VOL. 25, NO. 11 NOVEMBER 1970

Food Drug Cosmetic Law
JOURNAL

The Right to a Hearing in New Drug Revocation and Antibiotic Decertification Proceedings

. . . . . RODNEY R. MUNSEY

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

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

The FOOD DRUG COSMETIC LAW JOURNAL is published monthly by Commerce Clearing House, Inc. Subscription price: 1 year, $20; single copies, $2. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

November, 1970
Volume 25 • Number 11

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

FOOD DRUG COSMETIC LAW JOURNAL

Table of Contents . . . November, 1970

		Page
Reports to the Reader		475
The Right to a Hearing in New Drug Revocation and Antibiotic Decertification Proceedings	Rodney R. Munsey	476
AOAC: Why FDA Analyses Stick	Benjamin Adelman	487
Food Safety	Dale R. Lindsay	495

VOLUME 25 NUMBER 11

Printed in the United States of America

FOOD DRUG COSMETIC LAW JOURNAL

Editorial Advisory Board

REPORTS

TO THE READER

The Right to a Hearing in New Drug Revocation and Antibiotic Decertification Proceedings.—Beginning on page 476, *Rodney R. Munsey* discusses the controversy surrounding the validity of the May 8 regulations on hearing rights, or the lack of them, in proceedings to revoke approved new drug applications or antibiotic monographs. The author sets forth the terms, effects and background of the regulations in order to explain PMA's opposition to them. He says: "Our basic position in Wilmington is that the May 8 regulations, contrary to law, make the statutory test of substantial evidence of effectiveness the standard for determining whether a hearing will be held to determine whether that test is met. The manufacturer is required to convince the Commissioner of the ultimate result before the hearing, not as a result of the hearing." Mr. Munsey, Associate General Counsel for PMA, presented his paper at the Federal Bar Association Annual Meeting held in Washington, D. C., on September 18, 1970.

AOAC: Why FDA Analyses Stick.—Beginning on page 487, *Benjamin Adelman* discusses the operation of the Association of Official Analytical Chemists. This association is a scientific society that sponsors the development and testing of methods for analyzing many commodities and materials. AOAC methods are widely accepted because of its requirement for collaborative testing of methods before adoption. The author describes AOAC procedures, origin and development, and plans for further collaboration with foreign chemists' associations. Mr. Adelman is a manpower utilization officer in FDA's Bureau of Foods and Pesticides. His paper originally appeared in the September, 1970 issue of *FDA Papers*.

Food Safety.—The review of substances generally recognized as safe (GRAS), which was stimulated by President Nixon's consumer message of October 30, 1969, is discussed by *Dale R. Lindsay*, beginning on page 495. Dr. Lindsay, who is FDA's Associate Commissioner for Science, reviews the regulatory procedures for food additives and pesticide residues, then details the action upon a food additive or pesticide petition. He finds that "there is a real need for a streamlining of the application review processes in FDA." Specific problems in the review process are identified, and suggestions to correct them are offered. Dr. Lindsay concludes that although the GRAS list may be shorter after the review, new concepts of food safety demand that we use "the best science has to offer in our continued questioning of our man-made environment."

Vol. 25, No. 11 November, 1970

Food·Drug·Cosmetic Law
Journal

The Right to a Hearing in New Drug Revocation and Antibiotic Decertification Proceedings

By RODNEY R. MUNSEY

Mr. Munsey, Associate General Counsel for the Pharmaceutical Manufacturers Association, Presented His Paper at the Federal Bar Association Annual Meeting Held on September 18, 1970, in Washington, D. C.

HEARING RIGHTS, OR THE LACK OF THEM, in proceedings to revoke approved new drug applications or to revoke antibiotic monographs, are the center of a controversy concerning the validity of regulations issued in final form on May 8, 1970. This order, effective on publication, does two things: (1) it defines substantial evidence of effectiveness as studies meeting the requirements of adequate and well-controlled studies as set forth in the order, and (2) it enumerates the circumstances in which the Food and Drug Administration (FDA) will deny hearing rights in revocation proceedings.

Section 505 of the Food and Drug Act authorizes the Secretary of the Department of Health, Education and Welfare (HEW) (the Food and Drug Administration) to withdraw approval of a new drug application "after due notice and opportunity for hearing to the applicant" if he finds that there is a lack of substantial evidence of the

subject drug's effectiveness. Substantial evidence is defined to be "evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts . . . on the basis of which it could fairly and responsibly be concluded by such experts" that the drug is effective. The Secretary may remove a drug from the market pending a hearing only upon a finding of "imminent hazard to the public health."

Section 507(f) authorizes FDA to revoke an antibiotic monograph for lack of efficacy of the drug involved. A hearing must first be granted, however, if objections accompanied by a statement of reasonable grounds are filed. With one exception, the statute is silent as to whether the "lack of substantial evidence" rule may be applied to antibiotic monograph revocation proceedings. The one situation where the rule is expressly made to apply is the case of revocation proceedings involving antibiotics which were subject to new drug provisions prior to passage of the 1962 Drug Amendments. In that situation, lack of effectiveness means there is a lack of substantial evidence as the term is defined in the new drug provisions just referred to; that is, there is a lack of adequate and well-controlled investigations. Section 507 does not contain any specific provision for removal of an antibiotic from the market pending hearing on the monograph.

The May 8 Regulation

The May 8 regulation sets forth specific criteria that studies must meet in order to be considered adequate and well-controlled. Among other things, it specifies the type of controls permitted, requires procedures to assure comparability in test and control groups of pertinent variables, and requires a summary of the methods of analysis and an evaluation of data derived from the study, including appropriate statistical methods. Studies not meeting each and every element of "an adequate and well-controlled investigation" cannot be considered in determining whether substantial evidence of effectiveness exists. There are many who claim that no investigations conducted prior to 1962 meet this test. In any event, there is a substantial body of expert scientific opinion taking issue with the notion that a rigid set of criteria for adequate and well-controlled clinical

investigation can be prescribed. Further, there is no scientific consensus, in many cases, as to what constitutes an adequate and well-controlled test. The order provides that clinical experience may not be used for any purpose, and that uncontrolled and partially controlled studies can provide only *corroborative* support for a drug's effectiveness.

It is interesting to contrast this order with the assurances given industry on several occasions since 1962 to the effect that the technical requirements of substantial evidence would not be required in the case of pre-1962 new drugs as long as well-documented clinical experience existed.

The order does contain a provision for an FDA waiver of one or more of the rigid criteria for adequate and well-controlled studies on a showing that the study is, nevertheless, adequate and well-controlled. This provision will apparently result in little or no relief, however. The Commissioner, in a letter response to a Pharmaceutical Manufacturers Association (PMA) request, wrote that the waiver is intended primarily for future studies, not studies on pre-1962 new or antibiotic drugs. Further, he stated that there is no appeal from a denial of a waiver request. The provision does, however, unwittingly constitute an admission by the Agency that there can be no strict, rigid criteria for adequate and well-controlled studies that can apply in all cases. One can easily discern, however, where the industry is left. Since most pre-1962 new and antibiotic drugs do not meet each and every criterion, and FDA at its option will deny or grant waivers, the rights to continue to market these drugs are entirely left up to FDA. This position is buttressed by statements by the Agency in the preamble of the order that it will not require adequate and well-controlled studies where the National Academy of Sciences-National Research Council (NAS-NRC) evaluation is effective unless the Agency disagrees with the finding. Many NAS-NRC findings are based on only informed judgment of the panels. It is clear, then, that the rigid criteria for adequate and well-controlled studies have not been devised primarily as a scientific guide, but as a tool to enable FDA to have a free hand in deciding what drugs shall stay on the market,

using any criteria it sees fit. The second portion of the order establishes a mechanism by which FDA can accomplish its purposes without even a hearing, when it so chooses. It describes what must be done by a company in order to be granted a hearing at which he could attempt to show that substantial evidence of effectiveness, that is, adequate and well-controlled investigations, existed. The order requires that along with objections, a request for hearing must contain "a well-organized and full-factual analysis" of the clinical and other investigational data he is prepared to prove.

Denial of Hearing

A request for hearing, according to the order, will be turned down if it clearly appears from the data and from the reasons and factual analysis in the request for the hearing, that there are no adequate and well-controlled clinical investigations as these investigations were defined earlier in the order. This, according to FDA counsel, is a rule adopted directly from the summary judgment rule of the Federal Rules of Civil Procedure. After all, he stated, "a reported study was controlled—or it was not and no amount of cross-examination can convert an uncontrolled study into something it was not." If it is all that simple to decide when a study is adequate and well-controlled, why did the Agency decide that the regulation should provide a waiver process for studies that did not comply with the criteria but were nevertheless adequate and well-controlled? And why did the Senate Judiciary Committee in its final report in the Kefauver-Harris Drug Amendments of 1962 state: "The Committee recognizes that in the difficult area of drug testing and evaluation there will frequently if not usually be a difference of reasonable opinion"? And why did Dr. Louis Lasagne, a leading expert on clinical testing, state in testimony before the Senate Committee, "The emphasis should be on scientifically acceptable evidence *of whatever quality and quantity* required to give a reliable answer to the questions posed concerning the drug's effects"? He continued, "I would hope that if such a bill [the 1962 Amendments] were passed, that there would be every opportunity for flexibility of interpretation. I don't

believe it would be possible to write a bill that would spell out in detail all that one would like to say about efficacy concerning all the host of drugs that might be considered." It is clear that FDA counsel is wrong when he indicates that the determination of whether a study is adequate and well-controlled is, in all cases, a simple matter.

The PMA would have little objection to a true summary judgment procedure; that is, the denial of a hearing by an impartial arbiter where there is no genuine issue of fact. But that is a far cry from a rule which sets up criteria that many, if not most, pre-1962 new drugs cannot meet, and then grants the prosecutor unfettered discretion in deciding in which cases he will give hearings. We believe anytime it is shown that there exist clinical tests supporting effectiveness coupled with substantial clinical experience, a hearing should be held if requested.

I should mention here, however, that although we are extremely critical of FDA's actions in promulgating this order, there are many areas in which industry and FDA can, and have, cooperated to the advantage of the public, the Agency, and the industry. We intend to cooperate whenever it is possible to do so. We also can understand the Agency's desire, because of its personnel and budget limitations, to find shortcuts in implementing its drug decisions. But when we believe that the interest of the law, the industry, and the public so dictates, we will not, and have not, shied away from using the courts. It is a credit to all parties concerned, however, that resort to the courts has been infrequent.

Background of the Regulation

Before discussing the pending cases on the regulation and the legal issues involved, a brief rundown on the background of the regulation is in order.

The 1962 Drug Amendments, among other things, authorized the FDA, after a two-year grace period, to require substantial evidence of effectiveness for new drugs which were first marketed subject to effective New Drug Approvals (NDAs) between 1938 and 1962. FDA contends that similar authority exists with respect to anti-

biotics. In July of 1966, the Agency entered into a contract with the NAS-NRC for the conduct of an effectiveness review of the drugs. Over the next two years, panels of physicians selected by the NAS-NRC reviewed claims of effectiveness of more than 2,800 different products. Reports were prepared for FDA. Since completion of the review in 1968, the FDA has been evaluating the reports and has begun publishing in the *Federal Register* summaries of the reports on a product-by-product basis. In some cases, FDA has initiated proceedings to remove the products from the market on the ground of lack of substantial evidence of effectiveness. In two instances, the Agency was rebuffed by the courts in attempts to remove antibiotic drugs from the market in advance of acting on objections requesting a hearing. In both cases, the U. S. District Courts involved enjoined FDA from ordering the products from the market until 30 days after ruling on whether objections filed by the parties stated "reasonable grounds" for a hearing. In both cases, the Courts expressed concern that the Commissioner was requiring the parties to prove to his satisfaction that the evidence in support of the effectiveness of their products met the statutory requirement; that is, substantial evidence, as a condition of obtaining a hearing to determine that very issue.

On September 19, 1969, the Agency promulgated regulations similar to the ones currently in dispute. They were made effective on publication. In *PMA v. Finch*,[1] the U. S. District Court in Wilmington, Delaware, held the regulations invalid on the ground that, contrary to Section 4 of the Administrative Procedure Act, they were issued without notice of proposed rulemaking and an opportunity for interested persons to comment. The Court emphasized that the September 19 order represented a dramatic departure from past Agency practice and policy, that the regulations had a direct and severe impact on the industry, and that many of the questions raised in the lawsuit were ones that merited the consideration of the Commissioner. Consequently, on February 17, 1970, the Agency republished the order as a proposal.

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[1] *PMA v. Finch*, CCH FOOD DRUG COSMETIC LAW REPORTS, ¶ 80,292, (DC Del 1970) 307 F. Supp 858.

On May 8, the final order was published with minor modifications. Subsequent correspondence between FDA and PMA confirmed that the content and effect of the May 8 order are essentially the same as those of the September 19 regulation. We filed suit in the U. S. District Court in Wilmington on July 23. A case filed by Pfizer attacking the regulation as it was applied to one of its products is also pending. It will be argued before the U. S. Court of Appeals for the Third Circuit on September 30, the day before the PMA argument. First by court order, and then by agreement between the parties, the order against Pfizer's product has been stayed pending the decision.

Prior to May 8, in *Upjohn v. Finch*,[2] the Court of Appeals for the Sixth Circuit upheld an order of the Commissioner repealing certain antibiotic monographs and removing Upjohn's Panalba from the market without a hearing. The Court held that Upjohn had not established reasonable grounds for a hearing, as required by Section 507, because it had not established the existence of a genuine and substantial issue of fact as to the existence of evidence of effectiveness meeting the statutory definition of substantial evidence. In the course of its opinion, the Sixth Circuit stated, without any analysis and without reference to *PMA v. Finch*, that the September 19 regulations "correctly elucidate what Congress itself has plainly written in its definition of substantial evidence and constitute a correct application of the Congressional definition." Clearly, this decision hurts the *PMA* case, although it should not be controlling. We believe its one-sentence approval of the order can fairly be characterized as dictum unnecessary to its basic holding that the evidence submitted by Upjohn, accepted on its face, was clearly insufficient under the statute itself. In addition, the Court found "that the presence of novobiocin in Panalba makes these fixed combinations irrational and hazardous." That the Court was gravely concerned with the safety question is demonstrated by the fact that it alluded to the hazards associated with the use of novobiocin in no less than four different places in the opinion. There is, of course, no safety question in either the *PMA*

[2] *Upjohn v. Finch*, CCH Food Drug Cosmetic Law Reports, ¶ 80,301 (CA-6 1970) 422 F. 2d 944.

case or the *Pfizer*[3] case. In *Upjohn,* the company had been given a 120-day extension to gather relevant evidence, and while the company had not been given an evidentiary hearing, it had been given the right to make an oral presentation to FDA—a presentation which consumed some 117 pages of transcript. Thus, the Court had an ample record before it on which it could, and did, examine in order to ascertain whether Upjohn had shown reasonable grounds. Another distinction between the *PMA* case on the regulation itself and *Upjohn's* case on Panalba is that ours involves new drug revocation proceedings as well. As pointed out earlier, there are no "reasonable grounds" requirements in the new drug section. Incidentally, the Court in *Upjohn* incorrectly cited 505(h) relating to new drugs as its authority to review the antibiotic revocation proceeding. The authority is actually contained in Section 507. Further, the Court ignored the substantial differences in language and in purpose between the antibiotic provisions and the new drug provisions—specifically the omission of the adequate and well-controlled studies requirement in Section 507, except for antibiotics previously cleared under the new drug provisions.

PMA's Position

Our basic position in Wilmington is that the May 8 regulations, contrary to law, make the statutory test of substantial evidence of effectiveness the standard for determining whether a hearing will be held to determine whether that test is met. The manufacturer is required to convince the Commissioner of the ultimate result before the hearing, not as a result of the hearing. Further, as stated earlier, the rigid and exclusive definition of adequate and well-controlled investigations is inconsistent with the statutory definition of substantial evidence of effectiveness as elucidated by the legislative history of the 1962 Drug Amendments. I have previously mentioned some of this legislative history. Let me also quote the initial Senate Report on the 1962 Amendments as follows: "In such a delicate area of medicine, the Committee wants to make sure that safe new drugs become available to the medical profession so long as they are

[3] *U. S. v. An Article Consisting of 36 Boxes, More or Less, etc., Labeled in Part: "Line Away, Temporary Wrinkle Smoother, Coty, etc.,* CCH Food Drug Cosmetic Law Reports, ¶80,201 (DC Del 1968).

supported as to effectiveness by a responsible body of opinion." Quite apart from the legislative history, the final report of the NAS-NRC states that: "In a number of areas of drug action . . . there is no agreement on what constitutes a well-controlled investigation"; and as Goodman-Gilman, perhaps the leading textbook on pharmacology, states: "What constitutes an adequately controlled clinical trial necessarily varies depending upon the drug effect being evaluated."

We also object to the limited role of partially-controlled studies. Since they may be used only as corroboration of substantial evidence, they are not, for all practical purposes, being used at all. This is so because if you have substantial evidence, then no corroboration is required. It was not the intent of Congress that these studies should be ignored. Even if the rigid definition of adequate and well-controlled clinical investigations were a valid interpretation of the statutory requirement of substantial evidence, manufacturers should have been, at a minimum, entitled to be notified in advance of those products of which the effectiveness will be challenged and provided a reasonable period in which to conduct new clinical investigations of the kind required by the May 8 regulations. The regulations effect a material narrowing of the range of evidence which previously had been considered relevant in evaluating a drug's efficacy. Lulled into a sense of security by previous FDA assertions that technical requirements of substantial evidence would not be required of pre-1962 new drugs, and having placed reliance on other statements by FDA officials that hearings would be granted for drugs found ineffective as a result of NAS-NRC review, manufacturers of pre-1962 products must now conduct tests on all such products in order to be safe. Manufacturers have no way of knowing which products will be decided by FDA to become subject to the substantial evidence requirement. It also should be mentioned that in the past, FDA always gave hearings on new drug application revocation proceedings merely on request.

Whatever "reasonable grounds" the FDA may require to be shown in order to obtain a hearing prior to revocation of an anti-

biotic monograph, the situation is entirely different with regard to new drugs. There is nothing in the language of the legislative history of Section 505 that permits any qualification of this kind on what has always been assumed to be an absolute right to hearing before an individual new drug will be removed from the market. The language of Section 505(e) clearly indicates that a finding leading to withdrawal of approval of a new drug application can validly be entered only "after due notice and opportunity for hearing." Section 505(c)(2) makes clear that all the new drug applicant has to do to obtain a hearing is to "accept the opportunity for a hearing." Even where the Secretary finds that there is an imminent hazard to the public health, he is required by the statute to "afford the applicant an opportunity for an expedited hearing." Since the law requires that the Secretary establish "that there is a lack of substantial evidence" that the drug is effective, it is not surprising that the statute gives the affected manufacturer a right to a hearing at which the Commissioner may be given the burden of establishing his case. Of course, this is not to argue that an applicant may not forfeit the right to a hearing in circumstances such as in the *Dyestuff*[4] case where, even if an applicant proved his allegations, he could not, as a matter of law, prevail. But the right to a hearing, before an administrative agency resolves disputed questions of fact against a specific party, is a fundamental aspect of due process of law. It is clear that the May 8 regulation is not a summary judgment procedure, but one that contemplates a pre-hearing determination on the merits. Correspondence between FDA and PMA concerning the May 8 regulation leaves the inescapable conclusion that affidavits stating facts which, if true, would demonstrate that a material issue of fact exists, would not be sufficient grounds for a hearing even though it is well established in case law that such affidavits would be sufficient to defeat a motion for summary judgment. Indeed, the Commissioner stated, the objections must be accompanied by a substantially detailed factual discussion of the available data to allow "a medical judgment as to the conclusions that may be properly drawn from the data."

[4] *Dyestuffs & Chemicals, Inc. v. Fleming*, (CA-8 1959) 271 F. 2d 281; (US Supp Ct 1960) cert. denied.

All briefs in the case will be filed the last week of September. Oral argument before the court will be held on October 1. A discussion of FDA hearing procedures in connection with the withdrawal of drugs from the market would not be complete without brief mention of the *Hynson, Westcott & Dunning* and *Wm. S. Merrell* cases recently decided in U. S. District Courts in Baltimore and Wilmington, respectively. Both cases involved attempts by the companies to obtain adjudication by the Courts on the question of whether certain products were new drugs or were old drugs. If they were old drugs, then FDA could not initiate proceedings to revoke their new drug applications because their NDAs would no longer apply. The *Hynson, Westcott & Dunning*[5] case was dismissed on the basis that the plaintiff had failed to exhaust his administrative remedies. The Court, in the *Wm. S. Merrell* case, refused to extend a temporary restraining order against FDA issuing a notice withdrawing approval of the relevant new drug application and giving an opportunity for the filing of objections and requesting a hearing. The important aspect of both cases, however, is that apparently FDA will allow evidence on the new drug-old drug issue to be presented at a hearing, if one is granted. If no hearing is granted, the companies will be able to make a record for consideration by the Court of Appeals of old drug-new drug status. This, seemingly, would be a radical departure from previous FDA custom of not permitting evidence on what it considers to be purely "legal" issues at administrative hearings. Of course, the basic fear of both Courts was that they would be besieged by a great many manufacturers requesting an old drug-new drug decision prior to decisions allowing or refusing administrative hearings. Another case filed by USV Pharmaceutical Corp. and relating to bioflavonoids is also pending. It, too, is concerned with the determination of new drug-old drug status prior to an FDA decision on granting a hearing.

[The End]

[5] *Hynson, Wescott & Dunning, Inc. v. Commissioner of Public Health & another*, (Mass Sup Jud Ct 1964) 195 NE 2d 74, 346 Mass 606.

AOAC: Why FDA Analyses Stick

By BENJAMIN ADELMAN

The Following Article Appeared in the September, 1970 Issue of *FDA Papers*. Mr. Adelman Is a Manpower Utilization Officer in the Bureau of Foods and Pesticides, FDA.

ALTHOUGH THE ASSOCIATION OF OFFICIAL ANALYTICAL CHEMISTS (AOAC) is not well known to the public, it affects the daily life of every American. Its efforts result in monitoring of the food he eats, the medicines he takes, the diet of his pets, the pesticides he sprays in his garden, the cosmetics his wife uses, the water he drinks, and the air he breathes. It supplies the tested and approved methods of analysis used by the Food and Drug Administration's (FDA's) laboratories in their daily search for potential adulterants and contaminants.

The AOAC, as it is commonly called, is a scientific society of the United States and Canada that sponsors the development and testing of methods for analyzing pesticides, foods, food additives, color additives, drugs (both animal and human), animal feeds, cosmetics, liquors, beverages, fertilizers, hazardous household products, air and water pollutants, and many other commodities and materials. It does all this with a remarkably small administrative staff because the bulk of its activities, especially methods studies, is carried on by volunteers. The AOAC has no laboratories. Instead it relies on laboratories that require analytical methods and which cooperate to supply validated data required for AOAC's approval of the method.

The methods developed and approved by the AOAC are widely recognized in Federal and State courts and are used by food and drug regulatory agencies in countries throughout the world. The reason for this almost universal acceptance is the requirement for collaborative testing of methods before adoption, pioneered by AOAC.

Since the AOAC program covers thousands of products and the progress of science and technology introduces thousands of new commodities each year, there is a constant demand for the development of new analytical methods and updating of older ones. The AOAC supplies a coordinating system that avoids duplication of work by Federal agencies with common interests. For example, both the Department of Agriculture and FDA are interested in proteins, and FDA and the Internal Revenue Service in alcohol.

Procedure

The proposal to develop and test a new method or improve an existing one may be made to the association by a member, an industrial firm, a Federal agency of the United States or Canada, a university laboratory or occasionally by a scientist from some other country. The current 54 general referees, who are experts in their fields, such as in drugs, food additives, and pesticides, are each responsible for noting the needs for analytical methods, and each looks around for scientists who are qualified and willing to take assignments as associate referees. The latter may be employed by the Government, a State agency, a university, or industry. The executive secretary considers each proposal from general referees, officials in agencies, and other experts before he assigns it to an associate referee, who usually is already working in the field as part of his organization's program to design or develop a suitable method and arrange for interlaboratory testing.

The associate referee is the key man in the scheme of operations. He is responsible for finding an appropriate method in the literature, devising a new method, or modifying an existing one. His work usually begins with a thorough search of the scientific literature, followed by as much as two years of experimentation in the laboratory. After he has perfected or designed a method that he believes to be satisfactory, he writes the directions for the method and then lines up analysts in six or more laboratories who agree to serve as collaborators in checking the method.

The associate referee sends the collaborators at least four test samples, a description of the method, and directions for running the test. The collaborators analyze the samples exactly as directed and report their findings to the associate referee, who evaluates the data. If the analyses are satisfactory, he sends a report to the general referee recommending adoption of the method.

The general referee evaluates the associate referee's report and, if he is satisfied, recommends its approval to the appropriate subcommittee of the Committee on Recommendations of Referees, which in turn makes its recommendation to the association at its annual meeting. At this meeting, usually held in early October, the association votes on the proposed methods. Those adopted are designated as "official, first action," and are published in the following March issue of the *Journal of the AOAC*. After being used successfully by analysts for a year, a method may be voted "official, final action" at a subsequent meeting.

The approved methods of the AOAC are compiled in a treatise, "Official Methods of Analysis," which is revised and published in a new edition every five years. The 11th edition, due about November, 1970, will describe 1,550 analytical methods and run to over a thousand pages. The first publication of the AOAC in 1884 devoted three pages to methods for the analysis of fertilizers.

The 1908 edition, which was published by the Department of Agriculture, contained 272 pages and described 382 methods. It was highly regarded by the scientific community. Henry L. Lepper, president of the AOAC for the 1952 term, recalled in his presidential address that it was used as a supplementary text for one of his college chemistry courses:

> The impressive title, 'Provisional and Official Methods of Analysis of the Association of Official Agricultural Chemists,' promised a wealth of analytical methods which to us at the time was more than fulfilled by the text. I well recall our disappointment over the completeness of the book. Apparently, procedures had been perfected for all important foods and determinations. To us with the narrow vision of those just at the doorstep of their profession, the question arose as to what further opportunity could there be for further research and method development.

Relation of FDA and AOAC

The FDA has a strong interest in the AOAC and has always given it full support. Dr. Harvey W. Wiley, the chemist whose campaign for pure foods brought about the passage of the Food and Drug Act in 1906 and the establishment of the Bureau of Chemistry of the Department of Agriculture (which became the Food and Drug Administration in 1930), also was instrumental in organizing the AOAC in the early 1880's.

The connection between the two organizations is not merely historical. FDA is the major "producer" and major "consumer" of validated analytical methods for foods, drugs, and other consumer commodities in the United States. The tests it uses are essential to the enforcement of the Food, Drug, and Cosmetic Act and the other legislation for which the Agency is responsible. Consequently, it is important that the methods employed by its analysts to detect violations of the law be reliable, accurate, and accepted as valid by the courts.

In 1969, for example, the AOAC adopted 56 new methods. Of these, 34 were developed by FDA analysts, 15 by industrial laboratories, three by States and universities, three by the Department of Agriculture, and one by the Department of the Interior.

The Office of the Methods Research Coordinator in the Bureau of Foods and Pesticides is responsible for liaison between FDA and the Association of Official Analytical Chemists. The head of the office serves as executive secretary of the AOAC and is responsible for directing its day-to-day operations. FDA is heavily involved in the AOAC's activities. Of the 585 associate refereeships active as of last July, 298 were held by FDA scientists. These projects are part of their normal activities.

Origin and Development of AOAC

The reason for AOAC's origin dates to 1840 when the noted German chemist, Justus von Liebig, published a book, *Organic Chemistry in Its Application to Agricultural Chemistry and Physiology.* In it he recommended that mineral fertilizers be used to replace the elements in the soil used up by growing crops. His views were widely accepted and a new industry grew up to meet the demand for fertilizers, both in Europe and in the United States.

With the expansion of American agriculture after the Civil War, fertilizer production became a major industry, but it soon encountered a serious problem. The farmer needed to know how much nitrogen, potash, and phosphorus was in fertilizer he bought, but the analyses by the manufacturers' chemists and those by the State agricultural chemists did not agree, for each chemist used the analytical methods he preferred.

Dr. Wiley wrote of the time:

> The condition of analytical work may truly be described as chaotic. The result of such conditions is easily imagined. There was no standard of comparison or reference. Buyers and sellers were continually wrangling over analyses, which, made by different men, following different methods, did not agree. The sellers' chemists uniformly obtained higher results than the buyers' and thus the door to litigation was constantly open.

The obvious solution was for everybody involved to get together and reach agreement on the analytical methods to be used. On July 28, 1880, the first "Convention of Agricultural Commissioners and Chemists" met at the Department of Agriculture in Washington. This meeting led to the establishment of the Association of Official Agricultural Chemists (since 1965, the Association of Official Analytical Chemists), which first met in Philadelphia on September 8, 1884.

In time, the scope of the AOAC widened. Analytical methods for cattle feeds and dairy products were added in 1886, sugars and fermented liquors in 1887, soils in 1890, tanning materials and leather in 1894, insecticides in 1898, and food adulteration in 1901. Today, work is being pursued in nearly 600 different subjects grouped in 60 commodity areas.

Progress

The publication in 1908 of the "Official and Provisional Methods of Analysis of the AOAC" established the association as the world leader in its field. The contrast between the 1908 and 1970 editions of "Official Methods of Analysis" is enlightening. The methods described in the 1908 book are those of "wet chemistry," the chemistry of test tubes and beakers. About the only analytical instruments mentioned are the polariscope and refractometer. In the 1970 edition, wet chemistry is only the prelude to analysis by astonishingly sensitive equipment that was hardly imagined 60 years ago. Gas chromatography, atomic absorption, polarography, infrared spectrophotometry, ion exchange, electrophoresis, and fluorimetry are embodied in sophisticated analytical instruments, some of which can determine impurities in parts per billion. To put it another way, it would be impossible to enforce the present Federal food and drug legislation with the analytical techniques and methods of 1908. The successive editions of "Official Methods of Analysis" illustrate the progress of chemistry and physics and underline the need for continuing progress.

A striking example of this need is the analysis of modern organic pesticides. Before World War II, insecticides and fungicides were

mainly inorganic chemicals. The synthesis of DDT during the war stimulated the development of hundreds of organic pesticides that now dominate the field. During the growing season, the farmer often sprays several different pesticides on the same crop to control various pests. Methods for the analysis of each pesticide for each crop are too time-consuming, so in the last few years FDA chemists have worked on perfecting multiresidue, multiproduct methods that are now used regularly in laboratory practice. One method, for example, can determine the concentration of the pesticide residues of 12 chlorinated pesticides on 33 different crops, in dairy products and vegetable oils, and also seven phosphated pesticides on two crops. The accuracy and reproducibility of this method was demonstrated by FDA laboratories running many samples as unknowns. The results checked with each other to a satisfactory degree.

The volume of analyses grows yearly to keep up with the progress of technology and the introduction of thousands of new consumer-oriented products. In the first 10 months of fiscal year 1970 (July, 1969 through April, 1970), as an example, the FDA's 17 District laboratories, the National Center for Drug Analysis, the National Center for Antibiotics and Insulin Analysis, and the National Center for Microbiological Analysis ran approximately 100,000 examinations of samples. By far, most of the methods used were those approved by the AOAC and the United States Pharmacopoeia and the National Formulary.

The number of samples is so large and the advantages so great of examining samples "down the line" from the farm or factory to the retail supermarket or drugstore shelf that analyses in many laboratories are being automated. Automated analysis does not lessen the responsibilities of the analyst; on the contrary, it increases them, since he must devise new tests suitable to a new class of complex equipment and must be sure that the equipment operates reliably.

The AOAC cooperates with many other scientific societies to avoid duplicating analytical methods. It has established joint committees with the American Society for Testing and Materials, the American Association of Cereal Chemists, and the American Oil Chemists Society, and also has representatives on the Intersociety Committee on a Manual of Methods for Ambient Air Sampling and Analysis. The association has 34 liaison representatives with societies and committees such as the Council on Soil Testing and Analysis,

the Association of Food and Drug Officials of the United States, the American Society of Brewing Chemists, and the American Society of Enologists (enology is the study of wine).

International Collaboration

Although active membership in the AOAC is limited by its constitution to analysts employed in Federal agencies in the United States and Canada, it is actually an international scientific society of worldwide influence. The *Journal of the Association of Official Analytical Chemists* has a circulation of 3,900 copies of which 1,560 are mailed to foreign countries. The 1965 edition of "Official Methods of Analysis" had a sale of 13,130 copies of which 4,941 were sold to purchasers in 72 foreign countries.

Although the AOAC has been interested for a long time in expanding international cooperation, there have been serious obstacles. Shipments of samples from the United States could take weeks or even months to reach their destination, and deterioration, especially of foods, could be serious. For a valid collaborative study, it is essential that the sample be received by the collaborating analyst in exactly the same condition as shipped from the associate referee's laboratory. The slowness of communication, the multiplicity of languages, and the differences in instruments have made international collaborative studies difficult.

Fortunately the barriers to international cooperation in the development of analytical methods are dwindling. Samples can now be sent by air freight in a matter of days or even hours instead of weeks. Air mail has brought Europe much closer to the United States. Luther Ensminger, executive secretary of the AOAC, says his office in Washington now gets mail from Europe as quickly as from Los Angeles or San Francisco. English has become the leading language of science and most scientists are able to read English scientific papers in their specialty. Also, a foreign associate referee can recruit collaborators from his own or neighboring countries.

The remaining obstacle is passenger travel. Often a foreign associate referee may not be able to travel to Washington to attend the annual meeting of the AOAC. In that case, however, he can inform his general referee, who can arrange to have another scientist read his paper at the meeting.

The changing situation is beginning to have its effect. Last year, for the first time, the AOAC had associate referees in other countries besides the United States and Canada. Of the 19 non-U. S. associate referees now serving, 14 are Canadian. The associate referee for analysis of vitamin D by chemical methods is from the Netherlands; for carbaryl in corn and corn products, an Indian scientist; for diethylpyrocarbonate in beverages, German; for hydrogen cyanide, Australian; and for sodium, Mexican. It is expected that in the next few years the number of overseas referees will greatly increase.

The AOAC cooperates with several international organizations on the standardization of analytical methods. It has, for example, representatives on the Collaborative International Pesticides Analytical Committee (a European group) and works closely with that committee on development and joint adoption of methods for the analysis of pesticide formulations. The aim is to provide, in time, complete uniformity and standardization of pesticide analyses the world over.

The AOAC also has special consultative status with the Food and Agriculture Organization of the United Nations. Dr. Robert Weik, an FDA food chemist, represents the AOAC on the International Dairy Federation and International Standards Organization on the standardization of analytical methods for dairy products. Dr. William Horwitz, deputy director of the Office of Foods and Nutritional Science of FDA, represents the AOAC with the Office Internationale du Cacao et du Chocolat, which is concerned with the marketing of cocoa and chocolate. AOAC has five FDA scientists serving as its representatives with the International Association for Cereal Chemistry. Dr. John Howard is concerned with food additives and their residues, Milo Prochazka with cereal foods, Mike Deutsch with determinations of vitamins, William Eisenberg with tests for filth in cereals, and Dr. Robert Angelotti with microbiological contamination of cereals.

At the October, 1970 meeting of the AOAC, the executive secretary will propose changing the AOAC constitution to make official analysts in all countries eligible for active membership. The method of voting would be changed. At present, each State, Province, and Federal agency has one vote. This would be altered to extend one vote to each country other than the United States and Canada. To cast their votes, the scientists representing their countries would have to be present at the annual AOAC meeting. **[The End]**

Food Safety

By DALE R. LINDSAY

Dr. Lindsay Is Associate Commissioner for Science, FDA. His Paper Originally Appeared in the July-August Issue of *FDA Papers*.

IN HIS CONSUMER MESSAGE on October 30, 1969, the President asked that the list of substances generally recognized as safe (GRAS), and thus exempt from safety preclearances under the Food Additive Amendment of 1958, be fully reviewed and revised as necessary to assure adequate consumer safety. This request followed the October, 1969 action on cyclamates and similar public concern about monosodium glutamate.

The President's request stimulated a great many ideas as to the best method for accomplishing this review. Some interpreted it as a mandate to immediately begin acute and chronic animal studies for each substance on the GRAS list. Considering the Food and Drug Administration's (FDA's) limited staff, physical facilities, and budget it was quickly apparent that such a task was impossible, mandate or not. After getting the problem in better perspective, several things became clear:

- For a good many of these substances, and for the uses made of them, no cogent reasons existed for doubting their safety; no justification could be made for the funds required to test them.

- Many other substances were essentially proprietary compounds, the safety of which should be demonstrated by the manufacturer.

- There existed no readily available source of information about the totality of uses of many of these individual substances; for example, in which foods used, in what amounts, and constituting

what part of the human diet? Obviously this information was necessary to arrive at conclusions as to the risks that would be involved.

- For nearly 300 flavoring and extract substances, the Flavors and Extract Manufacturing Association was in the process of compiling an inventory of uses. The Association was gathering information on quantities used in specific foods and experimental evidence of safety.

- One important ingredient was missing; that is, how many additional substances were in general usage as food additives which were also exempted from the Food Additives Amendment of 1958 by virtue of a clause in the Food, Drug, and Cosmetic Act (S. 201(s)(4)) which exempted "any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act . . . or the Meat Inspection Act of March 4, 1907 . . . as amended and extended . . ."? Unfortunately, there are no complete records of these prior sanctions which could have been issued by either FDA or the United States Department of Agriculture (USDA).

On April 9, 1970, an FDA *Federal Register* notice appeared: "Food Additive Status Opinion Letters; Statement of Policy." It had a very simple purpose; in the absence of an established list of these sanctioned substances, this notice was intended to identify, through the procedure outlined in the notice, all of the prior sanctions that the holders of them cared to keep in force. It also very logically offered to update the opinions that had been issued in the original letter. To accomplish this, the *Federal Register* notice announced that these earlier opinions were thereby revoked and that they would be "replaced by qualified and current opinions if the recipient of each such letter forwards a copy of each to the Department of Health, Education, and Welfare . . . along with a copy of his letter of inquiry, within 60 days after the date of publication of this section in the *Federal Register.*"

It should be apparent that "qualified and current opinions" could not possibly be issued immediately upon receipt of the copy of the

original sanction. They will require, in many cases, a considerable amount of time. Meanwhile, the original sanction must apply at least until the further consideration reveals some reason to change it. In this sense, the "prior sanction" cannot be revoked simultaneously with the revocation of the opinions, even though these sanctions were based upon the opinions contained in the letters. The success of the venture lies in the wholehearted cooperation of industry.

Regulatory Procedures

Any current discussion of the GRAS list status requires an understanding of the regulatory procedures for food additives and pesticide residues.

The Food, Drug, and Cosmetic Act, as amended, is the basic law under which these products are regulated. Section 201(g) of this Act defines a pesticide chemical as any substance which, alone, in chemical combination, or in formulation with one or more other substances, is an economic poison within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (which is administered by the USDA) and is used in the production, storage, or transportation of raw agricultural commodities.

Section 201(s) defines a food additive and, in addition, specifies the circumstances under which exceptions to the Food Additives Amendment of 1958 may be recognized. The definition of a food additive will be considered below, as will the most important of these exceptions—those substances generally recognized as safe, or GRAS.

Section 401 authorizes the promulgation of regulations fixing and establishing for any food (with named exceptions) a reasonable definition and standard of identity, quality, and fill of container, whenever such action "will promote honesty and fair dealing in the interest of consumers."

Section 403(j) authorizes the promulgation of regulations for such labeling of special dietary food as is determined to be "necessary in order fully to inform purchasers as to its value for such uses."

Section 404 authorizes the promulgation of regulations for issuance of emergency permits providing for the conditions under

which a particular food or foods may be manufactured when it has been determined that an emergency situation warrants such action for the protection of the public health.

Section 406 authorizes the promulgation of regulations limiting the quantities of poisonous and deleterious substances added to food where such substances are required or cannot be avoided.

Section 408 authorizes the issuance of regulations establishing tolerances for the presence of poisonous or deleterious pesticide chemicals in or on raw agricultural commodities.

Section 409 authorizes the establishment of regulations prescribing, with respect to one or more proposed uses of a food additive, the conditions under which such additive may be safely used, and includes the famous Delaney Clause aimed at excluding the use of carcinogens.

Section 702(a) authorizes the promulgation of regulations governing sanitary and other conditions for plans under the seafood inspection service.

Section 706 authorizes the promulgation of regulations providing for uses of color additives.

In addition, section 3 of the Federal Hazardous Substances Act authorizes the promulgation of regulations declaring certain substances to be hazardous and establishing variations and exemptions.

Sections 4, 5, and 6 of the Fair Packaging and Labeling Act provide for the establishment of certain regulations relating to the packaging and labeling of foods, drugs, devices, or cosmetics.

The Shellfish Sanitation Program includes the publication of procedures in the National Shellfish Sanitation Program's Manual of Operation.

Model codes and other criteria and standards are issued under the FDA function in Food Service, Milk, and Interstate Travel Sanitation Operations.

Food standards (§ 401), pesticides (§ 408), food additives (§ 409), and color additives (§ 706), all involve premarketing clearance based on the submission of adequate data by a petitioner.

Course of Action

In the simplest of terms, the action upon a food additive or pesticide petition takes the following course:

A petition is submitted to FDA by the manufacturer, formulator, or processor of the food additive or of the food which may contain a pesticide residue. This petition must make a thorough case for the safe usage of a food additive substance or for the safety of the pesticide tolerance requested. It must describe the chemistry of the additive or pesticide, the analytical procedure most appropriate for its qualitative and quantitative assessment, its toxicity to experimental animals and any known human effects, its microbiological aspects where appropriate, and any special characteristics such as antibiotic or radioactive qualities. Unfortunately, neither nutritional quality nor essentiality of usage are requirements in issuing regulations insofar as the Food, Drug, and Cosmetic Act affects food additives or pesticide residues.

After the petition is numbered and logged it is prepared for the review procedure and sent to an appropriate "product manager" or project officer. Over two-thirds of the petitions received are found wanting in some essential feature. When this happens, a notification letter and two copies of the petition are sent to the petitioner and one copy placed on the "inactive petition" file. If the petitioner offers a supplement in accordance with the notification letter, then the petition is reactivated and continues on its way as though this interruption had not occurred. If the supplemental material still is inadequate, the petition is held inactive until such time as the requirements are met or the petition is withdrawn.

For petitions found acceptable for filing, a tentative draft of a regulation is usually prepared and sent forward for technical review and evaluation by toxicologists, chemists, pharmacologists, microbiologists, or other appropriate scientists. If the petition involves a pesticide, a certificate of usefulness is required of the USDA. The evaluations of all reviewers are forwarded, with the petition, back to the "product" or "project" manager.

If the reviewers decide that the scientific evidence presented supports the action requested, the project manager drafts the required regulation and briefing memorandum, considering, as appropriate, the comments that may have been received from other agencies that might be affected by the regulation.

After final drafting the project manager sends both the regulation and the briefing memo to the Associate Commissioner for Compliance, where, in turn, they are sent to the Office of the General Counsel for legal review. Upon its return, and if acceptable all along the line, the Associate Commissioner for Compliance may either sign the regulation or initial it and send it to the Commissioner for signature. The approved regulation is forwarded to the Office of the Secretary of the Department of Health, Education and Welfare, where it is certified and sent to the National Archives for publication in the *Federal Register*.

A petition may be found wanting at almost any point in the reviewing process, sometimes on technicalities that may be corrected, but sometimes because additional information has been received which requires additional testing, clarification, or other clearance procedures.

Problems and Suggestions

We have decided that there is a real need for a streamlining of the application review processes in FDA. The following is a summary of the problems that were identified in the previous procedure and some suggestions for correcting them:

1. Excessive handling time for processing petitions.

Food additive and pesticide petitions constituted the greatest workload. Average times required to review and dispose of petitions are not the best indices of efficiency, since a large number of simple and short-term disposals may more than offset a few very difficult petitions which have taken considerably more than the statutory time limit. However, the major delays have been identified.

One prime delaying factor in the past was the fractionation of organizational responsibility, and this is being corrected. Perhaps the

most important shortcoming that caused excessive delay at many levels was inadequate scientific planning for the types of testing and other data that would be required. The creation of "product managers" should result in either a more efficient review, or a change in managers. The use of a table of maximum times for each function, totaling no more than the statutory limitation, should be followed together with several other good management features.

2. Poor quality of petitions received.

Two-thirds or more of the petitions received during a test period last year contained insufficient data for favorable action without one or more amendments. The publication of revised procedural regulations is now in order since a proposal for them has already been published. This action, coupled with dissemination of educational materials and the development of a universal petition format, should improve the quality of food additive and pesticide petitions as well as to expedite their review.

3. Prompt availability of scientific data for reviewers.

An automated data retrieval system is needed to offset our shortage of personnel to search and review the literature concerning the substance under petition. A preliminary step in this direction has been made from 95 pesticide petitions which are stored in a computer, but much more is needed to implement an effective storage and retrieval system.

4. Improvement of scientific reviews and regulation adequacy.

When scientific reviews do not reach conclusions adequate to recommend an action, a considerable delay may result. The establishment of internal guidelines, together with a program of education in legal and scientific requirements, should produce a marked improvement, even in those reviews that are adequate.

5. Adequacy of pesticide fees.

Fee schedules should be adjusted to reflect necessary costs.

6. Storage of petition files.

Currently one official and two nonofficial files of duplicate material are maintained, placing a severe strain on storage space. When

action is completed on a petition, it should be reduced to microform, the original file sent to the Federal Records Center, and the microform file maintained for reference access by the Divisions concerned.

This is background for FDA's GRAS list review. As mentioned earlier, the review and inventory of substances generally recognized as safe by the Flavor and Extract Manufacturer's Association provides a basic format for reviewing the official GRAS list. After several preliminary discussions with a panel of the Food Protection Committee, FDA entered into a contract with the National Academy of Sciences in mid-April, 1970. The contract calls for development and field testing of a comprehensive questionnaire to be sent to the manufacturers and formulators making or using substances now on the GRAS list. In addition to the official GRAS list we will include the substances covered by prior sanction letters in conducting this review. This should be completed by November, 1970.

As soon as the questionnaire is developed and tested, a second contract will complete the survey. This second contract must include some of the information developed under the first contract. Concurrently with the letting of this second contract, or even earlier, we will begin the evaluation of the substances reported upon in the field test. In fact, we hope to issue a *Federal Register* notice in the near future, based upon the knowledge jointly available in FDA and in the Academy review panel, establishing the nucleus of a new GRAS list or its equivalent. It would contain substances that have long been in use and about which we know a great deal, such as salt, sugar, and vinegar under specific conditions of use.

In conducting and evaluating the survey of the known toxicity or other adverse effects of these substances, we may find some about which there is enough information to warrant regulations. However, if safety data appear to indicate significant doubt, then it may be necessary to remove substances from the GRAS list and force the submission of petitions.

Some think that when the job is done there will be no GRAS list. More likely there will be a much shorter GRAS list of items for which insufficient experimental evidence exists to warrant reg-

ulations, but where no questions of safety over many years of usage are found.

Advantages and Goals

The advantages of the Academy survey are many. First, it takes the job out of the pressure cooker—it should be free of the pulling and tugging of regulatory responsibilities. Secondly, it will enhance the probability of accurate reporting of the extent and volume of usage —thanks to the fine cooperation of the Industry Liaison Panel of the Food Protection Committee. Finally, among other things, it does not constitute an additional effort to be made by an already overworked FDA staff, but will be done by an experienced and proven team. By the time the final evaluation of findings is to be made, we will have worked out an orderly procedure for accomplishing this evaluation.

Some doubtful substances on the GRAS list will have to be reviewed by FDA. These will be substances manufactured or processed by many firms at marginal profits. When we find substantial consumer demand for the substance, FDA would undertake its testing in the public interest. This, like any of the research done by FDA, may be done either by our own scientists, or by scientists under contract. It is obvious that any large load of such research will have to be accommodated by contract, since our own facilities and personnel are currently overextended.

One such substance about which there is doubt is saccharin. We have not removed saccharin from the GRAS list and we are awaiting a review by the Nonnutritive Sweeteners Panel of the Academy's Food Protection Committee before making a decision. There is some legitimate doubt as to the incentive to the manufacturers of saccharin to conduct extensive tests. Actually, saccharin is more important economically to formulators using it than to the manufacturers of the chemical.

FDA should also continue to investigate the effects of cyclamates which are available as drugs for use by diabetics and others who cannot use sugar. In addition, we should better assess the risks that individuals face who have used cyclamates for the past decade or so.

We need to know more about monosodium glutamate. Other substances range from many of the pesticides to mercury, with the latter consideration including mercurial pesticides, alkyl mercury derived from metallic mercury, and mercurial drugs. The primary problem facing us in all of these substances is that of extrapolating from animal experimentation to man. We are in desperate need of proven methods which will permit us to test these substances over wider ranges, beginning with the often very low level encountered by man in his food and other environment, up to the no-effect level established in acute toxicity testing in two or more species of animals.

Review of the GRAS list, then, is but a part of the new picture of food safety. In the present decade we must not only use 1970 science to look at substances considered safe by more primitive standards, but we must also use the best science has to offer in our continued questioning of our man-made environment. **[The End]**

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION (Act of October 23, 1962; Section 4369, Title 39, United States Code)

1. Date of filing: Oct. 1, 1970. 2. Title of publication: Food Drug Cosmetic Law Journal. 3. Frequency of issue: Monthly.

4. Location of known office of publication: 4025 W. Peterson Ave., Chicago, Cook, Illinois 60646. 5. Location of the headquarters or general business offices of the publishers; Chicago, Ill. 60646.

6. Names and addresses of publisher, editor, and managing editor: publisher: Commerce Clearing House, Inc., Chicago, Ill. 60646; editor: Allen E. Schechter, Chicago, Ill. 60646; managing editor: George H. Harris, Chicago, Ill. 60646.

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8. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: None.

9. For completion by nonprofit organizations authorized to mail at special rates: Not applicable.

10. Extent and nature of circulation:

10A. Total number copies printed (Net Press Run): Average number copies each issue during preceding 12 months: 1,350. Actual number of copies of single issue published nearest to filing date: 1,300. 10B. Paid circulation: 1. Sales through dealers and carriers, street vendors and counter sales: Average number copies each issue during preceding 12 months: None. Actual number of copies of single issue published nearest to filing date: None. 2. Mail subscriptions: Average number copies each issue during preceding 12 months: 979. Actual number of copies of single issue published nearest to filing date: 954. 10C. Total paid circulation: Average number copies each issue during preceding 12 months: 979. Actual number of copies of single issue published nearest to filing date: 954. 10D. Free distribution (including samples) by mail, carrier or other means: Average number copies each issue during preceding 12 months: 34. Actual number of copies of single issue published nearest to filing date: 34. 10E. Total distribution (Sum of C and D): Average number copies each issue during preceding 12 months: 1,013. Actual number of copies of single issue published nearest to filing date: 988. 10F. Office use, left-over, unaccounted, spoiled after printing: Average number copies each issue during preceding 12 months: 337. Actual number of copies of single issue published nearest to filing date: 312. 10G. Total (Sum of E & F—should equal net press run shown in A): Average number copies each issue during preceding 12 months: 1,350. Actual number of copies of single issue published nearest to filing date: 1,300. I certify that the statements made by me above are correct and complete. (Signed) Allen E. Schechter.

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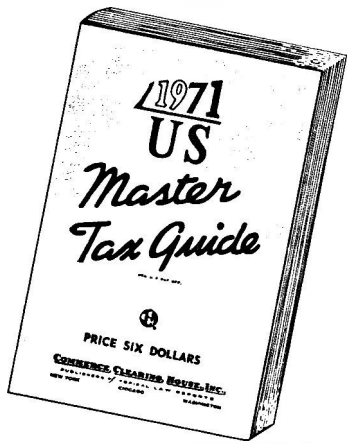

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