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Food Drug Cosmetic Law JOURNAL

Concluding Papers Presented at the 1965 Joint National Conference of The Food and Drug Administration and The Food Law Institute, Inc.

Papers Presented at the Twenty-first Annual Meeting of the New York Bar Association Section on Food, Drug and Cosmetic Law

A COMMERCE CLEARING HOUSE PUBLICATION
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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.

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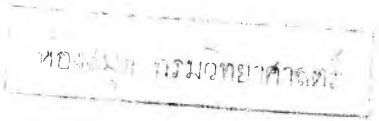

FOOD DRUG COSMETIC LAW JOURNAL

Editorial Advisory Board

REPORTS

TO THE READER

Drug Safety and the FDA.—The Food and Drug Administration and its role in the area of drug safety is the topic of the paper beginning on page 68 which was presented at the Symposium on the Safety of Foods and Drugs on November 22, 1965. The author, *Joseph M. Pisani,* discusses the legal procedures required of all new drug products, and the new amendments and regulations which have a bearing on drug safety. *Dr. Pisani* is the Deputy Medical Director of the Food and Drug Administration.

1965 FDA-FLI Conference.—The concluding papers presented at the Ninth Annual Joint Conference of the Food and Drug Administration and the Food Law Institute are featured in this issue of the JOURNAL. Previous papers presented at this Conference were in the January, 1966 issue.

The authors of these last three papers are *James L. Trawick,* Director of the Division of Consumer Education, Bureau of Education and Voluntary Compliance, Food and Drug Administration, *Mrs. Esther Peterson,* Special Assistant to the President for Consumer Affairs, and *Dr. Frances O. Kelsey,* Chief, Investigational Drug Branch, Division of New Drugs, Bureau of Medicine, Food and Drug Administration.

Beginning on page 78, in "Progress in Consumer Education," *Mr. Trawick* discusses the importance of educating the consumer for his own protection, and the role the FDA plays in this education.

"The Consumer's Interest" is the topic of the article commencing on page 92. *Mrs. Peterson,* the author, discusses the rights of the consumer as stated by President Kennedy in his consumer message to Congress in 1962. These rights are the right to safety, the right to be informed, the right to choose and the right to be heard.

Dr. Kelsey is the author of the article entitled "Investigational Drug Branch: Intra-FDA Relationships." This article, beginning on page 102, concerns the Investigational Drug Branch and the Investigational Drug Regulations, and the surveillance over a new drug from the first time it is tested on human subjects until it has received an approved new drug application, or testing in human subjects has been discontinued.

Twenty-first Annual Meeting of The Section on Food, Drug and Cosmetic Law of The New York State Bar Association.—Some of the papers presented at this meeting are featured in this issue of the JOURNAL. Additional papers will be published in a later issue. This meeting was held in New York City on February 1, 1966. The "Introductory Statement" given by *Franklin M. Depew,* Chairman of the meeting and President of the Food Law Institute, begins on page 109. A paper, "Artificial Sweeteners—Their Impact on the Food Laws," by *Murray D. Sayer,* an attorney for General Foods Corporation, which begins on page 111, discusses the long and controversial history of artificial sweeteners and the food laws. "The Proposed Alternative to Zero Level and No Residue Regulations," is the topic of the article beginning on page 124. The author, *Bernard L. Oser,* is with Food and Drug Research Laboratories, Inc.

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Drug Safety and the FDA

By JOSEPH M. PISANI

This Article Was Presented at the Symposium on the Safety of Foods and Drugs, Forming a Part of the Dedication Ceremonies for the New FDA Building on November 22, 1965. Dr. Pisani Is the Deputy Medical Director of the Food and Drug Administration.

PRACTICALLY DAILY WE ARE CONFRONTED WITH QUESTIONS such as "How safe are drugs?" "How safe is this drug or that drug?"

This matter of drug safety is most important. It is doubtful that any other area of responsibility receives as much attention in the Food and Drug Administration (FDA) either directly or through efforts in related fields as the safety of drugs.

While some other agencies of the federal government have regulatory functions in some drug matters, the FDA bears the major authority and responsibility in this regard. This authority and responsibility has been gradually extended and increased since the enactment of the first Pure Food and Drugs Act in 1906. Further, this extension in authority and responsibility has come about largely as a result of public demand.

The chief catalyst for the enactment of new major drug legislation has been Congress's concern with drug safety or more specifically drug hazards. A well known example is the Elixir of Sulfanilamide tragedy, causing over 100 deaths within a few weeks which furnished the impetus for passage of the 1938 Federal Food, Drug and Cosmetic Act which had been under consideration for the previous five years. Its major feature, added after the disaster occurred, was the provision which prohibited the marketing of a new drug in interstate com-

merce until adequate evidence was presented to FDA to show that it was safe when used as directed in its labeling. Another famous example was the thalidomide tragedy in Europe and certain other parts of the world which aided the enactment of the Kefauver-Harris Amendments of 1962. Fortunately, application of the new drug safety provisions of our 1938 law had prevented approval and widespread marketing of thalidomide in the United States.

We will not attempt to review in detail the investigational and new drug procedures or the law and regulations now in effect since this has been done many times previously. However, it may be helpful to some of those present who may be unfamiliar with our operations to make a general statement on the legally required procedures for their background information and then discuss some specific aspects of the law and regulations which are pertinent.

New Drug Procedures

A new drug product cannot be legally shipped interstate until a new drug application for it has been approved by the FDA. There are exemptions to this prohibition to allow shipment of an unapproved new drug for investigation by qualified experts under carefully controlled conditions designed to protect the public.

Under the FDA regulations a new drug intended solely for tests in vitro or in animals may be shipped interstate for such uses provided the following conditions are met: (1) The drug is labeled "Caution: New Drug—Limited by federal (or United States) law to laboratory studies in tests on animals. Not for human use." (2) Animals used in such tests or their products such as milk or eggs are not used for food purposes unless authorized by FDA under the food additive provisions of the act and regulations. (3) The shipper uses due diligence to assure that the consignee is regularly engaged in conducting laboratory studies or animal tests and that the new drug will be used for those purposes. (4) The shipper maintains records of each shipment and delivery for a period of two years and makes them available for inspection by an authorized representative of FDA. (5) The new drug is not intended for in vitro use in the regular course of diagnosing or treating disease.

Another exemption is reflected in the investigational drug requirements for tests in humans. Here the sponsor of the drug must file with FDA a "Notice of Claimed Investigational Exemption for a New Drug." These "notices" are known as IND's to distinguish

them from the NDA or new drug application. A "notice" includes information as to the identity of the drug, manufacturing controls, preclinical or animal studies, to demonstrate reasonable safety to initiate or continue human studies, the qualifications of the investigator, the plans of the investigations to be conducted and copies of the information concerning the drug supplied to the investigator. In submitting such a "notice" the sponsor agrees to abide by such requirements as the reporting of adverse reactions to FDA and to all clinical investigators and notifying the investigators when the investigation is discontinued or when a new drug application is approved. The sponsor is also required to obtain from his investigators signed statements concerning their qualifications for undertaking research and their agreement to report results and maintain records of the investigation and to obtain patient consent except where they deem it not feasible or in their professional judgment contrary to the best interests of the subject. When the sponsor has submitted his IND to FDA the investigation may proceed without approval. It may be terminated on a variety of grounds including lack of required information, inadequate preclinical testing and a failure to adhere to the specified conditions.

A new drug application is submitted by the sponsor when he believes he has accumulated adequate information to demonstrate the safety and effectiveness of the drug when used as he proposes in its labeling. Besides submitting the reports of animal and clinical investigations, the application must include a listing of all substances used in making the drug, whether or not they are still present in the final product, the complete quantitative composition, a description of the manufacturing facilities, procedures and controls, specified samples of the drug for the checking in our laboratories of its specifications and methods of assay and finally the proposed labeling. When the application is approved by FDA the applicant may market the drug in interstate commerce with the labeling and other conditions in the approved application.

The evaluation of a new drug application involves reaching a decision on whether or not the drug is safe for use. The Kefauver-Harris Amendments of 1962 also charge us with making a decision with respect to effectiveness.

Actually, safety and effectiveness are closely intertwined as has been explained on numerous occasions in the past. Those experienced in the field of drug therapy in humans, particularly physicians, do not

take issue with the concept that no drug is absolutely safe. A question naturally arising from this concept is the degree of hazard which can be accepted. Here, our staff is generally guided by the therapeutic values of the drug, weighing not only the degree of effectiveness but the condition for which the drug is effective. Generally speaking, a physician or his patient will accept a considerable risk of toxicity if they know that the drug has a high degree of effectiveness in a serious condition for which other effective drugs may not be available.

While realizing that all drugs are toxic to some extent, one of the objectives of the new drug application procedures is to assess the degree and nature of the toxicity, which can be done only through tests on animal and human subjects. Over the years the medical and scientific community has come to recognize the necessity for more demanding animal tests, and other requirements may later be recognized as proper as we learn more about how to measure drug effects. Hopefully, as science progresses we may be able to get more reliable information in some areas by substituting newer, less time consuming tests for older ones. In animal toxicity studies we require the tests now recognized by science as proper and necessary. For example: tests in newborn animals are being required for pediatric drugs. Reproduction studies are required almost routinely to detect adverse effects on any part of the reproductive process, including teratogenicity. It is realized that either positive or negative results of teratogenicity studies in animals cannot yet be extrapolated to the human with certainty. Positive animal studies in this area, however, are carefully studied, particularly if drug use in pregnancy is anticipated.

More information on drug metabolism in animals would be most helpful, particularly after determining which species of animal metabolizes the drug in the same way as man. Such information could well direct the course of other toxicity experiments and make them more meaningful. Drug metabolism studies are dependent on the availability of methods for determination of the drug or its metabolites in body media and apparently this is sometimes a major problem. At times it brings up the question as to what extent such information can be required, particularly if it might definitely delay the availability of a useful drug. In such situations, however, investigations of this type are, at the least, highly encouraged.

Increased demands for clinical investigation from the safety standpoint chiefly involve clinical laboratory studies such as liver and

kidney function tests, hematologic studies and endocrinological determinations. These tests may be of a routine nature, but more extensive tests pertaining to specific organs or organ systems may be requested because of the results of animal toxicity studies or the results of early clinical investigations or by previous experience with a drug of similar chemical structure. Generally speaking, investigational drugs are being tested in greater numbers of patients than they were in the past. This increase may often be due to the need for studies demonstrating effectiveness. Whatever the reason, the larger samples should disclose some of the less frequent adverse reactions before the drug is marketed than was previously possible.

Drug Labeling

At this point I would like to make some observations regarding drug labeling. We should keep in mind that all drugs and especially many of the potent newer drugs, have a potential for producing adverse effects of varying severity. The labeling of a prescription drug for the information of the physician should enable him to prescribe it with optimal safety. This means he should be furnished with "full disclosure" labeling, which is required for all prescription drugs, new and old, unless the effects of the drug are so well known that such labeling is not needed. Full disclosure labeling includes indications, effects, dosages, routes, methods, frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions. The approved labeling for a new drug is required to appear on or within the market package of a prescription drug and is usually in the form of a package insert. Other labeling such as promotional literature has to restrict its claims to those approved with a new drug application and is also expected to make a balanced presentation of the bad effects as well as the good.

This requirement for adequate labeling is regarded as an important measure in assuring the safety of drugs and can serve this function only if the physician reads and heeds it. The criticism is often made that the physician never sees the market package with its insert. While it may not be the ideal way to reach the physician with authoritative information, at the present time it is the one form of distribution of information which can be enforced. Before this was required, there was no assurance that the labeling as approved in any new drug application would be used in some instances. The physician now receives the package insert with sample packages of

drugs and with mailings to physicians, and full information on all prescription drugs is as near as the nearest pharmacy.

Let me now turn to some sections of the new amendments and regulations which also have a bearing on drug safety.

Investigational Drug Regulations

The investigational drug regulations contribute to the safety of drugs which are ultimately marketed. An example of this is the requirement for investigators to submit reports, particularly in the area of adverse reactions. Under the prior regulations reports were not always forwarded to the sponsor of a drug. In most instances this was probably due to the investigator losing interest in his study at the outset because of encountering adverse effects in one or more patients. Generally speaking, investigators are more interested in reporting positive results and new discoveries rather than negative findings, unless there is a requirement to do the latter. In addition, the regulations also specifically require reporting any adverse effect which may reasonably be regarded as caused by, or probably caused by a new drug. This latter phrase was undoubtedly included to encourage an investigator to think twice before deciding the observed effect was not drug-related and therefore not subject to report. It is recognized that many adverse effects occur which do not establish a causal drug relationship when considered singly; but if the same isolated adverse effect is reported from multiple sources it may then become quite significant. Thus, the failure to report undesirable effects which occur during drug testing could lead to the unjustified marketing of a drug or its distribution with inadequate information for the physicians' guidance.

Another important effect of the investigational drug regulations is the improvement in the quality of investigations. It is our impression that such improvement is occurring. More serious consideration is now being given to the qualifications and facilities of investigators; to more adequate planning and review of study protocols; and to more detailed recording and reporting of data. Thus when investigations have reached the point for submission of a new drug application, more complete information is available relating not only to efficacy but also to safety. While an improved quality of investigation does not make a drug safer by itself, the additional knowledge obtained, if adequately disseminated, should permit it to be used with greater safety.

Kefauver-Harris Amendments

A significant weakness in the Food, Drug and Cosmetic Act prior to the Kefauver-Harris Amendments was the lack of provisions for the monitoring of the safety of drugs after they had been approved for marketing. FDA was receiving very limited information on the occurrence of adverse drug experience. Reliance had to be placed on reports in the literature and the relatively infrequent direct reports by physicians and/or pharmaceutical firms. The major source of such reports was for the most part unavailable, namely the complaint files of the drug firms. As physicians encounter an adverse drug experience in a patient, they are likely to communicate with the distributor of the drug either to register a complaint or more commonly to inquire about any similar experiences of physicians or others. Detail men often transmit and follow-up on adverse drug experiences reported by physicians. In brief, the distributor of a drug knows more than anyone else about the marketing experience of that drug. On occasion such information would be furnished voluntarily to FDA when a firm realized it had a problem on its hands. Occasionally such information was furnished on request and at other times it was refused. In essence, FDA did not have legal access to such information and thus in many instances was unaware of its existence.

The amendments provided that the holder of an approved NDA must establish and maintain records of clinical experiences and other data and information received pertaining to the drug. These records and reports must be furnished to the Secretary as prescribed by regulation or by order as needed to facilitate a determination whether to withdraw approval of an application. They must also be made available for inspection on request. These requirements have resulted in a flow of information, including reports of adverse reactions which was not previously available. Thus, much closer surveillance of new drugs on the market is now possible.

The Pharmaceutical Manufacturers Association and a number of their member firms have sued for a federal court order that the reporting requirement should not apply to products which are not presently considered new drugs even though they were originally marketed as new drugs. On the other hand, FDA believes that the law requires reporting of adverse effects associated with the use of any drug first marketed as a new drug; this would permit, among other things, withdrawal of approval in the absence of substantial evidence of effectiveness or if new experience or data indicates that such action

is justified from the standpoint of public health protection. The litigation is still pending in the federal court in Wilmington, Delaware.

The Kefauver-Harris Amendments strengthened the authority to withdraw approval of a new drug application on the basis of lack of safety. Previously, the government was required in an administrative hearing to show on the basis of evidence not available when the application was approved that the drug was unsafe under the prescribed conditions of use. Now, the amended act allows withdrawal of approval also on the basis that considering the new evidence, the application does not show the drug to be safe under such conditions. In essence, a drug may be removed from the market not only on the showing that it is unsafe but also if it is demonstrated that there is a substantial question of safety.

Another new provision authorizes the Secretary to immediately suspend approval of an application without a prior administrative hearing if he finds there is an imminent hazard to the public health. Opportunity is then provided for a hearing after the drug is removed from the market. This procedure has not yet been used.

The Kefauver-Harris Amendments achieved a notable change in prescription drug advertising whether the products be new drugs, old drugs, or certified antibiotics. This is apparent to anyone who has read the advertisements in professional journals, before and since the amendments passed. The importance of advertising as a source of information for the physician is subject to debate. In any event, present prescription drug advertising generally presents a much better balance of the "good" and the "bad" of a drug than formerly. Current advertisements are required to include the same quantitative information on ingredients as is required on the labeling or package insert. If any information is given on indications for use or dosage, the advertisement must then contain a brief summary relating to side effects, contraindications, and effectiveness. Claims made in the advertising of a drug which is the subject of a new drug application must be within the limits of the approved labeling. Information as to side effects and contraindications from the approved labeling also have to be included. While it is probably impractical to try to estimate to what extent drugs have been misused with adverse effects as a result of lack of full disclosure or unsubstantiated claims in advertisements, nevertheless the new law does provide a safeguard against such occurrences. While on the subject, the enforcement of this provision for prescription drug ads is assigned to FDA. The Federal Trade

Commission (FTC) still has jurisdiction over advertising for over-the-counter drugs.

That portion of the amendments dealing with good manufacturing practices has a bearing on drug safety which is not usually thought of by the physician. The recall of batches of defective drugs is not a rare enough occurrence. During the last fiscal year for example there were over 200 drug recalls. About 90 of these involved products which were contaminated with penicillin. About 75 were due to label mixups. The other recalls were for various reasons such as low potency and variation of the potency of individual tablets, etc.

Formerly, FDA was able to take action against a defective product only after it was on the market. Now, action is possible under the adulteration section of the Act in the absence of "current good manufacturing practice," which requires a high standard of facilities, methods, and control procedures. This represents another step in assurance of drug safety.

Other illustrations of the importance of these amendments with respect to drug safety, which in the interest of time I shall just mention, are the extension of the certification requirement to all antibiotics for human use; the requirement of registration for all firms engaged in the manufacture, repacking, or relabeling of drugs; the authority to designate "established names;" and the strengthening of the authority to inspect factories producing prescription drugs.

Medical Organizations and Drug Safety

At this point, I would like to place special emphasis on a very important aspect of our program dealing with drug safety, namely, our collaborative effort with other organizations such as the American Medical Association (AMA) in programs devoted to the reporting of adverse experience with drugs. In our own program reports are collected from a variety of sources including approximately 195 nongovernmental teaching hospitals which are under contract with us and a large number of governmental units. Feedback to the contributors to our program is accomplished through monthly bulletins of suspected adverse reaction reports and also monthly reports of significant drug reactions. In addition, 250 medical journals are scanned each month by the Bureau of Medicine library for reports of adverse drug experience and abstracts of significant articles are also distributed.

We are in constant collaboration with the AMA Division of Drugs and the Council on Drugs for exchange of information. Arrangements are also being made with four large medical centers in the United States to develop a quantitative adverse drug experience reporting program which would include data on drug utilization as well as the number and type of reaction. With this approach the incidence of reactions can be then calculated and this will be much more meaningful than the isolated reports of adverse experiences.

Other very important projects in this area which involve collaborative and cooperative efforts among scientists in government, industry, universities, and other segments of the scientific community, both national and international, are the Registry of Adverse Tissue Reaction to Drugs established within the Armed Forces Institute of Pathology and the proposed international monitoring of adverse drug reactions which is approaching the planning stage. This latter project represents an ultimate objective which we should earnestly strive to achieve. Can anyone suggest a better alternative than such a world-wide early warning system to prevent another thalidomide tragedy? As a corollary, can anyone propose a workable alternative to the efforts I have described in the field of adverse reaction reporting? Can anyone suggest a practical alternative which would enable us to more effectively meet our duties and responsibilities under the law and regulations with respect to drug safety, particularly in the surveillance of drugs after they have been approved for marketing?

In essence, I have tried to convey in this article the fact that there is no simple answer to the question "How safe are drugs?" Effective drugs available today have varying potentiality for harmful effects. One might ask if drugs can be developed with such specificity that all effects but the one desired would be eliminated. This is something to strive and hope for but the reactive mechanisms of the body may also have limits of specificity. At the present time since we have to rely on new drugs which occasionally produce adverse effects, less difficulty will occur if the physician uses them wisely. We must do all that we can do to assist the physician in learning as much as possible about these drugs before he prescribes them and in turn continue to receive from him any additional information he has gained from his own experience in the use of them. **[The End.]**

Progress in Consumer Education

By JAMES L. TRAWICK

The Following Article Was Presented at the Food Law Institute—Food and Drug Administration's Ninth Annual Educational Conference at Washington, D. C., on December 6, 1965. Mr. Trawick is the Director of the Division of Consumer Education, Bureau of Education and Voluntary Compliance, Food and Drug Administration. The Two Succeeding Articles in This Issue Were Presented at the Same Meeting.

EVERY MANUFACTURER IS BOUND TO BE AN AUTHORITY on consumer education—else he would not have survived his competition. Every label he puts on his products, and every advertisement, every promotion, is a unit in consumer education. Consumer service people, market research people, various industry association programs—and certainly the Food Law Institute (FLI)—all are agencies of consumer education.

The Food and Drug Administration (FDA) is a newcomer to the field. But there is still much more that can be done to enhance the role of the consumer as a responsible free agent in our free enterprise economy.

I put it this way because consumers cannot be free agents—cannot make free choices—without adequate information. The consumer cannot be a free agent—or make a free choice—if his mind is captive to ignorance, false information, fear, prejudice, faddism, quackery, or unfounded suspicion of industry or of the government agencies created for his benefit. More than that—the consumer cannot participate effectively as a citizen in the democratic processes of our country if he is slave to ignorance or misinformation. Our consumer protection laws must ultimately reflect the knowledge perception, wisdom, and experience of the individual consumer as applied to the issues affecting his interests.

In some areas—as for example the inherent safety of necessary products such as food and drugs—the consumer cannot protect himself entirely—he must rely on the rules of society. In other areas—such as fraud, quackery, wise choice of products to meet his individual

needs—the well informed consumer can to a large extent be his own protector in the marketplace, and thus needs the least help from the government.

But so much for general philosophy. Perhaps we are all agreed that consumers should be well informed, if possible—and that's a big *if*. But all of this brings up a host of questions. What is the proper role of the FDA—a law enforcement agency—in consumer education?

What are our specific objectives? How are we going about our task? What have we accomplished? What are our problems? And how can industry and the public—and the FLI especially—be of help?

Consumer Education Mission

First, what is our role—our mission? Broadly stated, it is the same as FDA's mission: consumer protection. Consumer education complements law enforcement, just as does volutary industry compliance.

Here are some of the specific objectives of FDA's consumer education program:

The mission is to help consumers:

1. Buy wisely;
2. Avoid frauds, cheats, and quackery;
3. Use drugs safely and effectively;
4. Protect children from poisoning;
5. Evaluate and reject misinformation;
6. Exercise citizenship responsibilities;
7. Enjoy maximum benefits of laws.

Each of these objectives is a living, dynamic thing—affecting every American.

Let me illustrate. Take item 1—buying wisely. Visualize, if you will, the following scene—a true story from FDA files:

A visiting nurse has called on a destitute mother with four preschool children—one an infant only two weeks old. The visiting nurse is upset—so angry she is almost in tears. She has spent $8.00 of her own money to buy groceries for this family. All the food in the house when she arrived was one can of string beans. The mother, age 21, is trying to breast-feed the baby, with little success. She had been able to stay in the hospital only one day after delivery.

But on the shelf was a fresh package of a vitamin-mineral supplement being sold nationally by house-to-house canvassers at that time for $20.00 per package. The sales talk had persuaded the mother that she needed to take this vitamin supplement to help feed the baby. It was a mixture of the usual vitamins and trace minerals.

Now, let us ask, did this mother buy wisely? Without discounting the need for vitamin-mineral supplements in some cases, is this what this mother needed under the circumstances? What she really needed—but did not know it—was professional advice.

Many consumers today—much more sophisticated than this woman—are confused about the need and areas of usefulness of vitamin food supplements. There are people who make a business of spreading misinformation to confuse the consumer.

Take the next item—avoiding frauds, cheats, and quackery.

Despite the court actions in the last few years that have driven some of the major frauds and cheats off the market, misrepresentation and product quackery remain a major public health problem.

Through consumer education, we hope to make people aware of some of the hallmarks of quackery—the clues to probable misrepresentation, and how to check up before investing.

"Clues" to quackery:

1. Is the product or device based on some alleged new or secret principle known only to the sponsor or promoter?

2. How did you *hear* about it? Is it advertised or promoted with testimonials of users?

3. Is it claimed to treat a wide variety of conditions, including some for which medical science still has no cure?

If the answer is *yes* to any of these—*investigate* before *investing*.

Take the next item—poison prevention. Here's a rather typical story from our files. A California mother is in the bedroom with her youngest child. In another room the two-year-old daughter rouses up from a nap and wanders into the kitchen. On the kitchen table she sees a glass jar with liquid in it. The child thinks it is fruit juice—she is accustomed to juice in such a container. She takes a swallow. It is furniture cleaner. The original bottle was properly labeled with the legend "Keep Out of the Reach of Children." But, of course, this little girl could not yet read.

How many parents take such label precautions seriously? How can we make more people aware of the protection built into the Federal Hazardous Substances Labeling Act? How can we make this law more effective in reducing the hundreds of thousands of accidental poisonings that occur each year?

Let us look at just one more aspect of our consumer education mission—the mission to help consumers use drugs safely and effectively, and to avoid the misuse and *abuse* of drugs.

This subject has been underscored this past summer by the enactment of the Drug Abuse Control Amendments.

As for misuse of legally purchased or prescribed drugs, our experience tells us that there are millions of people who do not understand the importance of reading and following labels, or following precisely the doctor's instructions; and further, that injuries and medical failures result from misuse through inadequate information. Here consumer education can be effective.

However, I want to speak primarily to the drug *abuse* problem.

One of the major social tragedies of our times may well be in the making through the increasing involvement of teenagers and young adults with the habit-forming and hallucinogenic drugs. These are the barbiturates (sedatives, sleeping pills), the amphetamines (pep pills), and more recently, LSD and its companions of the dream world.

Here are a couple of case histories that illustrate the point:

In 1964, two boys, 18 and 21 years old, began a crime spree that took them across five states and ended with their being sentenced to death in the electric chair. They had been using amphetamines continuously for three months prior to their crime spree. One of them admitted being introduced to amphetamines at the age of 13. Detectives who apprehended the pair said they were so high on amphetamines that it took four days for the effects to wear off completely.

In February 1965, three youths, two aged 16 and one 17, assaulted a 65-year-old man on a Chicago street and fired eleven bullets into his body. The motive was robbery. They got $11.00. When apprehended, they admitted being under the influence of barbiturates. They explained that the money was needed to buy more pills.

For a number of years FDA has been grappling with the enforcement problems arising out of the illegal dispensing by pharmacists and the peddling by bootleggers of amphetamine and barbiturate drugs. The consequences to society have been seen in terms of juvenile delinquency, unemployment, highway accidents, broken health, broken homes, habituation, progression to hard narcotics, and completely wrecked lives, often beyond redemption.

Bad as this was, we are now confronted with a still more nightmarish situation arising out of the increasing use of the LSD type drug. The hallucinogenic drugs are more insidious and potentially much more dangerous in terms of damage to the mind than the barbiturates or the amphetamines.

The President's Advisory Commission on Narcotics and Drug Abuse two years ago urgently recommended a program of public and professional education to deal with the problem.

The Drug Abuse Control Amendments enacted this summer focused a major responsibility for both law enforcement and public education on the FDA.

The education responsibility is an awesome one indeed. In making our plans to carry it out, we are mindful on the one hand of the necessity *not* to excite curiosity and foster experimentation by young people who might not otherwise have been so inclined; and on the other hand *not* to create unnecessary fears and apprehensions on the part of the public at large that would interfere with the necessary prescribing and use of valuable drugs.

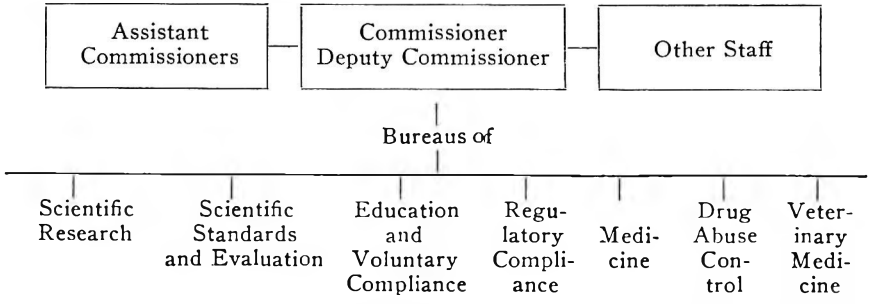
So much for the mission. The other items listed could be similarly illustrated.

It is evident that any one of these would require resources far exceeding the total now available, to do more than scratch the surface.

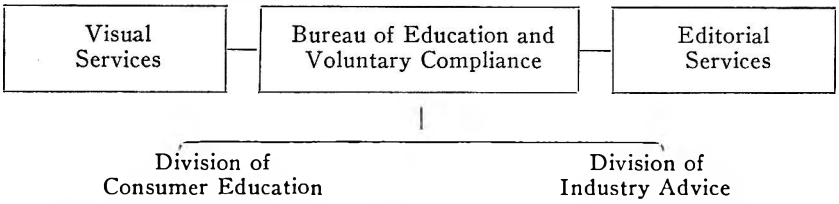
Organization for Consumer Education

Let us look quickly at the organization for consumer education, so you will know who we are and how we relate to the other FDA programs and to the mission as just outlined.

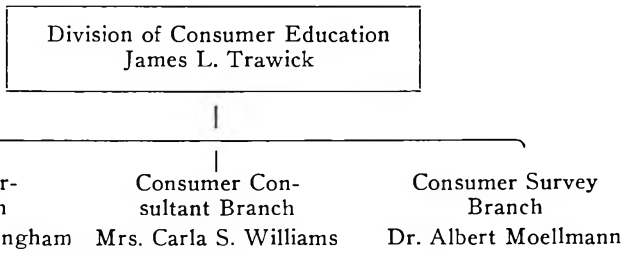
This chart shows the relationship of our Bureau of Education and Voluntary Compliance to the Commissioner, the Assistant Commissioners, and our six companion bureaus.



The next chart shows how our bureau is organized into two divisions—the Division of Consumer Education and the Division of Industry Advice. The two branches operating out of the Bureau Director's Office—Visual Services and Editorial Services—serve both divisions, and to some extent the rest of FDA as well.



Now we come down to our Consumer Education Division organization. We have three branches, each with its specific and separate functions.



Consumer Information Branch—Information *materials:*

- Publications
- Radio-TV spots
- Feature items
- Motion pictures (plans, scripts)
- Film strips, slides
- Special program materials
- Schools
- Aging
- Poison prevention
- Low-income
- Foreign-language

The principal job of the Consumer Information Branch is to produce the information materials for consumer education. Here are some of the types of things we are producing. Our major accomplishments to date in this area are as follows:

1. Publications Library

We now have achieved a publications library that contains at least some items in all of our "mission" areas. These include:

Pamphlets—dealing broadly with each subject area, for example, label-reading, food standards, pesticides and additives, poison prevention, quackery, and so on,

Consumer Memos—dealing with items of current or continuing interest,

Student Reference Sheets—for in-depth study or classroom projects for students,

Science Projects—laboratory experiments that deal with some phase of consumer protection, suitable for the high school science student, science fair, etc.

2. School Information Program

For several years we have received increasing numbers of requests from students and teachers about medicines, pesticides, food additives, fakes and swindles, and other areas of wise buying and health protection.

The student of today will be the breadwinner or the homemaker of tomorrow. About one-fourth of our total population is now in school. These people have the time, the inclination, the opportunity, and the setting for learning. This is not true of many of us as adults.

Taking the publications library just mentioned, we packaged it especially to serve the needs of teachers as reflected in requests being received. We designed a teacher's chart to illustrate how the subject matter fits into various curriculum areas—especially science, home economics, social studies, and career guidance.

The chart summarizes the subject matter and relates it to the curriculum course, and gives suggested class activities or projects. References for further study—including some of your very excellent industry materials—are provided in the packets. We also solicited suggestions from many of you here today, and received some very constructive ones, which we adopted.

These packets were pilot-tested in classrooms. The reception was good—teacher and student interest was high.

Because the potential demand for these packets was beyond our budget, we arranged for their sale by the Superintendent of Documents. The announcement went out about the time school opened this fall.

As yet we have only preliminary reports, but first indications are that the packets are popular items, despite the cost.

In order to get a more complete evaluation of this project, we have arranged for one major school system in the country to have every teacher try out the packets. We will be given a comprehensive report on the interest and usefulness of the materials. We hope to build evaluation reports right into all of our major projects of this kind in the future.

Also for the school information program, we are currently engaged in the preparation of a series of film strips for classroom use, along with more science projects and more reference sheets.

Before leaving the written materials category, I should mention that for the immediate future we hope to concentrate on special types of materials for the low-income population groups, including those who do not speak English. At the moment, we regard this as the most serious deficiency in our publications library.

3. Radio-Television-Motion Pictures

The only way we are going to be able to assist our 117 million adult consumers with health and pocketbook protection information is through the cooperation of the mass media—newspapers, magazines, radio, and television.

One major effort to date in this area is through the distribution of public service spot announcements for radio and television. Kits of these are now issued every two months to every radio and television station in the country which wants to receive them. Each kit consists of eight announcements. Sometimes we include feature items for editorial use.

Our latest evaluation returns show that 33% of the radio stations and 50% of the television stations are using these spots and many stations repeat them several times in the two-month interval during which they are current. Many of the stations have written complimentary letters thanking us for these materials.

In addition to these regular issuances, we have prepared a number of special items to help radio and television stations serve their audiences in this way. These include:

1. Two 60-second television film clips on quackery, one with Raymond Massey as narrator, the other with Commissioner Larrick,
2. A special 60-second television film clip on poison prevention,
3. A special 4-minute radio tape on quackery, jointly sponsored by FDA and the President's Committee on Aging,
4. A series of television film clips on the work of our field scientists, complete with script for use in either a 15-minute or a 30-minute live television interview with the District Director and the Consumer Specialist.

As for motion pictures, we have just completed our first new film, "A Reason for Confidence." It is a 28-½ minute color film about the work of the FDA, a basic item for our film library.

We now have under contract a second film, on the subject of fakes and swindles in the health field. It, too, will be a 28-½ minute film, in both color and black and white, aimed primarily at older Americans and tailored especially for television.

For our third film, we are trying our wings on an in-house production. Our first effort will be a 10-15 minute documentary on drug abuse.

Our fourth film, also to be produced this year, will be a longer, more comprehensive film on drug abuse, also tailored for television.

And we also hope to produce another on the same subject for the medical profession.

We are now arranging a comprehensive distribution program that will make films available on a free loan basis to every club, school, church, and civic group in the country, as well as to commercial and educational TV.

However, one of our major program deficiencies in the radio-television-motion picture area is that we have not as yet been able to take advantage of the opportunities in educational television. A number of ETV stations have expressed an interest in cooperating in the program. FDA does not have grant money with which to foster specific educational projects. The contract arrangement is somewhat more cumbersome for the accomplishment of educational television programs. But we recognize this opportunity and we are exploring ways to take advantage of the offers of cooperation extended. We will appreciate your suggestions.

So much for the materials being produced. How do we use them? What are the people-to-people channels through which we reach the general public and the special population groups? This is where our Consumer Consultant Program—and the Consumer Consultant Branch—come in.

Potential outlets for consumer education materials:

Newspapers
Magazines
Radio-TV
Educational TV
Professional journals
Textbooks
Encyclopedias
School magazines
Food package panels
(An industry suggestion)
Shopping bags
(An industry suggestion)
Consumer correspondence
Mailing lists

Potential distribution points for consumer education materials:

Schools—all levels
Hospitals
Doctors' offices
Drug stores
Supermarkets
Other retail stores
Libraries
Beauty shops
Barber shops
Theaters
Public housing projects
Senior citizen centers
Consumer information centers
County, state fairs
Science fairs
Buses, street cars
Museums
Public buildings

Outlets for consumer education materials—cooperating organizations

Consumer
Women's clubs
Home demonstration clubs

Professional
- Home economics
- Nurses
- Doctors
- Pharmacists
- Teachers

Industry
- Food
- Drug
- Cosmetic
- Other

Youth Groups
- Boy Scouts
- Girl Scouts
- 4-H Clubs
- Future Farmers

Civic and Service Clubs

Church and Religious

Cultural and Recreational

Government Agencies
- Federal
- State
- County
- Local

Now these are for the most part simply the normal channels by which people, government agencies, and business communicate with each other, and work together to get things done. I have listed them in order to make the point that our job is a big one, and the opportunities already extended to us are overwhelming in relation to our meager resources. I am reminded of the quip about the mosquito in the nudist colony. He knows what he wants to do, but simply cannot decide where to begin.

But we have made a beginning—a good beginning. Some of these contacts with the media and the organizations are carried out from headquarters; but this is also a major and continuing responsibility of the Consumer Consultant Branch and the Consumer Specialists in our 18 field districts.

This part of the program has been known since 1954 as the Consumer Consultant Program, because it was originally carried out by "consultants"—that is, professional women who worked only part-time, and who could actually be paid for only two to four days of work each month. (They actually put in more time than this, out of sheer dedication.)

Consumer Consultant Program

Community Liaison (Organizations-Media-Distribution Points)
Two-way Information Flow (FDA ⇄ Consumers)

This program is one of community liaison, working with the news media, the distribution outlets for materials, and with the community organizations already mentioned.

Consumer Consultant Program

Techniques:

- Speeches
- Workshops
- Radio-TV appearances
- Exhibits
- Demonstrations

The consumer specialists address club groups, hold workshops for teachers and group leaders, appear on radio and television, sponsor exhibits at large meetings and in public buildings and the like.

Even the part-time program, meager as it was, accomplished a great deal in terms of consumer education, goodwill for FDA, and feedback to FDA of the views and opinions of Mrs. Housewife and Mr. Breadwinner in person—the two-way flow of information, as we sometimes call it.

Beginning last year, fiscal 1965, our budget provided for a full-time Consumer Specialist in each of the 18 field Districts, in addition to the part-time Consultants. This has made for a tremendous increase in our accomplishments at grass-roots level.

Let me report a very few examples from dozens of similar projects last year, to illustrate the impact the Consumer Consultant Program is having.

As a part of FDA's contribution to the President's program on poison prevention last March, our Consumer Specialist in Detroit arranged a symposium in which thirty medical, public health, law enforcement, and community agencies joined as co-sponsors. More than 600 community leaders attended and were thus able to carry back and spread the information on how to protect children against accidental poisoning in the home.

As a part of FDA's contribution to the President's program during Senior Citizens Month, our Consumer Specialist in our Denver District held a series of seven conferences on quackery throughout the State of Utah. The conferences featured State and local health and medical authorities and educators, and altogether were attended by 1,885 people, mostly the Senior Citizens for whom they were intended.

The St. Louis District Consumer Specialist arranged for an exhibit at the "Governments at the Gateway" Exposition, worked with the University of Missouri in a six-weeks program for Older Americans, recorded several radio tapes and appeared on several television programs, and enlisted Senior Citizens Clubs in handling more than 3,000 requests for FDA publications.

The Kansas City District Consumer Specialist arranged for educational materials to be displayed in urban renewal centers, nursing homes, health departments, and 13 libraries. Special exhibits were created and displayed in many of these centers.

Our Buffalo Specialist arranged for a concentrated news media coverage during Senior Citizens Month; the Baltimore Specialist broadcast a series of public service announcements that reached an estimated 60,000 listeners during the same period. These broadcasts were heard and liked, as demonstrated by requests for more than 4,000 copies of one of our publications on quackery as a result.

Now if you multiply these typical single projects by 18 Districts on a year-round basis, it is evident that the Consumer Specialists are among the world's busiest people, and that they are doing the kinds of things the public appreciates—and they are making consumer protection come to life.

Our estimate of the total potential impact of the combined activities of the Consumer Information Branch and the Consumer Consultant Branch, in terms of number of people being reached through these activities is as follows:

Estimated audience potential—1965

MEDIUM	NUMBER OF PEOPLE
Publications	12 million
Radio-TV spots	62 million
Radio-TV appearances	9 million
Special programs	22 million
Magazines and news features	40 million
Exhibits, correspondence, and other	4 million
	Total 149 million

These figures do *not* include the many more millions who read regular news stories about FDA in the daily papers. If the figures look large to you, let me assure you that the only inflation in them is that many of these 140 million statistical people are of course counted more than once. If the same person, for example, hears three different spot announcements, reads a feature article in a newspaper, sees one of our exhibits, and hears one of our speakers at a club meeting, he would be counted six times. We simply have not as yet been able to devise a better measure of our impact, but we are working on it.

And that brings me to the third major activity area—consumer surveys. How do we know whether any of this is doing any good? How do we know our publications are read and understood? How do we know what people learn from a 10-second or a 60-second radio or TV announcement? Or whether it caused them to do anything differently?

For that matter, how do we know that consumers understand some of the words and phrases we require on labels? We may well need to re-evaluate our food, drug, cosmetic and household product labels in terms of what consumers really understand them to be saying.

We know what people tell us about our materials and activities —through our Consumer Specialists and our other contacts. However, we don't know as much about any of these things as we should, but we are now ready to start finding out more. Since last year's FLI meeting, we have recruited a fine professional staff for our Consumer Survey Branch. We have under contract a national pilot survey of consumer knowledge levels in our areas of interest, as a basis for further studies. We are currently working on a larger study to find out why people—especially older people—are susceptible to quackery and resistant to authoritative information.

We have plans for surveys to evaluate the effectiveness of our educational materials and programs; to explore the incidence of drug abuse, its sociological causes, and susceptibility factors; and to learn more about consumer attitudes and opinions on pesticides, additives, labeling, food standards, and many other facets of our program.

You in industry of course are way ahead of us on this—you have been researching consumer habits and reactions and motivations for years. Many of you have offered to give us the benefit of your experience in this area, and we want to accept these offers. I predict that the FDA will find this type of research just as valuable as industry does, and that very soon our small survey unit will be literally "snowed under" with projects along this line. I hope that by next year we will be able to report on the completion of at least one or two major research projects.

Now I have talked a great deal about consumer education, and how industry and FDA might work together in this endeavor. In fact, many of you have offered good suggestions for mutual projects which we have not been able to act upon, simply because we have more than we can do already. In fact, our major problem—our major danger—right now, as we see it, is that we may spread ourselves so thin and tackle so many jobs that we will not complete any of them satisfactorily. Nevertheless, we do appreciate your suggestions and offers of cooperation, and hope to be able to take advantage of them.

I also have a list of projects on which FDA and consumers might work together to improve industry practices and products in some respects, and I am not necessarily talking about compliance with

legal requirements, either. My wife frequently asks why somebody can't devise bread wrappers that you can put a few slices back into without their falling apart, and cereal packages that are easier to re-seal, moisture-proof, after opening. And I ask myself why my aerosol shaving lather can so often squirts out twice as much as I need, wasting half. But this list is the subject of another paper.

If I have created any impression that our tiny staff is busy, and that we are making some progress in getting a consumer education program under way—well, that's what I intended to do.

When I was a youngster, I remember that my father would keep a record of my and my two brothers' growth by making us stand up tall each birthday, and marking our height with a pencil on the kitchen door. Our names were placed alongside, and the next birthday a new measurement would be made and a new and higher mark added.

I know that if we were to make a figurative mark on the door of this auditorium to show where we are in consumer education today, it would be higher than last year's and the year before, but still pretty close to the floor. But I believe we have a mission to be proud of; we have made a good start; and the mark will be higher next year—with your help and cooperation. **[The End]**

DRUG ABUSE CONTROL REGULATIONS ADOPTED

Food and Drug Commissioner James L. Goddard has announced that final procedural regulations for depressant and stimulant drugs, implementing the Drug Abuse Control Amendments of 1965, have been adopted. They became effective February 1, 1966. These regulations explain the records to be made and maintained and the information required in the initial inventory which must list the type and quantity of all controlled drugs in finished form. Normal business records will comply with the law and regulations. Most licensed doctors are exempt from the record-keeping requirements. Physicians who hold small supplies of these drugs for administering in emergency or special situations will not be subject to record-keeping, but doctors who regularly administer the controlled drugs to their patients and charge them will be subject to the record-keeping requirements. FOOD DRUG COSMETIC LAW REPORTS ¶ 76,500.

The Consumer's Interest

By MRS. ESTHER PETERSON

Mrs. Peterson Is Special Assistant to the President for Consumer Affairs.

THE TOPIC I HAVE BEEN ASKED TO DISCUSS HERE is not the public interest, but the consumer's interest. Some maintain that the public interest is synonymous with the consumer's interest, because all of us are consumers. Obviously, however, this is not always true. The two interests do not correspond exactly, and often the consumer interest must yield to the public interest. It is not, for example, in the consumer's interest to pay increased taxes. Yet the public may dictate higher taxes to meet growing educational needs or to provide for the national defense or for any of dozens of reasons.

What then is the consumer interest?

The most concise and yet probably the most encompassing definition of the consumer interest was given by President Kennedy in his historic consumer message to Congress in 1962. This was the first Presidential message devoted exclusively to the consumer interest, and it has served as the foundation for the federal consumer program today.

Major Rights

In his message, President Kennedy spelled out the four major rights of the consumer. These rights are:

1. The right to safety
2. The right to be informed
3. The right to choose
4. The right to be heard

I would like to examine each of these rights closely, for I believe they have great relevance to those who serve the consumer in industry and those who serve him in government.

President Kennedy recognized that improvements were needed to bolster each of these rights. In particular, however, he saw that the consumer's right to be heard was the most neglected, so he acted,

in the body of this same consumer message, to close the gap. He established the Consumer Advisory Council, under the Council of Economic Advisers. President Johnson carried this concept of consumer representation one step further when he established the President's Committee on Consumer Interests and the post of Special Assistant for Consumer Affairs, which I hold.

The Right to Be Heard

These positions were established with the recognition that for too long the consumer, alone among the major interest groups, had gone unrepresented. The farmer, the laborer and the businessman—each had had special representation in Washington for decades. But the consumer had no one place where he could turn.

This is not to say that the consumer's interest was ignored by the federal government. Indeed, it was not, for the consumer was—and still is—served by many agencies—the Food and Drug Administration (FDA), the Federal Trade Commission (FTC), the Agriculture Department (DOA) and others. The deficiency was that there was not one agency where he could voice his problems and there was not one agency that took an overview of all government activity in the consumer's behalf and stated the consumer position in the policy-making process.

This was the gap that the President's Committee on Consumer Interests was created to fill.

The job has not been easy, for the consumer interest is very broad and complex. But we are guided by the thousands of letters we have received from consumers, by the advice of the Consumer Advisory Council, by the personal contact my staff and I have with consumers throughout the country, and by the many meetings we have held with consumers and consumer organizations. In addition, the President's Committee last year conducted, at President Johnson's direction, a series of four regional conferences through which we attempted to seek out the existing problems.

In all of our activity, we have adhered to the philosophy that more can be accomplished for the consumer by voluntary cooperation than by legislation. We have, to use Secretary Gardner's phrase, engaged in a "cooperative enterprise" with business. This policy has, I believe, paid off handsomely, for both the consumer and business, and I continue to receive splendid cooperation from business.

I should note, at this point, that one of the first offers of industry-related assistance I received after taking this office was from the Food Law Institute (FLI). Mr. Depew, its president, has been most helpful.

As a result of my contact with business, I have come to realize more than ever that the consumer interest and the producer's interest are two sides of one coin and inseparable. President Johnson is of the same belief and in a message to the Consumer Advisory Council several weeks ago, he stated his view most forcefully.

> I believe the time has come to bury the myth that furthering the interest of the consumer must be at the expense of the producer. There is, I am convinced, a common interest between Americans in their capacity as producers and in their capacity as consumers. This mutuality must be emphasized.

More and more businessmen are gravitating toward this view, I believe, and consequently the consumer is being listened to more carefully by business, as well as government. I noted with interest in the papers recently the comments of one prominent retailer to the effect that many stores are losing customers by failing to handle complaints quickly and efficiently. His contention is that the millions of dollars spent to create customer goodwill are being wasted by a failure to process complaints adequately.

This theory has an obvious application to manufacturers as well as retailers, and I hope this discussion in the business community will lead to more direct communication between business and the consumer. I know that firms welcome comments from consumers, because they can help improve a product or a service. Yet some companies fail, for example, to take the simple step of putting their address on their products, so that the channel of communication is closed to the consumer from the outset. I think all of you in industry can benefit from giving renewed attention to the consumer's right to be heard, and I hope you will do so. It would be in your best interest, as well, to be more consumer-oriented in your decision-making.

Progress is being made additionally on the state level. Seventeen states now have consumer representation, so that the consumer can now air his views more freely in these state capitals.

With clearer channels through which he can speak, the consumer is increasingly asking questions. Everyday's mail brings to my office new questions, and many of these questions pertain to the industries you represent. I would like to raise some of them here. I do not claim to have the answers. I am not a lawyer, a chemist or a marketing expert. I am a housewife—but I am a housewife with a responsibility to the consumer, as well. I feel it my responsibility to voice these concerns to you, in the hope that you—the lawyers and the chemists and the marketing experts—will find some of the answers.

The Right to Safety

Many of the questions consumers are asking relate to the consumer's right to safety. Consumers are concerned about auto safety and concerned about safety as it relates to foods, drugs and cosmetics.

Several weeks ago, I addressed the Nutrition Foundation in New York. At that time, I said that consumers were concerned about additives and such terms as "poly-unsaturates" and "low-sodium." After my talk, several persons expressed disbelief that consumers have misunderstood these terms. But the fact is that many of them have. Not only do they have a fragmented knowledge of these concepts, but many also exhibit the irrational fear that comes from misunderstanding.

Many equate the use of additives to adulteration. They fear that their health is endangered. Similarly, many believe that the consumption of poly-unsaturated fats and low-sodium products is essential to their health. Yet they are not sure just how, and some have begun to wonder whether foods which contain saturated fats or are high in sodium endanger their health.

I would recommend to you today, as I did to the Nutrition Foundation, that you extend your educational campaign to inform consumers of the exact nature of these food elements and how they relate to health and safety.

One woman mailed me a label that aroused her, and it is not too hard to understand why. Listed as ingredients in this product were: Sugar, non-fat dry milk, hydrogenated vegetable oils, precooked starch, gelatin, sodium caseinate, propylene glycol monosterate, adipic acid, sodium citrate, hydroxylated lecithin, sodium carboxymethylcellulose, malthol, salt, natural and artificial flavors, U. S. certified color and BHA added as a preservative.

To the layman, this can be a frightening array, indeed.

I do not think it suffices to dismiss such expressions of concern as the prattle of faddists. I think a real problem of understanding exists, and I recommend your attention to clearing up this misunderstanding.

Thanks to the FDA, of course, we can rest assured that unsafe drugs, foods or cosmetics are the rare exception, and not by any means the rule. Yet the FDA's educational efforts must be shared by industry. This is a job that cannot and should not be done by government alone.

A recent example that was called to my attention shows the need, I think, for manufacturers to examine some of their promotional campaigns. This concerns a sample of new children's cold capsule, that

was sent through the mail to consumers. Printed in very small type on the packet were warnings that children under three should not be given the tablet. In addition, it warned against giving more than one tablet to children under a certain age. Although it did not state specifically, swallowing all four tablets in the packet would presumably be extremely hazardous.

Yet all parents know how small children can get into things, and everyone knows that unsolicited mail is generally not stored away. It most often is left lying where children can easily get into it. In the eyes of small children, the colored tablets, I am sure, look appealingly like candy. I hope that this promotional campaign does not result in a tragedy.

I should note here that consumers should be grateful for the help many of you provided in getting Congress to pass legislation giving the FDA enlarged power to cope with the growing traffic in stimulant and depressant drugs. With this weapon, FDA now has a greater capability to insure the consumer's right to safety, but new scientific discoveries constantly challenge this capability.

Commissioner Larrick summed up this challenge in a recent magazine article.

> As drugs become more potent they show more dangerous side effects. As more chemicals are added to food, there is greater danger from misuse. As numerous synthetic materials are added to cosmetics, the need for careful safety-testing of each formulation increases . . . The question is whether our society is advanced enough to direct these scientific developments—as well as others—in the public interest.

I think our society will direct our scientific progress, instead of being directed by it. But I believe this effort requires a more unified approach among the states and the federal government than we have at present.

Adequate consumer protection in the food and drug field can only be achieved by enforcement vigilance throughout the entire course from production to consumption. But because of inadequate coordination between the enforcement activities of different governmental agencies, based frequently on differing food and drug laws, it seems apparent there is wasteful duplication of effort at some points and neglect at others. If we are to insure fully the consumer's right to safety, I believe we must close many of these gaps. I would therefore welcome renewed attempts to develop more uniform laws and more coordinated enforcement.

The Right to Choose

The right to choose was the third consumer right enumerated by President Kennedy. In his Consumer Message, President Kennedy defined this right as the right "to be assured, wherever possible, access to a variety of products and services at competitive prices; and in those industries in which competition is not workable and Government regulation is substituted, and assurance of satisfactory quality and service at fair prices."

There is no question that, generally speaking, the consumer has a wide variety of items to choose from. Indeed, it often seems that there is too much variety. The array of goods that line the shelves of supermarkets is a testimony to our prosperity. But having to make a choice among a shelf-long assortment of goods that make similar claims is sometimes a difficult chore.

The consumer's right to choose has also been complicated by the fact that products are becoming increasingly complex. There used to be a time, for example, when shampoos were all very much alike. But now lanolin and oils and detergent-like ingredients—yes, and even formula X—have been added to the product, with the result that the housewife cannot know how a shampoo will perform for her until she uses it. I have used some shampoos that have caused an irritation, and I wish I knew what caused the irritation, so I could avoid the substance. My choice of a shampoo, in other words, may be imperfect, because I do not have the knowledge of the complex ingredients that constitute the product. It is unreasonable to expect a housewife to have the knowledge of a chemist, and so I wish you would spell out for me—and other housewives—what the elements are in a good shampoo that we should be looking for. And I for one object to printing the ingredients on the back of a label, so the housewife must read it through the shampoo.

The growth of complexity of products, however, is by no means confined to shampoo. Thanks to our mastery of technology, products are frequently being improved, and many new products are appearing. But many consumers are wondering whether some of these new products are really new, or whether they are simply the old products with a new twist, that are being promoted as new, perhaps at a higher price. I receive letters, too, from consumers who question whether "new" applied to old products, always means the product is now better.

This is a very serious concern, because it puts into question whether we are using our resources in the wisest way.

I was disturbed recently by a charge made before the National Food Marketing Commission by a California consumer representative. "We are certain," this representative said, "that in recent years the cost of the average consumer's food purchases has been inflated by expensive forms of water, sugar, flour and artificial vitamins, used to make diluted, extended, or imitation foods."

She noted, for example, that a certain fruit juice drink often was found to contain more sugar and water than juice and hence less vitamins. The advertising for this product, however, stressed "more vitamins."

I do not know the answer to this charge, but I would like to hear the answer voiced once and for all, so that consumers will know the truth.

Similarly, I am concerned over the wide discrepancy that exists in drug prices. My concern in this area was revived by a recent report issued by the Citizens Committee for Metropolitan Affairs of New York City. The gist of this report was that the prices of the same drugs in Manhattan vary as much as 820 per cent. The difference is accounted for, of course, by the fact that a comparison was made between generic and brand-name drug prices. This is a thorny problem, of that there is no question. It would be naive, to say the least, for me to suggest that you who manufacture brand-name drugs, publicize the savings that are possible by purchasing generic drugs. I realize, in addition, that this is a problem that involves physicians and pharmacists, as well as manufacturers.

The Citizens Committee report noted, surprisingly, that middle-income consumers consistently pay more for identical prescriptions than rich or poor consumers. It noted, too, that poor consumers generally pay more than rich consumers. It is unfair that any group should pay more than another. But the middle-income consumer at least has a margin to absorb the higher prices, while the poor do not. Paying higher drug prices is an affront to the middle-income consumer, but it may be a disaster to the low-income consumer.

Just last week, a neighborhood poverty worker told me of an old woman in her 70s whose sole income is $92 a month from Social Security. Out of this meager income, she pays $70 a month for rent. This leaves her with a grand total of $22 to meet her living expenses. Amazingly, this woman has managed to survive on this below subsistance income. But the poverty worker recognizes ruefully that the woman will not be in good health indefinitely. When illness strikes, she is certain to have a hard time, indeed.

You in industry cannot be expected to remedy our social ills. You are not social workers; you are in business to make a profit—and this is proper and good. Increasingly, however, we must have the involvement of the private sector in our social problems. Many of you decry government power, but I would urge you to war against the problems and not the government.

Despite the obvious complications involved in the drug price situation, I think an effort must be found to better serve the consumer in this area. As a result of its study, the Citizens Committee is urging that New York City pass a law requiring pharmacists to state the price of a prescription before it is filled. Maybe such a law is an answer, but I would like to see an effort begun to solve the problem through voluntary means. You can be assured that we in government stand ready to assist in such voluntary efforts when called on.

The Right to Be Informed

The fourth and final right of the consumer that President Kennedy enumerated is the right to be informed. This means that the consumer has a right to be given the facts he needs to make an intelligent choice.

This right, I believe, is imperative if we are to have a vital and dynamic economy. Intelligent choice in the marketplace, just like in the polling booth, requires that the consumer know all the pertinent facts about the candidates—the products available to him. This does not mean that a manufacturer must proclaim the faults of his product as well as its virtues. It means only that the manufacturer should not spread fraudulent or misleading information about the product, and should give the consumer meaningful information, so he can make intelligent purchasing decisions.

The right to be informed, I believe requires that we enact a Fair Packaging and Labeling Bill.

But why, you may ask, am I advocating this bill if I truly believe in cooperative enterprise between government and business? The answer is that cooperative enterprise has been attempted for four years in this area, and the abuses persist.

Recently a label from a popular drugstore product was called to my attention that proclaimed "New! 12 ounces." I learned that the only thing new was that the contents of the bottle had been reduced by several ounces, with no change in price.

Cooperation would seem to have failed in this area, and so I am advocating that the Fair Packaging and Labeling Bill be passed. I hope that we can expect support from some of you who realize that the ground rules established by this bill will, in the long run, benefit you as well as the consumer.

I am well aware of the valuable work that you in industry have performed in cooperation with the National Conference on Weights and Measures, the Bureau of Standards and the Commerce Department in drawing up a Model State Packaging Regulation. The model regulation resulted from a meeting of men of good will on both sides of the issues, who were willing to work for a sound solution of all the problems. It is a good regulation and I am told that it has been implemented with success in many states. I hope other states adopt it. But I do not think the Fair Packaging Bill is in conflict with the regulation. I think the Hart Bill represents the culmination of the efforts you began in drawing up the regulation.

And so, these have been the four rights of the consumer that constitute the major portion of the consumer interest.

Obligations

Do not let me mislead you. The consumer does not simply have rights. He has obligations, too. And sometimes he fails to meet these obligations. Oftentimes, he fails to recognize that the vast majority of businesses are honest and fair-dealing and he condemns you all for the sins of the wayward few. This is a grossly unjust attitude, and one I have done my best to eliminate.

We in government have obligations, too, and we in government are not perfect, either. We have improvements that must be made, and we have new directions we should explore. I have already mentioned the need for more uniform food and drug laws and more coordinated enforcement. This is a goal that we in government, as well as you in industry, should be working for.

In addition, I think we might explore ways by which the food-standard establishment procedure might be speeded up, without sacrificing the welfare of the consumer or the interests of industry. The proceedings to establish a peanut butter standard have been in progress for four years without a resolution of the issue. I think it is proper to question whether such a prolonged procedure is efficient.

Conclusion

In concluding, I should note that I understand fully how it feels to be part of a regulated industry. In fact, just this week I have been accused of marketing a worthless patent medicine. In a business publication, a writer urged his readers to get the business message across to the public. If they do not, the writer continued, the public will turn to "Mother Peterson's Protective Balm for Skinned Consumers."

I have no comment—other than to say that I hope you in industry *will* address yourself more to the public. President Johnson has issued a challenge to all Americans to use their wealth to improve the quality of our national life. This goal will never be met if business—or any of the other sectors of our society—sits on the sidelines.

I urge you to get involved, to address the public. And, if the occasion arises when Government can cooperate, I say, let us work together.

[The End]

FDA SIGNS CONTRACT FOR NEW DRUG USAGE STUDY

Food and Drug Commissioner James L. Goddard has announced plans for a new study conducted for the Food and Drug Administration under a contract with the Kaiser Foundation Health Plan of Oakland, California. This study, which will take place at the Foundation hospital in San Francisco, is designed to help make decisions concerning the labeling of drugs for various diseases and directions to doctors in the use of drugs for better protection to the patient. The study will report on diagnoses of conditions and diseases and drug usage among patients receiving regular medical care, and the results will be analyzed to show if there is any possible relationship between drug-usage and increases in the frequency of diseases. Eventually, the study will include patients who are not required to be treated in a hospital. Findings from this study will be compared with similar studies on other populations.

THEODORE O. CRON NAMED ASSISTANT TO THE COMMISSIONER

Theodore O. Cron, former Deputy Assistant Commissioner for Information, U. S. Office of Education, has been named Assistant to the Commissioner for Education and Information, Food and Drug Administration. Mr. Cron, who joined the Office of Education in 1964, is the creator of "American Education," the official monthly magazine of the Office.

Investigational Drug Branch: Intra-FDA Relationships

By FRANCES O. KELSEY, PH.D., M.D.

Dr. Kelsey is Chief, Investigational Drug Branch, Division of New Drugs, Bureau of Medicine, Food and Drug Administration.

THE INVESTIGATIONAL DRUG BRANCH WAS ESTABLISHED in January 1963 as a part of the Division of New Drugs, Bureau of Medicine. The Branch has surveillance over a new drug from the first time it is tested in human subjects until the preparation has an approved new drug application or testing in human subjects has been discontinued. The basis of its existence rests on the revision of the Investigational Drug Regulations which followed the 1962 Kefauver-Harris Amendments of the Federal Food, Drug and Cosmetic Act. These regulations are directed toward improving the quality and the safety of the testing of drugs prior to marketing and thus to offer protection and assistance to the patient receiving the drug, to the physician administering it, and to the sponsor endeavoring to make generally available safe and effective new drugs at the earliest possible opportunity.

Prior to the 1963 Investigational Drug Regulations there was no requirement that the Food and Drug Administration (FDA) be notified that a drug was under test. In addition, no requirements were placed on the extent of the preclinical studies that should be completed before a drug was administered the first time to man. Furthermore, unless a New Drug Application (NDA) was later submitted for the product there was no means by which information might be generally available concerning the adverse effects associated with the drug in question.

Under the current Investigational Drug Regulations, before distributing an investigational new drug for clinical trial in man, some responsible firm or individual must file with us a Notice of Claimed Investigational Exemption for a New Drug (the so-called IND).

This Notice should provide us with the preclinical work and manufacturing control data that leads the sponsor to believe it would be safe to introduce this drug into man in the manner proposed. The extent of such preclinical data will depend in large measure on the nature of the drug and the proposed plan to study.

Three Phases of Clinical Investigation

The clinical investigation plan falls into three phases. The first two are described as clinical pharmacology. In the first phase, the administration of the drug may be to healthy volunteers, the primary object being to ascertain the pharmacologic activity in man. Such studies involve a comparative small number of subjects and are ordinarily conducted under carefully controlled circumstances by persons with extensive training and experience in clinical pharmacology. Nevertheless, even for such restricted studies we believe that as a minimum the acute toxicity should be determined in three or four species, that repeated administration studies of at least two weeks duration be done in at least two species, and that such studies should cover the route of administration that will be used in the human trials. We realize, too, that in the preliminary animal work the precise formulation of the drug would not necessarily have been determined and the proposed clinical plan should allow for considerable flexibility in this regard.

Following the completion of Phase I the sponsor may then proceed to Phase II, in which the drug is administered to a carefully controlled group of patients with a view to determining safety and effectiveness in the disease conditions for which the drug is proposed to be used. Before commencing such studies, the sponsor is expected to report in adequate detail the results of the Phase I studies together with an outline of the proposed Phase II studies. It is probable, too, that additional pharmacologic and manufacturing control data would be necessary to support safety for the extension of the studies.

Finally, if the data obtained in the Phase I and II studies support the safety and effectiveness of the compound, Phase III, or clinical trial proposals are in order.

While the Investigational Drug Branch believes that certain basic preclinical studies should be completed before a drug is introduced in man, nevertheless, we are fully aware that too rigid procedures could well stifle the introduction of new and useful drugs. We are, therefore, willing at all times to consider reasonable amendments to clinical plans and to discuss with the sponsor the appropri-

ateness of a proposed protocol. We further realize there may be situations in which the investigator can produce convincing evidence that the possible benefits accruing to the subjects from the use of an investigational drug might well outweigh the theoretical hazards.

The review of the original Notices and of subsequent amendments thereto are done as rapidly as possible by medical officers in the Investigational Drug Branch, by chemists of the Manufacturing Controls Branch, both of the Division of New Drugs and by pharmacologists of the Drug Review Branch of the Division of Toxicological Evaluation of the Bureau of Scientific Standards and Evaluation. Additionally, the submissions are reviewed by the Drug Indexing Branch of the Division of Medical Information who extract certain data and store it either in a manual system or in a machinable card file system. One of the main purposes of this latter step is that information on similar or related drugs may be readily recalled. Where deemed necessary or advisable, such information may be conveyed to the sponsor thus providing him with additional safety data.

Deficiencies in Notices

Deficiencies in the Notices are called to the sponsor's attention as rapidly as possible. If these deficiencies appear to offer a hazard in the continuation of the ongoing clinical studies, the sponsor may be ordered to modify his clinical plan or to discontinue clinical testing until further preclinical work has been done. An important function of our reviews is to inform the sponsor as to the further preclinical information that would be required before the clinical testing can be extended to another phase or to complete the requirements for an NDA. Thus, by the time a Phase III is well underway, it is not unreasonable to expect that the control data and pharmacologic studies required for a new drug application would be completed. In actuality, instances have occurred in which an NDA has been submitted before chronic animal studies have been completed and even before the deficiencies in either pharmacology or manufacturing controls that have been pointed out by the Investigational Drug Branch have been collected. It would seem unreasonable to hold the FDA responsible for any delay in the approval of such incompletely assembled new drug applications.

We believe that the surveillance of Phase III studies is an extremely important part of the work done under the Investigational Drug Regulations. Furthermore, the responsibility of the Investigational Drug Branch does not end when an NDA is submitted. Not only

may the new drug application not cover all the uses for which the drug may be under investigation but additionally should the Medical Evaluation Branch advise the sponsor that the NDA is incomplete, the Investigational Drug Branch will have the sole responsibility for the surveillance of the drug if clinical testing is to continue. It is essential, therefore, that the Investigational Drug Branch receive information concerning adverse reactions during Phase III studies and equally important that the Notice be promptly amended whenever a new investigator is added.

In regard to these Phase III studies, it is recognized that they should involve, in addition to experienced investigators, other licensed practitioners whose training and experience in drug evaluation has been less extensive, and whose facilities may not be so elaborate. The reason for this is that once a drug has been approved it may be used by anyone licensed to administer drugs in the state in which he practices. It is, therefore, of considerable importance for us to have some advance information as to the use of the drug by individuals with widely varying experiences, before the drug is placed on the market.

In order for Phase III studies to be meaningful, it is essential that they not be permitted to be so extensive that careful monitoring of the progress of the studies is impossible.

We believe that physicians cannot be included in such studies unless they are willing to keep careful records of use, and to make these available promptly to both the company and the FDA. We have had instances drawn to our attention recently in which the clinical investigator had failed to fulfill his obligations in this regard and even cases in which there was failure to report severe adverse experiences promptly to the sponsor. The investigator in completing form FD 1572 or FD 1573 undertakes a clear-cut obligation to furnish such reports. It should also be noted that the Commissioner may notify a sponsor that an investigator is not entitled to receive an investigational use drug if he repeatedly or deliberately fails to comply with the conditions of the exemptions. We will do all we can to assist the sponsor by encouraging the prompt and adequate reporting of drug experiences by the investigators.

Of the almost 3,000 Notices received to date, approximately 25% have been sponsored by individual investigators or by research institutes rather than by drug manufacturers. Such Notices usually cover a very limited use of an investigational new drug in human subjects, frequently as a research tool. However, many of the Notices are for Phase II, clinical pharmacology evaluation, for example, for drugs

used in cancer chemotherapy or for drugs used in unusual conditions affecting only the occasional patient.

In the case of limited Phase I metabolic studies we have accepted INDs in the form of a letter from the sponsor in which he described the nature of the drug, the preclinical findings that lead him to believe it would be safe to use and the circumstances in which he plans to use it.

Termination of Notices (INDs)

However, as with all Notices we are aware that our primary responsibility is the protection of the subject or patient. In this regard, it might be noted that more than two-thirds of the INDs which have been terminated to date have been submitted by individual investigators. A common reason for these terminations has been the virtual absence of any preclinical data relative to safety together with a plan for clinical testing that is acceptable under the present day standards for clinical investigation. We believe that clinical pharmacology has reached the stage today where some definite scientific criteria can be presented in regard to clinical testing designed to evaluate the safety and the effectiveness of a compound.

When a Notice has been terminated the drug in question may not be reintroduced into clinical testing in man until additional safety data has been submitted to the FDA and approved by the Commissioner. It should be emphasized that termination of a Notice does not necessarily mean that the drug may not be reintroduced into man. Recently, for example, we have terminated clinical studies with the drug, dimethylsulfoxide (DMSO). Notices for this drug had been filed by 13 drug firms and 3 individual investigators. Termination of these Notices was recently instituted because of reports of eye toxicity in animals. This toxicity, although not fully evaluated, appears to consist primarily of changes in the refractive index of the lens. It has been observed in dogs, rabbits, and pigs, following either the topical application, or the oral administration of the drug. The magnitude of the effect appears to be dose related and effects are first elicited with doses that are approximately in the range of those used in human studies. Factors leading to termination were not only the necessity of further evaluating this effect in animals but also the availability of this drug had lead to its widespread use not only by sponsors of INDs but also by unauthorized individuals, including physicians, who obtained this well known chemical through non-medical channels.

Probably the widest use of the drug has been in painful but relatively benign conditions, such as, acute strains and sprains and rheumatoid arthritis. Additionally, however, some unique uses for this drug were being explored. For example, in patients with scleroderma it appeared to heal ulcers which previously were resistant to all other forms of therapy.

Additionally, it appears to be a promising preservative for storing living tissues for implantation studies. It also has been used as a solvent for drugs not readily soluble in the more commonly employed solvents for parenteral use. In this connection, for example, it has been used in the therapy of certain malignancies with otherwise highly insoluble compounds. The FDA is aware that certain of the proposed investigational uses for this drug may well justify the continued use of this preparation even though the nature of the eye defects in animals may not be completely understood and there is a risk that man may also be liable to these effects.

The second problem concerns the mineral oil adjuvant preparations in which specific antigens or allergens are incorporated to form emulsions for use in the treatment in various allergies. While an NDA had been submitted for such a preparation, it was considered inadequate to establish safety and not approved. The applicant did not file an exemption to provide for additional studies to remedy these defects. As a consequence allergists throughout the country were unable to use this material legally in treating their patients. Subsequently, some 150 sponsors as individuals did submit INDs. Unfortunately, many of these failed to provide a clinical plan that might answer some of the questions that were raised concerning the safety and effectiveness of this product. Furthermore, there appeared to be little likelihood that any of these sponsors would ultimately submit an NDA for the product and clinical trial would be unduly prolonged.

In view of this, many of the INDs have recently been terminated. We have realized, however, there may be certain situations in which this type of treatment offers the possibility of unique benefits. Where the sponsor plans to restrict the use of the drug to such cases INDs have been allowed to remain active.

One of the consequences of the simultaneous termination of so many INDs has been the formation of one or more committees of

investigators. It is possible that such committees may, by a cooperative venture, provide the necessary background material for an NDA and will accept the responsibilities of monitoring the drug should it become marketed under acceptable labeling. Alternately, the restrictions now placed on the use of mineral oil adjuvant preparations may stimulate additional researches to develop a vehicle, better tolerated by the body tissues and at the same time offering the potential advantages of repository type therapy.

Conclusion

In conclusion, we are fully aware of the shortages of highly trained clinical pharmacologists and of facilities to undertake the studies of investigational drugs. Thus, we are concerned that a large portion of the clinical testing appears to be undertaken by a rather small number of investigators whose facilities and capacities may well become overtaxed. On the other side of the coin, we are encouraged when we hear of new activities both government and private, which are directed toward the training of additional pharmacologists or to the equipping of additional facilities for clinical pharmacology. A very large amount of additional effort along these lines is urgently needed.

In recent months physicians of the Investigational Drug Branch have visited an occasional sponsor or clinical investigator. In the future we hope to extend this appreciably. To date, unfortunately, such visits have generally been prompted by adverse reaction reports or by some indication of an irregularity in the investigational drug procedures. We are hopeful, however, that such visits will be undertaken also to familiarize our medical officers with the manner in which clinical investigations with investigational drugs are being carried out. We feel this would be most stimulating and most helpful to our staff and would also provide additional means of acquainting investigators, particularly sponsor-investigators, with the purpose and objectives of the Investigational Drug Regulations. **[The End]**

Introductory Statement

By FRANKLIN M. DEPEW

The Following Introductory Statement Was Given at the Twenty-first Annual Meeting of The Section on Food, Drug and Cosmetic Law of the New York State Bar Association. Mr. Depew Was the Chairman of This Meeting and Is President of the Food Law Institute. Succeeding Papers in This Issue Were Presented at the Same Meeting.

WELCOME TO THE TWENTY-FIRST ANNUAL MEETING of the Section on Food, Drug and Cosmetic Law of the New York State Bar Association. It would appear that we have now come of age. As you know, this section is the pioneer and oldest bar association group of lawyers in the food and drug field, and our membership is not limited to New York State, but, rather, is a nationwide one.

Our program today consists of eight interesting and valuable papers. I am confident that all of you will find them most rewarding.

One of the most important events during the past year has been the retirement of Mr. George P. Larrick as Commissioner of Food and Drugs. This event caused two immediate reactions. One was a widespread feeling of regret within government, and among lawyers and other groups whose activities are related to the Food and Drug Administration (FDA), that an outstanding service career was drawing to a close. The second was the hope that in the selection of a successor the Administration would recognize the major importance of the agency and would select someone who had the necessary character and professional qualifications.

The Honorable John W. Gardner moved quickly to give assurance on the second point by appointing a distinguished five-man committee headed by Rufus Miles, recently retired Assistant Secretary for Administration of the Department, to review the major organizational and substantive problems affecting the future of the FDA in the light of the increased statutory authority and greater resources available to it, and to present its recommendations regarding the

qualifications which should be sought in choosing a successor to Mr. Larrick. The subsequent appointment of Dr. James L. Goddard as Commissioner has met with universal acclaim, and I am confident that you all join me in wishing Dr. Goddard outstanding success in this new and responsible assignment. I am confident, too, that you, as lawyers, will work with him to the end that our great national food and drug law is effectively administered in the public interest. The strength of the FDA is one of our country's greatest assets.

Mr. Larrick has had a distinguished and historic career in the field of our national food and drug law. Under his able and courageous leadership the FDA has responded successfully to a decade of tremendous growth and expansion in both the food and drug industries. As a result the agency has grown in scope and prestige until today it is one of the most powerful and important agencies in Washington. Mr. Larrick's courage, skill and judgment in enforcing the law has served to protect the public and to assist industry. Throughout his term of office, conscience was his guide and an unswerving devotion to the public good his guiding principle.

This estimate of Mr. Larrick's capabilities and character is the universal one of all those who have any familiarity with his career and the burdens of his high office. In support of this I cite Secretary Gardner's statement that George Larrick has long been one of the nation's dedicated servants—that he has served in one of the most difficult spots in government and that he has served with honesty, judgment and courage.

During Mr. Larrick's term of office his associate, Deputy Commissioner John L. Harvey, was his strong right arm. He, too, merits our encomiums for his many years of honorable service in behalf of his country and its citizens. He concluded his government service last October on a most auspicious occasion in Rome, Italy, when he was serving as Chairman of the Joint FAO/WHO Codex Alimentarius Commission. In addition to a multitude of other duties, Mr. Harvey labored diligently and effectively to provide leadership in the simplification of international food standards.

A number of other key personnel in the FDA have retired as of the end of 1965. We sincerely hope that this will not handicap the new administration of Commissioner Goddard and trust that he will soon be able to build a highly qualified staff of competent and devoted people. [The End]

Artificial Sweetners— Their Impact on the Food Laws

By MURRAY D. SAYER

Mr. Sayer Is an Attorney for General Foods Corporation, White Plains, New York.

ARTIFICIAL SWEETENERS AND ARTIFICIALLY SWEETENED FOODS are widely used by American consumers today. A visit to the supermarket reveals a great variety of artificially sweetened products; the coffee break often reveals the weight conscious man or woman with his or her own private supply of artificial sweetener tablets; and restaurants frequently have packets of artificial sweeteners as readily available as the sugar bowl. With such wide distribution and usage, the average consumer could hardly suspect that artificial sweeteners were anything more than a normal ingredient of food.

Yet during their life span, artificial sweeteners have been the subject of much controversy and restrictive regulation. Over the years, artificial sweeteners have been characterized by laws, regulations, or official rulings with a number of unpleasant descriptions, such as: a poisonous and deleterious substance; an unsafe substance; a drug; and an economic adulterant. On the other hand, manufacturers of artificial sweeteners and artificially sweetened foods have promoted it as a boon to the diabetic, an aid to the weight watcher, and a substance which would make possible significant breakthroughs in food technology.

The Question of Safety

Normally, controversy over a specific substance tends to die down with long use and common acceptance. However, such is not the case with artificial sweeteners. Today, food and drug officials are still debating the appropriate uses of artificial sweeteners, the question of safety of artificial sweeteners seems to be raised regularly by scien-

tists or doctors, and food researchers argue that the restrictions imposed on the use of artificial sweeteners are unrealistic. In this paper, I propose to discuss some of the regulatory history of artificial sweeteners and touch on some of the knotty problems yet to be resolved.

The artificial sweeteners most commonly used today are saccharin and cyclamate salts, more commonly known as sodium or calcium saccharin and sodium or calcium cyclamate. Saccharin was discovered in 1879. In its salt form, it is about 300 times sweeter than sucrose. Cyclamate was discovered in 1942 and is estimated to be about 30 times sweeter than sucrose.

Regulatory History

When I started preparing this paper, I became curious as to how far back saccharin was actually used as a sweetening agent in foods. While there are no reported regulatory actions regarding saccharin prior to 1900, I did find a case decided by the Supreme Court in 1894.[1] It involved a dispute as to the duty classification of saccharin imported into the United States during the year 1887. In that case, the Court described the uses of saccharin as follows:

> * * * it is used as a sweetening agent in manufacturing purposes, such as soda water, liquors, wines, chewing tobacco, preserves, medicines, etc.; that it has no medicinal effect upon the human or animal system, and that its principal use is to sweeten articles of medicine or food in order to render them palatable. * * *

This case would indicate that saccharin was actually being used as a sweetener in foods less than 10 years after its discovery. Apparently, it did not take the states too long to step into the picture to regulate the use of saccharin. A review of early state food laws reveals that many of the states absolutely prohibited the use of saccharin in foods and beverages early in the 1900's, and perhaps earlier. For example, the Pennsylvania Food Law provided that an article of food would be deemed to be adulterated if it contained (among many other substances) any added saccharin or other added ingredients deleterious to health. Other states, while not prohibiting such products limited them to sale by Doctor's prescription only. For example, the Florida law read as follows:

> The sale of saccharin, a drug, or other artificial sweetener for use as a substitute for sugar, or the manufacture or sale of foods or drinks of any kind containing saccharin or other artificial sweetener as a substitute for sugar in part or in whole, is prohibited in the State of Florida. Provided, that saccharin or foods containing saccharin, shall be sold or dispensed only by duly licensed pharma-

[1] *Lutz v. Magone,* 153 U. S. 105.

cists, upon the written prescription of duly licensed practicing physicians, with the date and name of physician and of the person for whom prescribed and kept on file by the pharmacist.

Federal Ruling

Notwithstanding the many state restrictions against the use of saccharin, apparently there was still a sizable amount of commerce in artificial sweeteners and artificially sweetened foods during the early 1900's. In 1906, the Federal Food and Drugs Act was enacted. The first federal ruling with respect to saccharin was published by the Bureau of Chemistry of the Department of Agriculture, the predecessor to the Food and Drug Administration (FDA), on April 26, 1911. This was followed shortly thereafter by two other rulings which were intended to clarify the first ruling. Reading between the lines of these rulings, it is evident that even then there was considerable dispute over the use of artificial sweeteners and that the final ruling was something of a compromise position.

The conclusion of the April 26, 1911 ruling read as follows:

> Saccharin has been used as a substitute for sugar in over thirty classes of foods in which sugar is commonly recognized as a normal and valuable ingredient. If the use of saccharin be continued it is evident that amounts of saccharin may readily be consumed which will, through continual use, produce digestive disturbances. In every food in which saccharin is used, some other sweetening agent known to be harmless to health can be substituted, and there is not even a pretense that saccharin is a necessity in the manufacture of food products. Under the food and drugs act articles of food are adulterated if they contain added poisonous or other added deleterious ingredients which may render them injurious to health. Articles of food are also adulterated within the meaning of the act, if substances have been mixed and packed with the foods so as to reduce or lower or injuriously affect their quality or strength. The findings of the Referee Board show that saccharin in food is such an added poisonous or other added deleterious ingredient as is contemplated by the act, and also that the substitution of saccharin for sugar in foods reduces and lowers their quality.
>
> The Secretary of Agriculture, therefore, will regard as adulterated under the food and drugs act foods containing saccharin which, on and after July 1, 1911, are manufactured or offered for sale in the District of Columbia or the Territories, or shipped in interstate or foreign commerce, or offered for importation into the United States.

About 10 months later, on March 1, 1912, a revision of the previous ruling was issued. This ruling removed the absolute prohibition against the use of saccharin and saccharin sweetened foods but stated that such saccharin sweetened foods would be deemed drugs. The conclusion of the ruling reads as follows:

> * * * it is plain, from the finding of the Referee Board, that the substitution of saccharin for sugar lowers the quality of the food. The only use of saccharin

in foods is as a sweetener, and when it is so used, it inevitably displaces the sugar of an equivalent sweetening power. Sugar has a food value and saccharin has none. It appears, therefore, that *normal* foods sweetened with saccharin are adulterated under the law.

In making this decision we are not unmindful of the fact that persons suffering from certain diseases may be directed by their physicians to abstain from the use of sugar. In cases of this kind, saccharin is often prescribed as a substitute sweetening agent. This decision will not in any manner interfere with such a use of saccharin. The Food and Drugs Act provides that any substance which is intended to be used for the prevention, cure or mitigation of disease is a drug, and a product containing saccharin and plainly labeled to show that the mixture is intended for the use of those persons who, on account of disease, must abstain from the use of sugar, falls within the class of drugs and is not affected by this decision.

Three and one-half months later, on June 22, 1912, another ruling was issued which read:

There appears to exist a misconception of the position of the Department of Agriculture as to the use of saccharin in foods as announced in Food Inspection Decision No. 142. That decision prohibits the use of saccharin in foods. The law defines the term "drug" and it is considered that saccharin has its proper place in products coming within this definition.

It is recognized that certain specific products generally classified as foods, and sweetened with saccharin, may be required for the mitigation or cure of disease. It is not intended to prohibit the manufacture or sale of such products, provided they are labeled so as to show their true purpose and the presence of saccharin is plainly declared upon the principal label. This must not be interpreted to mean that the use of saccharin in foods prepared for ordinary consumption is permissible even if declared on the label.

This final ruling seemingly set the stage for future policy with respect to saccharin and artificially sweetened foods. Saccharin, per se, was to be considered a drug but it could be used in foods intended for the mitigation or cure of disease provided they were clearly labeled.

As the years rolled by, saccharin sweetened foods continued to be sold in modest quantities. Because of the widely varying restrictions in the states, these products were sold either in drug stores, specialty food stores, or even by mail. In some cases, these artificially sweetened foods were detailed to doctors. The indicated use for these products were for conditions calling for reduced carbohydrate intake, such as diabetics, obesity and its complications, and for those on reducing diets who wish to keep down their calories.

Special Dietary Regulations

The next important legal development was the passage of the 1938 Federal Food, Drug and Cosmetic Act. This Act contained a

new provision with respect to special dietary foods. Section 403 (j) of the Act provided that:

A food shall be deemed to be misbranded—if it purports to be or is represented for special dietary uses, unless its label bears such information concerning its vitamin, mineral, and other dietary properties as the Secretary determines to be, and by regulation prescribes as, necessary in order fully to inform purchasers as to its value for such uses.

With the passage of the new law, the FDA moved quite rapidly to promulgate special dietary regulations and these were published in the Federal Register on November 22, 1941. Two of these regulations affected artificially sweetened foods and reflected pretty much the policy established in 1912 by the Bureau of Chemistry.

The first regulation, Section 125.6, provides:

If a food purports to be or is represented for special dietary use by man by reason of its use as a means of regulating the intake of protein, fat, carbohydrate, or calories, for the purpose of controlling body weight, or for the purpose of dietary management with respect to disease, the label shall bear a statement of:

(a) The percent by weight of protein, fat, and available carbohydrates in such food; and

(b) The number of available calories supplied by a specified quantity of such food.

The second regulation, Section 125.7, provides:

If a food purports to be or is represented for special dietary use by man by reason of the presence of any constituent which is not utilized in normal metabolism, the label shall bear a statement of the percent by weight of such constituent, and, in juxtaposition with the name of such constituent the word "nonnutritive." * * * But if such constituent is saccharin or a saccharin salt, the label shall bear, in lieu of such statement and word, the statement "Contains . . . saccharin (or saccharin salt, as the case may be), a non-nutritive, artificial sweetener which should be used only by persons who must restrict their intake of ordinary sweets," the blank to be filled in with the percent by weight of saccharin or saccharin salt in such food. The provisions of this section shall not be construed as authorizing the use of saccharin or its salts in any food other than one for use by persons who must restrict their intake of carbohydrates, * * *.

With the establishment of a federal regulation which set up a special class of dietary foods, many of the states which had prohibited or restricted the sale of artificially sweetened foods began to amend their laws or regulations to conform in general with the federal regulations. However, some of the states went beyond the federal regulation. For example, Pennsylvania amended its food law. It still prohibited the use of saccharin in foods but added a proviso which read:

That any article of food containing saccharin or any artificial sweetening agent may be manufactured, transported or sold if it contains no added sugar,

honey or other natural sweetening agent, and the name of the artificial sweetening agent followed by the word 'sweetened' is placed upon the label each time the name of the article of food is mentioned, in type no smaller than the largest type on said label. Said label shall also contain such appropriate warning statement as shall be prescribed by the Department of Agriculture.

However, the regulation promulgated by Pennsylvania was unique among the various regulations existing at that time. The Pennsylvania regulation required the following statement:

> WARNING!
>
> This product contains the drug "Saccharin."
>
> CAUTION!
>
> Do not use this product unless advised to do so by your personal physician.

This warning statement had to be surrounded by a solid black border of not less than 12 points in thickness.

This type of warning statement was something of a marketing man's nightmare, but those who wished to sell in Pennsylvania complied with the regulation by having special labels for products sold in Pennsylvania. This regulation was declared invalid in 1955 as being "wholly unreasonable and unnecessarily alarming."[2]

Restricted Market

Up until the early 1950's, artificially sweetened foods had a relatively restricted market. The reason for this was that the only approved artificial sweetener, saccharin, had a decided bitter aftertaste. By this time, however, the cyclamates had made their appearance on the market and it was discovered that a combination of saccharin and cyclamates eliminated most of the undesirable off taste properties in an artificially sweetened food. The surge of artificially sweetened products began. The biggest single development in the artificially sweetened market was in the beverage field. This result is obvious today in any supermarket where the space devoted to artificially sweetened beverages appears to take almost as much space as sugar sweetened beverages. No longer is the artificially

[2] *Cott v. Horst,* 110 A. 2d 405.

sweetened food aimed primarily at the diabetic or persons who must restrict their intake of ordinary sweets, but rather at the calorie conscious.

This change of direction in the marketing of food products and the obvious desire of consumers for lower calorie foods was recognized by FDA when it published its proposed revision of the special dietary food regulations on June 20, 1962. These regulations would eliminate the labeling requirement of the old regulations which makes mandatory the statement that artificially sweetened food "should be used only by persons who must restrict their intake of ordinary sweets." In its place, there would be a series of other requirements. First, if a food purports to be for special dietary use by reason of the presence of an artificial sweetener, and is intended to be used by persons who wish to or who must restrict their intake of ordinary sweets, the label shall bear a statement "contains sodium saccharin and sodium cyclamate, nonnutritive artificial sweeteners." Second, the label must contain a statement of the number of calories in an average serving of the food and a calorie comparison of the artificially sweetened food with the same food when made with the sweetening ingredient that the artificial sweetener replaces. Tied in with these two provisions is an attempt to limit the use of artificial sweeteners in foods to those products in which the use of the artificial sweetener results in a substantial calorie reduction. The reason for this limitation is that FDA believes a great many of the artificially sweetened products today are not truly special dietary foods.

Also tied in with this regulation would be a revision of the old Section 125.6. This is the section aimed at special dietary foods used as a means of regulating the intake of protein, fat, carbohydrates, or calories; for the purpose of affecting body weight; or for the purpose of dietary management with respect to disease. Under this proposed regulation, if a food is offered for the purpose of affecting body weight, the label would have to bear this statement: "Useful only when used as a part of a calorie-controlled diet." If an article is described as "low calorie," it may not contain more than 15 calories in an ordinary serving and not more than 30 calories in the ordinary total daily intake. Products not meeting the "low calorie" designation may still be represented as "lower in calories" provided the labeling supplies a calorie comparison between the "lower in calories" food and the regular food to which it is compared.

It has now been 3½ years since the publication of these proposed revisions of the dietary regulations. There are indications that FDA

has made a number of changes in the proposed regulations and that they will soon be republished for further comment.

Problems of the Food Industry

From what has been presented so far, I believe it is obvious that artificially sweetened foods have had a long and controversial history. However, even if the revised special dietary regulations are adopted, the controversy will not be over. Up until recently, the struggle has been primarily to obtain acceptance of reasonable uses of artificial sweeteners in foods. We are now in a phase, I believe, in which much more difficult and sophisticated problems will have to be faced by both regulatory agencies and the food industry. I would like to touch briefly on what some of those problems may be.

Guidelines

1. Once the new regulations are adopted, what will be the guidelines for determining whether an artificially sweetened food is truly a dietary food within the meaning of the Law and Regulations? This question is extremely pertinent because the mere replacement of natural sweetener with artificial sweetener does not, in all cases, make the product a proper special dietary food. The new regulations, as proposed, really set up two primary classes of dietary foods. One class of foods is for those who wish to restrict their intake of ordinary sweets. This would encompass those products in the low calorie area intended primarily for the calorie conscious. The other class of foods is for those who must restrict their intake of ordinary sweets, the diabetics.

In that class of foods aimed at the calorie conscious, the mere replacement of sugar with an artificial sweetener will not necessarily have any significant effect on the calorie content of the product. As an example, let's take a look at cookies. A cookie weighing one ounce will have approximately 137 calories. This cookie will contain perhaps 25% sugar. If you displace the sugar with an artificial sweetener, without doing anything else, there is no real reduction of calories on an equivalent weight basis. The reason for this is that when you displace the sugar in a one ounce cookie some other nutritive substance, either a carbohydrate, fat, or protein, will have to replace the lost sugar in making a one ounce artificially sweetened cookie. The net result is that the sugar has been displaced by an artificial sweetener but the calories from the other nutritional substances replace the nutrients formerly provided by the sugar. In-

herent in this concept is the long held position of FDA that most calorie comparisons must be made on a weight for weight basis rather than volume for volume basis.

Now it is quite possible that other adjustments could be made to the cookie, such as lowering the fat content, which would result in an actual lowering of calories. But the mere replacement of sugar with artificial sweetener would not result in any significant reduction of calories and could even increase the calories on a weight for weight basis if the proportion of fat in the cookie were increased.

This does not mean that a cookie which merely replaces sugar with artificial sweetener could not be an appropriate dietary food for diabetics since it eliminates perhaps the most dangerous ingredient for the diabetic, sugar. But if a cookie is intended for the diabetic, how should the product be labeled so that the calorie counter will not mistake this product as a lower calorie cookie?

With respect to the artificially sweetened food which is intended as a lower calorie food, FDA in its proposed regulations has given a rather general guideline. The regulation provides that if there is an "insignificant" reduction of calories between the artificially and naturally sweetened food, the artificial sweetener should not be used. This leaves open the eventual determination as to what is a significant reduction of calories.

Regulatory Policy

2. What will be the regulatory policy of FDA with respect to special dietary foods which combine both artificial and natural sweeteners? This question itself has a long and interesting history. For a great many years, FDA has taken an official position that where artificial sweeteners are used in special dietary foods, the product may contain no added nutritive sweetener. This position had the effect of restricting the potential uses of artificial sweeteners in special dietary foods because some artificially sweetened products require a small amount of sugar for technological purposes.

In 1962, FDA apparently revised its long held position when it promulgated standards for artificially sweetened jams and jellies. In artificially sweetened jams and jellies, there is a need for adding an ingredient to aid in producing and maintaining a gel-like body or consistency. One of the approved gelling agents listed was pectin. Because the gelling strength of pure pectin will vary, it is common practice to standardize the pectin in order to achieve a specific gelling power. The normal standardizing ingredient in pectin is sugar or

some other nutritive sweetener. Therefore, the standards for artificially sweetened jams and jellies permit the use of a nutritive sweetener in pectin as a standardizing agent. However, the total amount of nutritive sweetener cannot exceed 1.32% by weight of the artificially sweetened jam or jelly.

In 1964, a new artificial sweetening product entered the market. This product was composed of sugar, plus sufficient artificial sweetener so that the product could be used on an equivalent spoon for spoon basis and provide the same sweetening power as sugar. Yet it claimed a 50% reduction of calories over that contained in sugar alone. At this point, FDA was faced with a choice of either litigating a declared policy of which they felt unsure or making a further change in their policy. They followed the latter route. Without publishing any formal policy statement on the matter, FDA indicated that they would not oppose a special dietary food which combined natural and artificial sweeteners provided that the food resulted in a significant reduction of calories. They indicated at the time that a 50% reduction would be considered significant.

The combining of artificial and natural sweeteners however, presents an additional matter of concern to FDA. Under their previous policy, an artificially sweetened food would normally have been safe for consumption by diabetics because of the absence of sugar. When natural sweeteners are combined with artificial sweeteners, this ceases to be true. It therefore becomes important to advise diabetics as to the true nature of the product. While the proposed regulations do not contain any warning requirement to diabetics, it is likely that the revised regulations will do so, provided FDA continues to follow its previously stated position that artificial and natural sweeteners could be combined in a special dietary food. Manufacturers of products containing both natural and artificial sweeteners are also alert to this problem and a recent entry on the market bears the following statement on its label. "NOTE TO DIABETICS: Contains 93.4% lactose, a natural sugar which should not be used by diabetics."

FDA Attitude Toward Technological Use

3. What will be the attitude of FDA with respect to technological use of artificial sweeteners in regular foods? From time to time over the past years, manufacturers approached FDA to try and obtain a ruling which would permit the use of artificial sweeteners in regular foods, as opposed to special dietary foods, where the artificial sweetener is used for technological purposes rather than for special dietary

purposes. By technological use, I mean the use of artificial sweeteners in regular foods where the desired end product can only be achieved through the use of artificial sweeteners and where the resulting use of artificial sweetener would have no significant effect on the nutrition of the product. In the proposed revision of the special dietary regulations, FDA did include a technological exception, which read as follows:

> If, however, the artificial sweetener is used for a technological purpose in food fabrication unrelated to nutritive value of the article and the use of the artificial sweetener results in no significant calorie reduction in the fabricated food, the presence of the artificial sweetener should be declared only by its common or usual name; e.g. "sodium saccharin." In such event, no representations, direct or implied, should be made in the labeling, based on the nonnutritive value of the artificial sweetener.

It is my understanding that FDA has had serious second thoughts about such technological use and that the exception will not appear in the regulations when republished. This does not mean that they have completely abandoned the technological exception. But their approach seems to be that if technological exceptions are granted, it will only be done on a product by product basis.

Artificial Sweeteners in Candy

4. Will artificial sweeteners be permitted for use in candy? On its face, this question might seem almost academic since almost every candy counter today seems to have a supply of candies which contain artificial sweeteners. The federal government and most states have laws which prohibit the use of most nonnutritive substances in candy. The federal prohibition is contained in Section 402 (d), and reads as follows:

> A food shall be deemed to be adulterated—if it is confectionery, and it bears or contains any * * * nonnutritive article or substance except authorized coloring, harmless flavoring, harmless resinous glaze not in excess of four-tenths of 1 per centum, natural gum, and pectin * * *.

In 1961, two things happened which were aimed at changing this section of the law. First, a bill was introduced in Congress which would appeal the prohibition against nonnutritive substances in confectionery. However, this remained essentially dormant in view of the second occurrence. FDA seized some dietetic milk chocolate flavored bars which contained artificial sweeteners. One of the charges made by FDA was that the product was adulterated in that it was a confectionery and contained a prohibited artificial sweetener. The court issued a ruling which held that the product was misbranded and it was therefore condemned and destroyed. However, in the process,

the court also ruled that section 402 (d) did not prohibit the use of artificial sweeteners in confectionery.

This decision was appealed by FDA and in 1963 the Court of Appeals dismissed the appeal on the grounds that the goods had been destroyed and the matter was therefore moot. However, in dismissing the appeal, the Court of Appeals[3] vacated that part of the judgment of the lower court which ruled that artificial sweeteners were not covered by the prohibition against nonnutritive substances. This left matters pretty much where they had been prior to the action.

In 1963, a bill to amend section 402 (d) was again introduced in Congress and was passed by the House in 1964. However, the Senate failed to act on the bill. In 1965 the bill was again introduced and passed by the House. Senate Hearings were held on the bill and passage looked favorable, but Congress adjourned before the Senate could act. The indications are that the bill will be passed by the Senate in 1966, either in its present form or slightly modified to prohibit the imbedding of trinkets in candy.

Safety of Artificial Sweeteners

5. Will the question of safety of artificial sweeteners finally be resolved to everyone's satisfaction? As early as 1912, the Bureau of Chemistry raised the question of possible gastric disturbances through over-consumption of saccharin. However, through years of usage, this artificial sweetener had come to be generally recognized as safe. In 1953, FDA submitted a request to the National Research Council asking for advice on the principles which should govern the use of artificial sweeteners in foods. In turn, the NRC set up an ad hoc committee to consider the question and its report was issued in 1955. The report of the committee stated that saccharin was safe. With respect to cyclamate, the committee's report stated that cyclamate "may not be classified as an unsafe chemical on the basis of present evidence. Nor can its safety at expected use levels be guaranteed until its tolerance level is known."

The recommendations of the National Research Council had little effect on the growing artificially sweetened food market, perhaps because the only known physiological effect was that over-consumption could have a mild laxative effect. When the Food Additive Amendment of 1958 was passed, both saccharin and cyclamate were listed by FDA as substances which are "generally recognized as safe" (GRAS).

[3] *U. S. v. 1200 Candy Bars* * * *, 313 F. 2d 219.

In September 1964, the publication known as *"The Medical Letter"* raised further questions as to the safety of cyclamate and saccharin. The publication did not charge that artificial sweeteners were harmful. It did question whether there was sufficient evidence to establish safety when artificial sweeteners are consumed at the current level.

On the publication of this letter, FDA refused to comment further on questions involving artificial sweeteners until they completed a study of data which had already been supplied by one of the prime manufacturers of cyclamate. In May of 1965, FDA issued a short report in which they stated: "A review of recent studies on artificial sweeteners show they are safe as presently used."

This report seemingly laid to rest any questions of safety under current conditions of use. However, five months later the Wisconsin Alumni Research Foundation published some initial findings in *Nature* reporting on some feeding studies with rats. This report indicated that rats fed calcium cyclamate at rates of 5 and 10 percent of their total diet showed reduced growth rates. No conclusions have been drawn on the basis of these studies and they are still continuing. Whether this study will have any effect on the ultimate use of artificial sweeteners remains to be seen. No one, except possibly the sugar industry, has expressed any concern over this report to date, probably because of the very high levels contained in the rats' diets. However, when the study is completed, the conclusions will unquestionably be evaluated, as they should.

These are only some of the questions which will be of interest with respect to the use of artificial sweeteners in the coming years. Other open questions of interest are: What will be the attitude of the various states where their existing laws or regulations will be in conflict with the new regulations and policies adopted by FDA?; What will be the approach of the Federal Trade Commission with respect to advertising of artificially sweetened products?; and What influence will philosophical objections have on the development of laws and regulations governing the use of artificially sweetened foods?

Conclusion

It is apparent from what has been presented here that artificial sweeteners have had a long and controversial history. Indeed, they seem destined to continue to be a controversial matter in the future. The resolution of these issues is bound to have a further impact upon the laws of this country, upon the food industry, and upon the eating habits of millions of American consumers. **[The End]**

The Proposed Alternative to Zero Level and No Residue Regulations

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IN 1954 I PRESENTED A PAPER entitled "The Interdependence of Law and Science Under the Food, Drug and Cosmetic Act" [1] in which I emphasized the fact that words not only have special connotations in various disciplines but meanings which change with time and conditions. In the light of subsequent events, it is apropos to quote again the comment of a famous English semanticist [2] ". . . how hard it is for the draftsman to foresee every possible path down which the judicial mind may be led by what he writes, . . . legal ambiguities are caused more often by over simplicity of diction than by over-elaboration."

Reinterpretation of Statutory Language

The Supreme Court of the United States is engaged in interpreting the language of the Constitution in light of the changing needs and conditions of society in an era of industrialization which could not have been foreseen by our founding fathers. In a similar fashion it becomes necessary for administrative agencies from time to time to reinterpret statutory language as its full meaning emerges in the light of situations encountered in the experience of enforcement.

Scientific Versus Legal Aspects of Legislation

Prior to the enactment of the Pesticides and Food Additives Amendments to the Food, Drug and Cosmetic Act there was consid-

[1] The Interdependence of Law and Science Under the Food, Drug, and Cosmetic Act presented by Bernard L. Oser before the Annual Meeting of the Section on Food, Drug and Cosmetic Law of the New York State Bar Association at New York City on January 27, 1954.

[2] Sir Ernest T. Gowers in *Plain Words —A Guide to the Use of English* (London, His Majesty's Stationery Office, 1948).

erable discussion of the scientific versus the legal aspects of the proposed new legislation.

When Congress introduced the "no residue" and "zero tolerance" concepts into law for the purpose of completely excluding unnecessary or extremely toxic substances from food, it failed to anticipate, first, that enforcement of these provisions necessitated the development and application of new analytical methods of much higher sensitivity than those in use at that time; secondly, that absolute proof of the absence of a substance is virtually impossible even by the most sensitive analytical methods; and finally, that the limit of detectibility by chemical or physical procedures is not fixed but becomes progressively lower with the availability of more sophisticated instrumentation and the discovery of new techniques. Thus it was not many years after these amendments became effective and certain pesticides were permitted for use on agricultural crops on a "no residue" basis, that advances in chemical analytical technology revealed the presence of finite residues of certain pesticides where none had previously been found. The situation reached the stage where seizures were made or threatened and dairy farmers sought monetary relief from Congress for losses incurred when milk was condemned despite the allegedly proper use of these pesticides on forage crops. It became obvious that there was serious trouble ahead so long as analytical methods of increasing sensitivity continued to be devised and the administrative interpretation of "no residue" continued to be an "absolute zero" basis.

Committee on Pesticide Residues

In response to the public reaction to Rachel Carson's *Silent Spring,* President Kennedy commissioned his Scientific Advisory Committee to review the uses of pesticides. Particular attention was directed to the "no residue" problem in the report of the special panel appointed for the purpose of this review. It recommended that the National Academy of Sciences-National Research Council be requested "to study the technical issues involved in the concept of zero tolerance and no residue with the purpose of suggesting legislative changes." Subsequently this study was requested by the Secretaries of Agriculture and Health, Education and Welfare, and a special Committee on Pesticide Residues was appointed to handle the assignment. On this Committee were represented the disciplines of analytical and agricultural chemistry, pharmacology, toxicology, oncology, food

technology, entomology, statistics, and law. After long deliberation its report was submitted last June and it has been published in several places including the FOOD, DRUG AND COSMETIC LAW JOURNAL.[3]

The terms "no residue" or "zero tolerance" cannot be interpreted literally for purposes of regulatory control. In the words of the Committee's report, "these concepts . . . are scientifically and administratively untenable and should be abandoned." The fact that negative concepts have different degrees of meaning is not uncommon. When a referee calls "no touchdown" he means precisely that, not "maybe a tiny little fraction of a touchdown;" in contrast, when a doctor says the patient has "no temperature," he means of course, "no fever" and could be discounting a fraction of a degree above normal.

Regulatory control requires that "no residue" as related to pesticides and "zero tolerances" for indirect food additives, such as veterinary drugs, be enforced by application of analytical procedures. Hence these provisions are perforce limited by the sensitivity of the means of testing. During the past ten years chemical and physical methods, particularly those involving the use of thin layer and gas chromatography, have improved to such an extent that the limit of detectibility has in some cases been reduced by several orders of magnitude. For instance no concentration of dieldrin or parathion less than 0.1 ppm could have been detected years ago, but it is now possible to detect as little as a few parts per billion, or a thousandth less. Chemists now recognize quantities in units of nanograms and picograms (billionths and trillionths of a gram), whereas only a few years ago the smallest unit used by analysts was a microgram (a millionth of a gram).

Since analytical procedures used for official control purposes were not specified in the regulations, it was not surprising to discover that newer methods revealed the presence of what might be considered to be infinitely small, though nevertheless finite, residues in commodities where they were neither permitted nor believed to exist.

Analytical Detectibility

No matter how sensitive an analytical method may be, it is not justified to conclude that because a substance cannot be detected, it is not present. For example, a method capable of revealing the pres-

[3] See 20 FOOD DRUG COSMETIC LAW JOURNAL 608 (November 1965).

ence of 0.1 part per billion of a given residue in food, would fail to disclose the presence of as many as two trillion (2,000,000,000,000) molecules in a 100-gram sample (about a 3-ounce portion) of the food. Even a thousand-fold improvement in analytical detectibility would not significantly increase the probability of stating with absolute assurance that no iota of the substance was present. Hence the cautious chemist reports a negative test as "none found" rather than "none present." It is worthy of mention in this connection, that at their minimum level of sensitivity analytical procedures are generally least reliable or reproducible, even in the hands of the most competent chemists using the best available equipment.

It is pertinent to recall the statutory conditions surrounding "no residue" regulations which have aggravated the administrative difficulty. When the conditions of use of a pesticide under good agricultural practice are such that "no residue" results on a particular crop (owing, for example, to the time interval between application and harvesting, or to washing, trimming or peeling of the vegetable or fruit) the Department of Agriculture may issue a regulation permitting its use without the necessity of a Food and Drug evaluation of the toxicity of the substance and the potential hazard of the residue. Hundreds of "no residue" regulations have been promulgated on this basis. On the other hand when a residue does result under the proposed conditions of use, the law requires that registration be deferred by the Department of Agriculture until the Food and Drug Administration (FDA) has evaluated the toxicological data and established a legally permissible limit (the so-called tolerance) for the pesticide on each raw agricultural commodity for which it is intended to be used. In the event that the substance is found to be carcinogenic or extremely toxic when fed to animals, the FDA may set the tolerance at "zero level." Thus the presence or "absence" of a residue involves not only a scientific determination, but a question of administrative jurisdiction, i.e. whether or not the USDA may act independently of the FDA. Under these circumstances the finding of finite levels of residue by an improved procedure where the previous method warranted a USDA "no residue" registration, has created an administrative dilemma.

Early in the deliberations on the subject it became apparent to the NAS-NRC Committee that the statutory "no residue" or "zero tolerance" provisions were intended not to challenge the ingenuity of analytical chemists, but to insure a degree of safety of edible prod-

ucts even greater than that implicit in finite tolerances. In essence, therefore, the matter hinges on toxicological considerations, rather than on chemical detection.

Solutions

Thus the simple pragmatic approaches to the problem were soon discarded. For example the defining "no residue" in terms of a specified analytical method, such as the one considered acceptable when the tolerance was established, could not be adopted, because this might not satisfy the desired degree of safety. The alternative of fixing the level corresponding to the limit of detectibility of a particular method, rather than the method itself, was likewise not acceptable in the absence of toxicological justification of its adequacy from the safety standpoint.

Still another alternative explored by the Committee was the establishment of some extremely low finite level, applicable across the board for all pesticidal substances, and far below the range of potential hazard, regardless of the chemical or pharmacological nature of the substance. This course has been adopted in Germany and certain other European countries, where zero tolerance terminology has been avoided and, indeed, is ridiculed by most toxicologists.

Another solution to the problem, and the one essentially embodied in Recommendation No. 2 of the report of the Pesticides Residue Committee, is to regard finite tolerances as "permissible residues," and to substitute for "no residue" or "zero tolerances" the concept of "negligible residues," the latter being so small a fraction of the maximum acceptable daily intake as to be insignificant from the toxicological standpoint.

Like a "permissible residue," a "negligible residue" would require a suitable analytical method for regulatory control purposes and would also be based on toxicological considerations. The recent amendment to the Delaney Clause established a precedent for this approach, since it permits the presence of a carcinogenic substance (i.e. an estrogen) in animal feed on the condition that it causes no harm to the animal and leaves no residue in any edible product derived therefrom. In this case the determination of "no residue" is according to a method specified by regulation of the Secretary of Health, Education and Welfare. Because of the virtual absence of risk (or, in effect, the greater margin of safety) involved in "negli-

gible residue" registration, it is felt that, at least provisionally, somewhat curtailed animal tests could be used to derive an estimate of the maximum acceptable daily intakes in such cases.

Some discussion of the term "maximum acceptable daily intake" is warranted. This may be regarded as the physiologically tolerable limit to the safe human intake. It is based on toxicological feeding tests of at least two species of animals from which is estimated the so-called no effect level, expressed in terms of milligrams per kilogram of body weight per day. It is beyond the scope of the present paper to enter into the details of the physiological, biochemical, pharmacological, and pathological procedures involved in these experiments, or to discuss the limitations of the method of establishing the no-effect dose for large populations and different species of animals. Suffice to say that in view of the uncertainties in the transition of data from laboratory animals to human populations, it is customary to apply a safety factor (generally 1/100) to the no-effect level observed in the most sensitive animal species tested, in arriving at an estimated no-effect level (also expressed in mg. per kg body weight per day) in man. Assuming the weight of an average man to be 70 kg (154 lb.), one can multiply the no-effect level by 70 to obtain the maximum acceptable daily intake of the substance in question in terms of mg per man per day.

This is, in effect, the safe tolerance and is quite distinguishable conceptually from legal tolerances. The latter are established for individual crops at levels no higher than necessary to accomplish their desired agricultural or technological purposes. Legal tolerances must, of course, be established, within the limits of safety. The margin of safety in the conversion of no effect doses from animals to man, as well as that implicit in the assumption of continuous daily intake throughout the lifetime of the species, is so great that it is grossly misleading to suggest that any excess of a residue in a given lot of food or feed above a legally established tolerance, involves peril to life or health. The legal tolerance is in no sense equated to the human tolerance.

Cumulative Effect of Tolerances

The cumulative effect of all tolerances (or of permissible plus negligible residues, in the proposed terminology) should not exceed the maximum acceptable daily intake.

As explained above, the maximum acceptable daily intake, expressed in relation to body weight, is converted to a limiting daily dose for an average 70 kg man. To relate the total intake of a given pesticide in various foods to the maximum acceptable level, one must consider not only the concentrations present in these foods, usually reported in parts per million (which is the same as mg per kilogram), but the actual amount of each such food eaten per day. For example 100 grams (0.1 kg) of food containing 5 ppm of DDT would represent 0.5 mg of this insecticide. Estimates of expected intake of the major categories of grains, vegetables, and fruits, are based on dietary surveys undertaken periodically and for various geographic regions, by the Household Economic Research Division of the U. S. Department of Agriculture (USDA).[4] As an added safety precaution data for high, rather than average, consumption levels have been used in estimating potential residue intake. However, the assumption that all such high levels are additive in the diet, or are consumed every day, is admittedly not supported by the facts. Furthermore it is unwarranted to assume that all permitted residues are actually contained in all crops from all sources and at all seasons. Hence the actual total intake falls well below the cumulative totals represented by the sum of the products of the tolerances and the high consumption levels.

Market Basket Surveys

Federal and state enforcement agencies are constantly sampling and testing agricultural commodities for compliance with pesticide regulations. In 1964, out of 32,678 samples analyzed by FDA, only 34 lots (about 0.1 per cent) were found to have exceeded the prescribed tolerances to an extent sufficient to warrant legal action. Even more significant are the so-called market basket surveys conducted by FDA in which the amounts and kinds of residue are determined in all types of food purchased bimonthly in three major cities, Boston, Kansas City, and Los Angeles. These foods are representive of the composition of the diet of a heavy eater, namely the young adult man. The foods are prepared for consumption, composited, and analyzed by methods capable of revealing some 50 pesticides, in the parts per billion range. A summary of the results of the 1964-65 surveys published last month [5] concludes that "The amounts of pesticide residues

[4] United States Department of Agriculture, Agricultural Research Office, Household Economics Research Division, Washington 25, D. C. (1960).

[5] Duggan, R. E., Barry, H. C., and Johnson, L. Y., Science, 151, 101 (1966).

found in the foods ready for consumption were very small; they were substantially less than the tolerances established for specific pesticides and products in those instances where the tolerances are finite."

Since the cumulative total of "permissible residues," results in a dietary intake far below theoretically possible levels, the effect of "no residue" or "zero tolerances" must indeed be insignificant. The realistic course is therefore to recognize the existence of "negligible residues" and be not deluded into believing that the residues are completely non-existent.

Like permissible residues, negligible residues would be predicated upon a knowledge of the toxicity of the substance in question. Like permissible residues, they would also be subject to regulatory control, which means suitable analytical methods must be available. However, the NAS-NRC Committee has recommended that when pesticides are registered by USDA on either basis, the analytical method should have the concurrence of both that Department and the FDA, and should be published. It recommended moreover that published methods should not be changed without notice and opportunity for comment by interested parties.

The Administrative Standpoint

From the administrative standpoint the Committee recommended that pesticide registration continue to be the responsibility of USDA and that a reasonable time schedule be adopted for an orderly adoption of its recommendations.

The report of the Pesticide Residue Committee was submitted to the Secretaries of Agriculture and Health, Education and Welfare and was released for publication. It has received commendation and support from agricultural and trade organizations, from the affected industries, from various state and local agencies, and from Congressmen who have urged its prompt implementation.

The National Agricultural Chemicals Association has offered its proposal for implementing these recommendations to the Secretaries of the two Departments most concerned. It suggests that negligible residues be set at low, "across-the-board" levels rather than on a crop-by-crop basis, i.e., for all raw agricultural commodities with the possible exception of milk which would be treated separately. These levels would be based principally on USDA and FDA evaluation of

short term (90-day) feeding studies and other information supplied by industry to the extent necessary.

It is understood that a proposal based on the Committee's recommendations has been under consideration by a joint USDA and FDA task force, with the aim of avoiding new legislation. It appears that in the view of legal advisors to these agencies, legislation would be necessary if the "no residue" concept were to be abandoned as recommended, and substituted by the more realistic concept of "negligible residues." Just why the statutory terminology cannot be administratively defined in interpretative regulations, this speaker fails to understand, particularly in light of the fact that no public health issue is involved. The inherent, unavoidable limitations in sensitivity of analytical control procedures must be recognized and adoption of the proposed concepts would in no sense be "letting down the bars."

It remains to be seen what course the government departments will suggest to implement these NAS-NRC recommendations.

[The End]

IDENTIFICATION SYMBOL FOR ABUSE CONTROL LAW DRUGS PROPOSED

The Food and Drug Administration has proposed that a distinctive product-identification symbol be placed on labels of all drugs covered by the Drug Abuse Control Amendments of 1965. This would apply initially to amphetamines, barbiturates and combinations of the two which are packaged after August 1, 1966. These drugs are the ones that are subject to inventory and record-keeping requirements on February 1, 1966. Any drugs that are brought under control after that date would be required to bear the symbol not later than 180 days after they become subject to control. This symbol would be placed on the principal panel of the label of each drug and would be of a contrasting color, large enough for easy identification. Food Drug Cosmetic Law Reports ¶ 80,120.

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