. 31, NO. 1 JANUARY 1976

od·Drug·Cosmetic Law JOURNAL

dditional Papers Presented at the 19th Annual Educational Conference of the Food and Drug Law Institute, Inc. and the Food and Drug Administration

gal Considerations in Establishing Third and Fourth Classes of Drug Products

. . . . . MAVEN J. MYERS and JOSEPH L. FINK

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 higest 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, $30; single copies, $3. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

January, 1976
Volume 31 • Number 1

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

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FOOD DRUG COSMETIC LAW JOURNAL

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REPORTS

TO THE READER

Maven J. Myers and *Joseph L. Fink* present the case for the establishment of third and fourth classes of drug products in an article beginning on page 4. Dr. Myers is Professor of Pharmacy Administration and Director of the Department of Pharmacy at the Philadelphia College of Pharmacy and Science. Dr. Fink is Assistant Professor of Pharmacy Administration at the Philadelphia College of Pharmacy and Science. Their article is titled, "Legal Considerations in Establishing Third and Fourth Classes of Drug Products."

"Current Topics in Canadian Drug Regulatory Affairs" is *Jan Apse's* analysis of issues important to the development and coordination of Canadian drug regulatory policy. Dr. Apse is Chief of the Drug Regulatory Affairs Division of the Drugs Directorate of the Health Protection Branch in the Department of National Health and Welfare of Canada. His article begins on page 11.

Nineteenth Annual Educational Conference of the FDLI and the FDA. The following papers were presented at the 19th Annual Educational Conference of the Food and Drug Law Institute and the Food and Drug Administration, which was held in Washington, D. C. on December 2 and 3, 1975.

In an article beginning on page 17, *John W. Farquhar,* Vice-President of Research and Technical Services of the American Frozen Food Institute expresses the frozen food industry's opposition to the microbiological quality standards proposed by the FDA. The article is titled "The Role of Microbiology in the Integrity of Foods."

Dee M. Graham analyzes the theory behind and the results of the 1970 GRAS pilot survey and the 1971 comprehensive survey conducted by the NAS. Dr. Graham is Assistant Director of Research of the Del Monte Corporation. His article, beginning on page 25, is titled "Review of the 1970 NAS GRAS Pilot Survey (Phase I) and the 1971 NAS Comprehensive Survey (Phase II)."

Robert L. Spencer is Chief of the Precedent Regulations and Legislative Activities Branch of the Bureau of Drugs in the Food and Drug Administration. In "Bioequivalence/Bioavailability—The FDA's Plans," he discusses the recently issued bioequivalence/bioavailability regulations. The article begins on page 32.

"Bioequivalence/Bioavailability — A Manufacturer's View" approaches the issue through exact definitions of terms. Written by *C. J. Cavallito,* Executive Vice-President of Scientific Affairs of Ayerst Laboratories, the article begins on page 39.

Stuart J. Land's presentation, beginning on page 46, questions the basic validity of the regulatory approach taken by the FDA with respect to the marketing of prescription drugs which were the subject of DESI review. Mr. Land is a member of the law firm of Arnold and Porter and his article is titled "Bioequivalence/Bioavailability—The Basic Legal and Philosophical Issues."

"Status of the FDA's Program on the Use of Antibiotics in Animal Feeds" is *Gerald B. Guest's* report on the FDA's watch over the various drugs fed to food-producing animals. Beginning on page 54, the article is written by the Special Assistant to the Director of the Bureau of Veterinary Medicine in the Food and Drug Administration.

James F. Mongiardo, an attorney with the Schering-Plough Corporation, takes issue with the FDA's regulatory program for animal drugs. Titled "A Response to New Approaches to Be Used in the Regulation of Animal Drugs," the article begins on page 59.

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Food·Drug·Cosmetic Law
Journal

Legal Considerations in Establishing Third and Fourth Classes of Drug Products

By MAVEN J. MYERS and JOSEPH L. FINK

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Dr. Fink Is Assistant Professor of Pharmacy Administration at the Philadelphia College of Pharmacy and Science in Philadelphia, Pennsylvania.

This Paper Was Presented at the Contributed Papers Session of the First Annual Meeting of the American Society for Pharmacy Law, which was held in San Francisco, California on April 23, 1975.

IT IS ESTIMATED that Americans spend more than four billion dollars each year on nonprescription (or over-the-counter (OTC)) drugs.[1] Estimates of expenditures in pharmacies for nonprescription drugs run as high as $2.6 billion,[2] or approximately two-thirds of the total spent. This estimate of market share is likely somewhat inflated because of the inclusion of "wets and dries, insecticides, and animal health goods" in the latter dollar estimate.

Once source has estimated that, in the market for "cold products" in 1972, pharmacies captured 56 percent of the total sales of $990 million.[3] Market shares ranged from less than 20 percent for throat lozenges to more than 80 percent in the fever thermometer market.

[1] Bowles, G. C., "Drugs Sold in the Community can be Source of Adverse Reactions in the Hospital," 119 *Modern Hospital* 108 (Dec., 1972).

[2] "Prescriptions and Sundries Show Best Gains," 170 *American Druggist* 39 (July 1, 1974).

[3] "Are You Ready for the 'Cold Season?'" 168 *American Druggist Merchandising* 45 (Oct. 1, 1973).

A popular cold capsule, introduced in 1961, was originally distributed only through drug distribution channels. By 1964, an estimated 15 percent of the sales of this product were in nondrug outlets. By 1969, the nondrug market share had increased to 45 percent.[4] In 1970, the company deleted its pharmacy-only distribution policy.

While precise figures are not available, it would seem that, in spite of inroads by nondrug outlets, around 50 percent of the sales of nonprescription drug dosage forms for human use occur in a pharmacy.

"Third" Class of Drugs and "Fourth" Class of Drugs

Present federal food, drug and cosmetic legislation divides marketed drug products into two categories: those that are safe and effective for use in unsupervised self medication and those that are safe and effective for use only under the supervision of a licensed prescriber.[5]

Suggestions have been made by the national professional society of pharmacists, [6, 7] a state board of pharmacy,[8] a state association,[9] and others,[10, 11] that a third category of drugs be established that would be available for self-medication, but requiring the supervision of a pharmacist to effect a purchase.

In 1969, the then Bureau of Narcotics and Dangerous Drugs officially created a third class of drugs with a regulation requiring that:

"A Class 'X' product may only be sold at retail without a prescription by a registered pharmacist and not by a nonpharmacist employee even if under the direct supervision of a pharmacist."[12]

The Food and Drug Administration (FDA) re-evaluated the status of these products, with a view to putting them on a prescription-only basis. The Agency reached the following conclusion:

"The Commissioner believes that most pharmacists are very diligent in exercising their professional responsibilities. Further, he notes that in many states where the products are OTC, pharmacists have apparently exercised increased responsibility resulting from a heightened awareness of the abuse potential of these products. Thus, voluntary self-regulation has contributed to reduction of actual abuse, while permitting freer patient access to the drugs than would be available under prescription status."[13]

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[4] "Men J Will Sell Contac to Non-drug Accounts." 161 *American Druggist* 36 (June 1, 1970).

[5] 21 U. S. C. 353(b).

[6] NS8 *Journal of the American Pharmaceutical Association* 362-3 (1968).

[7] NS7 *Journal of the American Pharmaceutical Association* 308 (1967).

[8] "'Third Class' Pushed in N. J.," 168 *American Druggist Merchandising* 26 (July 1, 1973).

[9] "'3rd Class' Sought to Curb Abuse," 163 *American Druggist* 37 (March 22, 1971).

[10] Neumann, "The Pharmacist as an Adviser on Vitamin Use," 170 *American Druggist* 13 (Oct. 1, 1974).

[11] Edwards Tells NARD He Supports 'Third Class of Drugs' Concept." 162 *American Druggist* 13 (Nov. 2, 1970).

[12] 34 *F. R.* 17106—7 (Oct. 22, 1969).

[13] 40 *F. R.* 12998—9 (March 24, 1975).

A less frequently heard, but equally significant, suggestion has been for the creation of a four-category system.[14-20] The fourth category would be dispensed at the request of a prescriber and renewable for a reasonable period of time at the pharmacist's discretion.

The Duffy Commission, created by a resolution of the California lower house, issued a report recommending that pharmacists be allowed, under certain restrictions, to prescribe some prescription drugs.[21]

The "Need" for Additional Classifications

The justification for a third class of drugs (safe and effective for use in self-medication under the supervision of a pharmacist) can rest upon either the desirability of increasing rational drug use by the patient or the attempts to reduce the misuse or abuse of drugs.

Rational drug use can be increased by using the professional knowledge of the pharmacist to benefit the patient in rational drug product selection. This includes selection of an effective drug for the patient's complaint, avoidance of undesirable potential interactions of the drug with other substances, and avoidance by patients for whom the product may be contraindicated. Proper use of the selected drug product includes establishment of the drug consumption regimen and provision of warnings as to use.

Because of the very nature of a drug product, one should be able to assume that a drug product available for nonprescription use is safe and effective for use in self-medication when used according to its labeling. The assumption must be made, however, that the patient reads, comprehends and complies with this labeling. This assumption cannot always be made. One trade organization, for example, launched a public service advertising campaign for the purpose of encouraging patients to read the labels on medicines before taking them.[22] A

[14] Bicket, "Autotherapy—'The Future Is Now,'" NS12 *Journal of the American Pharmaceutical Association* 560, 562 (1972).

[15] NS10 *Journal of the American Pharmaceutical Association* 348 (1970).

[16] NS9 *Journal of the American Pharmaceutical Association* 334 (1969).

[17] NS8 *Journal of the American Pharmaceutical Association* 382 (1968).

[18] NS7 *Journal of the American Pharmaceutical Association* 323 (1967).

[19] NS6 *Journal of the American Pharmaceutical Association* 314 (1966).

[20] NS4 *Journal of the American Pharmaceutical Association* 428 (1964).

[21] *Report to the Speaker of the [State of California] Assembly by the Advisory Commission on Pharmacy, Pursuant to H. R. 21 of 1973-74* (Nov., 1974).

[22] "'Read Label Before Taking Drugs!' Theme of Council on Family Health," 168 *American Druggist Merchandising* 45 (Oct. 15, 1973).

report of a study conducted by the FDA indicated that only half of the people interviewed regularly read the labels of drugs they used.[23]

An additional factor favoring pharmacist intervention in the consumer's purchase of self-medication products is that such intervention serves to emphasize the fact that the product actually is a medicine. Because of extensive advertising of some of these items, consumers may think of them as just another product, rather than medication.[24]

Personal Reinforcement

A final factor that may be mentioned is the impact of personal reinforcement of important labeling statements at the time of sale. The patient is more likely to remember and heed the statement if personally informed of it by the pharmacist at the time of sale.

The second justification for increased control over some nonprescription drugs is the reduction of misuse or abuse of these drugs. While these products are presumed safe and effective when taken according to directions, they may have other effects when not taken according to directions. The movement of paregoric from classification as an exempt narcotic (Schedule V) to a more tightly controlled prescription-only status provides one example.[25]

That highly alcoholic cough syrups can be purchased in a supermarket by anyone old enough to walk while most states prohibit the purchase of beer or liquor until age 18 or 21 presents an anomaly. Suspected misuse of nonprescription products containing antihistamines, non-narcotic cough suppressants, belladonna alkaloids, barbiturates or significant amounts of alcohol have led to requests that these products be placed under greater control.[26]

Some products currently requiring a prescription might be made available for self-medication under the professional supervision of a pharmacist and thus be transferred from prescription status to the "third class" of drugs.

Other prescription medications might be reclassified to permit, once a prescription has been written, renewals of the prescription over a reasonable time at the discretion of the pharmacist.

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[23] Novitch, "Self Medication: What's Right, What's Wrong, What's Next?" 17 *Wisconsin Pharmacy Extension Bulletin* 1, 3 (July, 1974).

[24] Kushner, "New Way to Think About OTC Drugs," 169 *American Druggist* 15 (March 15, 1974).

[25] 165 *American Druggist* 8 (April 17, 1972).

[26] "'Third Class' of Drugs Is Proposed in N. J.," 161 *American Druggist* 30 (June 1, 1970).

Inconsistencies in Current Classifications

The current classifications of drug products into those which are safe and effective for unsupervised use by patients (self-medication) and those which are safe and effective for use only under the supervision of a prescriber have created some apparent inconsistencies.

For years, a manufacturer has marketed an OTC cold preparation (Coricidin tablets) which contains in each tablet 2 milligrams of chlorpheniramine maleate with some aspirin and caffeine.[27] If the antihistamine per dosage unit is doubled to 4 milligrams, however, the product (without aspirin or caffeine) is a prescription legend drug (Chlor-Trimeton tablets). A patient desiring the more potent antihistamine effect, but not desiring to visit a prescriber for a prescription, would be able to obtain the effect simply by taking two tablets of the OTC preparation. The latter therapy might be considered preferable since the caffeine may overcome the mild drowsiness sometimes associated with the antihistamine.[28]

Legally, of course, the OTC product is considered safe and effective for unsupervised use when used according to directions. Practically, consumers may develop their own dosage regimens with these products.

A much clearer anomaly can be found with the treatment of two generically equivalent dosage forms of meclizine hydrochloride. Bonine, which contains 25 milligrams of the active ingredient, is available as an OTC product, while Antivert/25, which also contains 25 milligrams of meclizine hydrochloride, is limited to dispensing only on the order of a prescriber. Even more difficult to understand is the fact that Antivert (without any strength indication) contains only 12.5 milligrams of meclizine hydrochloride (therefore, being only half as potent as the OTC product) but is available only by prescription.

This quirk arose because the previous formulation of Antivert contained, in addition to meclizine hydrochloride, some nicotinic acid. As a result of a National Academy of Sciences-National Research Council review, the product was found ineffective as a fixed combination. This resulted in the reformulation of the product without the nicotinic acid; however, the marketer apparently did not petition for removal of the prescription-only status.

These two examples merely indicate that the current system of drug classification should be re-examined, if only for the purpose of removing inconsistencies such as those noted.

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[27] OTC or prescription status was determined by the designations given in *Physicians' Desk Reference* (28th Edition, 1974).

[28] Subsequent to presentation, the FDA moved Chlor-Trimeton (4 milligrams) to nonprescription status.

Methadone and Controlled Substances

In 1972, the Commissioner of Food and Drugs promulgated regulations limiting the distribution of methadone (a maintenance agent used in the treatment of heroin addicts) to approved maintenance programs, approved hospital pharmacies, and (only where hospital pharmacies are unavailable) to selected community pharmacies. The American Pharmaceutical Association challenged this regulation.[29] The District Court held that once the FDA had approved a new drug application (NDA) for the controlled substance, the Justice Department, not the FDA, had jurisdiction to determine permissible distribution.

In approving a NDA, the FDA does have the authority to limit the drug to use under the supervision of a prescriber.[30] The decision in the methadone case could be interpreted as a limit of the Agency's authority over distribution. In other words, once the FDA has categorized a drug as OTC or prescription, the drug is either available for sale in all outlets or, in the latter cases, in all outlets licensed to dispense prescription medication. With regard to a third class of pharmacist-only drugs, the methadone case is distinguishable in that it dealt with a drug subject to controls by the Drug Enforcement Agency (DEA) and classified as prescription-only. It is highly debatable whether a positive basis exists for the FDA to limit distribution of a drug classified as safe and effective for self-medication.

Section 352(f)(1) of the Federal Food, Drug and Cosmetic Act declares a drug to be misbranded unless its labeling bears adequate directions for use.[31] One might suggest that a product could be placed in the proposed third class by considering, as one aspect of adequate directions for use, use under the supervision of a competently trained health professional, that is, a pharmacist.

The current administration of the FDA, however, has indicated that it would not favor a third class of drugs at this time. Commissioner Schmidt has been quoted as saying he:

". . . categorically rejects the establishment of a third class of drugs at this time . . . . It would be inappropriate to restrict the sale of OTC drugs to pharmacies based on anything less than proof that a significant issue of safety was involved."[32]

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[29] *American Pharmaceutical Association et al. v. Weinberger et al.*, 377 F. Supp. 824 (DC DofC 1974). See also NS14 *Journal of the American Pharmaceutical Association* 400 (1974).

[30] See 21 U. S. C. 353(b)(1)(B) and (C).

[31] 21 U. S. C. 352(f)(1).

[32] "FDA Firmly Rejects Concept of 'Third Class' of Drugs," 170 *American Druggist* 29 (July 1, 1974).

Thus, while such a classification may be legally possible, significant additional proof that this would provide substantial additional protection to the public appears necessary.

As previously noted,[33] once the FDA has approved for OTC sale a substance which also is subject to DEA control, the DEA has successfully restricted these drugs to pharmacist-only sale. This was the case with the cough syrups which contain codeine.

State Regulation

It is well recognized that where the federal government has properly assumed control over a matter, a state government (with some limitations) may more strictly control that matter. The states, however, may not abrogate the federal control through legislation which provides less strict control.

Thus, in states in which an appropriate agency has the legislative authorization, a product which the FDA has approved for OTC sale could be restricted to sale by a pharmacist. In this way, some states may create a third class of drugs within the state.

The same cannot be said for the fourth class of drugs (those originally requiring a prescription, but refillable at the option of the pharmacist for a reasonable time). In this situation, federal laws requiring specific refill authorization are dominant. Thus, without modifications in federal law, the fourth class of drugs would be limited to those which, under federal law, are classified as OTC but which, through an appropriate state law, have been limited to fourth class status.

Summary

To provide better patient care and to increase their contribution to health services, many pharmacists and their professional organizations are seeking a reclassification of drug products. The current federal classifications contain several obvious inconsistencies.

The reclassification goals of pharmacy are hindered by ambiguous interpretation of current federal law and, more significantly, by the failure of pharmacy to present an uncontrovertible case for the public health benefit of reclassification.

A limited third class of drugs has been established by the DEA and could be established in some states. Without changes in existing federal legislation, a fourth class of drugs would be limited to additional state controls over products approved for OTC sale by the FDA.

[The End]

[33] *Supra* note 12.

Current Topics in Canadian Drug Regulatory Affairs

By JAN APSE

Dr. Apse Is Chief of the Drug Regulatory Affairs Division of the Drugs Directorate of the Health Protection Branch in the Department of National Health and Welfare of Canada.

This Paper Was Presented at the Annual Meeting of the Food, Drug and Cosmetic Law Committee of the Corporation, Banking and Business Law Section of the American Bar Association, which was held in Montreal, Canada on August 13, 1975.

WHEN I FIRST STARTED in this position in the Drugs Directorate, I thought the development and co-ordination of regulatory policy and regulations would be a simple and perfunctory task. Experience has taught me otherwise. I know now that policy design and execution is and undoubtedly will be a highly controversial matter for the foreseeable future. The bridge connecting the scientific data, the final policy and the regulation enshrining that policy is difficult to achieve. Scientific facts often are not clearly established, scientists may disagree and consensus on acceptable risks or degree of safety may be absent. However, the public pressure for a rapid resolution is enormous.

In this presentation, I will briefly decribe regulatory matters of current concern, considering proposed new drug, proprietary medicine and cosmetic regulations and dwelling briefly on the problems of labelling in a bilingual country of 22 million.

Proposed Changes to New Drug Regulations

Existing new drug regulations, which are contained in the Food and Drug Regulations, require a notice of compliance for a new drug before a person may sell or advertise the drug. However, an exemption is made for a manufacturer who wishes to conduct certain investigations of the new drug. Upon satisfactory completion of certain regulatory requirements, the manufacturer may sell a new drug to investigators qualified to use that drug.

In actual practice, it is possible to identify two stages in the clinical development of a new drug: clinical pharmacology studies and therapeutic trials. By way of explanation, a clinical pharmacology study is basically an examination of the pharmacology of a drug measured in man. In the proposed regulations, it is defined as follows:

"'Clinical pharmacology studies' means a test in humans, of a new drug, carried out by a clinical pharmacology investigator in an institution having special facilities for the study of new drugs, and includes studies on the route of administration, pharmacological and toxicological actions and initial studies in disease states."

Therapeutic trials, on the other hand, fall into quite a different category. The purpose of these is to determine the conditions of therapeutic use of the new drug. The drug is put in a suitable formulation and, under carefully defined conditions, is given to groups of patients with illnesses for which the new drug might prove of value. In this case, the investigator best qualified for the therapeutic trial may be a physician with a good knowledge of the clinical specialty involved. The proposed regulations will contain a definition of therapeutic trial to the following effect:

"'therapeutic trial' means the testing in humans of a new drug by clinical investigators to determine its efficacy for a proposed use and its safety under the proposed conditions of use."

As a matter of actual practice, the present regulations have been interpreted and administered in such a way that the amendment of the new drug regulations will, in effect, formalize the principle of clinical pharmacology studies and therapeutic trials.

Development of New Drugs

The information required from the manufacturer in order to permit the continuation of the development of a new drug will be set out in somewhat greater detail than in the present regulations.

Under the proposed regulations, a manufacturer will be required to satisfy the Health Protection Branch (HPB) that all the conditions necessary to conduct the study or the trial are such that they may go on without undue foreseeable risk to humans. From a technical point of view, the present regulations are somewhat vague in this regard.

Without going into great detail, permit me to dwell on the subject of "product monograph." The proposed regulations contain a rather detailed definition but, generally, it is defined as a document devoid of promotional material describing properties, claims, indications, and conditions of use of the drug required to provide adequate

directions for safe and effective use of the drug. Before the issuance of a so-called "sales certificate," the Director must be satisfied that a number of conditions have been met, including the development of a satisfactory product monograph. The monograph must accompany the sales certificate of the drug.

Product Monograph

The new regulations provide that HPB may require the manufacturer to provide every practitioner with a copy of the product monograph before advertising or selling the drug to the practitioner. This would mean that, in circumstances determined by HPB, a copy must be supplied to every physician before the drug is advertised or sold.

Our present regulations apply to new drugs for humans and animals. Our proposed regulations will separate the new drug regulations into drugs for use in humans and drugs for use in animals. This, I hope, will be a forerunner of a complete separate set of veterinary drug regulations. We will require much the same data with some important differences. Instead of clinical pharmacology studies, we will have an "experimental studies section." This, and other sections, will contain regulatory requirements which address themselves to the drug residue problem. For example, a therapeutic certificate will be issued only if the proposed therapeutic trial can be conducted without undue foreseeable risk to humans or animals or contamination of the environment.

In summary, our new drug regulations are in the process of revision to the following extent:

(1) Separate new drug regulations for drugs for use in humans and drugs for use in animals.

(2) Express provision for clinical pharmacology trials and therapeutic trials.

(3) Introduction of the product monograph concept.

We will, before the end of the year, I hope, provide industry with drafts of the regulations for comment. With any luck, they will be law by this time next year.

Cosmetics Regulations

Permit me now to turn to cosmetics and cosmetics regulations. The Consumer Packaging and Labelling Act and Regulations apply to consumer products. Drugs, devices and all products manufactured for commercial or industrial enterprises or institutions for use by such

institutions without being sold by them as prepackaged products to other consumers are exempt from the operation of the Act. In such instances, the requirements for labelling under the Food and Drug Act still apply. The Food and Drug Act continues to control all aspects of cosmetics involving health considerations, as well as cosmetics for commercial and institutional use.

Our cosmetics regulations, presently consisting of only four pages, will be revised to bring them into line with the soon to become effective Consumer Packaging and Labelling Regulations.

Our present concept of the revision of the cosmetics regulations involves bringing together into a self-contained unit all regulations applicable to cosmetics under the Food and Drug Act.

As I have already said, HPB is charged with the responsibility over health aspects of cosmetics. With the ever increasing complexity of products and the question of safety, there is a need to have adequate information to enable the Branch to react quickly when new hazards from ingredients are identified and to place such problems in a proper perspective. Additionally, there is a need for information to build scientific and well-reasoned regulations, should they be needed.

Notification System

In order to achieve this end, the Branch advised industry by information letter, as is our custom, that we would be proceeding to a system of notification for cosmetics whereby the industry would supply the Branch with certain information.

We see the system not as a clearance or approval mechanism, but as one providing information. After due deliberation with industry, we have developed draft regulations relating to notification which require the submission of data including:

(1) The name and address of the manufacturer as defined by our regulations.

(2) The name of the cosmetic. The function of this is the identification, without question, of the product that is being notified.

(3) The function of the cosmetic. This is primarily to assist the Branch in understanding the nature of the product in question. It relates more to the manufacturers' concept of it than to the claims. If it becomes necessary to review the safety of the product, it puts into perspective what might be considered normal and intended use.

(4) Formula. Industry is concerned about submitting a detailed description about the formula of products, particularly because of the trade secrets aspect. At this time, it would appear that, in our role as health protectors, the use of ranges of concentration of substances may be sufficient to identify any concern we may have about a particular substance.

Broad Regulatory Power

We believe—and hope—that, in typical "Canadian fashion," we can overcome the difficulties inherent in such a system through the wise use of our broad regulatory power.

The Proprietary or Patent Medicine (PPM) Act was introduced in 1908 to protect the public from the hazards of nostrums and cure-alls.

If I may be permitted to quote from a statement made on the introduction of a bill to repeal the Act by the Honorable Marc Lalonde, the Minister of National Health and Welfare:

"Some of the most romantic and colourful aspects of the early days of patent medicines in this country were the names of the products themselves and the claims made for them. Our grandfathers and grandmothers guzzled, smeared or otherwise employed such exotic concoctions as Lydia Pinkham's Compound; Green Mountain Vegetable Ointment for piles, sore throats and swelled breasts; No-To-Bac, 'to be used faithfully by those who desired to free themselves from the bondage of the tobacco habit'; Pratts' Healing Ointment, for Man and Beast; Munyon Pills-ads for which trumpeted the advice of 'Doctor yourself; there's a Munyon Pill for Every Ill'; and last but not least, Dr. Pierce who offered $500 to women who could not be cured of female weakness by taking his medication. I suppose one might regretfully infer from the latter that in Dr. Pierce's day, as in our own, 'female' and 'weak' tended to be synonymous all too often."

The Act, the repeal of which becomes effective July 1, 1976, has served the Canadian public well. It is now taken to cover products intended for the relief of symptoms associated with minor ailments such as headaches or indigestion. It is unique in that it permitted manufacturers to avoid the listing of medical or active ingredients. In contrast, the Food and Drug Regulations require such listing on both inner and outer labels.

Consumer-Oriented Society

In keeping with today's modern consumer-oriented society, it was felt that the secrecy aspect was outdated. However, the Canadian government recognizes that there should be a class of products that can be used, without undue risk, by the general public for self-medi-

cation. Such self-medication has an important place in the total health care system and serves to ease the pressure for services on health care professionals.

Because of the impending repeal of the Act, a division for proprietary medicines was created in the regulations under the Food and Drug Act. As a result, every proprietary medicine will require a quantitative listing on the label of all medicinal ingredients.

The new regulations contain provisions allowing HPB to adapt rapidly to the scientific and technological progress made in pharmaceutics. They permit close scrutiny of the product:

(1) on first registration;

(2) as the need arises during the valid registration period of the proprietary medicine;

(3) as the manufacturer submits information with respect to any change in the product that might affect its innocuousness and its efficiency or might provide for a schedule of drugs that may not be contained in proprietary medicines.

Place of Sale

An important element in the regulation of drugs is their place of sale. This has been traditionally controlled by the provincial pharmacy statutes. In the past, proprietary medicines under the PPM have been exempt from the provincial requirement that all drugs be sold in pharmacies. As one can imagine, a great deal of close cooperation is required between the provincial and the federal government in order to effect the smooth transition of proprietary medicines from the PPM to the Food and Drug Act.

Finally, a reference to a matter which I am informed is uniquely Canadian. Division 9 of Part C of the Food and Drug Regulations provides a kind of an inventory to the Drugs Directorate on drugs currently on the market. These regulations require every manufacturer of a drug to advise us prior to first sale of a drug, upon withdrawal of the drug from the market, and when a change in formulation, recommended dosage or use occurs. Additionally, the manufacturer must, once a year, furnish certain information to HPB which indicates any changes in the data previously supplied. **[The End]**

The Role of Microbiology in the Integrity of Foods

By JOHN W. FARQUHAR

Mr. Farquhar Is Vice-President of Research and Technical Services of the American Frozen Food Institute.

IN SEPTEMBER of 1972, the Food and Drug Administration (FDA) first proposed the establishment of "Microbiological Quality Standards for Frozen Cream-Type Pies and Food Grade Gelatin." These are the first specific quality standards for which there are no standards of identity. The development and content of this proposal and the subsequent finalization of the rule-making in 1973 have created the following problems:

(1) misunderstandings between the food industry sector and the FDA;

(2) differences in interpretation and/or implementation of micro standards versus micro guidelines among regulatory agencies;

(3) some confusion among various international standards programs.

A hearing has been requested by industry and the regulation, at this time, is stayed.

From the standpoint of the frozen food industry, the American Frozen Food Institute (AFFI), one of the principals in requesting the hearing, was completely disoriented as to a number of programs which were ongoing joint FDA and industry projects. At that particular time, industry was working jointly with the Agency in developing criteria for the FDA Hazard Analysis of Critical Control Points (HACCP) through a series of Technical Service Bulletins as well as participating in supervisor/inspector workshops. Secondly, and most important, was that the AFFI had signed with the FDA a formal memorandum of agreement to establish a cooperative quality assurance program

with a commodity group, namely, onion products. Both of these projects were essentially outcroppings of the recommendations of the 1971 Food Protection Conferences. However, the concept of these newer cooperative quality assurance programs were different from FDA self-certification. Instead of an agreement between the Agency and a particular company, the cooperative quality assurance program was to be more extensive since it involved a number of companies. Thus, an entire industry quality control approach was standardized and/or upgraded.

Up to the time that the FDA proposed to establish microbiological quality standards at the retail level, the industry emphasis via the Food Protection Conference recommendation was to be on microbiological guidelines which were to be implemented through good manufacturing practices (GMPs) or an FDA cooperative quality assurance program. This program would have identified the various critical control points and would have been monitored by the Agency's field inspections (HACCP).

Initial Survey

Interestingly enough, the initial survey for the frozen onion ring industry had already begun. Samples were being collected from the processing plants at various critical points of the production as well as just prior to shipping the product. The design of the microbiological survey was much like the continuous sampling program operated jointly by the United Kingdom Association of Frozen Foods and the Camden Food Preservation Research Association. Over the past ten years, many thousands of samples of United Kingdom produced sauced vegetables and prepared meat and fish products have been analyzed.

Ironically, the next product line that was to have been incorporated in the FDA-industry quality assurance program series was frozen soft-filled bakery products (which include cream-type pies), with certain potato products following. In retrospect, had the FDA's left hand known what the right hand was doing, the Agency could have had all the data it wanted. But at that point, the microbiological quality concept was introduced.

In addition to the promulgation of microbiological standards on the finished product at the retail level and the obvious de-emphasis of in-plant compliance was the introduction of a single number approach. This also caused some confusion, particularly for those who were actively developing the international microbiological guidelines.

It was a well-known fact that the International Commission on Microbiological Specifications for Foods of the International Associa-

tion of Microbiological Studies (of which the FDA was a part) was developing a recommendation for the first time—an opportunity to apply a system of international surveillance of foods through the use of standard sampling plans. The Commission also was going to provide a rational basis for microbiological guidelines, which were to be made more or less stringent as circumstances warranted. These specific recommendations were earmarked, however, for monitoring microbiological safety rather than quality. They could be modified if necessary. Again, it was emphasized that control of processing and handling at the source offers better consumer protection.

Two-Number Approach

The International Commission on Microbiological Specifications for Foods recommended a two-number approach: (1) a target number to designate compliance; and (2) an upper control limit (larger number) to suggest a definite question as to the acceptability of the lot of product. The plan allowed for deviation above the target number but did not allow for any sample exceeding the upper control limit. The concept was designed to handle, on a product-by-product basis, the extreme variation in the food as well as the normal variability which occurs between the method and/or analyst.

Nevertheless, the word from the Agency was:

(1) the FDA has authority under the law to set quality standards;

(2) microbial status of a food is an attribute of quality and the FDA has the authority to set microbial standards;

(3) the FDA can pick up and evaluate foods from plant to retail but is most interested in quality at the retail level;

(4) the FDA can only enforce one number (quality standard) under law.

Thus, the line had been drawn.

The industry's position is basically that opposition to the standards in no way indicates opposition to sound microbiological controls in food production. To the contrary, most, if not all, manufacturers use sophisticated microbiological procedures to eliminate not only the health related pathogens, but also to control the non-health related bacteria which are the subject of the proposed standard. Bacterial tests for the latter are used routinely as an indication of GMPs in the plants.

Foods Processed on Open Lines

Frozen food microbiologists feel that frozen products can be divided into two classes, those which are given a heat process before freezing and those which are not. This fact has an important influence on bacterial counts. In many foods processed on open lines under normal conditions, the great majority of total aerobes originates from the surfaces of equipment. Despite frequent cleaning procedures, minor foci of infection arise (sometimes in machines, sometimes on belt surfaces) and small aggregates of bacteria are dislodged, from time to time, into the product. This mode of infection may contribute to the fact that only in very rare exceptions are bacteria distributed evenly through the bulk of material on the production line. Adjacent samples or even samples from a single frozen block frequently show widely varying counts. Thus, a single sample cannot be regarded as representative of the production as a whole.

Included in the class of products which are heat treated before freezing are vegetables, some meat products and some fish products. In vegetables, the organisms present at the time of freezing are almost entirely confined to the initial infection from the equipment, air or personnel. The time interval is too short and the temperature too low between post-blanch cooling and freezing for growth to occur on the product. It is, therefore, not certain that organoleptic quality losses occur even when the counts approach the 10^6 level.

It must be remembered, however, that the surfaces of equipment could be contaminated with types of bacteria which produce end products of an objectionable nature. Carried over in very small quantities, these could result in off-flavors. Although the possibility cannot be ruled out that growth on the product might take place due to accidental holdup of material through plant breakdown or manual topping up of cartons with held-up vegetables, it can be said that, in general, the total aerobic count from freshly produced vegetables provides a direct indication of the cleanliness of the line and personnel.

Pre-Cooked Meat and Fish

In pre-cooked meat and fish products, cooling is unavoidably less rapid than in blanched vegetables. Also, mixing is required with some made-up or comminuted products. In these conditions, growth may occur after infection in the post-cooking line and high counts could, in some cases, affect the general quality. The counts of total aerobes for freshly frozen pre-cooked meat and fish products are, therefore, an indication of the general process sanitation.

In products which receive no preliminary heat treatment or only a slight surface heating, such as raw meat, poultry and fish products, bacteria on or in the material as it enters the factory may form a high proportion of the flora. Again, this infection may be augmented by contamination from the equipment and personnel or by growth during the process. The total aerobic count may, therefore, be an indication of the quality of the raw material as well as a measure of process hygiene.

In each of the above types of production, the source of abnormally high total counts, when encountered in routine control, may be pinpointed by sampling at various points on the line. With unheated products, samples from incoming raw materials may also require investigation.

Temperature of the Sample

When evaluating counts from stored products, whether from factory stores or retail cabinets, a knowledge of history of the sample is a great asset, if not a necessity. During storage at temperatures of —20°F (—29°C) or 0°F (—18°C), many types of bacteria show a reduction of viable cells. When the temperature of the sample is raised, the death rate increases, until at temperatures in the region of 20°F (—7°C), over 80 percent of the organisms may die in a period of six months. This fact was illustrated in the work by Michener *et al.* (1960) as well as others who found that fluctuations in temperature between 0°F and 20°F during storage exerted the same effect as continuous storage at 20°F. It is apparent, therefore, that long periods at the recommended temperatures, together with the slight rises in temperature which are normal during transport and retail cabinet life, can have a profound effect on the flora. The total counts are reduced and, as some species show a greater persistence than others to survive these conditions, the bacterial spectrum tends to change, with the predominant species sometimes finally assuming a lower position in the order of count magnitude.

How the regulatory agency is going to identify the party guilty of mishandling through the distribution chain has never been explained. It is not uncommon to have as many as six different parties handling the same frozen product enroute to the consumer. The current regulation is aimed directly at the manufacturer. If the product fails to meet the standard, the manufacturer is the one who must label it, "Below Standard in Quality—Contains Excessive Bac-

teria." Essentially, the manufacturer is penalized if the product left the plant in good condition but was mishandled by someone else. Oddly enough, however, high counts at time of processing can readily be reduced in storage and distribution because of bacteria die off. This means the whole concept of microbiological quality standards will not hold up if applied throughout distribution.

While there are legal questions at issue regarding the proposed standard, I will sum up only scientific issues here. The points of industry disagreement are:

(1) Contrary to FDA assertions, there is no direct relationship between normal levels of bacteria in food and the "quality" of such food.

(2) The proper application of microbiological guidelines or GMPs should be at the point of manufacture, not at the retail level.

(3) Microbiological guidelines or GMPs developed from retail samples are meaningless to the manufacturer. Bacterial populations in most non-sterile foods are not static. Normally, they will decrease or increase by the time they reach retail, depending on the nature of the product, its method of distribution and the time elapsed since the product was manufactured.

(4) Microbiological standards applied at distribution and retail levels will present an undue burden on retailers and distributors since they have no way of determining whether products delivered to them are in compliance with the standards.

(5) If regulatory actions occur as a result of such standards, consumer anxiety about the safety of the food supply will undoubtedly increase, even though no question of safety is involved.

(6) The need for microbiological quality standards at the retail level and the consumer benefit to be derived therefrom have never been defined by the FDA.

(7) The regulation requires that products which exceed the standards may be sold only if the label contains a bold warning which reads:

BELOW STANDARD IN QUALITY
CONTAINS EXCESSIVE BACTERIA

We believe that most consumers will totally misconstrue this statement as a health hazard warning when, in fact, there is no health hazard involved.

(8) The adoption of microbiological standards will almost certainly lead to a significant increase in the cost of many foods without any commensurate benefit to consumers.

Request of Data

In addition to considering the above points, one has to question why dry food grade gelatin and frozen cream-type pies were selected, given their excellent health track record. In the case of cream-type pies, survey results published in a technical magazine clearly indicate that all of the major producers could, at the time, meet the proposed criteria. Incidentally, the data from that survey plus the additional supportive data, which set the criteria, were requested by industry lawyers. Essentially, the track record on that request went as follows:

On October 16, 1974, industry wrote the FDA requesting copies of the study and supportive data which provided the basis for the proposed establishment of microbiological standards of quality. This request was made pursuant to the Public Information Act.[1] The materials sought were described in the *Federal Register*,[2] which referred both to data being actively accumulated by the Agency for the establishment of these proposed standards and to survey data and other available information including supportive studies by the FDA and other interested parties which purportedly substantiated the proposed standards. At page 20039, it stated that the data are on file with the Hearing Clerk and are available for review Additionally, another *Federal Register*[3] made further reference to data and information used by the Agency to set the proposed quality standards and stated that additional information was being gathered.

In response to the request of October 16, 1974, industry was directed to the Office of the Hearing Clerk at the FDA's headquarters in Rockville, Maryland to view the referenced data. In Rockville, only copies of objections and correspondence with respect to the proposed standards and a copy of an article reprinted from *Food Technology*,[4] were made available. We were informed by the Hearing Clerk that no other data supporting the proposed standards were on file in that office.

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[1] 5 U. S. C. 552, 45 CFR 5.1—5.85 (1973).

[2] 37 *F. R.* 20038—20039 (Sept. 23, 1972).

[3] 38 *F. R.* 20728—20729 (Aug. 2, 1973).

[4] Leininger, H. V., Shelton, L. R. and Lewis, K. H., "Microbiology of Frozen Cream-Type Pies, Frozen Cooked Peeled Shrimp, and Dry Food Grade Gelatin," 25 *Food Technology* Vol. 3.

On November 21, 1974, industry lawyers visited the FDA in Washington, D. C., presenting industry's dilemma and reiterating the request to view and copy the data referred to in the *Federal Register* as supporting the proposed microbiological standards. The Agency stated that it would attempt to locate those data and any other data or information since gathered in support of the microbiological standards. Upon locating any information the FDA would allow industry to view and copy what was deemed necessary. Furthermore, the Agency stated that it would probably take a few days to locate the data and it would notify industry when it had done so.

Entire Survey

On November 22, 1974, industry was told that the aforementioned *magazine article* constituted the *entire* "survey and supporting data" upon which the proposed microbiological standards of quality were based.

It is extremely difficult to believe that a federal agency such as the FDA is proceeding with the proposed regulation of various food products on a theory that microbiological levels are indicative of quality and is relying for support solely on an article appearing in *Food Technology* with no apparent verification data.

Therefore, in summary, I wish to offer an alternate course of action that we, as part of the affected industry, may pursue cooperatively with the FDA and other interested parties for the purpose of advancing the development and promulgation of microbiological quality standards for foods.

Alternate Course of Action

We believe that there are a number of critical factors which must be thoroughly considered in establishing microbiological guidelines for foods. These factors include such things as:

(1) industry capability to meet the standard (GMP);

(2) the bacteriological profile during the process of distribution;

(3) scientifically valid and statistically acceptable methods of sampling foods and assaying them for their microbiological content.

Failure to consider these and other factors could lead to unrealistically stringent standards which could result in unnecessary waste of wholesome foods and increased costs to consumers.

Therefore, we propose to establish a standing technical committee made up of experts in food microbiology from academia and industry. This committee would be charged to perform the following functions:

(1) identify the foods most likely to benefit from microbial standards and the priority order for such standards;

(2) identify the microorganisms for which standards should be established for the identified foods—namely, total aerobic plate count, coliform organisms, staphylococci, etc.;

(3) identify the sampling plan, sample size and analytical methods to be applied in determining the numerical standard(s) for microorganisms of concern;

(4) identify methods for obtaining microbiological data from all appropriate sources on the level and type of organisms in the identified foods—namely, industrial data, FDA data, academia data, etc.;

(5) propose a microbiological quality standard for each of the identified foods after appropriate thought has been given to all of the considerations listed above.

We feel it essential that there be participation for appropriate Department of Agriculture and FDA representatives in the deliberations of this committee. We hope that the committee, through the sharing of data from industry, academia and government, could function to provide a basis from which regulations could be issued with input, cooperation and relevant information from all affected parties.

FDA Position Paper

Since the committee will need some bench marks from which they begin their activity, we urge that an FDA position paper be developed that would define microbial quality, the regulatory disposition toward developing and promulgating standards, and some indication of intended application. Again, speaking for AFFI, better understanding on these subjects could well lead to withdrawal of our objections to Subpart A.

We do not intend to retract our objections to the microbiological numerical value for frozen cream-type pies as issued under Subpart B until the committee described above makes its recommendations relative to these products. Nor do we waive rights to a hearing on this subject should it be advisable from our point of view to exercise this right at some point in the future. **[The End]**

Review of the 1970 NAS GRAS Pilot Survey (Phase I) and the 1971 NAS Comprehensive Survey (Phase II)

By DEE M. GRAHAM, Ph.D.

Dr. Graham Is Assistant Director of Research of the Del Monte Corporation.

OPERATING UNDER A PRESIDENTIAL DIRECTIVE, the United States Department of Health, Education and Welfare in 1969 began a re-evaluation of the safety of substances generally recognized as safe (GRAS) for use in food. The Food and Drug Administration (FDA) subsequently requested the National Academy of Sciences (NAS) to develop and test a format and survey procedure that could be used to gather the information required in performing the safety re-evaluation. A special subcommittee, chaired by Dr. Herbert E. Carter and under the general direction of the Food Protection Committee, carried out this assignment. The activity of this committee has come to be known as the NAS Phase I GRAS Survey.

Purpose

Early in its deliberations the committee arrived at several purposes for the initial survey:

(1) To develop estimates of usage of GRAS substances in foods. This required information on specific uses and use levels wherever GRAS substances were used.

(2) To provide a basis for re-evaluating the GRAS status of individual substances.

(3) To provide data on potential individual intakes. This was not an attempt to arrive at probable or even average daily intakes but, rather, it was an attempt to measure the extent of potential individual exposure of consumers to GRAS substances.

(4) To provide a basis for subsequent toxicological evaluation of safety.

It is very important that these purposes be clearly understood for they guided the entire design and development of both Phase I and Phase II questionnaires. Incorrect interpretation of purpose no. 3, particularly, has led, in some cases, to overextension and incorrect usage of the Phase I and Phase II data.

Plan

The Phase I NAS Survey Committee recognized the enormity of its task at the outset. Among the several different alternatives considered were the following suggestions:

(1) Select a "market basket" sample of representative foods and analyze them for content of GRAS substances. This alternative was considered impractical because of its obvious cost, the wide number of choices of foods which would have to be analyzed, the logistics of collecting such foods for analyses, the limits on analytical capability and the inherent inaccuracies involved in selecting an appropriate sample.

(2) Survey the amount of each additive produced and then allocate these to per capita intake. This approach was considered unworkable since many GRAS substances have both food and non-food uses. Thus, in many cases, total production figures were not meaningful. Manufacturers often were not certain of the ultimate use of the substances they produced. In addition, there was no satisfactory way to relate total production to food intake.

(3) Survey only the users of GRAS substances, that is, food processors. This approach provided no way of checking the data against any realistic bench mark of production. Furthermore, in most cases, safety data on food additives resided primarily in the hands of the additive manufacturer and the availability of such data became an increasingly important factor in the committee's opinion.

(4) Survey both chemical manufacturers and food processors concurrently. This approach was selected because it provided information on usage from those who used GRAS substances—

food processors—and it provided some basis for judging the validity of total consumer exposure by relating calculated consumption to estimates of production of GRAS substances. While this could not be done for all substances, there were enough possible situations to make this a meaningful internal check on the survey procedure.

Design of the Survey

A first essential step was the development of a complete list of GRAS substances. While the charge to the committee was to survey the GRAS list, there was at that time no readily available complete list of GRAS substances. The original list published in 1960 had received both additions and deletions over a decade.[1] Each of these additions and deletions had been published appropriately in the *Federal Register* but were not assembled in any one place. Further, there were a number of prior sanctioned items which had been cleared for individual processors on the basis of "prior sanction letters." Because of limited applications, in most cases, these were never published in the *Federal Register*. The identity, purity and proper names of many GRAS substances also required resolution. Perhaps one of the major contributions of the Phase I survey was the development of a single complete list of GRAS substances.

In a similar way the appropriate technical effects of GRAS substances were defined. Since intended technical effect was the primary basis for the approval of food additives, this same approach was used in organizing data for the GRAS survey.

The variety of individual foods available in the United States food system is almost infinite. Classification of individual foods into appropriate food categories was considered an essential step in making the survey task manageable. The committee eventually selected 28 food categories for this purpose.

Estimate of Consumer Exposure

To arrive at an estimate of consumer exposure, some estimate of food consumption was required. After careful study, food consumption data from the United States Department of Agriculture 1965 survey was considered the best available source of portion sizes. However, it did not provide adequate information on frequency of

[1] 21 CFR 121.101(d).

eating. The 1967 menu census data developed by the Marketing Research Corporation of America was selected for this purpose.

An appropriate questionnaire, designed to provide information on annual usage of GRAS substances, the specific foods in which GRAS substances were used, specific use levels and ranges, additional data on specifications, safety information and effects of processing, was developed. Comprehensive instructions explaining how to use the questionnaire were prepared. In view of the scope and the variety of both the manufacturers of chemical additives and the food processors who would be responding, explicit detailed instructions were necessary.

The committee was impressed with the extreme sensitivity of the kind of information it would be requesting in the questionnaire. Therefore, a system of data collection and coding which would ensure the confidentiality of individual responses was required. Such a system was developed through the offices of the NAS and functioned effectively.

Implementation of the Survey

The Phase I pilot survey was intended primarily to test the workability of the questionnaire and its instructions. Also, it was planned to gain some idea of how many firms would need to be surveyed. The cooperation of the chemical and food industry to this pilot survey was extremely gratifying. Within 90 days after the questionnaires had been mailed, 42 firms had responded with reports on 282 individual substances. The reports generally were very complete. The critiques and telephone questions to the Academy Office proved invaluable in correcting the major procedural deficiencies in the Phase I survey. The Phase I survey report was submitted to the FDA in December 1970. Early in 1971, the NAS was asked to expand the pilot survey to a full-scale survey which has come to be known as the Phase II NAS GRAS Survey. This task was undertaken by a reformulated committee, chaired by Dr. L. J. Filer under the general direction of the Food Protection Committee. Recipients of the Phase II survey were selected to provide as wide as possible coverage of the food industry within the bounds of practicability. Respondents were chosen with the aid of many major trade associations within the food industry. In addition, the survey was announced in the *Federal Register* which invited any interested respondent to contact the NAS if they did not receive a questionnaire and wished to have one.[2] Again response to the full survey was extremely gratifying. Of the 750 ques-

[2] Vol. 36, No. 206 (Oct. 23, 1971).

tionnaires mailed out, 382 firms reported on 479 substances for a total of 5,449 reports submitted within the allowable time. A separate NAS survey on infant formula products and baby foods collected 304 reports. Compiled with additional surveys conducted by the Flavor & Extract Manufacturers Association, the Chewing Gum Manufacturers Association and the candy industry, a total of 24,184 reports were received and processed. Compilation of these data proved to be a major task. One criticism which the NAS committee received at the completion of the survey was that a copy of the final report was not provided to each respondent. I think I can answer that question most effectively by pointing out that the two complete copies of the final report weighed approximately 50 pounds when delivered to the FDA. Subsequently, summaries of appropriate tables of data were compiled in reduced type size and made available through the National Technical Information Service (NTIS). The NTIS document is available to any interested party who wishes to purchase it.[3]

Evaluation of the Phase I and Phase II Surveys

The weaknesses of the Phase I and Phase II surveys quickly became apparent. The data did not provide good estimates of average daily intakes of individual additives. This specifically was not one of its original purposes. A more critical weakness related to the lack of precision in developing the major food categories. The categories were entirely too broad and gave an exaggerated idea of the usage of GRAS substances in some areas. This is true particularly when an attempt is made to use data from the Phase I and Phase II surveys for estimating average daily intakes. The very broad food categories assumed the usage of an individual additive in every food within the category. Even though this might be the case, it is obvious that no individual would ever consume every food within a food category within one day or even within one year. Thus, while the Phase I and Phase II data provided a basis on which to judge potential consumer exposure, the bias for intakes on the high side limits the usefulness of the data. On the other hand, any substance judged safe in subsequent safety evaluations based on data from the Phase I and Phase II surveys would necessarily enjoy a substantial margin of safety.

The strengths of the Phase I and Phase II surveys included the compilation of a complete GRAS list and a better understanding of the importance of frequency of use of individual foods. It also pro-

[3] No. PB-221939 (Feb. 1973).

vided enough perspective on potential individual exposure to prove that reasonable estimates of intakes can be obtained.

The data emphasized to me the extreme importance of consuming a balanced diet from a large variety of foods. Certainly, restriction of intake of foods to a smaller number of food choices increases the exposure to individual GRAS substances, as well as posing the obvious risk of nutritional inadequacy.

Another major contribution from the GRAS surveys, in my opinion, resides within the industry itself. Completion of the laborious task related to this survey required the development of information systems within the participating companies showing clearly the location and use of additives throughout the food industry. This in itself does much to assure our confidence in the safety of the American food system. **[The End]**

FD&C RED NO. 2 SHOWN TO BE CARCINOGENIC IN FDA STUDY

The carcinogenicity of the color additive FD&C Red No. 2 has for the first time been clearly demonstrated, according to Dr. D. W. Gaylor of the Food and Drug Administration's (FDA's) Toxicological Advisory Committee. Dr. Gaylor reached this conclusion from a biostatistical analysis he completed on data from the most recent FDA study of the color additive. The biological assumptions upon which Dr. Gaylor's analysis is based are presently being evaluated by FDA, members of the Toxicological Advisory Committee, and a consultant from the National Cancer Institute. Two additional analyses will be completed as part of the Toxicological Advisory Committee's review of the FDA study.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,543

Bioequivalence/Bioavailability—The FDA's Plans

By ROBERT L. SPENCER

Mr. Spencer Is Chief of the Precedent Regulations and Legislative Activities Branch of the Bureau of Drugs in the Food and Drug Administration.

IN THE *FEDERAL REGISTER* OF JUNE 20, 1975, the Food and Drug Administration (FDA) proposed regulations regarding bioavailability and bioequivalence. A review of the more than 80 comments submitted in response to the proposed regulations indicates that, in spite of the somewhat lengthy preambles, the intent of the proposals and the FDA's plans to handle bioavailability/bioequivalence problems are not completely understood. Therefore, I would like to take this time to restate the intent of the proposed regulations and to reflect on a few of the comments submitted in response to the proposals. In addition, I will discuss the FDA's plans regarding bioavailability and bioequivalence.

The June 20th proposal contains two separate but nonetheless related regulations. The first of these proposes to define the term "bioavailability," to establish acceptable methods for the conduct of *in vivo* bioavailability studies, and to specify those *in vivo* bioavailability studies requiring submission of an investigational new drug (IND). This proposal also requires that any new drug application or supplemental application which concerns a significant change in product formulation and which is submitted after a specified date contain either evidence of bioavailability or information to permit waiver of this requirement. The intent of this last requirement is to establish basic data whereby formulation changes may be adequately reviewed to assure that the reformulated product is equivalent to the original

product shown to be safe and effective in clinical trials. Without such data, clinical evidence of safety and effectiveness of the reformulated product may be needed.

The second regulation proposes to define certain terms relating to bioequivalence, to establish criteria to identify drug products having bioequivalence problems, and to establish procedures to assure that, if a bioequivalence problem is identified, each manufacturer marketing the drug product obtains data necessary to show that its product is bioequivalent. This second proposed regulation describes procedures only. It does not, in itself, establish a requirement that a person must submit evidence that his product is bioequivalent.

Specified Standards

The proposed regulations do not attempt to equate evidence of bioavailability with evidence of therapeutic effectiveness. All drug products are required to meet specified standards to assure that they have their purported identity, strength, quality and purity. Traditionally, these standards have used physical and chemical tests to characterize a drug product. However, with the development of the sciences of biopharmaceutics and pharmacokinetics, it is now possible to characterize a drug product more fully by measuring its bioavailability as well as its physicial and chemical characteristics. The intent of the proposed biovailability/bioequivalence regulations is to establish methods and procedures for implementing this additional means of assuring drug product quality and performance.

Bioavailability and bioequivalence studies are intended to establish *in vivo* performance. In the case of bioequivalence studies, we intend to utilize, as the reference material, drug products that have been shown to be safe and effective in clinical trials. We believe that bioequivalence studies are the most accurate methods of showing product comparability. Furthermore, we are not aware of any instance where clinical or therapeutic differences have been demonstrated between products producing comparable blood levels *in vivo*.

Let me now turn to what we believe are some of the more significant comments that have been submitted in response to the proposed regulations. Brief mention of a few of these comments is warranted in order to clarify the intent of the proposals and to highlight the scientific issues involved.

Legislative History

Several of these comments raise the question of the FDA's authority to issue bioequivalence requirements and argue that the intent to require evidence of bioavailability and bioequivalence flies in the face of the legislative history that specified that the authority to require proof of safety and effectiveness not include the issue of relative effectiveness. We believe that such a narrow interpretation of the Federal Food, Drug and Cosmetic Act subverts the intent of Congress to assure that marketed drugs meet appropriate standards of quality, and are safe and effective. In addition, it is our opinion that the issue has nothing to do with the concept of relative effectiveness. The Act clearly requires that every dosage form of each drug be formulated and manufactured in such a way as to meet appropriate standards, and be safe and effective. For some drug products, in addition to evidence that the products meet appropriate physicochemical standards, a necessary part of this assurance is evidence that each active ingredient is bioavailable to a uniform and acceptable degree. It is difficult to understand how an argument can be made that a scientific consideration of the quality, safety and effectiveness of a drug product need not include the question of its bioavailability.

There is no single provision of the Federal Food, Drug and Cosmetic Act which specifically outlines the FDA's authority to issue bioavailability and bioequivalence regulations. Rather, the Agency's authority in this area derives from several provisions of the Act—the new drug provisions, the authority to develop antibiotic regulations, and the drug adulteration and misbranding provisions that can be implemented either on a case-by-case basis through court actions or by regulations for the efficient enforcement of the Act under Section 701(a). We believe that, through use of the authority cited, we can establish such bioavailability and bioequivalence requirements as are necessary to assure that a drug product meets appropriate standards of quality and is safe, effective and neither adulterated nor misbranded.

In Vitro Tests

A number of comments expressed concern over the use of an *in vitro* test, not correlated with *in vivo* data, to establish bioequivalence. We believe that efforts should be made to develop *in vitro* tests that are valid predictors of bioequivalence. An *in vitro* bioequivalence standard that has been correlated with *in vivo* data will assure not only the bioequivalence of different drug products but also batch-to-batch uni-

formity of the same drug product. However, we believe that if an *in vitro* bioequivalance standard does not exist, an interim solution is, where practical, *in vitro* testing alone using a current method specified by the FDA and/or a requirement for *in vivo* testing. We believe that this interim requirement should be imposed only until an *in vitro* bioequivalence standard is available.

The FDA intends to use a current *in vitro* test (usually a dissolution test) as an interim measurement of bioequivalence only in selected cases where findings suggest that a class of drug products has a potential bioequivalence problem. The *in vitro* test would serve to screen out "poor" products. It has been the Agency's experience that poor bioavailability has been associated with poor dissolution. Where the FDA has performed both dissolution studies and blood level studies on the same lots of different brands of the same drug product, substantial differences in disssolution rates were associated with substantial differences in blood levels. We are not aware of any instance where products with high dissolution rates were not also bioavailable.

Careful Dosage Control

A current *in vitro* test not correlated with *in vivo* data will not be used to establish the bioequivalance of drug products with a documented bioequivalence problem or if the products have a narrow safety-toxicity range necessitating careful dosage control and patient monitoring.

The FDA is developing a program to obtain dissolution data for approximately 40 multisource drug products listed in the proposed regulations as having potential bioequivalence problems. These data will enable the Agency to determine the practicability of using dissolution testing as an interim bioequivalence requirement for these drug products.

The majority of the more significant comments concerning the proposed bioavailability regulations addressed the proposed guidelines for the conduct of *in vivo* bioavailability studies. It is appropriate to point out that these proposed guidelines are intended to be just that—guidelines. A protocol for the conduct of a bioavailability study must be tailored to the drug product to be studied and to the scientific questions to be answered. However, rather than simply requiring evidence of bioavailability and letting the manufacturer determine how the bioavailability studies are to be conducted, the FDA decided to provide some detailed suggestions as to the basic design of a bioavailabilty

study. The Agency also recommended, in the proposed regulation, that the protocol for a bioavailability study be submitted for review prior to the initiation of the study. The recommendation was made because the FDA knew it could not write specific regulations covering the types of protocols required for all bioavailability studies. The Agency also wished to avoid the conduct of an improper study and unnecessary human research.

Brand Name Products

There have been a number of questions raised regarding the list of drugs in the proposed bioequivalence regulations. Concerns have been voiced that some purchasers of these drugs will limit their selection to brand name products only. The significance of the list was also the subject of a statement by the Commissioner before Senator Nelson's Select Committee on Small Business on November 11, 1975.

The list was published to announce to the industry, to the scientific community and to the public those drug products that we believe, on the basis of current evidence, fall within the criteria set in our proposed regulations for requiring proof of bioequivalence.

We felt it necessary for the industry, the public and experts in biopharmaceutics to understand the Agency's views in applying the criteria for the selection of products presenting real or potential bioequivalence problems so that they could better evaluate the criteria before commenting on the regulations. We also believed that it was important to inform drug firms that they should initiate efforts to study the bioequivalence of their products on the list, if they have not already done so.

The proposed list includes:

(1) all drug products for which any positive evidence has ever been developed that a bioinequivalent product has been produced by one or more manufacturers; and

(2) all drug products that have, in our view, a potential for bioinequivalence on the basis of chemical structure and/or physicochemical features.

Liberal Inclusion Policy

In identifying drug products for inclusion on the list, we accepted each one if there was any question about its potential for bioinequivalence. Such a liberal inclusion policy was adopted to provide as

much advance notice as possible to the drug industry and the scientific community of the drug products that the Agency was considering covering by its bioequivalence regulations. It was our view that a more timely solution to any problems of bioequivalence would occur if we included, at the start, all drug products with any potential for bioinequivalence than if we added drug products later in a piecemeal fashion.

Inclusion of the drug products with potential problems on the list in no way implies that we have positive evidence of bioinequivalence among the various brands of these drug products currently on the market. Where specific examples of nonbioequivalent products are discovered, it is our policy to take enforcement action on a case-by-case basis.

In the public debate which has surrounded the bioequivalence issue during the past year, a simple fact has been all too often ignored. This is that the FDA has for a number of years required bioavailability data on all antibiotics and on virtually all of the multisource drugs on the list published on June 20, 1975. This means that manufacturers who hold approved new or abbreviated new drug applications (NDAs) have, for the most part, already submitted bioavailability data on their products to the Agency. The major exceptions are those cases where methodology for such testing is not available.

List of Manufacturers and Distributors

To those charged with purchasing these drug products, we would recommend a simple policy—that is, to purchase these drugs from firms holding approved NDAs or abbreviated NDAs. To aid such purchasers, the FDA is making available a list of all firms that are authorized in an approved NDA, an abbreviated NDA or a supplemental application to manufacture and/or distribute the drug products listed in the proposed bioequivalence regulations. The list will include manufacturers, repackers and own-label distributors. We recognize that, until bioequivalence requirements are established, this list of manufacturers and distributors will have to be updated periodically to include new firms that obtain approval to distribute these drug products.

We are in the process of preparing the final bioavailability and bioequivalence regulations. As is our practice, we are carefully reviewing each of the comments we have received regarding the proposals, and these comments will be addressed in the preambles to the final regulations. Although there will be revisions of the regulations to re-

flect these comments, we do not anticipate any major changes in approach or direction. The procedures for identifying bioequivalence problems and for establishing bioequivalence requirements will be essentially as set out in the proposed regulations. Bioequivalence requirements will be established under the basic rule-making procedures. Therefore, the public will have the opportunity to comment on the drug products identified as having bioequivalence problems and on the kinds of studies needed to assure the bioequivalence of these products. Where drug products are listed because they are a member of a particular chemical class (for example, sulfonamides), we will endeavor to deal with them on a class basis rather than on an individual product basis. Our highest priority is the establishment of bioequivalence requirements for those drug products used for the treatment of serious disease in which dosage control is critically important.

The FDA's Responsibility

Let me close by reflecting on one of the other comments that we have received regarding the proposed regulations. This comment stated that the proposed petition procedures for establishing a bioequivalence requirement shift to manufacturers the FDA's responsibility for monitoring the safety and effectiveness of their competitors' products. This comment, in our opinion, wrongly implies that once the regulations are made final, the FDA is going to sit back and wait for manufacturers to submit data on their competitors' products. This is not the case. The FDA will continue to conduct studies to determine if bioequivalence problems exist with multiple source drug products. The FDA itself will propose to establish bioequivalence requirements for drug products if the data needed to establish such a requirement are known to the Agency. It would be naive to believe that many manufacturers do not routinely test their competitors' products. In the past, manufacturers have submitted data to the FDA showing that there are bioequivalence problems with their competitors' products. The petition procedure is not to transfer to anyone the FDA's responsibility to assure the safety, effectiveness and quality of drug products. The purpose of the procedure is to provide an orderly process for any person to submit evidence of a bioequivalence problem to the FDA and to assure that such evidence is scientifically valid and available for public scrutiny and is not simply an attempt to make it harder for competitors to market their products. **[The End]**

Bioequivalence/Bioavailability—A Manufacturer's View

By C. J. CAVALLITO, Ph.D.

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EXAMINATION OF ISSUES that have controversial implications might best begin with a discussion of what is meant by certain key words and expressions.

A definition of "bioavailability" that is consistent with general usage is that it is "a measure of the rate and extent of absorption of a *drug* from an administered dosage form, usually estimated from concentration-time relationships of the drug or its metabolites in the systemic circulation." The proposed rules of the Food and Drug Administration (FDA), published on June 20, 1975,[1] define bioavailability as "the rate and extent to which the *therapeutic moiety* is absorbed from a drug product and becomes available to the site of drug action, usually as estimated by its concentrations in body fluids, rate of excretion, or acute pharmacological effect." This would be more acceptable with deletion of "to the site of drug action" since we do not know the quantitative relationships between rate or extent of absorption and that of delivery or availability of drug to site of action. Most bioavailability questions relate to orally administered dosage forms.

Before defining "bioequivalence," some other reference terms should be described. One of these is "chemical equivalents." The Office of Technology Assessment (OTA) Drug Bioequivalence Report[2] defines these as "drug products that contain the same amounts of the same therapeutically active ingredients in the same dosage forms *and that meet present compendial standards.*" This definition may have served a

[1] 40 *F. R.* 26161 (1975).

[2] Drug Bioequivalence. A Report of the Office of Technology Assessment Drug Bioequivalence Study Panel. U. S. Government Printing Office, Washington, D. C. (1974).

purpose in the context of that report but, to a pharmaceutical chemist, it is unacceptable. Chemical equivalence relates to conformance with the physical and chemical specifications of a reference drug substance. Further, compendial standards, of necessity, lag in time behind the relevant advances in technology and do not always fully describe the chemical composition or specifications of the drug substance, let alone the drug product. In addition, they tend to be minimal common denominators for specification of a drug substance. It is not unusual for manufacturers to develop additional or more definitive specifications characterizing the drug substance. Not all drugs, of course, are included in the compendia.

Equivalents and Alternatives

Two other terms introduced more recently are "pharmaceutical equivalents" and "pharmaceutical alternatives." Pharmaceutical equivalents are defined by the OTA Report[3] as "drug products that contain the same amounts of the same therapeutically active *ingredients* in the same dosage form *and that meet standards to be established on the basis of the best available technology.*" The FDA-proposed definition[4] is expanded with reference to conformance with compendial or other applicable standards. Pharmaceutical alternatives are described by the FDA as ". . . drug products that contain the identical therapeutic moiety (or its precursor), but not necessarily in the same amount or dosage form, or as the same salt or ester."[5] The expressions "pharmaceutical equivalents" and "pharmaceutical alternatives" are obfuscating, if not misleading in implications and have doubtful scientific need or value.

Now let us look at "bioequivalents." The OTA defines these as "chemical equivalents which, when administered to the same individuals in the same dosage regimen, will result in comparable bioavailability." The word "comparable" reflects the uncertainties that exist at this time as to the biomedical and therapeutic implications of degrees of deviation from identity or superimposability of bioavailability curves. The FDA defines "bioequivalent drug products" as ". . . pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a statistically significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions."[6] The inclusion of phar-

[3] See footnote 2.
[4] 40 *F. R.* 26165, 26168 (1975).
[5] See footnote 4.
[6] See footnote 4.

maceutical equivalents and alternatives in a definition of bioequivalence may serve some regulatory rather than scientific purpose.

In Vitro Bioequivalence

An expression introduced in the June 20, 1975 proposed regulations is that of *"in vitro* bioequivalence" standards for drug products.[7] More than 75 drug products were listed in a category requiring such standards. Left to the future was the establishment of the standards and a clarification of the incongruities of the expression.

The ultimate objective of our concern is that of assuring clinical or therapeutic equivalence of purportedly equivalent or interchangeable products, be they derived from different manufacturers or the same manufacturer at different times. Although "clinical" and "therapeutic" often are used interchangeably, "clinical" is more widely applicable since not all drug products are "therapeutic." All other measures of equivalence are abbreviated approximations of these. Therapeutic equivalents are defined by the OTA as "chemical equivalents which, when administered to the same individuals in the same dosage regimen, will provide essentially the same efficacy and/or toxicity."[8] This language is built on the OTA reference to chemical equivalents as products rather than as drug substances. Therapeutic or clinical equivalence should relate to product dosage forms, not to drug substances.

From the foregoing discussion, it appears that there are more proposed categories of equivalences than are necessary, and that those we need could be more clearly defined.

Use of Human Subjects

There is general agreement that the use of human subjects in drug testing should be kept to an essential minimum, including use for evaluation of equivalence among drug products. There also is agreement that the original product must be shown to be safe and effective by adequate and well-controlled clinical studies. The original product becomes the reference for subsequent comparisons of equivalence. The word "equivalent" implies something less than identical. Opinions differ as to how product equivalence assessed by less than therapeutic experience is to be approximated and how much of a statistically significant deviation from a reference is therapeutically significant for each product. The answer is that we usually do not have an adequate correlative data base from which to define acceptable limits of devia-

[7] See footnote 4.

[8] See footnote 2.

tions. It is generally accepted by pharmaceutical scientists that chemical and/or compendial equivalence of drug substances is not adequate to assure product equivalences. Bioequivalence as reflected by appropriate bioavailability tests permits a closer approximation. However, one controlled bioavailability test would not answer questions such as the following. How many lots of each manufacturer's dosage form should be tested to detect lot-to-lot variations? At what frequency should this testing be done? Does bioavailability of each manufacturer's dosage form remain unchanged during product shelf life? Do variations in excipients influence allergenicity? Do taste and odor differences among products influence patient compliance in practice? The latter is an effect not reflected in controlled bioavailability test subjects.

It is not always possible to assess bioavailability by the amount of drug or metabolites appearing in the circulation. Analytical methodology may be inadequate. Urinary excretion profiles or measurement of an acute pharmacological response may be utilized. However, these are less desirable.

Bioavailability Tests

The qualification "adequate and well controlled" usually prefaces reference to acceptable therapeutic trials for evidence of efficacy and safety. No less significant is this qualification to bioavailability tests used to assess bioequivalences. However, even best effort bioavailability tests may retain uncertainties as to best design, their significance and circumstances of need. For example: Will results observed with normal test subjects be indicative of the product's bioavailability in patient populations? How are results influenced by the subject's sex, age, weight, race, etc.? What are the effects of real life environmental variables compared to controlled test environments? Are single or multiple dose administrations more meaningful? Should a steady state be achieved before the test dose is administered? When are crossover or parallel studies appropriate? What are the significances to equivalence of areas under the curve, peak concentration time and level, and rate of drug disappearance? Do food and beverage intake variables among patient populations influence bioavailability differently among purportedly equivalent products?

It would be morally unjustified and economically prohibitive to satisfy all questions of equivalence by resorting to a large variety of bioavailability tests and clinical trials. Ideally, if therapeutic performance were correlated with bioavailability, which in turn was correlated

with *in vitro* laboratory tests, our problems would be simplified. We are a long way from having such correlations. Unfortunately, merely expanding the number of uncorrelated *in vitro* studies is a dubious substitute for bioavailability tests. At this time, a bioavailability test may be more likely to detect possible inequivalences among products than to assure equivalence of performance among a variety of patients under the variable conditions in practice.

Multiple Source Products

I would like to propose another form of equivalence, which if assured would provide more confidence in the quality of multiple source products on the market; namely, regulatory equivalence.[9]

Regulatory equivalence among multiple source drug products requires at least uniform application of the requirements for a new drug application (NDA) or an abbreviated NDA, uniform enforcement practices, equivalent inspection surveillance and consistent application of principles in regulations. (An illustration of an inconsistent application of principles may be drawn from the June 20 proposals which would require bioavailability testing for any reformulations of a new drug, including changes in dyes, flavors or preservatives.[10] However, for older drugs, the regulations would be less strict. This ignores the fact that it is just as likely for an inexperienced manufacturer to prepare a poor dosage form from an old drug as from a new one.) In the past year, the existence of regulatory inequivalences has become much more widely recognized, and is inconsistent with FDA assurances (such as those made before Senator Kennedy in 1974) of uniform quality of marketed products under a proposed Maximum Allowable Cost (MAC) program. The inability or reluctance of the FDA to remedy regulatory inequivalences can be read by comparing the scope of the initial bioavailability proposals of January 3, 1973[11] with the conglomeration of other issues intermingled with the June 20, 1975 proposals relating to bioavailability.

Governments, of course, can arbitrarily dictate or establish certain situations by fiat. The old drug or new drug status of a marketed product or the requirement of a full NDA as against an abbreviated NDA may be based on regulatory expediency as much as on scientific and medical considerations. The justification of a need for a bioequivalence showing *via* bioavailability tests and the design of such studies

[9] NS13 *Journal of the American Pharmacy Association* 698 (1973).

[10] 40 *F. R.* 26160 (1975).

[11] 38 *F. R.* 885—887 (1973).

also can be rationalized to accommodate temporal objectives of government. However, time and experience can dispel illusions, including the one that multiple source products can safely be considered to be equivalent until proven to be different.

Appropriate and Adequate Evaluations

Does a particular segment of the pharmaceutical industry have a uniqueness in its total product quality that others could not match? Of course not. If an organization is willing to commit the resources necessary to provide the qualified personnel and facilities and to conduct appropriate and adequate evaluations and controls of its products, it should be able to meet the requirements that add up to therapeutic equivalence—or even superiority. No manufacturer can achieve perfection in total product quality, but, until every manufacturer's best effort is equal, multiple source products are unlikely to be consistently equivalent in performance. Although the FDA cannot assure that every manufacturer's quality is equivalent, the Agency should assure, through the exercise of regulatory equivalence, at least a minimum common denominator of current good practices.

Attempts to achieve and demonstrate consistent therapeutic equivalence among multiple source products will exact a high price. Proposed programs, such as MAC, project savings based on selected present prices with the assumption that regulatory equivalence exists and bioequivalences can be assured with little impact on price differentials. The economic impact of a MAC program has not been documented adequately.

Seven years ago today, I gave a talk before an industry group on the then emerging controversial subject of therapeutic equivalence.[12] By 1968, the Academy of Pharmaceutical Sciences had already taken a position on the multiple source drug product quality issue (also adopted in 1969 by the American Pharmaceutical Association).[13] That same year, the Department of Health, Education and Welfare Task Force on Prescription Drugs stated "that lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health."[14] The word "major" involves a value judgment and provides a basis for per-

[12] 91 *Journal of the National Association of Retail Druggists* 29—34 (1969).

[13] "Drug Product Quality," Academy of Pharmaceutical Sciences and American Pharmaceutical Association, Washington, D. C. (1969).

[14] Task Force on Prescription Drugs. Second Interim Report and Recommendations, Aug. 30, 1968, p. 72. Office of the Secretary, U. S. Department of Health, Education and Welfare, Washington, D. C.

petual interpretive accommodation. On June 20, 1975, the FDA published a list of more than 60 drugs, for whose dosage forms an *in vivo* bioequivalence requirement was proposed. Although the basis for selections and exclusions was not described, it may be a sign that we are coming closer to a recognition that a question ignored is not a question answered.

Conclusion

In conclusion, bioavailability evaluations have evolved as approximations of bioequivalence, which in turn are suggestive of therapeutic equivalence among multiple source products. The most appropriate design of a bioavailability study and the circumstances and frequency of its need to monitor equivalence are matters still under examination. There remain elements of total product quality incorporated in the course of the development, manufacture and control of each manufacturer's product, and delivered with a degree of consistency that is variably unique for each product and each manufacturer. These elements cannot be measured by an occasional bioavailability test. We are similarly distant from having correlations of bioequivalences with simpler *in vitro* assessments among multiple source products. When a specific product that has an established record of performance is substituted for one of a different source, there may be differences in price and quality. However, one cannot place a value on these trade-offs in the absence of equivalent experience. **[The End]**

EFFECTIVE DATE OF CANNED FRUIT LABELING REGULATIONS EXTENDED

In response to requests from the canned fruit industry for additional time to deplete its existing label inventories, the Food and Drug Administration (FDA) has extended the effective date of amendments to a number of canned fruit standards of identity. The FDA stated that, due to problems in obtaining supplies, a number of manufacturers have apparently been led to maintain larger than normal packaging inventories. The extension, which postpones the effective date of the amendments from January 1, 1976 until January 1, 1978, applies to the canned fruit labeling requirements for peaches, apricots, prunes, pears, seedless grapes, cherries, berries, fruit cocktail, plums and figs.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,542

Bioequivalence/Bioavailability—The Basic Legal and Philosophical Issues

By STUART J. LAND

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FROM A LAWYER'S STANDPOINT, the proposed bioequivalence and bioavailability regulations raise a number of legal issues, both procedural and substantive. But I believe it would be most fruitful to focus on a central question encompassed by the proposals. This concerns the basic validity of the regulatory approach which the Food and Drug Administration (FDA) is taking with respect to the marketing of prescription drugs now on the market which had been the subject of the Drug Efficacy Study Implementation (DESI) program. Consideration of this approach is important not only with respect to DESI drugs, but also because the Agency, in the future, may try to follow the same course with many post-1962 new drugs in the future.

The proposed regulations on bioequivalence and bioavailability are integral parts of the Agency's overall regulatory mechanism for these drugs, set forth in the extensive texts, prefatory comments and proposed regulations published in the *Federal Register* on June 20, 1975. In my view, the key to the regulatory scheme set forth in the publication—and the perspective from which the proposed bioavailability and bioequivalence regulations must be examined—is contained in Section 310.7 of the proposed regulations. This provides for "the conditions for marketing a human prescription drug product" which had come under DESI review. In this provision, the Agency declares that, in effect, drugs which have undergone DESI review may be marketed without a submission or approval of any kind of new drug application (NDA) unless the FDA has specifically designated the drug as one

for which either a full NDA or *in vitro* or *in vivo* data is necessary. Thus, if these regulations become effective, the Agency, in one fell swoop, will have established a drug regulatory system under which, except for the 190 or so drugs identified as subject to such testing, DESI drugs can be marketed by any manufacturer without obtaining FDA approval of a NDA of any kind.

DESI Programs

In his recent testimony before Senator Nelson's Senate Monopoly Subcommittee concerning the bioequivalence/bioavailability regulations on November 11, 1975, Commissioner Schmidt stated that drugs cleared under the DESI programs and not among those listed as requiring submission of NDAs can be lawfully marketed without approved NDAs because "they meet the test of general recognition of safety and effectiveness."

It is important to note that under this approach the Agency's long-heralded prescription drug monograph system is of no real significance. Its pendency will not affect the legal status of the marketing of non-listed drugs without an approved NDA since these will now be regarded as "old" drugs. This regulatory approach is in sharp contrast to the Agency's over-the-counter (OTC) rule-making proceedings. In that instance, the FDA took the position that an OTC product remains a "new drug" unless it falls within the confines of final monographs establishing conditions for marketing various therapeutic classes of OTC drugs. The monographs themselves become final only after a thorough rule-making proceeding which is bottomed on the recommendations of an expert panel as modified by the Agency after consideration of comments submitted by all interested parties.

By contrast, the FDA proposes the immediate release from new drug status of all prescription drugs which have been through the DESI process unless they are listed as having a multi-bioavailability or bioequivalence problem or unless some special manufacturing conditions are applicable. Thus, for most prescription drugs, old drug status will be declared prior to the adoption of any considered system of regulation akin to the OTC monographs.

Old Drugs

Moreover, once the Agency declares that a prescription drug is an "old drug," any subsequent monograph establishing conditions for marketing by therapeutic class or otherwise is of questionable legal

effect. If a prescription drug as now marketed is declared to be generally recognized as safe and effective (GRASE), what power does the FDA have, monograph proceeding or otherwise, to require such a product to be marketed under different conditions?

The FDA justifies this sweeping regulatory approach on the grounds that:

(1) the experts in DESI review have found these various compounds effective;

(2) there have been only a few cases in which drugs of the same chemical compound made by different manufacturers have been proven to be significantly different from a therapeutic standpoint with adverse effects to the public; and

(3) the list of drugs set forth in the Agency's proposals encompasses all of the drugs which the Agency believes by reason of chemical structure can have a reasonable possibility of raising therapeutic equivalence problems.

The Commissioner further believes that through the drug listing act, factory inspections and drug monitoring, the public health will be protected against substandard drugs. The Commissioner sees the proposed bioequivalence regulations as buttressing this regulatory approach because the regulation includes a mechanism under which any manufacturer (as well as the FDA) can petition to establish bioequivalence requirements for a compound.[1] The thinking behind this is that present manufacturers of the drugs will have the incentive to carefully monitor competing versions of the drugs produced by other manufacturers. If significant differences between these competitive versions are detected, the manufacturers will have the opportunity to bring the facts to the Agency and to make the case for the establishment of bioequivalence procedures.

Legal Requirements

The first question which must be addressed is whether the proposed system which I have so briefly outlined meets the legal requirements of Section 505 of the Federal Food, Drug and Cosmetic Act.

We must not lose sight of some elementary facts which were brought home in the recent *Hoffmann-La Roche* case before Judge Green in the District Court of the District of Columbia.[2] Unquestionably,

[1] See proposed Section 320.3.

[2] *Hoffmann-La Roche v. Weinberger et al.*, Docket No. 75-0270, (DC DofC July 29, 1975).

Congress intends the strict regulation of new drugs on the market. Section 505(a) specifically proscribes the marketing of new drugs without an approved NDA. This is above and beyond the general prohibitions against the violations of the Act set forth in Section 301. The legislative history reinforces this strong statutory language. Prior to 1962, the law provided that new drugs would be permitted on the market after submission of a NDA unless the Agency disapproved the application within the 180-day review period. In 1962, Congress changed that to specifically require approval by the Agency. Congress wanted the Agency to go on the line.

Measured against the terms of the Federal Food, Drug and Cosmetic Act and this legislative history, the Agency's approach can be questioned.

New Drug Status

1. First, consider the procedure. When the FDA published its DESI notices (in the not too distant past), the Agency itself specifically recognized that those drugs were considered "new" drugs. The notices are replete with such a finding of new drug status. Accordingly, one may ask whether it is proper now for the Agency, through the mechanism of these regulations, to make a broad finding that all of these drugs, except for the ones designated in the June 20th notices, are no longer new drugs and, therefore, can be marketed without approved NDAs. To ensure that the Congressional mandate is honored, one may ask whether or not the Agency should proceed on a systematic basis releasing these drugs from new drug status only after a proceeding on each drug or perhaps group of drugs involved.[3]

2. These procedural issues overlap a basic substantive question. Will the clear Congressional directive regarding new drugs be honored if prescription drugs reviewed under the DESI program can be put on the market without approval of the Agency, in the absence of any data purporting to show equivalence of various versions and without pre-clearance of manufacturers, as in the case of NDA approvals? The issue here is compounded by the Agency's reliance on a finding by the National Academy of Sciences-National Research Council of a drug's effectiveness made in the context of a system of strict regula-

[3] A subsidiary issue—but one that must be raised—is whether the Agency, in any event, is complying with the law at this time and requiring approved NDAs for such drugs prior to the final promulgation of the proposed regulations. If not, serious questions would be raised as to whether the Agency is breaching the order of Judge Green in the *Hoffmann-La Roche* case which prohibits it from permitting the marketing of prescription drugs previously declared to be new drugs without approved NDAs.

tion. The drugs which were the subject of DESI review were drugs which had been the subject of approved NDAs and prior Agency clearance. DESI findings by experts of effectiveness were based on data submitted by manufacturers who were subject to this regulatory control. Can the judgment of these experts in this context be considered a judgment of GRASE generally, or GRASE as to every version of a drug, regardless of the regulatory control over their manufacturer, and without regard to bioequivalency data?

Pre-Clearance Control

3. Moreover, given the strong legislative mandate for strict Agency control of new drugs, is the Agency right in relinquishing pre-clearance control of so many prescription drugs and relying on drug inspections and monitoring to ensure public safety? Certainly, the Agency's prior record of post-marketing surveillance of drugs is not too comforting. Thus, we note the General Accounting Office (GAO) report which indicated that one-fourth of the drug firms monitored by GAO had not been inspected within a two-year period.[4] We also note a most recent report by a House Appropriations Subcommittee which stated that the FDA failed to inspect adequately 5,000 out of 8,000 drug firms to determine compliance with good manufacturing practice (GMP).[5] With respect to reliance on sampling, the Office of Technology Assessment[6] reports that over a million lots of capsules are produced each year and the FDA's monitoring (by their own estimates in the June 20th publication) will cover only 20,000 of these.

4. Another question concerns reliance on the inclusion of the immediate and 15-day reporting requirements of Section 10.300(b)(1) and (2) of the Agency's current regulations applicable to new drugs for DESI drugs which the Agency proposes to release from new drug clearance requirements.[7] The Agency's authority to require such reports is subject to legal challenge because the most obvious authority for such reporting requirements is Section 505(j) which deals with new drug provisions. Therefore, if the products are no longer considered new drugs, the power to require such reports may also vanish. One may wonder whether the Agency, by insisting on these reports, really regards these compounds as old drugs.

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[4] B-164031 (March 1973).

[5] House Appropriation Subcommittee Hearings on Agriculture and Related Agencies Appropriations for 1976, Part 5, p. 531.

[6] Office of Technology Assessment Report, p. 34 (July 1974).

[7] See proposed Section 310.7(A)(4).

Barriers to Entry

In prefatory comments, the Commissioner further justified the elimination of pre-clearance controls on the ground that this eliminates barriers to entry and, therefore, increases competition in the marketing of these drugs. However, a case can be made that the Agency's failure to give full sanction to the approved NDA concept envisioned by the Federal Food, Drug and Cosmetic Act will not only add risks to public health but also may constitute a disservice to companies which began to manufacture new versions of DESI compounds. This is the very group which the Agency is trying to benefit. It is apparent that the Agency's abdication of its responsibilities under the new drug provisions, as demonstrated in the *Hoffmann-La Roche* case, has led to great confusion and uncertainty. This cannot help but injure manufacturers bringing new versions of DESI drugs into the market. One only has to look at the hearings before Senator Nelson to see the point. At the hearing, the testimony focused on the State of Arkansas which recently repealed its anti-substitution laws under a statute calling for the promulgation of a so-called negative formulary, that is, a listing of those generic drugs which were not subject to substitution on the ground that they were not equivalent. The state officials classified all 190 drugs proposed by the Agency in the June 20 publication as subject to *in vitro* or *in vivo* testing as ineligible for substitution. It is possible that other states will take similar positions. The significant point is that this negative formulary was made applicable even to drugs manufactured pursuant to approved NDAs. Commissioner Schmidt promised Senator Nelson that the FDA would try to persuade states that those versions of drugs subject to approved NDAs should be exempt from the negative formularies. But it is clear that the Agency's past practices have led to the point that whether or not a drug possesses an approved NDA is no longer considered of much significance as a bench mark of a drug's safety and efficacy or of its legal status. This is indeed ironical since the new drug law explicitly provided a comprehensive regulatory system designed to make approved NDAs a pivotal factor in determining drug safety and efficacy.

Regulatory Framework

In an address to the Food and Drug Law Institute in December of 1972, the former General Counsel of the FDA likened the Federal Food, Drug and Cosmetic Act to a "constitution" which gave the Agency broad authority to devise regulatory systems to meet the

objectives of the Act.[8] Such a concept provides the Agency with great flexibility in establishing a regulatory framework; it also permits it to more readily accommodate other governmental policies such as the Department of Health, Education and Welfare's strong interest in reducing drug costs to the government for Medicare/Medicaid purchases as reflected in the Maximum Allowable Cost (MAC) regulations. However, one invariably pays a price for exercising broad gauge discretion. The rules become unclear and the potential for uncertainty and confusion is increased.

I would submit that a strong commitment to statutory requirements—the warp and woof of administrative law—may in the long run produce more lasting benefits than the "constitutional" approach taken by the Agency. It would provide more certainty as to the rules. It would provide more assurance as to the safety and efficacy of drugs generally, as well as to the comparable equivalence of different versions of the same drug. Indeed, generic manufacturers themselves may strongly benefit from this approach. After all, if the FDA required approved NDAs for their versions of these DESI drugs, the Agency imprimatur would clearly help them in gaining acceptance of these products in the marketplace. If approval of NDAs were required before marketing (which should also include a prior FDA inspection), there would be more assurances that the new versions going on the market were made in accordance with GMP. Where bioavailability data can reasonably be developed, a requirement that the data be included in the abbreviated NDA would provide further assurance as to the overall quality of a drug and the equivalence to established versions of the drug. I should add that bioavailability or bioequivalence requirements would provide safeguards to the public health. Compliance by a manufacturer would supply strong indicia that the company had the requisite degree of technical competence appropriate for responsible functioning in this field.

Knotty Problems

This would not solve all of the knotty problems. For example, one must still be concerned with the resources of the FDA to effectuate this approach. However, I am somewhat skeptical about the Agency's perennial plea of limited resources. An argument was made in the *Hoffmann-La Roche* case that the fact that the FDA was unable

[8] Hutt, Peter Barton, "The Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act," 28 FOOD DRUG COSMETIC LAW JOURNAL 178 (March 1973).

to process all of the pending abbreviated NDAs for generic drugs justified drugs being marketed on the mere filing of abbreviated NDAs. However, the statistics in FDA annual reports to Congress and the testimony of Dr. Marvin Siefe of the Agency's Generic Drug Division in a deposition in the *Hoffmann-La Roche* case strongly undercut the Agency's position.

In sum, in dealing with these regulations, one must carefully consider whether the Agency has given due deference to the Congressional intent of the new drug law to eliminate risks and to assure that new drugs available in the country were safe and effective for the purposes intended. It is from this perspective that one should evaluate the validity of the proposed bioavailability and bioequivalence regulations. **[The End]**

SOURCE LABELING REQUIREMENT FOR FATS AND OILS ISSUED

Regulations have been issued by the Food and Drug Administration (FDA) to require that fats and oils be identified specifically by origin on all food labels. Presently, fats and oils can be listed simply as being of animal, vegetable, or marine origin, or in some cases only as "shortening." Under the new requirements, which take effect on January 1, 1978, fats and oils must be identified by name—for example, "cottonseed oil," "corn oil," "soybean oil," "beef fat." The term "vegetable oil" or "vegetable shortening" can still be used on the label, but only if it is followed by an identification of the specific oils used. In addition, some ingredients will be permitted to be declared by class names: for example, milk, concentrated milk, reconstituted milk, and dry whole milk may all be declared as "milk."

The new regulations also provide an alternative method for declaring the ingredients of a standardized food when that food is used as an ingredient in another food and establish a common or usual name for mixtures of edible fat or oil and olive oil.

Over 300 comments were received by the FDA in response to the new regulations, as proposed. Some 80 changes were suggested, but the Agency made only a few revisions, mostly of a technical nature, in the final regulations. Consumers, an FDA spokesman stated, "have a basic right to know the source of the fats and oils in the food they eat, and have overwhelmingly requested that the labeling of fats and oils be more specific. This is a major addition to the Agency's policy of providing more informative food labeling." Manufacturers, the FDA emphasized, may start using the new labeling immediately.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,539

Status of the FDA's Program on the Use of Antibiotics in Animal Feeds

By GERALD B. GUEST, D.V.M.

Dr. Guest Is Special Assistant to the Director of the Bureau of Veterinary Medicine in the Food and Drug Administration.

ANTIBACTERIAL DRUGS HAVE BEEN USED in the feed of food animals in this country for the past 20 to 25 years for the purpose of increasing rate of gain, increasing feed efficiency, and for prevention and control of animal diseases.

When looking at safety considerations which are concerned with the use of drugs in food-producing animals, there are two issues which should be understood and separated as much as possible. One concern, one which the Food and Drug Administration (FDA) and the United States Department of Agriculture (USDA) spend a great deal of time on, is drug residues in meat, milk and eggs. Drug metabolism studies, adequate drug withdrawal times before slaughter and proper labeling are all a part of this concern which deals entirely with the presence of the drug or drug metabolites in food for man.

The second issue is the one which I will discuss in this presentation. This issue concerns the effect of antibacterial drugs on bacteria in the gastrointestinal tract of animals, the development of drug resistance, and resistance transfer between the intestinal bacteria.

I believe that this audience understands generally the separation of the two issues. I mention the distinction because on many occasions I have heard individuals speak of the Swann Committee Report of England and the United States Task Force on Antibiotics in Feeds when discussing issues concerning drug residues in animal-derived products. It is important to remember that both the Swann Committee and the Task Force made only passing mention of drug residues.

As you recall, the Task Force on Use of Antibiotics in Animal Feeds filed its report to the Commissioner in January of 1972.

Recommendations of the Task Force

The recommendations of the Task Force were based on the conclusions that use of certain antibacterials in feed does cause the intestinal bacteria in the animals to become resistant to the antibacterial used. Many times these bacteria are resistant to more than one antibacterial and usually the resistance can be transferred by the R-factor.

The major concerns expressed by the Task Force and our major emphasis in review of the use of these products are:

(1) *Salmonella reservoir.* We know that food-producing animals constitute a major reservoir of certain bacteria, particularly salmonella, that are capable of causing disease in humans. Evidence suggests that some antibacterial drugs may promote an increase in the reservoir of gram-negative bacilli in animals.

(2) *Transfer of drug resistance.* We know that exposure to antibiotics can promote drug resistance in some bacteria. In many cases, this resistance is transferable to other bacteria. The Antibiotic Task Force concluded that a potential hazard exists since these bacteria may be transmitted to humans. Additional work is needed to more fully categorize this hazard and to further determine the frequency of this occurrence.

(3) *Treatment of clinical disease in animals.* The basic question is whether use of subtherapeutic levels of an antibacterial drug in feed compromises the subsequent treatment of clinical disease in the animal should disease occur. Are the same drugs effective for treatment? Or must other drugs and sometimes those not approved for food animals be used?

With these items as our major concerns, the FDA, on April 20, 1973, published a Statement of Policy which essentially provided for a two-year period of additional drug industry research in order to answer the questions raised by the Task Force. Very specific guidelines in the way of health safety criteria were developed by the Agency.

Intermediate Deadline

An intermediate deadline in the program called for firms which market tetracyclines, streptomycin, dihydrostreptomycin, penicillin and sulfonamides to test the effect of the use of these products on the salmonella reservoir in animals within one year. Data from the studies were received in April of 1974.

These studies tell us that, when animals fed antibiotic drugs in subtherapeutic dosages are exposed to infecting numbers of drug-resistant salmonella organisms, the animals will likely shed increased

numbers of salmonella organisms. Animals under the same antibiotic feeding conditions which are exposed only to drug-sensitive salmonella organisms will be likely to shed decreased numbers of the organisms. These findings must be evaluated in light of the FDA's current information concerning salmonella organisms. The published literature contains information from surveys conducted on salmonella organisms isolated by diagnostic laboratories. These surveys indicate that a substantial number of such isolates are resistant to one or more antibacterial drugs.

We have been and are presently continuing to gather what information we can on the drug-resistant versus the drug-sensitive status of Salmonella *sp.* from clinically normal animals. Some very preliminary information leads us to suspect that, in general, salmonella are not good recipients of drug resistance transfer. It appears that, perhaps, only a limited number of phage-types may readily accept and retain the genetic material which codes for drug resistance.

Salmonella Reservoir

The particular criterion concerning the effect of these drugs on the salmonella reservoir was given a great deal of emphasis by the Agency. In the early phases of the program, we felt as though salmonellae shedding and salmonellae drug resistance could be, relatively, easily quantitated. This measure appeared to be an excellent first step in assessing the effect of the drugs. The question concerning the drug-sensitive versus the drug-resistance status of the challenge organisms and other questions have made the salmonella issue not quite so clear-cut as we had anticipated. We are continuing to assess the significance of the salmonella data for each drug, in light of what we know about salmonellae in the animal population. Sponsoring drug firms have added much information to our knowledge of the salmonellae population by submitting data on organisms isolated from clinically normal animals.

Data on all other aspects of the program were required by no later than April 20, 1975. The data which were received have essentially been evaluated in the Bureau of Veterinary Medicine.

We knew when we were developing the program that we were dealing with a young science. We knew that some of the studies would not be conceived easily. Most of the studies we were requesting had no model systems developed nor precedent in the literature. We started early with our own contract research and overcame some of these problems in the early part of the program. Even so, we

know that conclusive answers to all the questions raised will not be available.

Members of the Subcommittee

Because of the nature of the project and the importance of decisions which must be made, we plan to take selected issues to a committee of outside individuals in order to benefit from their advice. This group will be a subcommittee of the National Advisory Food and Drug Committee. The members of the Subcommittee on Use of Antibiotics in Feeds are: Dr. Jacob Mosier of the Veterinary College at Kansas State University; Dr. Nelson Fernandez, a physician with the Department of Nutrition and Biochemistry at the University of Puerto Rico; and Ms. Camille Haney, an individual with a consumer affairs and public relations background from Milwaukee, Wisconsin. The expertise of these individuals will be supplemented by four consultants to the Subcommittee. Those who have been invited to participate are: Dr. William Flatt, Director of the Agricultural Experiment Station at the University of Georgia; Dr. Edward Hook, Professor and Chairman of the Department of Medicine at the University of Virginia School of Medicine; Dr. Stanley Falkow, Professor of Microbiology at the University of Washington School of Medicine; and Dr. George Poppensiek, Professor of Microbiology at the New York State Veterinary College at Cornell.

In addition to these consultants, Dr. Howard S. Teague of the Food Animal Research Laboratories, Clay City, Nebraska, will participate in the deliberations of the Subcommittee as a representative of USDA.

The Agency is scheduled to meet with this Subcommittee for the first time in January of 1976. Meetings will follow during the year with final decisions expected by the end of calendar year 1976.

I also wish to mention what I see ahead and discuss some personal philosophies and hopes for the future.

Future Plans

I believe that the future will bring continued emphasis on the use of animal drugs on a herd or flock basis, but with more sophisticated innovations in the patterns of use. We will see more drugs used at higher levels and for periods of time which are less than the life of the animal or bird. This approach is particularly indicated during "stress" periods and at other times during the early part of the animal's life. In addition to the high-level, short-term use of drugs, there may be an increased need to alternate drug products during an

animal's time in the feedlot. In this way, a drug exhibiting a higher potential for human hazard might be used early in an animal's life, with a switch to another product in the finishing phases prior to slaughter. We will continue to urge drug firms to develop products useful in promoting increased weight gains, while at the same time not interfering with disease therapy, should disease occur. Let me emphasize this need. I believe that it is very important that future products used for growth promotion should be used exclusively for that purpose. Care should be taken that these products are not used for treatment of disease in humans or animals. They must not create cross-resistance with drugs used in human or veterinary therapy. In this regard, individuals should be looking for alternatives to the traditional growth promotant drugs. Certainly more basic work is needed on the understanding of the mechanism of growth promotion.

I believe there will be increased demands in the area of documentation of efficacy of growth promotant drugs, particularly the combination products. We are presently reviewing the efficacy data on antibiotic combination products now on the market. The data, for the most part, which we have on file, will not meet today's standards of full factorial studies and the additive effect policy as it exists in our current guidelines. It is not likely in the present climate that standards will remain static. Tomorrow's standards will be more demanding than today's.

More Prescription Drugs

Continuing to look at the future, I believe that we should expect to see fewer food animal drugs available for over-the-counter sale. More prescription drugs probably will be used in the future.

Up to this point, I have given my view of the future from a regulatory standpoint. I know that this is not the whole picture. I believe that in animal science, the feed industry and the food animal industry, we are going to see continuing and increasing efforts in the area of genetic improvement, improved husbandry practices and food animal nutrition in an effort to meet this country's and the world's needs for animal protein. These improvements may offset the need for continuous medication of animals.

It is also apparent that the drug industry will continue to seek alternatives to the traditional growth promotant drugs. I am hopeful that vaccines, other biologicals, enzyme inhibitors and other innovations might be developed to control disease and increase weight gain. These advances do not come quickly or easily, but I am confident that some will be a help in the future. **[The End]**

A Response to New Approaches to Be Used in the Regulation of Animal Drugs

By JAMES F. MONGIARDO

Mr. Mongiardo Is an Attorney with the Schering-Plough Corporation.

AS A MATTER OF FIRST IMPRESSION, the concept of establishing particularized regulations which will set forth standards permitting sponsors of new animal drug applications (NADAs) to understand the "rules of the game" in withdrawal proceedings appears to be both cogent and forceful. At first review, it further appears that the use of summary disposition procedures to resolve disputes where there are no genuine issues of fact are equitable and reasonable to both the sponsor attempting to keep a product on the market and the Food and Drug Administration (FDA) attempting to remove that same product from the market. However, as with any mechanism to implement statutorily defined powers, it is necessary, before accepting the mechanism as proper, to review the underlying authority for implementation and, further, to examine what, in real terms, these mechanisms create.

What has been presented as "New Approaches to Be Used in the Regulation of Animal Drugs" is the culmination of several years of effort within the FDA to change the focus of its regulatory power from a case-by-case approach to a broad regulatory framework covering classes of products, be they new animal drugs or new drugs for humans. Many of the details are similar to the internal guidelines for withdrawal proceedings involving new drugs for humans in the proposed FDA Administrative Practices and Procedures regulations. The "new approaches" make two basic assumptions which should first be reviewed in order to establish a framework for analysis of these mechanisms for regulation.

Broad Regulatory Schemes

The first basic premise made is that the only effective method of regulating new animal drugs is through the promulgation of broad regulatory schemes which will effectuate rule-making to permit the removal of products on an industry-wide basis. Implicit in this assumption is the premise that the Federal Food, Drug and Cosmetic Act empowers the FDA to use such broad regulatory schemes in a way which will further the purposes of the Act in a meaningful and lawfully permissible manner.

The second basic premise made is that there is little value which can be ascribed to a hearing with its attendant right to cross-examination when a sponsor wishes to contest the withdrawal of a product from the market. This prejudice against the use of hearings is well known to the regulated industry. The true extent of this presumption against the usefulness of hearings is succinctly but thoroughly set forth in the preamble to the proposed Administrative Practices and Procedures regulations:

"The Commissioner has concluded that, since the use of oral direct testimony and the use of cross-examination have been the principal causes for delay of Food and Drug Administration hearings in the past, most of the hearings should be developed through the submission of written documentary and testimonial evidence. Oral evidence should be permitted only where necessary for a full and true disclosure of relevant evidentiary facts. . . .

". . . the burden shall be on the party involved to justify cross-examination in each instance in which it is requested. Ordinarily, cross-examination is justified when it relates to witness perception or credibility, but not when it relates to a judgment based on scientific, medical, or technical data."[1]

Pyramid of Paper

The net result of the interaction of these two assumptions is the creation of a pyramid of paper which, when analyzed, relates not to the substantive issues involved in withdrawal proceedings but, rather, to the procedural questions involved in such proceedings.

Until the recent advent of "new approaches" to regulating new animal drugs, food and drug law from an attorney's viewpoint appeared to be quite basic and straightforward. A NADA—as well as a new drug application—is a private license. A sponsor has to prove the safety and effectiveness of his product based upon given standards which are known. The FDA's "new approaches" program has attempted to change this, despite the fact that there has been no

[1] 40 *F. R.* 22970, 22971 (May 25, 1975).

change in the underlying statutory authority from which this basic law is derived.

An examination of Section 512 of the Federal Food, Drug and Cosmetic Act still supports the concept of private licenses with respect to new animal drugs. While it is permissible to proceed against a class of products if the Commissioner believes all are deficient and must be removed from the market, each member of the class has individual standing and must be removed as an individual entity based upon information directly applicable to that product. This private license concept is supported by Section 512(i) of the Food, Drug and Cosmetic Act which provides that:

"When a new animal drug application . . . is approved, the (Commissioner) shall by notice, which upon publication shall be effective as a regulation, publish in the *Federal Register* the name and address of the applicant and the conditions and indications of use of the new animal drug covered by such application. . . ."

Conversely, when a new animal drug is removed from the market, the regulation must be revoked.

Requirement for Individual Approval

This requirement for individual approval is not intended to be mere window dressing for a grand regulatory scheme. It is a very real constraint on the power of the FDA. This has recently been reinforced by the *Hoffmann-La Roche v. Weinberger* litigation in the Federal Courts for the District of Columbia.[2] Judge Green held in this case that "the FDA's policy of permitting new drugs to be marketed without an approved new drug application contravenes the clear statutory requirement of preclearance mandated by 21 U. S. C. § 355 (1970) (Section 505 of the Food, Drug and Cosmetic Act)." Thus, the cornerstone principle that NADAs require individual review, individual clearance and individual removal remains basic law.

The second basic assumption made in the "new approaches" to animal drug regulation is also suspect. Once again reference to the Federal Food, Drug and Cosmetic Act is appropriate. Section 512(c) provides that:

"Within one hundred and eighty days after filing of an application . . . the (Commissioner) shall either (1) issue an order approving the application if he then finds that none of the grounds for denying approval . . . applies, or (2) give the applicant notice of an opportunity for a hearing . . . on the question whether such application is approvable."

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[2] *Hoffmann-La Roche v. Weinberger et al.*, Docket No. 75-0270, (DC DofC July 29, 1975).

In order to circumvent the statutory requirement for a hearing and to comply with court-imposed notice requirements, the Commissioner has in the name of expeditious review in withdrawal proceedings instituted a jungle of paper work in order to permit him to use his summary judgment powers in a procedurally permissible manner.

Summary Judgment

One need only examine the litany of paper required to invoke summary judgment to conclude that this entire procedure is extremely tedious, burdensome, wasteful of valuable resources, and not directed toward eliciting discussion about substantive issues. After a general notice is published proposing to withdraw a product, the sponsor may respond and request a hearing. If such a request is made and is accompanied by either new data or reference to data already on file, the FDA may not summarily reject the request for a hearing since a genuine issue of fact may be raised. To properly deny a request for a hearing and invoke summary judgment, the Commissioner must conclude that no genuine issues of fact are raised. This requires that the request for a hearing, together with the data in the NADA file, be analyzed and an order prepared demonstrating the inadequacy of the entire submission. But this order cannot be published in final form since it constitutes the particularized notice which must be given to the sponsor before summary judgment can be invoked. This means that the draft order must be sent to the sponsor giving the sponsor adequate time to comment and respond. Only after these comments have been received can a final order be published and the product removed from the market. It is axiomatic, of course, that the comments of the sponsor will be rejected since it is impossible to challenge the underlying thinking of the FDA in an exchange of paper where, in reality, only conclusions are discussed.

No Opportunity for Cross-Examination

Nowhere in this entire exchange of paper is there an opportunity for one party to cross-examine the other. Nowhere is there a provision to challenge the assumptions and prejudices which underlie the government's decision to remove the product. Nowhere is there an opportunity for a dialogue which would bring out into the open the true concerns of not only the government but, also, of regulated industry and other interested individuals or concerns.

It seems that the resources of both the sponsor and the FDA could be put to better use through an administrative hearing. Instead of an exchange of paper, which has no real meaning to the Agency since the exchange does not provide for any challenge to its judgment on scientific, medical or technical data, a hearing would provide an opportunity for a true review of the strengths and weaknesses of each party's position and, as a consequence, focus upon substantive issues. The argument that, in the past, hearings and the use of cross-examination have created undue delays is specious and fails to take into account the very real possibility that some substantive issues are extremely difficult to resolve. A competent Administrative Law Judge can responsibly and adequately control the scope of cross-examination and the conduct of a hearing.

As a practical matter, most hearings would require the expenditure of much less effort by both the FDA and sponsor since each would have only one opportunity to present its best case. This is in marked contrast to the present open-ended paper debate which may continue *ad infinitum* if the sponsor continually adds new information to the proceedings. Further, in situations where substantial issues must be resolved in order to determine whether a product should be removed from the market, the granting of a hearing and the use of cross-examination would permit public debate and the review of major FDA policy decisions which is not present when summary disposition is used. One need only examine the diethylstilbestrol (DES) litigation to conclude that summary judgment disposition does not result in the resolution of true substantive issues as a hearing would.

Underlying Statutory Authority

In effect, what has happened under these "new approaches" is an effort to broaden the regulatory control of the FDA without first expanding the underlying statutory authority to encompass such regulation. While the FDA has significant regulatory powers, a NADA is still a private license which must be approved or denied based upon its individual merits. Efforts to regulate on a class basis are certain to encounter difficulties, given the present FDA attitude to avoid hearings at all costs. A veritable quagmire of procedural and administrative red tape is created every time an effort is made to remove a class of products through the use of summary disposition. There can be no short cuts in a withdrawal proceeding since the statute requires that each approved product be removed on an individual basis.

It is apparent that the Commissioner, through these "new approaches," has created a wall of paper to insulate the FDA from a hearing. This is most unfortunate since the only way to have open, honest debate over fundamental issues involved in a withdrawal proceeding is through a hearing. The paper pyramid created by these "new approaches" serves no purpose other than to focus subsequent litigation on issues of procedure rather than substance. Thus, I respectfully voice my opinion that the good intentions of these "New Approaches to Be Used in the Regulation of Animal Drugs" are belied by statutory difficulties and the absence of pragmatic impact in expeditiously moving withdrawal proceedings to ultimate resolution.

[The End]

FDA PROPOSES TO WITHDRAW APPROVAL OF NEW ANIMAL DRUG APPLICATIONS FOR DES

Based on continued findings of residues of diethylstilbestrol (DES) in the livers of cattle and sheep, the Food and Drug Administration (FDA) has issued a proposal to withdraw approval of all existing new animal drug applications (NADAs) that provide for the use of DES in animals used for human food. DES, a synthetic estrogen marketed since the mid-1950's as a growth promotant in cattle and sheep, has been established as a carcinogen in mice and linked to the occurrence of a rare form of cancer, adenocarcinoma, in humans.

In 1972 and 1973, the FDA withdrew approval of DES for use in animals intended for human consumption. The courts, however, overturned the decision on the ground that the FDA had not allowed DES manufacturers adequate opportunity for a hearing. Since the resumption of the use of DES, residues have been detected by the United States Department of Agriculture (USDA) through the use of new scientific methods. Previously, only one of the 36 residues now detected by the USDA could have been detected by official methods of detection. The FDA therefore proposed to revoke the approved methods for identification and measurement of DES residues on the ground that such detection methods are outdated and inadequate. After having reviewed a number of comments submitted on that proposal, the FDA has decided to revoke the old detection methods for DES when final action is taken on the current proposal to withdraw approval of the NADAs for DES.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,541

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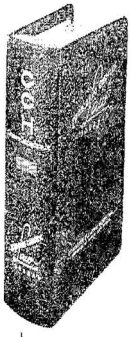

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