Waiver of:

(1) drug is a solution intended solely for intravenous administration which is identical to an approved drug subject to a full NDA;

(2) topical drugs intended for local therapeutic effect;

(3) oral dosage form not intended to be absorbed;

(4) inhalant, such as, anesthetic, in the same dosage form as an approved new drug;

(5) oral solution, elixir, syrup, tincture, etc. in the same concentration as approved new drug that contains no inactive ingredient that is known to significantly affect absorption.

Table 9

Section 320.22(c)* Permits Waiver of:

DESI effective—solid oral dosage forms of drugs (. . . other than enteric coated or controlled release dosage form) not listed in the January 7, 1977, *FR* publication (p. 1649)—

—provided *in vitro* data, such as dissolution, is provided by the firm—

less than effective drugs—raised to effectiveness will be addressed prior to publishing the DESI notice—bioavailability requirements will be included in future DESI notices where deemed necessary by the Agency.

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* Note: The preamble #21 states that this part 320 supersedes all previous DESI Notice, but additional *in vitro* data can be required to assure drug quality.

Table 10

Section 320.22(d) Permits Waiver of:

(1) drug product is one for which an *in vitro* bioequivalence requirement has been imposed by the Agency;

(2) the drug product is the same dosage form, having a similar formulation but different strength made by the same manufacturer having demonstrated bioavailability for one strength and meeting an *in vitro* test specification approved by the FDA;

(3) drug product meets an *in vitro* test specification which assures bioavailability, that is, *in vitro* data correlated with *in vivo* bioavailability;

(4) drug product is reformulated product that is identical except for color, flavor or preservative made by the same manufacturer who has demonstrated bioavailability and meets an *in vitro* test approved by the FDA;

(5) drug product is identical dosage form, and strength as a drug subject to full NDA or an ANDA and both products meet an *in vitro* test that has been approved by the FDA.

Now just a few words on the guidelines for conduct of *in vivo* bioavailability. It should be kept in mind that these sections are "guidelines" and not "road maps" and that the guiding principles are best exemplified in Table 11.

Table 11

Guidelines for Conduct of *In Vivo* Bioavailability Study

Guiding Principles

(1) no unnecessary human research should be done;

(2) study can be conducted in animals where an appropriate animal model exists;

(3) ordinarily performed in healthy normal subjects under standardized conditions;

(4) in some instances, preferable to be done in suitable patients.

(5) critically ill patients shall not be included unless attending physicians determine that there is a potential benefit to the patient.

The basic design of bioavailability study is determined by (Table 12).

(1) Scientific question to be answered;

(2) Nature of the reference material and the dosage form to be tested;

(3) Availability of analytical methods;

(4) Benefit-risk considerations.

At this time I wish to state that the Agency will shortly amend the 356H form in order to facilitate efficient quality review of all pertinent data. We have, therefore, elicited those elements key to the bioavailability/pharmacokinetic review and will require that a separate document containing those elements be submitted as part of the NDA package. While we recognize the additional work necessary on the part of the firms, we believe that it will have the offsetting benefit of allowing the Division of Biopharmaceutics to receive and review all relevant material in a single package sooner.

Generic Drugs

I am going to use my remaining time to discuss some aspects of the issue of bioequivalence of generic drugs. In my dealings with State Officials who have the responsibility to comment on or implement drug legislation associated with drug formularies, drug substitution, etc., I am continually asked to clarify a variety of divergent viewpoints.

Opponents of drug substitution bills cite the list of drugs in the January 7, 1977, *Federal Register* statement as proof of an industry-wide problem. On the other hand, proponents of generic drug substitution cite the Department of Health, Education and Welfare publication entitled "Holders of Approved New Drug Applications for Drug Presenting Actual or Potential Bioequivalence Problems" as a source of interchangeable drug products. Others have even interpreted the latter list of drugs as non-interchangeable drugs and further state that this list is simply the tip of an iceberg. The facts are that each of these oversimplifications is totally misleading to all concerned.

Opponents of state drug substitution legislation continue to cite the list of drugs which the Agency indicates present actual or potential bioequivalence problems as a primary basis that not only are generic drugs not interchangeable, but as proof that generic drug products are inferior to brand name products. This allegation in the last few years has placed great emphasis on the fact that holders of deemed approved applications had the first and only products to demonstrate safety and efficacy for their respective products. This

same message has even been nurtured by the Agency itself. I believe that one important point has been too long overlooked. Although the DESI process, applied to establishing immediate recognition of efficacy, was satisfactory and logical, it no way equates with the current post-1962 drug applications process applied for efficacy determination today.

The National Academy of Sciences-National Research Council set up 30 panels of experts to review the submitted data and advise the Commissioner on the status of these drugs. Most of the emphasis was placed on the active ingredient and general route of administration of these "deemed approved" drug products rather than an evaluation of precise studies to elucidate and define dosage form performance. The simple reason for this was that the latter types of studies usually did not exist. The Agency recognized this fact and attempted to cure these shortcomings by imposing the requirement that such products raised to effective status should also provide proof of biologic availability as a condition of approval. It is especially important to note that it was never intended that such biologic availability considerations be limited to subsequent firms entering the market (in other words, there was no intent to exclude deemed approved application holders from this requirement).

At the time of the Drug Efficacy Study Report, bioavailability was still in its infancy and with the exception of antibiotics which relied on microbiological assays, methodology was generally lacking to detect the minute amounts of drug and/or metabolites in blood and urine. Therefore, for many drugs, approval was granted based on submission of *in vitro* data or pharmacological data, such as, urinary excretion of electrolytes in the case of thiazide. The bioavailability requirement was deferred in the application for many drugs pending methodology development. It should be further stated that the issue of drug bioavailability was not widely recognized as a possible concern in drug approval by the Agency, drug firms, and all but a few scientists until about 1970. Also, when imposed, the bioequivalence requirement was applied to drugs which did not pose a bioequivalence problem, for example, anti-helminthics. In looking back, a major deficiency in the original Agency approach was the indiscriminate use of the biological availability requirement for deemed approved drug application holders as well as new applications. For example, such requirements even extended through various DESI announcements to many intravenous products.

Biopharmaceutics Program

Let me now return to more current times. In developing its biopharmaceutics program with regard to generic drug products, the Agency was faced with two major tasks. The first was to identify those drugs which presented a bioequivalence problem and impose a bioequivalence requirement on all products approved after that date. The second task was the need to recycle products previously approved prior to the introduction of the new bioequivalence requirement.

Hence, the Agency developed the bioequivalence procedural regulations and published the "infamous" list of 173 drugs with known or potential bioequivalence problems using the criteria previously described in the bioequivalence procedural regulations. In identifying drugs for inclusion on the list, we accepted each one if there was any question about its potential for bioinequivalence. It is the Agency's view that drugs of similar structural and physicochemical characteristics should be included if related to a drug of known documented bioinequivalence. Thus, for instance, a positive finding of a bioequivalence problem with tetracycline would certainly make oxytetracycline suspect. Similarly, a documented problem with prednisone indicts all glucocorticoids. I might point out the inclusion of drugs with potential bioequivalence problems on one list was not without controversy. It was the view of the Agency that a more effective way of dealing with the bioequivalence problems would be to include all drugs with any potential for bioinequivalence rather than dealing with them in a piecemeal fashion.

I must strongly emphasize that including the drugs on the Blue Book list in no way implies that the drugs are bioinequivalent. Nor should it imply that all such drugs are non-interchangeable. To categorize all such drugs as non-interchangeable is utterly ridiculous. It is particularly noteworthy that of the 173 drugs (each representing dosage forms of various active ingredients) listed in the Blue Book, such as, nitrofurantoin capsules and nitrofurantoin tablets representing two such listed drugs, 85 drugs are marketed by a single approved manufacturer, and 4 drugs are no longer marketed. Of the remaining 84 drugs, 30 are marketed by only 2 firms and many of these are marketed under licensing agreements. Thus, only 54 drugs are truly multiple source drugs produced by as many as 3 firms. To further clarify this list, the Agency is taking steps to identify those drugs where bioequivalence has been demonstrated by all approved firms, for example, quinidine sulfate, chlordiazepoxide,

as well as those drugs for which bioavailability has not been demonstrated by any firm, such as, reserpine. At a later date we will identify the mixed-bag; where bioavailability has been performed by some manufacturer.

Single Source Drugs

For those of you who wonder about single source drugs being on the bioequivalence problem list, it should be noted that if a particular drug ingredient in a specified dosage form is amenable to a bioequivalence problem, it remains on the list until proven otherwise. The innovator himself cannot be presumed to be immune from the problem. Moreover, additional producers can come on the market at any time. Furthermore, for several drugs, for example, warfarin sodium, firms were required to demonstrate clinical safety and efficacy under a full NDA, but not necessarily interchangeability between name brands. The new bioavailability/bioequivalence regulations finalized on January 7, 1977, will address these issues by requiring all firms including the innovator to establish proof of bioavailability and possibly bioequivalence relative to specified standards.

Where bioequivalence is an issue, until such time that bioequivalence has been demonstrated for all manufacturers of a generic drug, the Agency obviously cannot assure the interchangeability of all producers of that drug. Drugs such as reserpine and certain glucocorticoids are particularly difficult to assure interchangeability at this time since both *in vivo* and *in vitro* methodology is not yet defined. However, for these approved drugs the Agency can assure that all approved firms who market drugs in compliance with compendial and NDA specifications meet the same high standards currently imposed by the Agency, including GMP's manufacturing controls, etc. It should be noted, however, that it is not an issue of "brand name" versus "generic brand" since bioavailability/bioequivalence has not been defined for any drug, and there is no apparent scientific basis suggesting that the patient is offered greater protection by dispensing one brand in preference to another.

It is my recommendation that physicians and pharmacists should continue to prescribe and dispense generic drugs, but should not interchange brands when dealing with drugs with known or potential bioequivalence problems. This is particularly applicable to critical dose drugs, such as anticonvulsant, anticoagulants, antiarrythmics, etc., those that necessitate patient titration. Once a patient is titrated on a particular brand, innovator or otherwise, the physician and

pharmacist should continue to use the same brand in dealing with the above drugs. It is important to note that I am referring to the same manufacturer and not distributor or repacker. The obvious exception is any drug reviewed by the FDA for which a Maximum Allowable Cost program is established or an Agency determination is made that all approved manufacturers have demonstrated bioequivalence.

In dealing with critical dose drugs, such factors as stress that might ensue in a patient upon switching brands should be anticipated and the patient should be fully informed by the physician and/or pharmacist. For certain drugs, such as phenytoin, theophylline, warfarin, etc., where switching of brands and dosage forms occur, it is best accomplished by careful monitoring of drug blood levels.

In conclusion, it is my view that the Agency presently cannot assure the interchangeability of certain drugs without some measure of bioequivalence, but that they are manageable. The practicing physicians and pharmacists should continue to prescribe and dispense drugs respectively consonant with their scientific judgments. It is my view that the pharmacists should not be required to dispense drugs at the lowest cost contrary to his professional judgment. At times, the pharmacist may be aware of specific product defects that would preclude him from dispensing a specific product. Our file of over 20,000 drug problems reports is testimony to this fact. On the other hand, I personally am opposed to state legislation that would automatically preclude a pharmacist from substituting generically a different brand than that prescribed by the physician simply because the drug appeared on the "bioequivalence problem" list.

[The End]

Priority Setting in the Real World

By DONALD KENNEDY, Ph.D.

Dr. Kennedy Is Commissioner of Food and Drugs of the Food and Drug Administration.

FOLLOWING, AS I DO, a series of technical approaches to the evaluation of mutagenicity and carcinogenicity, and preceding some specific agency approaches to policy formulation, I take as my obligation the definition, in rather broad strokes, of how a public agency decides *which* things to do in a world that offers too many of them.

I would like to begin with some observations—which I suspect may be unpopular—about the tools we have to work with. In the course of running or helping to run three major analytical exercises for the Academy—one on pesticides, one on world food and nutrition, and one on the health sciences—I have had what I think is a fairly complete outsider's view of the biological disciplines that are critical to the major applications of medicine and agriculture. I am bound to observe, as a result of this exposure, that only nutrition approaches toxicology in terms of being in basically bad shape. In common with nutrition, toxicology suffers from its own transdisciplinary character, and from that peculiar kind of academic neglect that characteristically falls upon any specialty that does not fall neatly within Departmental lines laid down half a century ago. As a result, pharmacologists and biochemists vie to see who can neglect it most shamefully. Toxicology is similarly mistreated by the so-called basic research agencies of this government, with the result that it is not gathering its fair share of support nor its aliquot of the best people. Perhaps it is not surprising that one hears as much fact in search of theory as we have heard in this symposium.

Priorities

The first priority, then, is for the basic research agencies to supply a little more of the kind of innovation potential that they have made so readily available to, say, the development of therapeutic agents by the private sector. The first fact of life about toxicology testing in this country is that it simply cannot meet its obligations. Our current testing capacity is far below what it must be if we are to deal with the fruits of the synthetic organic chemical revolution in anything like our present way. I suppose that the various agencies will give you, in what follows, their own scorecards for meeting the testing requirements. To the best of our knowledge, the presently developed testing capacity out there in the private sector is adequate to perform about 800 long-term carcinogenicity studies at any given time. If you add the major public-sector laboratories like The National Cancer Institute and our own National Center for Toxicological Research and assumed that they only did routine testing on new chemical entities, you would have a capacity of perhaps 50-100 studies at any given time. The number of new molecules with potential activity being produced is now at least 1000 per year. Not only is there a backlog; we are losing ground. This mismatch is made worse by the fact that in our Bio-Research Monitoring Program, we are slowly but surely discovering that the existing testing establishment is sloppy much of the time, and frequently even corrupt. On past occasions when I've pointed out these difficulties, some cheerful soul has always suggested that now that public support of basic research in the universities has tailed off, those institutions will no doubt be glad of this opportunity to put their scientists and laboratories to work. Unfortunately the universities do not wish to do this kind of work, which may explain why, when they try it, they do it badly: Poor as industry is at meeting Good Laboratory Practice Standards, institutions of higher education have a distinctively worse record. So we cannot expect to be rescued by the academic cavalry this time.

I am afraid, therefore, that my view of the nation's capacity for chronic toxicology testing is a little bit like that of the football coach who was asked by the press to comment on his prospects after he had had a chance to observe his troops for two weeks of fall practice. "We may be small," he said, "but we're slow."

Rationing of Resources

So we have all of the elements of a classic resources dilemma: needs are piling up faster than our ability to meet them, and we must

engage in a sensible rationing of resources. In such a real world, what guideposts are there for the intelligent setting of sub-priorities? And to what extent will external events allow rational processes to exert their influence in the allocation of that resource? My long-range goal is to increase the resources so that the choices are less constrained. In the meantime, our task is to make the best of difficult choices.

As a primary approach to transfer this problem, we need to distinguish between different categories of substances, the kind and degree of hazard that each poses to people, and the political concerns generated by the threat to remove them.

Obviously there are a number of classes of chemicals out there, and each regulatory agency has statutes that treat them in a different way. Toxic substances added to the environment may be required to be registered under one law; but they escape that statutory boundary and enter another when, as a consequence of accident or design, they enter the food supply and become subject to regulation under the Federal Food, Drug, and Cosmetic Act. The way in which each law treats a compound has important implications for the priority-setting process. Moreover, even within a single law the treatment of different kinds of compounds may be highly inconsistent. Let me provide two examples.

Some food additives have not been subjected, under the law, to the same kind of scientific scrutiny as others. This is because, in the terms of the Federal Food, Drug, and Cosmetic Act, they have a "prior sanction"—that is, their use had been explicitly permitted by the Food and Drug Administration (FDA) or by the U. S. Department of Agriculture (USDA) at the time the food additive provisions of our law were enacted. Because such compounds are in an important sense beyond the reach of the law, they have not characteristically been accorded high priority by regulatory agencies. But that situation can be changed dramatically. A recent illustration is provided by the use of nitrites as color-fixing agents and preservatives in poultry products. We were recently informed by the Department of Agriculture that they no longer believed they had a prior sanction for such use, although they and the FDA had both always assumed such a prior sanction existed. That news immediately produced a consideration on our part of the options available to the FDA and the USDA in designing a regulatory strategy for these compounds, and in effect it also produced a retrospective elevation in the priority of these compounds

for scientific analysis. It just so happened that a chronic carcinogenicity test for nitrites had already been in progress, and that the FDA and others had been examining meat products in which nitrites were used for preformed nitrosamines. But there is no doubt that the sudden change in status of a compound under the law can produce, and often does produce, a swift reordering of priorities.

Indirect Additives

A second illustration has to do with the status of compounds that enter foods as indirect additives. Their regulatory status can change as a consequence of changing circumstances. In the incidence of the past four years involving polybrominated biphenyls (PBBs) in Michigan, that kind of change in status occurred. An initial accident in the packaging of an industrial chemical as livestock feed resulted in a local contamination. At that time, the incident could fairly be regarded as an avoidable contamination, and the compound as an adulterant. Over time, the highly persistent PBBs in effect spread themselves out over a wider area, and PBBs became a low-level contaminant in dairy and meat products. At some point that defies precise definition, the PBBs became unavoidable contaminants—poisonous and deleterious substances—subject to regulation by a different part of our law. We did not, of course, change our view of the importance of knowing as much as we could about the toxicity of PBBs; but clearly our *need to know* changed both as a result of an accident and then again as a result of a change in legal status.

Perhaps the most fundamental single issue impacting upon priorities is whether a compound is new or has already been marketed for some time. One has only to look at the saccharin example to realize how much more difficult it is to take a product off the market than to prevent it from reaching that market in the first place. Patterns of use often generate public dependencies that differ markedly from what anyone would expect. In 1958, when Congress passed the first of the so-called Delaney clauses, it in effect made a prospective risk-benefit judgment: it concluded that no food additive could possibly have a benefit commensurable with the risk of carcinogenicity. At that time the proposition must have seemed safe enough: who could imagine that a food additive would ever have a health benefit? But over time, the pattern of saccharin usage evolved into one that raised serious questions of health risks associated with its proposed removal.

Use and Exposure

To the extent that widespread use means widespread exposure, there is an argument for allocating high priority to the testing of familiar compounds for chronic risks. There are certainly enough things already out there to worry about, because both the advancing front of science and the changes in the status of chemicals as the law evolves have left strange constellations of relatively untested compounds behind. These salients of chemical anachronisms occur as a result of various legal "grandfathering" operations, or when testing technology has advanced to the point where new standards badly need application to a group of old molecules. In short, many compounds are a little bit like those of us in academic life who obtained tenure in the 1950's.

Despite this inclination to give toxicity reviewing high priority—as it is in the FDA's programs for cyclic review of food additives, for over-the-counter drugs, and for colors—there is at least one major reason why any regulatory agency might hesitate to do so. That has to do with the enormous leverage that the results have on the allocation of agency resources. Once a toxicity problem is identified with an old chemical, we are no longer in control of our own allocation process; the issue becomes a priority in somewhat the same sense that a cowbird's egg is a priority in a sparrow's nest. I could cite example after poignant example of this kind of leverage; perhaps it will suffice if I simply describe the amount of paper work that is necessary if we are to sustain such an action in the courts. For example, because of data showing that acrylonitrile could cause birth defects in animals, we announced last March 7 our intent to suspend on March 11 marketing approval for beverage containers made from this plastic. That order was stayed by the U. S. Court of Appeals, and we were ordered to hold a hearing. The hearing ended June 27, and supported our initial finding. But that does not end the matter. The parties had until August 15 to appeal this initial decision by filing exceptions. These were filed, and we then had until August 22 to submit replies. We did. I then had until September 19 to submit my decision to the court. In the preparations of evidentiary material for another hearing—just the first step in the unfolding of due process—our Bureau of Veterinary Medicine produced multiple indexed copies of 67,000 pages on diethylstilbestrol. The FDA is in danger of becoming the law's way of making more laws.

The Courts and the Regulatory Process

Nor is the federal appetite for due process in administrative law the only way in which other people get hold of our priorities. Of late the courts have developed an increasing taste for assuming the executive role and doing the Agency's business for the Agency. Along with their sporadic attempts to manage the welfare system and the schools, the district courts have recently shown a disturbing interest in the regulatory process. These black-robed Agency managers would have done well to listen to Judge Henry Friendly who knows a good bit of administrative law and who once said: "The best Agency to improve Agency performance is the Agency itself." As a result of the 1962 amendments, the FDA is responsible for demonstrating that drugs are both safe and effective for their intended use. Drugs marketed prior to the passage of these amendments often lacked efficacy data, and we established a drug efficacy study implementation program, involving a major commitment of Bureau of Drugs' personnel to clean up this huge salient. The American Public Health Association, feeling that our priorities were misplaced and that the study was not moving fast enough, sued us in court; and since 1972 the judge of the U. S. District Court of the District of Columbia has been obtaining reports from us at six-month intervals and encouraging us, in the way only Federal Judges can, whenever we show signs of flagging.

Conclusion

I hope these examples have served to illustrate some of the complexities an agency faces in setting its own priorities. The fact is that the great many processes entirely external to our Agency play a critical role in deciding what we study next. These include the peculiarities in our laws that set up different standards for different compounds; the accidents of history that create groups of substances having special status; the intervention of special interests, the Congress, and even the courts in managing our priorities for us; and the political leverage that can be generated by the public's interest in the benefits from a particular compound.

But I would return to the point at which I started, and remind you that the main reason all this is of concern is because the resources supplied to regulatory agencies, and available in the rest of our society, are simply inadequate to the task the public expects them to perform. Until we can generate a basic research establishment that provides useful shortcuts to what is now a hopelessly unimaginative

and time-consuming process, until we can rebuild and improve the private-sector testing establishment, and until we can develop similar capabilities in the public sector to monitor and extend it, we will continue in the uncomfortable position of having to choose where there really is no choice. In a rational world we should not have to decide whether old dangers are worse than new dangers, or familiar dangers worse than unfamiliar ones. That we now must do so is primarily a fact of political life. To cure it will require first, a greater public understanding of the problem, and second, the kind of science and resources base that relieves the need of making one Hobson's choice after another. **[The End]**

CONCERN OVER PROTEIN DIETS SPURS ACTION

In the belief that liquid protein diets have contributed to serious illness and death due to heart irregularities in a number of dieters, the Food and Drug Administration (FDA) is embarking on a labeling program and an investigation of the diets. The FDA is checking the accuracy of existing labels and developing a mandatory label warning against the use of the diets by infants, children, and pregnant or nursing women, and by persons taking prescription medication who do not have medical supervision for the diets. Manufacturers are currently being asked to use warning labels voluntarily.

Pending completion of plant inspection and investigations into the makeup of the liquid protein diets, the FDA is urging those considering, or presently on, such a diet to see their physician for strict monitoring. Various experts on obesity have cautioned that vitamin and mineral supplements, especially potassium, should be carefully prescribed. In addition to those special groups to whom the label warning is directed, the elderly, and those having kidney, liver, or heart disease or high blood pressure have been advised by the agency to avoid this form of protein diet.

CCH Food Drug Cosmetic Law Reporter, ¶ 42,100

In Vitamins, It's a "Paine-ful" Solution: Common Sense by Court Order

By MILTON A. BASS and JOSEPH J. BIANCO

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ON JUNE 7, 1977, the curtain closed on the third Act of complex Second Circuit litigation concerning the propriety of certain Food and Drug Administration (FDA) rules involving vitamin classification. In *National Nutritional Foods Association (NNFA) v. Matthews*,[1] the Court vitiated FDA regulations[2] which, *inter alia*, classified those preparations of Vitamins A and D containing unit dosages in excess of 10,000 International Units (IU) and 400 IU, respectively, as "drugs" and "prescription drugs" under Section 201(g)(1) and Section 503 (b)(1) of the Federal Food, Drug, and Cosmetic Act (the "Act").[3] The regulations were the subject of two earlier appeals involving the same parties. In *NNFA v. Weinberger* (1973),[4] the Court affirmed the District Court's initial denial of preliminary injunctive relief. On second appeal, *NNFA v. Weinberger* (1975)[5] the Appellate Court reviewed the lower court's dismissal, which found that the regulations in ques-

[1] 557 F. 2d 325 (CA-2 1977).

[2] 21 C. F. R. Sec. 250.109 and 250.-110 (1976), originally promulgated as parts 3.94 and 3.95, which first took effect on October 1, 1973.

[3] 21 U. S. C. Sec. 321(g)(1); 21 U. S. C. Sec. 353(b)(1).

[4] 491 F. 2d 845 (CA-2 1973), *aff'd* 366 F. Supp. 1341 (D. C. S. D. N. Y. 1973).

[5] 512 F. 2d 688 (CA-2 1975) reviewing 376 F. Supp. 142 (D. C. S. D. N. Y. 1974); *cert. denied sub nom. NNFA v. Mathews*, 423 U. S. 827 (1975). *See* the comment on this case published by the senior author hereof at 30 Food Drug Cosmetic Law Journal 448 (Aug. 1975).

tion satisfied the relevant "arbitrary or capricious" standard. But the Second Circuit remanded, holding that the Commissioner of Food and Drugs had not sufficiently exposed to the reviewing Courts his rationale in promulgating the regulations, and requiring that the lower court conduct a review based on the entire administrative record, invoking the hearing requirement first enunciated in *Citizens to Preserve Overton Park v. Volpe (Overton)*.[6] Specifically, the case was remanded "with directions to conduct an *Overton*-type hearing (including such affidavits or testimony as to the Commissioner's reasoning as the court deems necessary) for the purpose of determining, upon the entire administrative record before the Commissioner, which the court should scrutinize. . . . whether the Commissioner acted rationally in classifying the higher . . . dosage levels as 'drugs.' "[7]

General Dietary Supplement Regulations

Thus the question on appeal in this most recent case was whether or not the District Court complied with the directives of the 1975 remand, that is, was the classification properly upheld? In deciding that it was not, the Court reviewed the administrative history of the subject regulations, and traced the parallel development of the FDA's general dietary supplement (GDS) regulations[8] which became effective on January 1, 1975. The GDS regulations promulgated new U. S. Recommended Daily Allowances (U. S. RDAs) of all essential vitamins and minerals, and classified all preparations containing unit dosages in excess of the upper limit U. S. RDA as "drugs." Upon direct review of the GDS regulations, the Second Circuit held, in a related and often cited opinion, that the evidence supporting the blanket "drug" classification was insufficient, and stayed the effect of the GDS regulations.[9]

It was, *inter alia*, on the basis of the staying of the GDS regulations that the Second Circuit remanded the specific A and D classifications in 1975, thus setting the stage for the Court's decisive action in the instant case.

The latest opinion, at bottom, holds that the Commissioner's classification of the subject preparations as "drugs" was an interpretation so

[6] 401 U. S. 402 (1971).

[7] *NNFA v. Weinberger*, *supra*, 512 F. 2d 688, 703.

[8] 21 C. F. R. Sec. 125.1(h) [1975].

[9] *NNFA v. FDA*, 504 F. 2d 761 (CA-2 1974), *cert. denied*, 420 US 946 (1975). This decision was widely acclaimed, in these pages and elsewhere. *See* Vincent A. Kleinfeld, "Overview of Some Recent Developments in the Drug Field," 30 FOOD DRUG COSMETIC LAW JOURNAL 458 (Aug. 1975).

at odds with the statutory definition as to be "arbitrary and capricious." Intimately related to that holding is the recent amendment to the Act, adding Sec. 411[10] which specifically limits actions of the Secretary[11] in this area, as follows: "(B) the Secretary may not classify any natural or synthetic vitamin or mineral (or combination thereof) as a drug solely because it exceeds the level of potency which the Secretary determines is nutritionally rational or useful." The next paragraph of the Amendment limits the foregoing by excepting any vitamin or mineral "which is represented for use by individuals in the treatment or management of specific diseases or disorders, by children, or by pregnant or lactating women."

Rulemaking Authority

The Amendment, which was passed by Congress on April 12, 1976, was correctly interpreted by the Court as confirming the Second Circuit's action in staying the GDS regulations. Interestingly, the legislative history of the Amendment[12] focuses more directly on the issue discussed in the 1975 remand of this case than did the instant opinion. As authority for the specific A and D regulations, and for the GDS regulations, the Commissioner had relied on Section 701 (a) of the Act,[13] a general grant of rulemaking power, to promulgate the substantive vitamin regulations.[14] The senior author of the present work has commented[15] that such action tended to obliterate the classic distinction between substantive and interpretive rulings in judicial review of administrative actions. Indeed, the legislative history of the Amendment takes elaborate pains to note that the substantive rulemaking authority of the Commissioner, pursuant to Section 701(a), has been recognized and remains untouched by the

[10] 21 U. S. C. Sec. 350 (1976).

[11] The "Secretary" referred to above and in the Act is the Secretary of Health, Education, and Welfare, who has delegated his authority thereunder to the Commissioner of Food and Drugs pursuant to 21 C. F. R. Sec. 2.120(a)(1) [1976].

[12] PL. 94-278. *See* 1976 U. S. Code Cong. and Adm. News, pp. 709 *et seq.*; H. Rep. 1005, 94th Congress, 2d Session.

[13] 21 U. S. C. 371 (1974).

[14] The FDA, in promulgating the GDS regulations, utilized full-hearing adversary proceedings of the type specified in Sec. 557 and Sec. 558 of the Administrative Procedure Act (APA). For the A and D regulations, however, conventional notice-and-comment rulemaking was employed, pursuant to Sec. 553 of the APA. This fact was relied on to a certain extent by both Second Circuit benches in justifying the application of the "arbitrary and capricious" rather than "substantial evidence" standard of review to the A and D regulations.

[15] See *Bass, supra*, as to the important distinction of substantive vis-à-vis interpretive rulemaking, and its relation to effective procedure and review.

Amendment.[16] Since the latest opinion relies on the "arbitrary and capricious" rather than the "substantial evidence" standard of review, it too would seem to posture the regulations as "substantive" and based on the authority of Section 701(a). Yet the thrust of the opinion is that the agency erred in its *interpretation* of the statutory definition of "drug," leading us to wonder as to why a more rigorous substantial evidence test was not applied.[17]

Objective Therapeutic Intent

But despite the theoretical problems, the heart of the latest decision rests on the Court's exhaustive treatment of the Agency and District Court proceedings that precipitated the third appeal. The Court concluded that while the process utilized was sufficient, the inescapable evidence was that preparations of A and D were not "drugs" which are defined by the Act as follows:

"(g)(1) the term 'drug' means (a) articles recognized in the official United States Pharmacopoeia, Official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (b) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals. . . ."[18]

In supporting his position, the Commissioner argued that the subject products were being sold with the "objective therapeutic intent" described in (b) above because

(1) there exists widespread promotion and advertising to the effect that high potency A and D preparations were useful in the treatment of various specific ailments;

(2) there exists no recognized nutritional utility to such high doses; and

(3) there exists a potential of toxicity from the ingestion of large doses over extended periods.

Further, the Commissioner argued that A and D are recognized in the United States Pharmacopoeia and the National Formulary in therapeutic dosages.

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[16] H. Rep. 1005, *supra*, at 27-28. Cf. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U. S. 609 (1973).

[17] The test purportedly applied by the court is found in 5 U. S. C. Sec. 706(2)-(A), although a reading of the entire opinion seems to blur the distinction between the tests actually applied. Judge Lumbard, in his concurrence to *NNFA v. Weinberger*, *supra*, 512 F. 2d 688, 704-705, also found that the 1975 court, while purporting to apply an "arbitrary and capricious" standard, in fact conducted a substantial evidence-type review. Judge Lumbard also recognized, reluctantly, the Secretary's authority to adopt binding, substantive regulations under Sec. 701(a).

[18] 21 U. S. C. Sec. 371 (1974).

Essentially, then, the Commissioner argued that large dosages somehow transmogrified that which was admittedly a "food"[19] at U. S. RDA levels of potency to a "drug" at the subject levels. In rejecting the Commissioner's specific arguments, the Court held that the vitamins were not sold with an "objective therapeutic intent" since

(1) there was no evidence that the "widespread promotion" of the products emanated from the manufacturers;[20]

(2) lack of nutritional value is by itself more or less irrelevant;[21] and

(3) toxicity is relevant only as to whether a product can be marketed without prescription—it is irrelevant to the nature of that product, that is, as to whether or not that product is a "drug."[22]

Furthermore, since salt is also mentioned in the compendia, and since Vitamin C is listed therein in "therapeutic" doses (neither of these having been classified "drugs"), it was held that the evidence upon which A and D could be statutorily denominated "drugs"—thereby subjecting the manufacture and marketing thereof to the burdensome provisions of Title V of the Act—did not exist.

Conclusion

The decision of the Second Circuit is a paragon of logic in a desert of absurdity. Stated in most elementary terms, it means that the consumer who so desires can choose to take one harmless pill of dosage x in lieu of two harmless pills of dosage ½-x each. The Court, and, by and large, the present work, have refrained from taking a strictly common-sense approach, despite the amusing possibilities. But strictly from a rule-of-law approach, the opinion is noteworthy in several respects. Firstly, the appellate decision, which vacated the lower court's dismissal and remanded with instructions to enter summary judgment for plaintiff, takes a refreshingly direct approach to

[19] 557 F. 2d 325, 336.

[20] The Court correctly interpreted the Act in focusing on the intent of the vendor and/or the manufacturer in their promotional campaigns as the key element in the statutory definition, citing, *inter alia*, *Rutherford v. U. S.*, 542 F. 2d 1137, 1140 (CA-10 1976). And, of course, the court tended to disregard any "subjective" intent, relying instead on methods of constructing "objective" intent. In sum, the Court found that the subject preparations were in fact marketed as "dietary supplements." 557 F. 2d at 335.

[21] The Court specifically concluded that the Commissioner's finding of "objective intent" was based largely on this lack of nutritional value, and the toxicity issue, *infra*.

[22] The court noted that toxicity was again erroneously relied upon as demonstrative of "objective intent," and really was not well distinguished by the Commissioner from his lack of nutritional value argument.

the requested remedy—barring Supreme Court action. This litigation has taken only four years—unfortunately a relatively short time for resolution of issues of this type. Secondly, it is a truism that Court decisions openly labeling any agency action "arbitrary and capricious" are rare and precious. Thus, the implications of this decision in terms of the general body of administrative law may well be significant.[23] Thirdly, the substantive impact of the Court's rationale—if sustained—may go far in untangling the skein of bureaucracy and regulatory confusion historically attending "drug" regulation. And, finally, particularly in light of the opinion taken in the context of the 1976 amendment to the Act, there could be no more compelling polemic in support of clear legislative delineation of the role of the FDA, or, for that matter, any agency in fulfilling its public mandate. A clear and precise law, expostulating, for example, that which is substantive and that which is interpretive, could eliminate burdensome litigation and waste of public monies in pursuit of ephemeral goals, which situation would work, of course, to the benefit of all. **[The End]**

[23] Outside the scope of the present work are two questions of administrative law. First, the question raised by Judge Lumbard, *supra*, note 17, in 1975, as to which test was actually applied in these NNFA cases? Secondly, which test should have been applied? *See generally* B. Schwarz *Administrative Law* Sec. 238 (1976), suggesting that a uniform standard of review—the "reasonableness test" should be applied to cases of this type regardless of the nature of the subject rule, and the method by which it was promulgated. This second question hinges directly on issues raised in the companion case to *Hynson, supra, Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U. S. 645 (1973). In the *Bentex* opinion, in the course of recognizing the FDA's power to promulgate binding, substantive regulations under Sec. 701(a), the Court argued that the FDA, by virtue of its expertise, was better equipped to make decisions of this type than any court. Hence arises the issue, much debated in administrative law, as to exactly how much weight should be given to the agency's "expertised" opinion. That issue is relevant here because the 1977 NNFA decision, unlike *Bentex*, impliedly stands for the proposition that agency expertise can be virtually overlooked in favor of objective evidence. These issues of general administrative law affected by the NNFA cases are deserving of exhaustive analysis, in a more appropriate forum.

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(Required by 39 U.S.C. 3685)

1. TITLE OF PUBLICATION	2. DATE OF FILING
FOOD DRUG COSMETIC LAW JOURNAL	OCT 1 1977

3. FREQUENCY OF ISSUE	A. NO. OF ISSUES PUBLISHED ANNUALLY	B. ANNUAL SUBSCRIPTION PRICE
MONTHLY	12	$40

4. LOCATION OF KNOWN OFFICE OF PUBLICATION *(Street, City, County, State and ZIP Code) (Not printers)*

4025 W. PETERSON AVE., CHICAGO, COOK, ILLINOIS 60646

5. LOCATION OF THE HEADQUARTERS OR GENERAL BUSINESS OFFICES OF THE PUBLISHERS *(Not printers)*

CHICAGO, ILLINOIS 60646

6. NAMES AND COMPLETE ADDRESSES OF PUBLISHER, EDITOR, AND MANAGING EDITOR

PUBLISHER *(Name and Address)*

COMMERCE CLEARING HOUSE, INC. Chicago, Ill. 60646

EDITOR *(Name and Address)*

Donald Wenzel Chicago, Ill. 60646

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