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Food Drug Cosmetic Law JOURNAL

The Decline of the Honor System

. . . . . MERRILL S. THOMPSON

The Proposed "Food, Drug, Cosmetic Amendments of 1963"—Are They Necessary? . . . VINCENT A. KLEINFELD

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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

The Decline of the Honor System

By MERRILL S. THOMPSON

This Talk Was Presented Before the Annual Conference of the Association of Food and Drug Officials of the United States, in Lansing, Michigan on June 18, 1963. The Speaker Is Merrill S. Thompson of Chadwell, Keck, Kayser, Ruggles & McLaren, Attorneys at Law, Chicago.

WHEN LAST OCTOBER your vice-president asked me to speak to you, I am certain that his theory was that as a young attorney in the food and drug field I might have views completely unprejudiced by experience. Since I was asked to speak because of my youth and my profession, I felt that my subject today should in some way reflect the untrampled ideals which go with youth, applied to food and drug law. The decline of our honor system immediately came to mind.

Concept of Honor System

I think of the honor system as the fundamental approach to our American way of life. It consists of freedom, under law, to do what is right, and the *presumption* that each of us, whether lawyer, businessman or government official, *will* do what is right. This concept has historically permeated each of our basic institutions, whether it be marriage and the home, or our great country's constitutional form of government. The concept of individual honor and dignity has in the past been the starting point for the enactment of laws of all kinds. It is not trite to say that under criminal law, you are innocent until proven guilty. It is not mere chance that our tax laws place great reliance upon the *self*-reporting of income by each and every one of us.

Ours is a government of laws—not individuals. No *person* is or should be the law. Law is today the most important single force affecting our lives. We rely upon it implicitly for the protection of our personal liberty, our rights in property and the future of our children. For these reasons we must be very sure that no change in the law made by any legislature, and no application of the law by any official, tears the seamless web which binds our society together in harmony, health and honor. Laws which result in the erosion of our honor system, and enforcement activity, or the lack thereof, which causes individuals and corporations to discard the honor system, seriously weaken the fabric of our nation, for it is our honor system more than anything else which distinguishes our form of government from the totalitarian governments of other lands.

It was Chief Justice Charles Evans Hughes who said:

> We have in this country but one security. You may think that the Constitution is your security—it is nothing but a piece of paper. You may think that the statutes are your security—they are nothing but words in a book. You may think that the elaborate mechanism of government is your security—it is nothing at all, unless you have sound and uncorrupted public opinion to give life to your Constitution, to give vitality to your statutes, to make efficient your government machinery.

It is the function of law, and the responsibility of law enforcement officials, to sustain an atmosphere in which honor, decency and fair play may *voluntarily* flourish and grow from within. If industry is permitted the self-respect which comes with freedom, and the assurance that our laws are just and will be justly enforced, it can and must be able to take it from there. The honor system will then work. The need for complex laws and regulations directly intruding upon day-to-day business decisions vanishes.

Any other approach to government is to me unthinkable. We can ill-afford to legislate, administer and enforce on the assumption that any representative group of citizens, such as the food and drug industry, will as a group intentionally or through negligence harm and defraud others; because at that point we would be admitting to ourselves that adequate protection would require a complete loss of liberty for all.

For these reasons, *all* of us must recognize that the honor system in industry is essential to this nation's welfare. Its preservation is fully as important to the consumer as any other goal towards which any legislature or official is working.

Fate of Honor System Depends on Enforcement Officials

Now, no one will deny that our honor system is sick. You might even believe it is dead if you rely only upon newspaper reports and other publicity in recent years. I do not believe it is dead. But whether the system lives or dies in large part depends upon the road traveled by you as enforcement officials and by the legislative bodies from Maine to Hawaii.

I said that the honor system is sick. This is apparent from several practices followed by too many members of industry which cannot be condoned. Neither can they be dismissed as the bad apples you will find in any lot. Ethical brinksmanship has become too commonplace.

For example, I have noticed that a food manufacturer, in the regular course of business, distributes an otherwise identical food item in two sizes, one weighing 12 per cent less than the other. But for the net weight declaration, the two packages and their labels are identical. Both bear the same printed price marks. Who but a food and drug lawyer or an enforcement official would ever compare the net weight copy on otherwise identical products purchased at two or more retail outlets. Yet there is a 12 per cent difference in the weight of these food items sold to customers who almost certainly believe that the same product at the same price means the same value. Since the two weights are probably never sold side by side, and the product may frequently be consumed soon after purchase, the consumer is given almost no opportunity to compare value. The reason given for this practice by the manufacturer is that certain retailers *demand* the low-weight item, at a lower cost. It seems such retailers need a higher than normal profit margin but are reluctant to charge more than the established price.

Senator Hart's Committee has of course in recent months brought to the public's attention other industry practices which the Committee considers less than forthright. Moreover, I have heard no industry representative state that there are no evils to cure. Many have acknowledged that *some* action must be taken if our honor system is to be saved. The only real controversy is over what action is to be taken, and by whom.

Primary Cause for Decay

Logic tells us that the cure for sickness should be directed to the cause. In my opinion the primary cause for the decay of our honor

system has been the developing disrespect for the laws as enforced. I believe that this growing disrespect is the result of two factors: namely, (1) the complexity of our existing laws, and (2) their erratic enforcement by multiple jurisdictions.

With respect to the first factor—the complexity of our laws—I think we are suffering from an abandonment of the type of written law which is designed in broad patterns incorporating basic precepts not bound to present technology. This old type of law reflected a faith in wise administration, and even more important, a reliance upon our judicial branch of government to apply the law equitably and fairly on a case-by-case basis. Most federal and state laws and regulations promulgated today are specific and detailed in nature, reflecting a reaction to a particular concern. Such are the laws and regulations promulgated as the result of "scares." These laws are sometimes passed in a hurry and not well thought out.

Recently Chairman Harris of the House Interstate Committee acknowledged that his Committee has been enacting food and drug legislation on a piecemeal basis, and conceded that even he was not able to keep up with what is going on. Because such laws are so detailed and specific, numerous administrative, enforcement and compliance problems are created. Enforcement officials are forced to interpret their way out of embarrassing situations. And such laws become outdated in some respects almost before they become final. Amendment and reappraisal are required constantly.

Disadvantages of Complex Form of Statute

More specifically, the adoption of such laws gives rise to the following major disadvantages affecting our honor system.

The complexity of such laws makes more severe the repercussions stemming from the lag between law and science. As in most areas of science, vast progress has been made in the production, packaging and distribution of foods and drugs. If the consumer wants a product, industry has through science and ingenuity found a way to get it to him in the best possible condition, in or out of season, and wherever he may live.

However, such progress in technology clashes head-on with detailed food and drug statutes and regulations which have the effect of binding the production and distribution of products to techniques

and knowledge soon outdated. Standardization of identity, quality, and even packaging is an increasingly popular example of the detailed type of law I have been referring to. It is being espoused by both legislators and administrative agencies alike. This approach to law obviously has merit—but only if the jurisdiction promulgating standards is able to and does keep them up to date. The *principle* of standardization will not withstand the pressures of progress unless the standards keep pace with progress. Is it any wonder that business executives and scientists lose some measure of respect for the law when they are told they cannot legally sell a significantly improved and wholesome product in one or more states because it does not comply with existing standards? Watch for the time when industry is driven to the point of popularizing the term "imitation." When the stigma presently associated with that term is gone, what effect will standards then have? Where will we go from there? And it is not unreasonable to believe that this stigma may disappear if the word "imitation" is widely used upon wholesome, nutritious and economical food products which would otherwise be barred from the market by inadequate standards?

Still another disadvantage of the complex form of statute is the fact that such laws form a roadblock on the path leading towards uniformity. In our shrinking world, uniformity of laws on a national basis is more important than it used to be. Citizens of every state are today consuming and enjoying products from every other state in the union. And I doubt that there is any state which would like to do without the present free exchange of goods in interstate commerce.

When I was in law school, the only 48-state survey I every heard of was with respect to the Securities Acts or Blue Sky Laws of the several states. I have since learned what it means to try to clear a new food product and its label for sale in our 50 states. You should be commended for the tremendous strides which have been taken to make more reasonable the state-imposed burdens on goods in interstate commerce. Commercial animal feed is a notable example, as is margarine as well. Michigan should be commended for its new margarine act. Moreover, I understand that steps are now being taken to improve conditions affecting the interstate sale of fruit juice beverages. A great deal has been accomplished by your Association and its committees. But I am sure you would agree that much work remains to be done.

To get back to my point, experience has shown that 51 legislatures find it extremely difficult to agree on the many terms and provisions making up a detailed, complex statute. The strain on uniformity is great. On the other hand, it is not nearly as difficult for all legislative bodies to agree on the terms of a general statute providing, for example, that no label should be false or misleading.

Why Uniformity of Law Is Desirable

Businessmen can give you many reasons why uniformity of law is desirable, but as a lawyer I suggest that the primary reason is the loss of dignity which the law suffers in the eyes of laymen when jurisdictions seriously differ over what is right, and what is wrong.

What is a layman to think when he is told, for example, that a wholesome cheese product, which under federal law *must* be labeled as an "imitation pasteurized process cheese spread," cannot be sold in a particular state because it *is* so labeled, whereas the same product could be sold in that same state if it were produced locally and sold under another name. The institution of law is bound to suffer, and the honor system with it.

Lack of uniformity is not only a *state* problem. Multiple jurisdictions exist on the federal level as well. A label may be acceptable to FDA, but not to the Poultry Division or the Meat Inspection Division of the Department of Agriculture. Conflicts between the Federal Trade Commission and FDA are not unheard of. Such conflict and complexity breeds confusion, and confusion breeds ill-will and disrespect.

Before leaving the subject of written laws and their relationship to our honor system, I think a direct comparison is in order.

A prime example of the old type of law is Section 403(f) of the Federal Food, Drug and Cosmetic Act. It provides in part that a food is misbranded:

> If any word, statement, or other information required . . . to appear on the label . . . is not prominently placed thereon with such conspicuousness . . . and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

This statute simply requires basic honesty. It is a rule of reason. It will apply without amendment for all time. It does not infringe upon legitimate progress in label and packaging design and develop-

ment. It relies upon enlightened enforcement under the surveillance of our courts of law. Certainly no new legal or moral standard is needed. Compare this section with Senator Hart's "Truth in Packaging" Bill. It is written in specific terms against a background of present day practices and technology. It contemplates an abandonment of the case-by-case determination of what constitutes misbranding. In short, it is designed to foster further standardization and conformity within boundaries limited by the imagination of its draftsmen. In application it must certainly appear stifling and arbitrary to *every honest* businessman. It groups the honest with the dishonest, instead of segregating them. For that reason, it cannot help but create further disrespect and resentment for the law. Such a law should only be adopted as a last resort.

I have thus far suggested that the adoption of complex written laws and regulations has contributed to the growing disrespect for the law and the accompanying deterioration of our honor system.

Responsibility of Enforcement Officials

My second explanation for the increasing disrespect for the law is in my estimation the more crucial. It relates to enforcement. Law enforcement must be just, it must be prompt, and it must *be*. If law enforcement is neither prompt nor just, the law abiding businessman is placed at a serious disadvantage. What can be more demoralizing to the business society than to lose faith in its policemen. There is *nothing* that can cause decay and chaos in human relations and in our honor system faster than the knowledge that wrongs will be righted, and virtue not rewarded.

This point was brought home to me very clearly in my law school experience. At our law school we had no proctors during our final examinations. The professor would hand out the examination papers and go back to his office. If there was any unethical conduct on the part of a student, it had to be reported, if at all, by some other student—and to a student Ethics Committee. I was a member of that Committee for three years. I could not fail to notice that as the respect for our committee increased, or suffered, so also did the effectiveness of our honor system. From that brief exposure I became everlastingly impressed with the transcending responsibility which enforcement officials such as yourselves have for the ethical tone of the business community.

As pointed out earlier, the ethical tone of our business community is perhaps not as high as we would like it to be. Though the borderline practices so publicized of late do not fairly represent the attitudes of the food and drug industry as a whole, they are troubling, and *should* cause us to re-evaluate our law enforcement practices.

Before I go further, please bear in mind that I am by no means casting my aspersions upon the personal integrity or intentions of any enforcement official, whether in this audience or elsewhere. It has been my experience that you are dedicated public servants doing the best job possible with the facilities at hand. I might add that during my six years of practice, I have not once come in contact with even a suggestion of personal impropriety or corruptness on the part of an enforcement official.

Yet, I must say that despite your calibre, the enforcement of food and drug laws and regulations is not as *just*, or as prompt, as it should and could be. A primary example of injustice to industry is the lack of uniformity in the interpretation and enforcement of laws by responsible agencies.

Uniformity of Interpretation Prerequisite to Justice

So much has been said about the importance of uniform state and federal laws, and much has been done in that direction. But uniform laws are of little benefit in the absence of uniform interpretation. For example, approximately two years ago a state official whom I admire for his convictions (and that is not intended as a pun) advised a client that labeling on a nationally distributed salad dressing product must be revised because the placement of the signature clause and ingredient clause on the back panel violated the section of his state s law which is identical to Section 403(f) of the federal act. That section, you will recall, establishes the criteria for judging the required prominence of mandatory labeling. This same section is repeated in many state laws. The same criteria had existed for many years. And the same client had had several similarly split-labeled products on the market for quite some time. What were we to do?

At only two supermarkets I was personally able to purchase 173 food items then being marketed by 121 different food manufacturers and distributors. Each item bore what we now call split-labeling. This was a strong indication that on a company-by-company basis, split-labeling of food products was the general rule. Under

such circumstances, would it be just to insist that a single company be an exception to the rule? Surely not, and after submitting the results of our survey to him, the state official involved agreed. In essence, he acknowledge that uniformity of *interpretation* was a prerequisite to justice under the circumstances.

Law Must Be Uniformly Applied

Uniformity of *enforcement* is another phase of the basic concept that a law, to be just, must be uniformly applied to those subject to its terms. Discriminatory enforcement of food and drug laws on the basis of broad policy considerations or limited enforcement resources is intolerable. Such laws must be applied uniformly to the rich and poor, and the big and small of industry. If it is a sin to defraud, it cannot be condoned no matter who practices the fraud—and this is especially true under highly competitive circumstances. Ill-gotten gains by one constitute a loss of legitimate sales by another.

In effect, this means that food law enforcement officials must not adopt the same philosophy as the traffic cop on the corner. A traffic cop can with some justification say to himself "I can't catch all the speeders, so I'll slow them down by giving a ticket to the president of Hometown Industries. His case will get into all the newspapers." An enforcement official might *feel* himself driven to that approach by the inadequacy of personnel and facilities, but think of the disrespect for the law and the cynicism such a practice engenders. How could an industry-wide honor system receive nourishment from such a selective application of the law.

Now of course some of the feeling of being singled out which does exist is due simply to the *delay* in enforcement activities against competitors. I stated earlier that law enforcement, if it is to be just, must be prompt. This is important. In my own State of Illinois, we recently adopted a constitutional amendment modernizing the Illinois court system. One of the factors which prompted the amendment was the six-year backlog of cases in some of our courts. One of our campaign slogans was: "Justice delayed is justice denied." The same slogan applies to food and drug law, only again because of keen competition, with a sharpened thrust.

Take, for example, the battle of the polyunsaturates. Very early in the game, industry was told by FDA, in a formal opinion, that the role of fats and oils in heart and artery diseases has not been estab-

lished and that any labeling claim, direct or implied, that products containing certain fats and oils will mitigate diseases of the heart would constitute misbranding. Picture yourself in my place. I advised clients that they must not violate the letter or the spirit of this pronouncement. They followed this advice—but for only so long. Daring competitors immediately started walking the legal tightrope. Our clients were assured their competitors would be prosecuted. To date, with few exceptions, they have not been. Instead, their claims became more bold. In the meantime, a particular client's position in the national market for a major product became seriously endangered. The client finally reached the point of sink or swim—and then swam with the tide. It is conceivable that if the axe ever does fall, our client will be among those hurt.

It does not really matter what is causing the delay. The damage to the image of law is done. The next time such a situation arises and I am called upon for legal advice, could you blame this client if he reacts on a note of cynicism? He has lost some of his respect for the law.

Change Law or Enforce It

The last comment I have concerning the enforcement of the law is probably the least significant at the present time. It is simply that if there is a law on the books, either change it promptly or enforce it. Disregard for the law by officers of the law cannot help but have a subtle and insidious effect upon a citizen's respect for the law. I consider it an unhappy occasion when I must advise a client that a state or federal law or regulation clearly prohibits an act, but because the law is outmoded or the enforcement agency is irresolute, the enforcement officials are disregarding it. It is not only dangerous for an official to exercise such discretion, but it also encourages a poor attitude on the part of businessmen.

Thus far my comments have been on the negative side. I have said that our written laws may already be too complex. I have also stated that their enforcement is not always just, is not always prompt, and does not always occur. Our honor system has suffered as a result. But surely we have not yet reached the point where the honor system deserves to be abandoned. An attempt should first be made to revitalize it.

Industry Must Act Affirmatively

In *my* opinion, the place to start is to give you and your responsibilities the recognition they warrant in the areas of compensation, on-the-job training, personnel and facilities. Industry can and should help in this task. It should use its resources to persuade consumer groups, legislatures, and the public as a whole to upgrade the quality and effectiveness of our enforcement agencies. To be *against* ill-advised measures is not enough. Industry must act affirmatively if it is to preserve the right to do business under laws promulgated on the presumption of voluntary compliance.

If the food and drug industry's honor system is faltering, let us not unthinkingly make written law the scapegoat. We know that it is relatively inexpensive in terms of dollars and cents to promulgate new regulations. It is true that in the short run it costs the taxpayer less to place an entire industry behind bars than it does to bolster our police force to the point where it can effectively root out lawlessness within that industry. But where freedom is involved, our way has been to spend billions in money and millions in lives to preserve it. We have not accepted the easy way out.

Why should we as a nation now accept searching parties in the form of factory inspection simply to make enforcement easier? Why should we all not flinch at further specific and detailed laws and regulations when they are proposed because an enforcement agency has not been able to persuade our courts of law to agree with it as to what is and is not misbranding? Are we so convinced that our courts are incompetent? Why should we as a people collectively turn our backs on our right to be *judged* individually rather than merely *sentenced* individually by a court of law?

More and more regulation is not the answer to our ills. Distrust of industry, and abandonment of our reliance upon the judicial branch of our government, are paths to be followed only with great reluctance. Our existing laws have not been tested and proven inadequate. I submit that our past unwillingness to allocate sufficient manpower, money, and prestige to law enforcement is simply catching up with us. What good can come of further laws and regulations if we do not first improve our facilities for their enforcement?

Of major concern to us all is that enigma, the consumer. I have read no proposals which have not revolved about the interests of

consumers. But we should not lose sight of the fact that *every* man in this country is a consumer, and consumers are in fact enforcement officials, lawyers, stockholders, business executives, day laborers, as well as housewives. We all have a stake not only in a safe food supply and honest labeling, but also in the preservation of the way of life which we have known and which we want our children to enjoy.

Conclusion

The food and drug industry's remarkable and praiseworthy service to consumers has progressed and developed under a system embodying freedom under law justly enforced. Freedom, law and enforcement are the ingredients. We should proceed cautiously when adjusting their proportions. When the formula is right, our honor system will work. **[The End]**

CLEAN WHEAT PROGRAM YIELDS GOOD RESULTS

The Clean Wheat Program, a joint effort by federal and state agencies and the grain and milling industries to improve the quality of grain, continued to yield good results in fiscal year 1963.

Food and Drug Administration district offices collected and examined more wheat samples during the year and found less rodent and insect contamination than in any previous year.

Out of a total of 2,190 samples collected at random from interstate shipments and examined for rodent contamination, only 17, or 0.8 per cent, was found violative because of rodent contamination. This compares with a rate of 1.3 per cent for random samples collected in fiscal 1962. This rate has declined consistently each year since 1959, when it was 3.3 per cent.

Altogether, FDA collected and examined 2,486 samples, including 296 "planned" samples (where there was reason to suspect rodent contamination), and found 64 shipments to be in violation. Forty shipments were seized and 24 voluntarily diverted or referred to state officials for diversion from human food channels.

A total of 2,216 samples of wheat were examined by FDA for insect damage. Only four, all collected at random, were found to be in violation on that score, compared to 12 samples found to contain excessive insect damage in fiscal 1962. One shipment was seized and the other three were referred to state authorities or voluntarily diverted to non-human use.

FDA districts increased their examinations for "pink" (mercury contaminated) wheat to 2,243 samples in fiscal 1963 from 1,667 samples in 1962. Ten shipments of wheat with mercury contamination were seized.

One shipment of barley containing mercury and one shipment of treated shelled feed corn containing captan were also seized.

The Proposed "Food, Drug, Cosmetic Amendments of 1963" Are They Necessary?

By VINCENT A. KLEINFELD

The Author, a Member of the Washington, D. C. Law Firm of Bernstein, Kleinfeld & Alper, Presented This Paper at the Annual Meeting of the Federal Bar Association in Philadelphia, Pennsylvania, on September 26, 1963.

THE ANSWER TO THE QUESTION of whether the proposed further amendments to the Federal Food, Drug and Cosmetic Act contained in H. R. 6788 (introduced by the Chairman of the House Committee of Interstate and Foreign Commerce and apparently containing the recommendations of the Food and Drug Administration) should be enacted is not an easy one. The reply depends in large part on one's philosophical approach to the place of government in our society. The amendments would probably give the consumer some greater protection than he now has. But is this sufficient reason for exercising the greater control over the affected industries that would result from the passage of the bill?

Presumably, if one is of the view that the greatest possible protection must be extended to our citizenry in all areas, including the vital field of foods and drugs, the state must enter into the picture in an almost unlimited manner. For example:

We would amend the Securities Exchange Act so as not to limit its coverage to making certain that representations with respect to a stock issue be completely accurate and that there be no failure to disclose material facts. We would broaden its scope by providing that the Securities and Exchange Commission should have the authority to determine whether the sale of the stock promised to be a beneficial investment for the purchaser and to forbid the transaction if it appeared to be a foolish one from his viewpoint.

The Federal Communications Commission would presumably be authorized to decide what types of TV and radio programs should be permitted.

The Federal Trade Commission would examine all advertising of all commodities offered to the consuming public before it is employed.

And to solve in a realistic manner the continuing and costly farm programs, the government would tell each producer what and how much he might grow and probably would not permit the marginal farmer to continue in his vocation at all.

Complete Government Control

If our aim is to convey to the consumer the utmost possible protection, every food, drug and cosmetic company would have to be licensed by the government after demonstrating that it possessed the necessary capital, background and personnel with the requisite qualifications and integrity. As a matter of fact, to round the picture out nicely, it would seem that the state might determine what drugs are necessary in what areas of medicine and itself exclusively perform all pharmacological and clinical research. Since we know that, unfortunately, some doctors use potent and sometimes dangerous drugs such as certain of the antibiotics when they should not, it may be that, to protect the consumer further, a law should be enacted setting forth the particular conditions for which specific drugs may be prescribed.

If we do not wish to reach what, I hope, are these absurdities, then somewhere along the road of consumer protection we must pause and query whether the additional protection contemplated (and it presumably would constitute a further shield) may not be outweighed by unnecessary encroachment on private enterprise and the liabilities which must necessarily go along with overly big government.

Compromises Necessary

In the passage of social legislation, compromises are frequently inevitable if some law is to be passed. When the Federal Food, Drug and Cosmetic Act was finally passed in 1938, after five years of legislative maneuvering, many consumer groups were aghast at some of the compromises which were essential at that time if any law were to be enacted.

Actually, there were a number of weaknesses in the Act, but it nevertheless was a much stronger vehicle than the prior Food and

Drugs Act of 1906. In any event, the expressed desire of the courts, including the Supreme Court, to construe the 1938 Act liberally, added to the policy of the FDA to interpret the Act in such manner as it believes will inure to the benefit of the consumer, has converted a statute which many thought weak into a potent weapon for public protection.

Interpretation by the Courts

The courts have tremendously strengthened the coverage of the Federal Food, Drug and Cosmetic Act. Thus, the Supreme Court has sustained the manner in which "labeling" has been construed by the FDA so that the term includes literature shipped many months apart from the drug, if it is demonstrated that there is a textual relationship between the drug and the literature. Again, although Congress had thought that "advertising" was to be within the jurisdiction of the Federal Trade Commission and "labeling" within the jurisdiction of the FDA the courts have held that a drug is misbranded and its distributor subject to criminal prosecution if its labeling does not contain adequate directions for use of the product in the conditions for which it is advertised. Of course, by this ingenious device, once the conditions are set forth in the labeling, the government contends that a false and misleading claim may thereby be made.

Discussion of Cases

A brief mention of a few cases may be helpful to indicate the broad coverage given to the Federal Food, Drug and Cosmetic Act by the courts, even in criminal prosecutions. In the *Sullivan* case, sulfathiazole pills had been shipped by the manufacturer from Illinois to Georgia. A small retail druggist in Georgia purchased a portion of the tablets in that state and sold a few of them in his store in that state to a FDA inspector without getting a prescription. The regulations, which were ambiguous, required a prescription. The five years of legislative history of the Act contained not the slightest mention of the prosecution of retail druggists. Sullivan's conviction was affirmed by the Supreme Court as a violation of a section of the Act which made it an offense to alter, mutilate, destroy, obliterate, remove in whole or in part the labeling of, or the doing of any other act with respect to a food or drug that had been shipped in interstate commerce which caused it to become misbranded.[1]

[1] CCH Food Drug Cosmetic Law Reports, ¶ 2171.701, 2231.033, 70,151.91, 71,031.27, 332 U. S. 689, 68 S. Ct. 331 (1948).

In the *Spectrochrome* case, Olsen, in Oregon, purchased a fantastic device from its manufacturer in New Jersey. False and misleading therapeutic claims had been made for the device by the manufacturer. Olsen paid for the device and kept it in his home, where it was used only by him and his mother. It was seized in his home since the seizure section of the Act provided that a drug or device shipped in interstate commerce in a misbranded condition could be seized "at any time thereafter." Solely because of that language, the United States Court of Appeals for the Ninth Circuit found no difficulty in declaring that the seizure and condemnation of the device was proper.[2]

An Important Decision

The rationale of these cases, and an indication of the urgent desire of the courts to close "loopholes" in the 1938 Act, is best set forth by a leading case decided by the Supreme Court, involving the criminal prosecution of a small corporation and its president for having shipped a misbranded drug in interstate commerce. The president had had no direct or active part in the shipment and in fact was out of the state when the offense occurred. What little legislative history there was on the problem indicated that Congress had probably decided not to provide for the prosecution of corporate officers and agents in such circumstances. The Supreme Court in a five-to-four decision affirming the conviction of the officer, said in part:

> The purposes of the legislation thus touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of Government and not merely as a collection of English words.

In the same case, the Supreme Court also held that the government need not prove intent in order to obtain a conviction on a criminal charge. This rule of absolute liability is based, of course, on the public policy consideration that, in the area of foods and drugs, the public is entitled to great protection.

Amendments to the 1938 Act

In addition to the many judicial holdings which have immeasurably increased the coverage of the 1938 Act, subsequent amendments have also greatly broadened its scope. More and more, the Act is

[2] *United States v. One Article of Device Labeled "Spectro-Chrome,"* CCH FOOD DRUG COSMETIC LAW REPORTS, ¶ 2231.88, 161 F. 2d 669 (CA-9 1947), rev'g DC Ore.

being transformed from a punitive to a licensing statute. In 1948, the Miller Amendment was passed. The effect of this was to bring within the coverage of the law virtually every drugstore, restaurant, grocery store, beauty shop and barber shop in the country. This is because both the language of the amendment and its legislative history reveal that if a product covered by the Act once moves across a state line it is forever after subject to the provisions of the statute. The Pesticide Chemicals Act of 1954 strengthened the statute with respect to the use of pesticidal chemicals and their residues in or on agricultural commodities.

The Food Additives Amendment of 1958 provides that before an additive is utilized in our food supply it must be shown to be safe. In addition, the manufacturer must demonstrate that the use of the product does not violate the Act. This, of course, transferred the burden of proof to the manufacturer. In 1960, the Color Additive Amendments were enacted, providing similarly but going further with respect to all colors for use in foods, drugs and cosmetics.

The 1962 Amendments

Then came thalidomide and the inevitable passage of the far-reaching Drug Amendments of 1962. These amendments conveyed tremendous authority to the FDA and, as is customary, the regulations issued under the amendments tightened even further the control exercised over drugs, particularly prescription drugs.

The Drug Amendments of 1962 are extremely broad in scope. They define a drug as adulterated if it is manufactured in a plant which is not equipped and operated in conformity with good manufacturing practices to assure that the drug meets the requirements of the Act as to safety and has the identity, strength, quality and purity it is represented to possess. No new drug may be introduced into interstate commerce unless it has the prior approval of the FDA with respect to both its safety and effectiveness. A summary and immediate suspension of an approved new drug can be accomplished if the Secretary of Health, Education and Welfare determines that "there is an imminent hazard to the public health." The Secretary may also withdraw approval of a new drug if "there is a lack of substantial evidence that the drug will have the effect" claimed for it.

The FDA is authorized to require all holders of approved new drug applications to maintain records and file reports relating to

experience with the drugs, and the failure to maintain the records or file the reports is grounds for suspension of the new drug application and also constitutes a criminal violation. These records must be made available to FDA inspectors for examination, verification and copying. The amendments also create very strict control over the distribution of drugs for investigational purposes before they are commercially marketed in an attempt to avoid another thalidomide tragedy. Certification or exemption of batches of every antibiotic for human use is provided.

Every concern producing drugs, whether it is engaged in interstate or intrastate commerce, must register annually with the FDA and must be inspected at least once every two years. The advertisements of a prescription drug must include its established name in type at least half as large as the proprietary name, the quantitative formula of the drug to the extent required on its label and a brief summary setting forth the drug's side effects, contraindications and effectiveness. Even before the passage of the Drug Amendments of 1962, the FDA, by regulation, had required that the labeling of every prescription set forth in a full disclosure of all side effects and contraindications.

FDA and the Courts

The FDA customarily proceeds in the courts rather than by administrative proceedings. If a product is alleged to be adulterated or misbranded, seizure or injunction proceedings may be instituted, and the burden is on the government to establish its case by a preponderance of the evidence. Of course, if criminal proceedings are initiated, the government must prove its charges beyond a reasonable doubt. At first glance, this may seem to place an undue burden upon the government in the highly important and technical food and drug field, involving the protection of both the consumer's health and purse. By reason of the zeal and energy of the agency and the "liberal" construction of the Act by the courts, the government is very rarely defeated in the courts, no matter what position it takes. And when the most unusual case involving a really important issue is lost, the FDA (like Antaeus the wrestler who became more powerful each time he was thrown to the ground) goes to Congress to turn that most important defeat into victory. Why, then, is there a necessity for the passage of the Food, Drug and Cosmetic Amendments of 1963?

Objectives Sought by Proposed 1963 Amendments

The major ends sought to be accomplished by the proposed amendments are: (1) extending the factory inspection authority to include all products rather than merely prescription drugs; (2) providing for the premarketing clearance of cosmetics for safety; (3) requiring the premarketing clearance of therapeutic devices for safety and efficacy; and (4) providing for cautionary labeling of foods, drugs and containers with respect to possible accidental injury.

Of course, it is pleasant from any agency's viewpoint to have the authority to enter a plant and examine every paper and record, including formulas which may contain trade secrets. No necessity from the public health viewpoint, however, has been demonstrated. Reports have been made to Congress of the considerable number of instances in which requests for information and examination of records by inspectors have been denied by the owners of food, drug and cosmetic establishments. No mention is made of the fact that these refusals occurred because the law did not authorize such requests. Otherwise, those who refuse would be subject to criminal prosecution. In other words, the inspection authority must be increased because the government is held to the inspection authority conveyed by Congress.

Procedure Under Existing Law

Under existing law, inspectors are authorized to enter establishments and examine the sanitary conditions and all equipment, finished and unfinished materials, containers and labeling. Samples may be obtained. These, of course, are subject to the expert analysis of the government. Foods, drugs and cosmetics are subject to seizure and condemnation (and their manufacturers liable to criminal prosecution) not only if they consist in whole or in part of any filthy, putrid or decomposed substance but also if they have been prepared, packed or held under insanitary conditions whereby they may have become contaminated with filth or rendered injurious to health. In the case of prescription drugs, new drugs and antibiotic-containing drugs, the inspection authority is vast, encompassing virtually everything, including books and records, within an establishment. There seems to be no real need, in view of these circumstances, for granting further authority for unlimited fishing expeditions into the books and records of a manufacturer of foods, devices, cosmetics and old drugs.

New Provisions Largely Unnecessary

New food additives, colors, new drugs and antibiotics must be demonstrated to be safe before they are marketed, and the impelling consideration of safety would appear to require that new cosmetics and new devices must also be demonstrated to be free from hazard before they are placed in the channels of commerce. Particularly with respect to cosmetics, however, the complicated provisions in H. R. 6788 are, to a large extent, unnecessary. It is to be hoped that amendments will be made to the bill carrying into effect the major and beneficial aim of providing in a clear and simple manner for clearance by the FDA of the safety of new cosmetics and devices before they are distributed in interstate commerce, but not taking advantage of this opportunity by imposing further unnecessary restrictions.

In the case of cosmetics, for example, is it essential to provide that a new cosmetic application may not be approved if the data before the Secretary shows that the proposed labeling of the cosmetic is false or misleading in any particular or that the cosmetic "would otherwise be misbranded or adulterated." The Federal Food, Drug and Cosmetic Act has always provided that a cosmetic is illegal if it is adulterated or misbranded, including "if its labeling is false or misleading in any particular." The government has had no difficulty in prevailing when it has chosen to institute suit on charges of adulteration or misbranding. As a matter of fact, usually the mere threat of regulatory action, with the attendant publicity, is sufficient to correct the situation. In addition, the definitions in the Act of "drug" and "new drug" are so broad as to bring into those categories, with the tight controls which presently exist for those categories, many cosmetics employing physiologically active ingredients and for which grandiose claims are made.

Is it essential, with respect to cosmetics, for further limiting the concept of "generally recognized as safe" so that it will not necessarily include the best possible factor, use of the product on and by the only really reliable test animal—human beings? In the vital area of "new drugs," the term, with respect to safety, is defined essentially as a drug which is not generally recognized as safe by qualified experts. What compelling need exists for defining a "new cosmetic" as a cosmetic which is not generally recognized by qualified experts as having been adequately shown, "through scientific investigations," to be safe?

As I indicated at the beginning, there is more than one public policy consideration to be borne in mind in connection with the passage of remedial social legislation. Of course, by far the most important objective is to protect the health of the consumer, who is particularly an amateur in the essential field of foods, drugs, devices and cosmetics. But do we wish to go so far as virtually to create a complete licensing system in this area? Do we seek to impose requirements upon industry which do not in reality give sufficient additional protection to the consumer to outweigh the complications, delay, and confusion which must ensue, together with the inevitable increase in costs which sooner or later are borne by those whom we are endeavoring to protect? Do we not wish to reach some point where we hesitate to give more power even to Big Brother?

Towards the end of the nineteenth century, Thomas Henry Huxley is reported to have said:

> If some great power would agree to make me always think what is true and do what is right, on condition of being turned into a sort of clock and wound up every morning before I got out of bed, I should instantly close with the offer.

Is this our goal? [The End]

HAIR DYE EXEMPTION

The Food and Drug Administration's recent regulation limiting the exemption for hair dyes under the Federal Food, Drug and Cosmetic Act applies immediately only to new hair dye formulations coming on the market, according to Commissioner George P. Larrick. Products currently being marketed will not be affected until June 22, 1965.

This announcement was made in connection with an order in the *Federal Register* of October 3, dropping a former definition of a hair dye in FDA's color regulations.

The deleted regulation (21 CFR 1.200) was superseded by new regulations (Section 8.1(u)) published June 22, 1963, under the 1960 Color Additives Amendment.

The "hair dye" exemption applies to hair dyes which would otherwise be banned by the Act as containing poisonous or deleterious substances, provided the products bear specified caution labeling and adequate directions for patch testing.

The patch test does not afford protection against all types of possibly harmful ingredients of hair dyes, the FDA said, and the new regulation limits the exemption to products for which the patch test would be meaningful.

The deletion of the former definition clears the record to avoid possible confusion, the FDA explained.

FDA's Regulations Under the Kefauver-Harris Drug Amendments of 1962

By WILLIAM W. GOODRICH

The Assistant General Counsel for Food and Drugs of the United States Department of Health, Education and Welfare Delivered This Address at the Annual Meeting and Seminar of the Drug and Allied Products Guild, Inc. in Ellenville, New York on June 20, 1963.

THE FINAL REGULATIONS drawn to put fully into effect the new provisions of the 1962 Drug Amendments are carried in the *Federal Register* of June 20, 1963.

Here is what we have done—and why.

QUALITY CONTROLS

The first set of regulations describes what we regard as minimum conditions of current good manufacturing practice. Under the new law, a drug is deemed adulterated if the methods, facilities and controls used in manufacture, processing, packing and holding do not conform to or are not operated in conformity with current good manufacturing practice to assure the safety and integrity of the finished product. The purpose of this provision is to require that all drugs—not just new drugs as in the past—are prepared in proper facilities, with adequate equipment, and with all needed control procedures. If they are not, the drugs are deemed adulterated although the particular products may not fail in routine tests or assays. The point is that failure to meet minimum standards involves a constant risk of failure of the drug—a risk that can and should be avoided.

The regulations published on June 20, 1963, apply to the preparation of drugs in final dosage form. Bulk pharmaceuticals and medicated feeds will be the subject of later regulations, following in general the pattern that has been established but with some needed modifications for special problems for those products.

What These Regulations Cover

Briefly, these regulations deal with the buildings, equipment, key personnel, the handling and control of components, production and control records and procedures, the product containers, packaging and labeling controls, laboratory procedures, distribution records, stability testing and producing outdating, and the complaint file.

There was surprisingly little controversy over the content of these regulations. They have been adjusted to take care of certainly most of the apparent defects in the proposal draft published last February. And there were a number of minor language changes—such as changing "insure" to "assure"—to clarify our intent.

As to matters of substance, first it is made clear that automation is proper and permissible in drug production and control. But there has to be adequate inspection and checking on the machines to see that they are functioning properly.

Second, the provision in the proposal relating to building design has been eliminated. So long as the building is suitable in size, construction, and location to permit proper maintenance and orderly and sanitary operations at all of the critical stages, it can be used though not specifically designed as a drug processing establishment.

Third, the provisions relating to nonreactive and nonabsorptive surfaces of machinery and equipment were clarified to require that they be nonreactive, nonadditive, and nonabsorptive to the extent that they do not significantly affect the components and the finished drugs.

Fourth, key personnel may qualify by training or experience or both. The important point is that they be properly qualified.

Fifth, the record requirements were clarified to make clear that the master formula record did not have to be kept at a single place, and that code numbers did not have to be placed on invoices when the manufacturer or distributor had another suitable method of identifying the drugs he has shipped should a recall become necessary.

Finally, two new provisions were included. These require the maintenance of reserve samples and a complaint file.

LABELING AND ADVERTISING

The second set of regulations is in two parts, dealing with the presentation of proprietary and established names of drugs and ingredients of drugs on the labels and in labeling and with the content of prescription drug advertising.

There were two major points of controversy about these regulations.

Objection was taken to the requirement that the established name be presented each time the trade name of a drug or ingredient is used on labels, in labeling, or in prescription drug advertisements.

And the provision calling for preclearance of some prescription drug advertisements was challenged as both unnecessary and unauthorized.

There were, of course, other points but these were by all odds the most critical.

The law behind the "each time" requirement is this: the label of any drug must bear, to the exclusion of any other nonproprietary name, the established name of the drug, and if fabricated from two or more ingredients, the established name of each ingredient; if the drug is a prescription drug its established name, and the established names of its active ingredients, are to be printed prominently and in type at least half as large as that used for any proprietary name of the drug or any of its ingredients in any label, labeling or advertising.

The vital language here is that the established name must appear in type at least half as large as that used for presenting "any proprietary name."

We had many submissions on the plain meaning of this provision. "Any" was said to mean any one proprietary name; the manufacturer was claimed to have the right to present the established name with any presentation of the proprietary name, so long as he met the requirement of prominence. And clearly, it was argued, there is nothing in this statute which commands the repetition of the established name everytime the proprietary name is used.

We concluded that the plain intent of the Congress was to the contrary. The regulations require the "each time" presentation.

The Senate's report, filed in August, explained that its bill would require that on labels or any labeling, wherever a trade or brand name is used, the established name must also be shown in type at least half as large.

In the House of Representatives, a floor amendment was adopted to change this—to require that the established name be presented with the trade name at the first place the trade name was used and at the most prominent place if other than the first place.

The Conference Committee eliminated the House proviso, returned to the original Senate version, and Senator Kefauver in pre-

senting the Conference Report on the Senate floor explained that the House Amendment had been rejected as an unacceptable limitation on the number of times that the established name should be presented. The established name was to appear "wherever" the trade name was used.

So with the evident intent of the Congress before us and with the obligation to specify how the trade and established names were to be related, we adopted the "each time" requirement. The law permits exemptions to be made if it can be shown that this requirement is impractical in any special circumstances.

Mandatory Preclearance of Advertisements and "Extraordinary Circumstances"

Mandatory preclearance of prescription drug advertisements is expressly prohibited "except in extraordinary circumstances." The regulations have undertaken to describe what we regard as such circumstances. You will recall that we are talking about the brief summary relating to side effects, contraindications, and effectiveness, which may be required to appear in prescription drug advertisements and descriptive material.

Preclearance of the content of any such advertisement is required only in the extraordinary case where the drug has the potentiality of causing death or serious injury, where the danger is of recent origin or has not been widely publicized in medical literature, *and* where FDA has notified the sponsor by certified mail that advertisements must be approved before dissemination.

There were two basic objections to the regulation as originally proposed. The first was that almost any drug has this potentiality—especially if misused—and the second was that the sponsor had no opportunity for a hearing on the preclearance requirement.

We believe that relatively few drugs will fall into the extraordinary circumstance class. We certainly have no intention of requiring any large volume of advertisements to be precleared. We have undertaken the responsibility of both defining the class in general terms and of identifying to the sponsor the particular drugs that must be precleared. No drug advertisement has to be precleared until the certified letter is received. Any drug advertisement may be submitted on a voluntary basis for review.

But does this deny the sponsor his opportunity to contest the issue of needed preclearance? As a practial matter, we think not.

The content of the labeling and advertisements of all new drugs is established through the new drug procedures. Ample opportunity for a hearing and for judicial review exists when the drug is being approved for marketing or when a supplement to warn of new and unexpected dangers is being processed. All that preclearance is intended to do is make sure the ads for especially dangerous drugs actually contain adequate information about serious dangers that are of recent origin and have not been widely made known to the medical profession. If a second hearing had to be held at this stage to establish the need for preclearance, we would have no alternative but to require withholding of all ads until the hearing could be completed. We think the final draft offers a practical way to proceed with advertising without undue delays and with assurance that the extraordinary hazards which sometimes attend the use of prescription drugs will be promptly and effectively brought to the attention of the medical profession.

Advertising Content

You may be asking at this point how the content of the prescription drug advertisement is controlled through the new drug procedures. Actually Congress provided that the brief summary information should be presented as required by the Department's regulations. The regulations allow advertising claims which have been approved in new drug applications and in labeling approved for use with certified drugs. In other words, the drug may be advertised only for conditions for which it has been approved for marketing. If the article is not a new drug or a certifiable drug, the regulations permit it to be advertised for those conditions for which it is generally recognized as safe and for which there is substantial evidence to support the claims of effectiveness. The pinch of this last regulation is that some claims protected by the Grandfather Clause in the labeling cannot be used in prescription drug advertising because they cannot be regarded as true statements of the drug's effectiveness.

Time does not permit a detailed discussion of the other features of this group of regulations, which cover such things as the required prominence of ingredient and formula information, the use of misleading proprietary names, certain exemptions for labels for small packages, and the prominence and the balance between good and bad that is to be achieved in presenting all prescription drug advertisements regardless of their size.

To avoid confusion as to what is advertising, which requires only the brief summary, and what is labeling, which requires the so-called full disclosure, the regulations have specified that brochures, price lists, catalogs, house organs, literature reprints and similar pieces of promotional material are regarded as labeling.

NEW DRUG PROCEDURES

Perhaps the most important of the three sets of regulations are those revising the existing new drug regulations. Their essential purpose is to specify the kinds of information and the quality of data that is to be presented to support the claims of effectiveness, to establish the rules as to what records are to be kept and the what and when of the reporting responsibility, and to change the automatic clearance procedure of the past into an affirmative approval for the marketing of new drugs.

The major objections to the regulations as proposed were that they called for too much data in the new drug applications and in supplements, that they perpetuated the "incomplete filing" procedure, and that the reporting provisions demanded too much information too soon.

New Drug Form Redesigned

As to the content of new drug applications and supplements, the new drug form has been redesigned to merge with the investigational use regulations we placed in effect in February. More data is required about the preclinical and the clinical investigations to bring to us "substantial evidence" that the drug will in fact have the effectiveness claimed for it. The regulations have been clarified to make it clear that what is called for is all of the information obtained by or otherwise reported to the applicant with respect to the particular drug and any relevantly related drugs. As originally written, the regulations required all information available to the applicant, and some persons regarded this as a requirement that we be supplied a search and summary of the world's literature. We have now provided that we must have, in addition to all tests and clinical studies conducted by or otherwise obtained by the applicant, adequate background from the literature about the particular drug and any others that are relevantly related. This is nothing more than is customarily acquired by any prudent drug manufacturer.

Since the law was originally enacted in 1938, we have, as a matter of administrative practice, refused to file new drug applications that

fail to contain information essential for action on them. This has allowed for informal negotiating for additional needed information without the stress of deadlines. You will recall that the thalidomide application was called incomplete several times and the matter was pending for a good deal longer than 180 days.

The drug industry now contends that, since the automatic effectiveness provided for under the original Act has been eliminated, we should eliminate the incomplete filing provision. They argue that any application, no matter what its content, is entitled to filing and that we are required to approve it or deny it. Plainly, if the application simply leaves out certain information that is expressly required by the Act, it may be called incomplete. But the issue arises sharply when the application appears to be complete but a cursory examination shows that its content is seriously deficient in some of the important substantive respects.

"Incomplete Filing" Provision Retained

The new draft retains the "incomplete filing" provision where the information is so inadequate that the application clearly is not approvable, but provides that whenever an applicant is notified that we regard his application as incomplete, he may request a filing over protest, in which case the matter will be reviewed within 30 days and the application approved or the applicant informed as to his opportunity for a hearing. This technique will continue to permit considerable informal handling of new drug applications up until the time of filing over protest when they become matters for administrative adjudicatory hearings. The regulations as revised will avoid any undue delays in taking action on applications.

The reporting requirements were objected to, as I have said, as calling for too much information too soon. We have changed the requirement for reporting unexpected side effects within five days and have substituted a 15-day date. Information as to drug mix-ups, contamination, or unusual failures are to be reported as soon as received by the applicant. Unexpected side effects have been defined to mean side effects not previously encountered or an unusual incidence of side effects that were not expected. The three-months report called for during the first year of marketing of a new drug will have to report all side effects encountered so that we may have a better idea of the incidence of expected side effects.

There was some objection to our requirement that all promotional pieces and advertising used after the new drug application is approved be submitted to us. Since these promotional pieces are circulated widely to the medical profession, we believe it essential that this information be sent in for incorporation in the new drug files.

Grandfather Clause

Finally, may we say a few words about the Grandfather Clause.

If a drug is one that is generally recognized as safe and effective for its intended use, it is not a new drug under the new definition and requires no preclearance of its claims.

If it is a new drug either because not generally recognized as safe or not generally recognized as effective for its claimed uses, it must be submitted as a new drug with an adequate application.

The effectiveness provisions were delayed for a period of two years from October 10, 1962, for all products covered by a new drug application. As we read this, the holder of new drug application has about 16 months to assemble and present the substantial evidence to support his claims. Perhaps the application itself already contains such data. If it does, you need do nothing. But we would strongly recommend a review of these old applications to be sure that they contain the needed medical data. In October 1964, we will be free to proceed against any application on the ground that it does not contain substantial evidence to support the claims.

What is the status of a drug that was once a new drug but has been declared no longer a new drug? This product is covered by a new drug application in the sense that its labeling pattern was established through the new drug procedures. After October, 1964 we can move against the old new drug applications and if suspended all similar products will be affected though they themselves were never specifically the subject of a new drug application.

As to drugs which were commercially available last October 9, which were not new drugs on that date, and which had never been covered by a new drug application, these drugs may continue to be marketed by anyone without proof of safety or effectiveness, so long as the old claims are used for products of identical composition with the one that was commercially available on October 9.

This Grandfather Clause applies only with respect to the problem of efficacy. We can proceed to suspend any new drug application at

any time by proving that clinical experience has shown it no longer to be safe. And the new law allows suspension on the ground that the claims are false and misleading in any particular and were not corrected within a reasonable time after receipt of notice that the claims are regarded as false or misleading.

There is much more that could be said, but the clock is racing and I have already talked longer than I like. Thank you for inviting me to to meet with you. **[The End]**

CARBONATED SOFT DRINK STANDARDS PROPOSED

The *Federal Register* of September 14 contained definitions and standards of identity for nonalcoholic carbonated soft drinks as proposed by the American Bottlers of Carbonated Beverages.

At the same time, FDA further extended the industry's exemption from the requirement that soft drink labels list ingredients required by law for unstandardized foods, pending an opportunity to consider the proposed standards. The exemption would have expired September 15. All interested persons are invited to present views and comments in writing within 60 days of publication in the *Federal Register*. These should be addressed to the Hearing Clerk, Department of Health, Education and Welfare, Room 5440, 330 Independence Avenue, S. W., Washington, D. C. 20201.

The proposed standards would cover plain soda water (or club soda), soda water sweetened with one or more nutritive sweeteners and flavored and colored, and soda water artificially sweetened and flavored and colored.

"Soda water" would be identified as "the class of food characterized by its carbonation," and would contain not less than the amount of carbon dioxide the beverage would absorb at atmospheric pressure and 60 degrees Fahrenheit.

Natural flavoring ingredients would be derived from fruits, vegetables, berries, buds, roots, leaves and similar plant materials.

Products described by names which include "cola," "kola," "cola beverage," "cola-type beverage," "pepper," "pepper beverage" or "pepper-type beverage," would contain caffeine in a quantity not exceeding 0.02 per cent by weight. (This is about half the amount of caffeine in a cup of coffee or tea.)

The proposed standards would permit the optional use of ingredients either generally recognized as safe or subject to safety requirements of the Food Additives Amendment. These include a variety of acidifying, buffering, emulsifying, stabilizing, viscosity-producing, and foaming and anti-foaming agents, and one or more of 17 chemical preservatives. Also permitted would be carriers for flavoring agents, including ethyl alcohol in an amount not exceeding 0.5 per cent, and one or more of the nutrients ascorbic acid (Vitamin C) or thiamine hydrochloride (Vitamin B_1).

The products proposed to be called "artificially sweetened soda water" would be sweetened with one or more of the non-nutritive cyclamate and saccharin salts permitted in certain other foods.

New Drugs and the Statistician

By EARL L. MEYERS

The Author Is Chief of the Controls Evaluation Branch, Division of New Drugs, Bureau of Medicine, Food and Drug Administration, United States Department of Health, Education and Welfare. He Presented This Talk at the Fifteenth Rutgers All-Day Conference on Quality Control and Statistics in Industry, of the American Society for Quality-Control, September 7, 1963, at Rutgers University, New Brunswick, New Jersey.

IT IS INDEED A PLEASURE to be here today for your Fifteenth Annual Rutgers Conference on Quality Control and Statistics in Industry. I would be less than truthful if I did not express my appreciation of the cordial invitation to participate in your program. Although this is the first time that I have attended one of your meetings I have met a number of you personally on past occasions and it is good to renew acquaintanceships.

I am not here to urge you forward in your use of statistics. The literature in your field makes it evident that there is no need for me to do so. Rather, I would like to discuss some of the broad aspects that you, as a statistician will be involved in as a member of the team of chemists, pharmacologists, clinicians, and management in investigating, developing and marketing new drugs.

The development of so many new drugs, the financial growth of the pharmaceutical industry, and the increasing sophistication of the public in all phases of science has attracted interest in drugs and the drug industry. So it is that continuing success in the development and distribution of new drugs presents a serious challenge to the many segments involved in this complex and dynamic process. For the research chemist, the pharmacologist, the clinical investigator, and the statistician, there are unique problems and responsibilities.

In my discussion today, I will generally confine my remarks with respect to the problems and responsibilities of the statistician to the areas of new drug animal studies, clinical studies, quality control studies, and marketing experience (adverse reactions).

Review of Principles Under Present Operation

It might be prudent at this point to review with you the principles under which we now are operating the new drug provisions of the Food, Drug and Cosmetic Act in these areas.

The philosophical approach to the control of new drugs by the Food and Drug Administration can perhaps best be related to the intent of the law as it was passed. Basically, it is to insure that adequate safety and effectiveness testing of new drugs have been accomplished before marketing. This is achieved by prohibiting interstate commerce of new drugs until approved as safe and effective in use under the conditions prescribed in the labeling.

One of the major changes brought about by the Kefauver-Harris Amendments to the Federal Food, Drug and Cosmetic Act is in the definition of a "new drug." "Effective" has been added to the definition (Section 201(p)). The term "new drug" now means any drug which is not generally recognized as safe and effective by experts qualified to evaluate the safety and effectiveness of drugs when used under the conditions prescribed, recommended, or suggested in its labeling, or which is recognized as safe and effective as a result of investigations but has not been used for a material time or to a material extent under such conditions.

It is important to emphasize that a new drug has a different meaning than before passage of the Kefauver-Harris Amendments. In other words the investigational drug requirements apply to the clinical study of any drug not generally recognized as effective as well as safe for the intended use.

Although the law prohibits interstate distribution of a new drug without an approved application, it does allow an exemption for shipping it solely for investigational use to experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs (Section 505(i)).

More Important Provisions of the Investigational Drug Regulations

Now, let us consider some of the more important provisions of the investigational drug regulations. Prior to distribution of a new drug for clinical testing in man the sponsor of the investigation is required to submit to the FDA certain specified information as part of a "Notice of Claimed Investigational Exemption for a New Drug," (Form 1571). This includes:

(1) The name, dosage form, components, quantitative composition and the chemical structure, if known, of the new drug substance.

(2) A description of the source and preparation of any new drug substances and the methods used to ensure the identity and uniformity of the new drug.

(3) The methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality and purity for safety and to give significance to the clinical investigations made with the drug.

(4) Adequate information on preclinical testing to show that it is reasonably safe to initiate the proposed clinical studies.

(5) The labeling or other information to be furnished to investigators.

(6) The name and a summary of the training and experience of each investigator or expert.

(7) An outline of the planned investigations, which may be submitted by phases. Phases 1 and 2 cover the clinical pharmacology with administration of the drug in a closely controlled scientific environment to a limited number of patients and under professional controls which assure a large measure of safety. Phase 3 covers the clinical trial in which the drug is used with a larger group of patients by different physicians following substantially the same investigational procedures.

(8) If the drug is sold, a full explanation of why sale is necessary.

It should be noted that when the sponsor files with the FDA the notice of claimed investigational exemption for a new drug, he and the investigators are free to proceed without notification. If, however, there is failure to comply with the conditions of the exemptions and failure to correct the situation on notification of it, the Commissioner may notify the sponsor of the termination of the exemption.

Each investigator involved in clinical pharmacology (Form 1572) or clinical trials (Form 1573), is required to submit the following information to the sponsor of the investigation:

(1) A statement of his education, experience, and the facilities he will employ in the investigation.

(2) An outline of the plan for his investigation.

(3) Statements showing he understands the conditions governing the use of investigational drugs, including the maintenance of records, and the submission of reports to the sponsor.

The intent both of the regulations and of the law is to ensure, among other things, that the pharmaceutical manufacturer who wishes to have his product tested on man will conduct adequate preliminary studies to justify clinical testing, and will make the results of these tests available to the expert investigator and to the government before the drug is administered to man. The manufacturer will have to develop a scientifically sound program for the clinical tests he proposes. He will have to see to it that the new drug is turned over to qualified investigators who will test it on patients under their personal supervision or under the supervision of qualified investigators responsible to them.

Reasonable flexibility of a plan of investigation is provided for. An investigator may pursue promising leads that may emerge in the early stages of his investigations, and he may modify experimental design on the basis of experience, advising the sponsor in progress reports.

The sponsor is required to monitor the progress of the investigations and currently evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigators. Accurate progress reports of the investigations and significant findings, together with any significant changes in the informational material supplied to investigators, are required to be submitted to the FDA at reasonable intervals. In time the FDA will have received a large portion of a new drug application before the application itself is filed.

Purposes and Substance of a New Drug Application

Let us now explore briefly the purpose and substance of a new drug application. The Act, (Section 505(b)), provides that an application shall contain (1) full reports of investigations which have been made to show whether the drug is safe for use and whether the drug is effective in use; (2) a full list of the articles used as components of the drug; (3) a full statement of the composition of the drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug; (5) required samples of the drug and its components; and (6) specimens of the proposed labeling for the drug.

The significant purpose for the processing of new drug applications is contained in Section 505(d) of the Act which provides that an application may be refused, after giving the applicant notice and opportunity for a hearing, if it is found that (1) the submitted reports of investigations do not include adequate tests by all methods reasonably applicable to show whether the drug is safe for use; (2) the tests show that the drug is unsafe or fail to show that it is safe; (3) the methods, facilities, and controls used for the manufacture, processing, and packing of the drug are inadequate to preserve its identity, strength, quality and purity; (4) there is insufficient information to determine whether the drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling; (5) there is a lack of substantial evidence the drug will have the effect it purports or is represented to have under the conditions prescribed, recommended or suggested in the proposed labeling; or (6) the labeling is false or misleading in any particular.

Let us consider more specifically the contents of an application for a new drug. A new drug application form is available on request from FDA. It furnishes a detailed outline which should be followed in assembling the data for the application. "Assembling" is used advisedly and applies to the case of the applicant who employs able pharmacologists, clinicians, pharmacists, chemists, bacteriologists, statisticians, possibly other scientists, and production employees, and who has or contracts for the facilities essential to new drug research, development, manufacture, and control. Such an applicant will have developed substantially the same information as is required in a new drug application to satisfy himself of the safety, usefulness, integrity, and stability of the new drug, and need only assemble it in the form of an application to be submitted to FDA. There will probably be little or no differences of opinion between the conclusions that are drawn by an able group of nongovernment scientists and by the FDA scientists who review an application developed on this basis.

The investigations of the safety of the drug should include adequate tests by all methods reasonably applicable. There must also be "substantial evidence" of the effectiveness of the drug. The reports should contain detailed data derived from animal and clinical studies in which the methods used and the results obtained are clearly set forth. The kind and the amount of information required will depend on several factors, such as the nature of the drug and its indication, and must be determined individually for each new drug.

The applicant is required to submit detailed information on the components, the composition, the facilities and the controls that are used in the production of the drug. The synthesis of new drugs, information in the area of drug stability and dissolution and information derived from newer technics in analytical procedures are all incorporated in what we feel to be necessary information in a new drug application.

The application must include specimens of the proposed labeling including a package insert for prescription drugs. Package inserts must consist of so-called full disclosure information which includes indications, effects, dosages, routes, methods and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use it safely and for the purposes for which it is intended.

A new drug remains a matter of concern to us even after it is the subject of an approval application and is marketed. We follow with interest and continuing concern the marketing experience with the drug.

Records of Clinical Experience Necessary

Persons holding approved new drug applications now are required to keep records of clinical experience, (Section 505(j)). They will be required henceforth to make reports (130.13), as experience accumulates and advise us when they receive reports of adverse reactions, untoward reactions, contraindications, and the like, when attributed to their new drugs and antibiotics. This will enable more prompt detection of the relatively infrequent cases in which a product, despite the most careful premarket testing, shows undesirable side effects when widely used. This will shorten the time lag between the occurrence of adverse reactions and the decision as to what corrective action is needed. These reports and records are to be designed to facilitate a decision as to whether the drug should be continued on the market without change, labeling changes should be required, or the product should be recalled.

Deliberate or repeated failure to establish or maintain these records, or to make any required report, or to permit copying of these records will constitute grounds for withdrawing approval of the new drug application to which the records apply.

Under the new amendments, all antibiotics to be administered to humans, (Section 507(a)), were brought under the certification pro-

gram which, up to May 1, 1963 covered only five antibiotics and their derivatives. The law, (Section 507(c)), provides some of the guidelines which may be used to decide that because of its production record an antibiotic no longer needs certification. An antibiotic which is exempted from the certification procedures and which is a new drug becomes subject to the new drug provisions of the Act, (Section 507(e)).

Present Role of Statistician

Let us now consider the role of the statistician in new drug development and marketing against this abbreviated backdrop of the Act and the regulations.

The accelerated discovery and development of new drugs present serious problems with respect to their introduction to therapeutic use. The elimination of drugs with harmful side effects depends upon the insight into the drug action gained by pharmacologists, physiologists and biochemists. We cannot expect complete success here, so we rely to a considerable extent on the detection of these effects by the pharmacologists, clinicians and statisticians involved in animal and clinical testing. Their teamwork and close understanding of one another are most important.

In considering the methods for the appraisal of the safety and effectiveness of new drugs, it is desirable to consider the over-all problem from the standpoint of: (1) What are the hazards? (2) What are the methods of appraisal? (3) What extrapolations can be made from the sample studied? It is then apparent that the over-all problem has both a biological and statistical component.

We would like to know how well the predictive procedures employing humans match up in practice. How good is the correlation between what is predicted by a given procedure, and what happens when the drug is tried clinically?

In addition, we would like to know how the various technics compare. Is one of them more efficient, so that either we could use smaller samples or we could have greater confidence that the results obtained with this procedure would actually be borne out with the widespread use of the article?

It is not possible to design a single protocol of the studies that is necessary and sufficient to establish the safety and effectiveness of new drugs in general. The nature and extent of the investigations reasonably applicable are related to the nature of the article under

investigation and its intended conditions of use. The FDA scientists cannot reasonably make an advance commitment that a specified group of studies will be sufficient to establish the safety and effectiveness of a given article, but will furnish comment on proposed plans of study before or during the course of investigations. It is frequently desirable in the course of such investigations to modify the plan of study on the basis of preliminary results obtained.

On the statistical side, it should be remembered that the first step in any investigation is the proper design of the experiment. There are two important aspects in a study that should not be overlooked. First, the population used must be representative; that is, the sample to whom the test is applied is a reasonable cross section of the ultimate population for whom the product is designed. Second, the test procedure must simulate use conditions.

The formulation of the questions to be answered must be made explicit by the protocol of the study. The statistician member of the team has the responsibility for anticipating the form that the experimental results will take and for ensuring that the design of the study will permit a meaningful analysis. Since the type of statistical analysis appropriate at the end of the experiment is contingent upon the manner in which subjects were selected and the manner in which the data were collected, the statistician should participate in the study from its inception or discussion stages. One of the primary purposes of a statistician is to get the investigator to think and thus, more efficiently plan and conduct his study. At times he will perform somewhat like a lawyer in drawing out the pertinent special knowledge of the other team specialists, and in helping to form a clear statement of the problem before any attempt is made toward design and solution. In this interplay of a multiplicity of ideas and approaches to understanding, responsibilities and objective, it is natural that the statistician must make every effort to make his own viewpoint, strictly as that of a statistician, known, clearly understood, and accepted so far as possible. His main contributions to design of an experiment will be in the areas of careful examination of the objectives of the experiment, insistence on randomness, awareness of the many kinds of bias that may afflict a study, and mobilization of the technical tricks of experimental design.

Selection of a drug through the screening process does not mean that it should be submitted to clinical trial. There is a need to investigate toxicity by means of animal studies.

To date there has been no adequate study correlating the results of drug effects in animals with those obtained from later clinical tests

on human beings. However, a booklet, "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics," prepared by the staff of the Division of Pharmacology, Food and Drug Administration, and published in 1959 by the Association of Food and Drug Officials of the United States, contains useful information with respect to views of the FDA concerning safety studies.

It is not possible in a general outline to design a single program that will apply to each and every new drug. Many times, even after an experiment has begun, we observe changes in animals which cause us to change the approach.

In many instances we are dealing with a desired demonstration of safety for a small amount of a chemical which may be consumed by man for a long time. Therefore, chronic toxicity studies may be required. However, before such studies are started other data, such as acute and sub-acute studies, are necessary. Records of the observations on each individual animal and statistical treatment of the data as a whole are needed to reach a conclusion.

In the last analysis the caliber of the team conducting the various experiments and making the evaluations determines to a large extent the nature and usefulness of the animal toxicity tests.

Foolproof Experiment in Man Impossible

Clinical experimentation in man is one of the most difficult fields. It is almost impossible to set up a really foolproof experiment. And it is almost inevitable that there should be some differences of result and differences of opinion in these clinical fields of experimentation.

Sir Austin Bradford Hill and other statisticians have amply demonstrated that the careful planning of clinical trials is essential. Several factors, once hotly debated, are now widely accepted as important in the planning of any clinical trial. Some of these factors are:

(1) Randomization to minimize the biased selection of a sample from the population.

(2) Blind and double-blind and control (placebo) studies.

(3) Replication in separate, independent laboratories by different investigators.

(4) Altering such variables as the dose regimen and the method of administration.

Use of Matched-Pair Studies

Many clinical plans utilize matched pairs of subjects in the evaluation of new drugs, such as age, sex and the severity of the disease. Its purpose is to enable better comparison between the treated and control groups, since one patient of each pair receives the drug and the other is an untreated control. The disadvantage of matching lies in the rather extreme conditions for the model. Patients do not remain the same over periods of time; neither do conditions. There may be carryover of the effects of a drug, either physical or psychological. A recent study of the problem by computer model-simulation technics and by covariance analysis indicated that there is remarkably little advantage to the use of such matched-pair studies.

Phase I, Phase II and Phase III Investigations

It may not be generally appreciated that the regulations make a distinction between the type of information that must be provided to the FDA for the clinical pharmacology studies referred to as Phase I and Phase II, and the clinical trial, referred to as Phase III. In a Phase I study, possibly only one or two subjects may be involved. Initially small doses of the drug in question may be given, different routes of administration explored, and the subject followed closely with the appropriate pharmacologic studies. For this purpose it would not be necessary that exhaustive animal toxicities be done. For example, LD_{50} determinations and short-term subacute studies might suffice. In Phase II, studies would be extended to include the initial therapeutic trials on a limited number of patients and may require additional animal studies beyond those considered adequate for Phase I. Considerable leeway during Phase I and Phase II would be permitted in regard to the plan of investigation and such details as the route of administration and the physical form in which the drug is administered. Thus, although a drug might be intended primarily for oral use, during this period an investigator could undertake studies with a parenteral form of the drug provided preliminary animal experimentation had been done to indicate the safety of this route, and information was available concerning the nature of the solvent.

In the case of Phase III investigations, which involve relatively less exacting studies undertaken, often over prolonged periods of time, by clinicians of varying research experience, it is expected that considerably more preliminary animal work would be done and that the route of administration and the formulation of the drug would be more

or less standardized. Even in Phase III investigations, however, the regulations permit reasonable variations and alternatives in the proposed protocol. A reasonable degree of freedom for the investigator is essential if the full potentialities of a drug are to be developed.

Sometimes we find that only a limited amount of clinical data can be obtained; for example, only a small number of patients have a disease. A competent statistician can be very helpful to the clinician in utilizing to the best advantage the initial numbers available. The appropriate statistical design may decrease the amount of observations involved while increasing the amount of information that can be obtained.

Use of Double-Blind Procedure

At times it is wise to use a double-blind procedure so that the people actively involved in the investigation will not be aware which is the drug and which is the placebo (or standard). In this connection, the Food, Drug and Cosmetic Act requires that the labels of drugs moving in interstate commerce give certain information including the identification of the drug. A frequent suggestion is that for double-blind studies, the firm be allowed to ship drug and placebo identified by code numbers only, the key to the latter being held by the firm. Such a procedure would however be in violation of the Food, Drug and Cosmetic Act and would result in an unnecessary risk to the public. It is possible to aid double-blind studies, however, by the use of some sort of tear-off or folded label and suitably coded containers. A nonparticipant of the study located at the site of the test, such as the pharmacist, could then remove and retain the tear off portion of the labels and be responsible for keeping the key to the identity of the drug and placebo, furnishing it immediately to the physician should the necessity arise.

While the primary motive of the investigator may be satisfaction of his own personal intellectual needs, in many instances, the investigation is undertaken for eventual submission of the results to the FDA as part of a sponsor's "Notice" or a new drug application. It is therefore proper to view submission of the results as an integral part of conducting the investigation. If interpretation must begin with the making of the observation, then the level to which interpretation must be carried depends upon the kind of submission being made. The investigator has a responsibility to digest the data, extract the findings that appear consequential, and to present these simply and clearly. Charts and graphs should be simple, clear, adequately labeled, and to

the point. The complete data should always be retained in their entirety so that they can be re-examined, if necessary.

We find the tabulation of data is very helpful in terms of summarizing such information as the number of patients, their ages, the duration of the treatment, the dosages used, control measures, the frequency of adverse effects, the therapeutic results, method of assessment of subjects at the end of the trial, and the statistical techniques employed. However, this would be in addition to the needs of our medical officers to have available for review and evaluation the investigator's case reports, the over-all conclusions of each investigator, the design of each individual investigator's experiments, and the criteria used for each investigator's evaluations.

Reports from Investigator Must Be Evaluated

The reports from each individual investigator must be evaluated. We cannot delegate our responsibility of evaluating a new drug to a sponsor or to an applicant.

Sometimes we receive incorrect results on clinical trials because of ignorance, error or fraud. For example, one glaring instance of incorrect interpretation or combination of results has come to our attention. Five different clinical studies were conducted, comparing a new drug with one already on the market. The five results were then averaged. Upon critical examination of the raw data by our statisticians it was found that the five potencies they were combining were of the order of magnitude of 25 per cent, 66 per cent, 75 per cent, 95 per cent and 250 per cent, where the lowest and the highest were extrapolated way beyond the two levels of drug used in the investigations.

Our statisticians help us evaluate the design of the clinical tests found in sponsors' "Notices" and in new drug applications. Also in these areas they assist in the arrangement and, of course, the evaluation of the statistical analysis. Often we find too much statistical analysis; unfortunately, too much statistical manipulation is usually a sign of poor clinical work. Sometimes a simple graph of the results would have been sufficient.

Dr. Louis Lasagne has cited an instance where an elaborate report with beautiful charts, tables, and analysis of variance was received by a pharmaceutical firm from an investigator. However, upon checking to see what levels of the drug were used at a specific time, it was learned that, through oversight, the drug had never been sent to the investigator!

To control the identity, strength, quality and purity of new drug substance and the dosage form of an investigational as well as the marketed new drug, pharmaceutical firms employ a control system of which a part is the quality control laboratory. The laboratory, in collaboration with those who have developed the drug, must establish specifications to define the identity, purity and potency of the new drug substance and the drug's dosage forms. These specifications must in turn be supported by analytical methods by which conformity to specification can be determined. Usually one or more new methods must be developed for this purpose. In many instances, methods suitable to the drug in its pure state must be modified or replaced by other methods when working with the dosage forms of the drug.

As the new methods are developed and old ones are modified it is the constant job of the statistician to design experiments and to evaluate the results from the standpoint of accuracy, precision and limits of sensitivity, so that the chemist may compare the new method or modification with the one presently accepted. The statistician is often applying or developing mathematical formulas for the evaluation of various methods particularly those of biological assay.

Statistical technics form an integral part of every effective quality control program. The statistician can support the new drug quality control team with respect to physiological availability, uniformity, and stability of the drug.

The new legislation recognizes the obligation of the applicant and the FDA to follow the course of the new drug once an application is approved. One of the salient features is the requirement that the applicant maintain adequate records on clinical and marketing experience with a new drug and submit the reports to the FDA in order to recognize at an early date the need for corrective action when the accumulated evidence of side effects with a particular drug appears to make this desirable. The evaluation of these reports is frequently a statistical problem.

When new drugs enter wider distribution as a result of commercial distribution new toxicities may be uncovered for the first time. In a sense these kinds of toxic reaction are predictable although their incidence is not. Rarely a novel toxic effect is discovered such as thalidomide. The sooner knowledge such as this is available the quicker can counter-measures be taken.

The applicant should encourage physicians to report every instance of unexpected or unexplained symptoms during an extended

period following administration of the new drug. In order to avoid overlooking the novel or rare side effect, emphasis should be on reporting any unusual phenomena, whether or not the physician personally believes them to have been caused by the drug.

Early information of marketing experience and analysis of the data may suggest labeling revisions or profitable retrospective studies of the drug to the clinician-statistician team.

The fear has been expressed that the new regulations will result in valuable drugs being withheld by the FDA because of toxicity encountered during investigational trials. However, safety will certainly be evaluated in terms of potential clinical usefulness. Further, the new regulations with their emphasis on properly qualified investigators and adequate quality control during production may well reduce the number of drugs withdrawn because of toxicity resulting from improper, inexpert, investigational trials, or from poor manufacturing practices.

Conclusion

The involvement of statisticians in new drug work is still in its infancy. Some pharmaceutical firms are using them and many are not. A large number of the new drug applications we receive indicate that applicants are not making use of statistical technics in the design, analysis and interpretation of the animal, clinical and control data. We do find more use of statistical design in animal studies than in clinical studies.

This has been a brief resume of the new legislation and regulations which may affect your investigation, development and marketing of new drugs. The new legislation is designed to promote the development of safer and more effective drugs. Many problems lie ahead for both the pharmaceutical industry and the FDA. It is hoped that it will provide a better understanding of the role and function of the FDA in its regulation of new drugs and in turn assist those who have a responsibility for developing them. **[The End]**

Milk and Other Dairy Products: What Is Proclaimed– What Is Proper to Proclaim

By K. L. MILSTEAD

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I HAVE BEEN ASKED to explain the attitude of the Food and Drug Administration toward nutritional and health claims for dairy products. This request is disturbing for it implies that the unique contribution of milk and other dairy products to the adequacy of our diets has been challenged, and that your industry wants to know what it can say about your products to restore lost consumer confidence in "the perfect food." This is not a simple task because it involves some basic attitudes of consumers about their health, and the requirements of the Federal Food, Drug and Cosmetic Act as interpreted by the courts.

The American consumer has become health conscious, diet conscious, weight conscious, vitamin conscious, mineral conscious, fat conscious and protein conscious, but he has limited knowledge with which to deal with these new concepts. He has been made aware of important nutritional factors and developments, but his knowledge has not reached the point where he can distinguish between sound nutritional advice and nutritional nonsense. He hears the words vitamins, minerals, protein, polyunsaturates, and so forth, so often that he feels much happier if he sees one or two of them on the label of any food he buys. In addition, he is being constantly told that he must improve his diet with some type of "food supplement" if he is to enjoy good health. As a result, many consumers find it very difficult to make a rational choice of their foods.

The Supreme Judicial Court of Massachusetts in considering a question about food misinformation recently summarized the situation as follows:

We are not unmindful of the fact that questions relating to public health and nutrition are of public concern. It would be difficult to imagine anything more so.

Requirements of Federal Food, Drug and Cosmetic Act

Bearing in mind these attitudes of consumers, let us turn now to the requirements of the Federal Food, Drug and Cosmetic Act. The basic provision of the Act, dealing with labeling claims, prohibits any claim in the labeling of a food that is "false or misleading in any particular." The Supreme Court of the United States interpreted this language in a case under the Food and Drugs Act of 1906 as follows:

> The statute is plain and direct. Its comprehensive terms condemn every statement, design, and device which may mislead or deceive. Deception may result from the use of statements not technically false or which may be literally true. The aim of the statute is to prevent that resulting from indirection and ambiguity, as well as from statements which are false. It is not difficult to choose statements, designs, and devices which will not deceive. Those which are ambiguous and liable to mislead should be read favorably to the accomplishment of the purpose of the act.

More recently the same philosophy was expressed by a federal judge in a case involving false and misleading claims for a drug product. He said:

> When representations in the labeling of a product go beyond what has been established to be the fact, according to the recognized standards in the particular field for the determination thereof, such representations must be considered as false and misleading.

These decisions make it clear that the law sets very high standards for health claims on foods. It prohibits not only false claims, but misleading claims and claims that have not been established and accepted by recognized scientific authorities in the field. In other words, in considering whether the claim is justified, we must consider not only the scientific facts available, but also gaps in scientific knowledge about the particular matter.

What Is Proper to Proclaim?

With this background in mind, you will appreciate why it is difficult for me to answer the second question in the title of my talk: What is proper to proclaim for dairy products? This depends on many factors in addition to the attitude and understanding of consumers, such as, the way the claim is stated, the type of product involved, its method of marketing and promotion, failure to reveal material facts, and the status of scientific knowledge in the area involved.

Generally speaking, you may claim anything for a dairy product that is true and is supported by sound scientific evidence. This includes its established nutritional value, and information about its flavor, appearance, texture, palatability, versatility, wholesomeness, and so forth. Certainly you can continue to proclaim the superior value of milk and other dairy products based on their content of such important nutrients as calcium, riboflavin, and protein. And the value of dairy products in special diets for the young and old is so firmly established that reasonable claims in this area can be supported.

Now I recognize that these are general statements and that you would be happier if I could be more specific. I am sorry that I cannot, but I can tell you that we will be happy to consider any specific claims you have in mind and give you our views if you will send us proposed labeling. As a general guide, you should confine your claims to those that are proper for basic, nutritious foods. If you make drugs out of your products by curative or health claims, you are in a dangerous area.

What Is Proclaimed?

Now let us turn to the first question in the title: What is proclaimed for milk and dairy products? This question is easier to answer because we are dealing with specific claims and we can discuss these claims and our views about them. This will also be helpful in answering the second question or, at least, my discussion will give you some idea of the type of claims we think should not be made.

Claims Based on Vitamin and Mineral Content

The sensible enrichment of some of our basic foods has the approval and support of nutritionists and public health officials. The wasteful, irrational addition of vitamins and minerals to foods merely for sales promotion is disapproved by all scientists and public health officials. The food industry is now carrying on a competitive battle of therapeutic claims based on the addition of vitamins and minerals to foods. Consumers are being urged to select foods on the irrational basis of vitamin addition. The industry must accept its share of the blame for the "vitamania" being suffered by consumers, and the reaction that will inevitably occur. We hope the dairy industry will not contribute further to this confusion by the addition of unnecessary substances to your products merely to form a basis for health claims.

The Food and Nutrition Board of the National Research Council and the American Medical Association have endorsed the following fortification of dairy products: Vitamin D to milk, fluid skim milk and nonfat dry milk, and the addition of Vitamin A to fluid skim milk and nonfat dry milk. (I should point out, however, that the present Congressional definition for nonfat dry milk does not provide for fortification with Vitamins A and D.) Further enrichment of dairy products is not indicated at the present time.

Notwithstanding this, efforts are continuously made to market preparations to add other vitamins to milk and also iron and other minerals, protein, and so forth. The purpose of this is clearly to promote the fortifying product, and to provide a basis for claims for the modified milk. While there is no legal basis for preventing the sale of these so-called milk fortifiers, although they are generally unnecessary from a nutritional standpoint, we can act against unwarranted claims for them. During the past year, we seized shipments of four of these milk fortifiers because their labels claimed they would "promote healthy teeth and gum formation, resist infection, promote growth in children, sturdy bones, healthy blood, nerves and skin, and cause the blood and body cells to release energy." We do not believe that such claims are proper on any dairy product or any article that is intended to be added to a dairy product.

Here are a few examples of dairy products that were being promoted by what we consider to be exaggerated and unwarranted claims based on added vitamins and minerals.

Fortified Milk.—This article contained many added vitamins and minerals although there is no substantial scientific support for the addition of any vitamin or mineral to milk except Vitamin D. Leaflets distributed to promote the sale of this "super" milk represented it to be effective to promote clear skin; resist infections; prolong life; promote good health, good appetite, digestion, steady and healthy nerves, vigor, good teeth and rich, red blood; to regulate the thyroid gland and prevent goiter and to promote a personality sparkling with a healthy glow.

Milk with Multi-vitamins and Minerals.—This was another "super" milk that was actively promoted by means of a leaflet delivered to route customers. The same type of claims were made as mentioned above for the fortified milk.

2 Per Cent Milk with Added Vitamins.—We seized a shipment of this product because the labeling claimed the article would be effective for anemia, skin hemorrhage, loss of appetite, lack of proper growth, proper function of the nervous tissues, infertility and poor resistance of infection.

We think that health claims of the types that were being made for these dairy products are highly improper. They are not supported by sound scientific facts and they are contrary to the best interests of the dairy industry. They are similar to claims made by food faddists and "health hucksters" to promote their "health" foods.

Weight Control Claims

Nutritionally speaking our number-one problem in the United States is obesity. We eat too much of the highly nutritious foods that are readily available to practically everybody. It is no surprise, therefore, that your industry, along with most of the others in the food business, has shown an increasing tendency to promote dairy products for reducing. Consider, for example, these label statements that have been quite widely used and that have been involved in actions under the Federal Food, Drug and Cosmetic Act: "skim milk for that slim trim look," "low calorie creamed cottage cheese," "low calorie ice milk," "promotes slimness," "take off weight without tears," and "build strength not fat."

What does the term "low calorie" and similar statements really mean? To have any meaning it must be considered relative to other specific foods; there must be a frame of reference. Articles like ice milk and cottage cheese may be lower in calories than ice cream and creamed cottage cheese, respectively, but they are higher in caloric content than many other foods. Also, the use of "low calorie" and similar statements on such standardized foods, disparages similar foods distributed by other firms.

This does not mean that you cannot use truthful, non-misleading label statements as to the caloric and other nutritive values of your dairy products. You can state the calorie, protein, carbohydrate and fat content. If it is an excellent source of certain vitamins, minerals, and protein, these can also be listed. You can compare the caloric and other nutritive content of certain dairy foods with other foods, dairy or otherwise, of about the same uses in the ordinary diet. But be careful. It would not do, for example, to compare the caloric value of creamed cottage cheese with oleomargarine. They are used differently.

It would not do to compare the calories of ice milk with orange juice. In other words, we believe that references to calories should be generally limited to an appropriate statement of the calorie content of the food and to non-misleading comparisons with other foods that are used in a similar way in the ordinary diet.

And then we have those label statements—they pal around like the "Gold Dust Twins" we used to talk so much about—"High Nutrition—Low Calorie" or the variant "High in Protein—Low in Calories." And to clinch its meaning, we now see some firms adding statements about how wonderful the touted food is for "weight watchers." This is sheer nonsense. After all, if it is high in nutrition or protein it isn't low in calories. It is not true to say or imply, in general, that foods are of special value in weight-reducing diets because they supply significant amounts of nutrients in quantities which are low in calories.

Before leaving this subject of weight control claims, let me point up the problem a little more specifically by giving you the details on a few cases in which such claims were involved:

Slim Cheez.—This article contained about 2 per cent fat and the carton bore these claims, "Lower In Calories. Small Curd, Uncreamed Low-Calorie Cottage Cheese." The product was not cottage cheese and it was not low-calorie.

Instant Nonfat Dry Milk.—The label "Non-Fattening," "Excellent for Weight-Watchers," "Perfect for High Protein, Low Fat Diets," "So Necessary for Growth, Strength, and Sound Teeth. Gives Sparkle and Vitality."

Yogurt.—The labeling stated, "Take off Weight Without Tears." What a promise!

Ice Milk.—The label bore a vignette of a shapely female standing on bathroom scales and the statement, "Add Charm to Your Diet." Another very fascinating promise.

Also, "Low-Calorie Diet Lunch—Keep the calories down at noon yet satisfying your appetite," are promises that ice milk would have difficulty fulfilling.

Slenderizing Brand Nonfat Dry Milk.—The name and the vignette of a shapely woman on the label both suggested that the article would in some way slenderize you, which we think is untrue and misleading.

There is no short cut to weight control. The overweight person must suffer to control his weight by reducing his caloric intake. Milk products are suitable for use in calorie controlled diets for reducing. But they have no special or specific effect in the process of losing weight.

Other Borderline Health Claims

Here are some additional health claims that are being used on the labels of different foods, including dairy products, that we consider in the gray or doubtful area, because in the context used their meaning cannot be supported and thus they serve only to confuse and mislead: "body building," "bone strengthening," "energy producing," "now enriched," or "now fortified," "provides health," "high nutrition," "less calories per bowlful," "quick energy," "improve your complexion," "builds strong teeth," "extra nourishing," "healthful," "significantly greater in vitamins and minerals," "rich in healthful vitamins," "12 less calories per pat," "17 calories less per pat" and "eases nervous tension."

Advertising agencies refer to such claims as mere "puffery." We think they are false and misleading. We would suggest that you avoid vague and meaningless health claims of this type.

Misleading Cholesterol Theory

No discussion of what is being proclaimed about dairy products and what is proper to proclaim would be complete without commenting on the current misleading promotion of food products based on their fatty acid content.

Experimental observations during recent years have suggested that serum cholesterol may somehow be related to coronary heart disease. How it is related has not been established. Nevertheless, on this unproved theory there has developed one of the greatest food fads that has ever confused the American public. The consumer has been led to believe by many and devious ways that the most important thing from the standpoint of his health is to reduce the cholesterol level of his blood. First he was bombarded and exploited with various products bearing claims such as, "low in cholesterol," "lower in cholesterol," "less cholesterol," and so forth. But then it was determined that levels of blood cholesterol are relatively independent of dietary cholesterol and therefore such claims were not only patently false in

many cases, but grossly misleading, so something else had to be substituted.

By this time, some scientific reports were appearing that indicated that the type and amounts of fat in the diet have an influence on the blood cholesterol level in those persons with an elevated serum cholesterol. It was observed that certain unsaturated fats tend to lower blood cholesterol under carefully controlled conditions. So a new basis for continuing the fad to the general public was found. It was and is based on the unproved theory that diets high in saturated fats increase blood cholesterol which in turn favors the development of atherosclerosis, which in turn leads to coronary artery disease.

I need not tell you how this "theory" has been used not only by the food faddists and "health food" promoters but by some members of our major food industries to promote the sale of their products. You are painfully aware of the changes that have been brought about in the dietary habits of the American people as a result of this promotion. And all this, notwithstanding the repeated admonitions of the Food and Nutrition Board of the National Research Council, the American Medical Association, the United States Public Health Service, and others, that major changes in the American diet are not recommended.

We are now in what might be considered the third phase of this "medicine man" approach to food merchandising and that is that the people are being told that it is not the cholesterol in the diet that is important, it is not the amount of unsaturated fats, but it is the degree of unsaturation or the ratio of unsaturated fats to saturated fats or something else. Confusion reigns and new promoters with new theories and new advertising gimmicks appear and disappear. We detect a growing dissatisfaction on the part of consumers to all this and a return to a more sensible approach to their food selection. They are beginning to realize that the substitution of exotic and strange foods for basic foods of proven nutritional and health value is unwise. Perhaps before too long the consumer, as Dr. Bauer, Director of Health Education Emeritus of the American Medical Association recently suggested, will be able to return to the good old-fashioned custom of eating three square meals a day without fear and without anxiety.

The dairy industry, on the whole, has shown commendable restraint in the face of this prolonged campaign to degrade its products.

The FDA stated its position on this question in a policy statement on December 10, 1959, which was and is that all statements, words, or designs in the labeling of a fat or oil, or any other food for that matter, which represent or suggest that the article is effective for the prevention or treatment of heart or artery disease are considered to be false and misleading and consequently in violation of the Federal Food, Drug and Cosmetic Act.

We have no doubt that we can enforce this policy in court and we are proceeding against products where the labeling represents the article to be of value in the prevention or treatment of heart or artery disease, including claims that the article will lower the cholesterol level of the blood. Most of you are no doubt familiar with the many actions that have been taken against safflower oil products promoted by the book "Calories Don't Count," written by an M. D., Herman Taller, a gynecologist and obstetrician, and published by Simon and Schuster.

Dr. Taller represented safflower oil capsules for weight control; lowering of the cholesterol level of the blood; treatment of arteriosclerosis and heart disease; improving the complexion; increasing sexual drive and for other purposes. But no one came to the defense of Dr. Taller's theories in federal court, and the actions have been terminated in favor of the government.

But this did not stop the promotion of safflower oil for "drug" and "health" purposes. It is being aggressively promoted not only by "health food" zealots but also by large food manufacturers. We have already brought action against a shipment of "Safflower Shortening," based on claims of its value for heart and artery disease. We are hopeful that this action will serve as a restraint on the very aggressive promotion of this oil and that our food manufacturers who are selling safflower oil products on the basis of "drug" claims will promptly return to the food business.

What about other claims such as "polyunsaturated," "not hydrogenated," "double the unsaturation," "rich in linoleates," and so forth. We think they are misleading but it is a question of fact in each case. We are in the process of taking a good look at the promotion, labeling, and so forth, of all products and all firms that are promoting their products on the basis of such claims and we hope to help bring some order out of this chaotic situation before too long. It is long overdue.

CONCLUSION

I have dealt with the unsaturated fat problem in some detail not only because of your interest in it, but also because I hope my comments may offer some guidance to those of you who have or may be thinking of entering this twilight area. We sincerely hope that the dairy industry will continue to promote its products on the basis of their established nutritional and other values and their unique contribution to the adequacy of our diet and that you will leave the treatment of heart and artery disease to medical experts where it belongs.

I would remind you of the accepted fact that the American food supply is unsurpassed in volume, variety, safety, cleanliness and nutritional value. Americans generally have to go out of their way, nutritionally speaking, to avoid being well-nourished. Deficiency diseases in our population are now almost unknown. The dairy industry can take considerable credit for the part it has played in bringing about this desirable state of affairs.

But notwithstanding the abundance and quality of our food supply, consumers are being constantly barraged by exaggerated claims and misconceptions distributed, not only by food faddists and nutritional quacks, but by some of our principal food manufacturers. "Fashions" in foods come and go. They are a poor substitute for staple and proven nutritious foods that are the foundation for our health and strength.

On the whole the dairy industry has not participated in this "medicine man" type approach to merchandising its products. We hope you will continue to shun this approach and continue to market your products on the basis that they are good, clean, wholesome, attractive, tasteful, nutritious foods. With this approach, you will have no difficulty so far as the Federal Food, Drug and Cosmetic Act is concerned.

For those of you that are inclined to follow some other course, I would suggest that you ponder the words of Walter Weir in his book, *On the Writing of Advertising*. He said:

> We may say to ourselves that little harm is done, through overstatement or misstatement, if we cause someone to part with a dime or quarter for a product that will not do all our advertising claimed it would do. But we are not dealing in dimes and quarters; we are dealing in belief. And no matter how legally we deceive, we break a thread in the whole vast tapestry of belief that is our civilization.

[The End]

Research Efforts on Pesticides by FDA Division of Pharmacology

By ARNOLD J. LEHMAN, M. D.

This Statement Was Delivered by Arnold J. Lehman, M.D., Director of the Division of Pharmacology, Bureau of Biological and Physical Sciences, Food and Drug Administration, Department of Health, Education and Welfare, Before the Subcommittee on Reorganization and International Organizations of the Senate Committee on Government Operations on October 7, 1963.

AS INTENSIFIED AGRICULTURAL PRACTICES led to increased insect problems and in turn to greater use of insecticides there developed a growing concern that the residues of these insecticides remaining on the crops at the time of harvest might be harmful to the consumers. In January 1927 when the Food and Drug Administration was a part of the Department of Agriculture, it was recognized that there was not sufficient information on the toxicity of lead and arsenic, components of the principal insecticides of that era, to permit establishment of satisfactory tolerances for these chemicals.

Division of Pharmacology Established

Accordingly, the Department called on a committee to advise it as to just what levels of lead or arsenic in food or drink could be considered free from hazard. The committee recommended temporary tolerances for lead and arsenic and in addition recommended a study of chronic intoxication by both lead and arsenic in the form in which they were used in sprays and consumed with fruits and vegetables. In 1935 funds for such an investigation finally became available, and a Division of Pharmacology was establish in the FDA.

Research Efforts on Pesticides

The first research problem assigned to the new Division was the study of the chronic toxicity of lead and arsenic. The test was done on rats and dogs and involved administering the compounds at several

dietary levels with observation of the effects on vital organs, reproduction and survival. The degree to which the chemicals were stored in the tissues was also measured. Considerable progress was made but all work on the problem came to a stop on June 30, 1937 when the current agricultural appropriation bill forbade the use of funds "for laboratory investigations to determine the possibly harmful effects on human beings of spray insecticides on fruits and vegetables." Not until 1943 when we undertook an investigation of the newly discovered DDT for the Office of Scientific Research and Development was our work on pesticides resumed.

Much of what is now known about the effect of DDT on warm-blooded animals was discovered in our laboratory. Many of the insecticides developed in the immediately ensuing years were also studied. Finally with the passage of the Miller Amendment in 1954 it became the responsibility of those seeking a tolerance on a new pesticide to present data showing that the proposed tolerance would be safe.

Thus it was no longer necessary for the Food and Drug Administration to conduct toxicity tests on each new pesticide as it was introduced. Instead we occasionally checked a finding presented in a pesticide petition, and devoted our main attention to the development of improved procedures for evaluating the safety of pesticides. Where it seemed desirable we have gone back and reinvestigated some of the pesticides in commercial use with present-day methods.

Examples of research work on pesticides currently in progress or recently completed in the Division are as follows:

Demyelinating agents.—Certain types of chemicals, notably the organic phosphates and the carbamates, are in some instances capable of injuring nerves and causing paralysis. A pathological process known as demyelination is associated with this injury. We have been testing those pesticides which have not previously been examined for this kind of toxicity. We have been trying several different species of animals in such tests so as to select the one or ones most efficient in detecting this kind of toxicity. Possible antagonists to the demyelinating compounds are also under study as an aid to understanding the latter's mechanism of action. The anatomical basis for this nerve injury is being explored in cooperation with scientists of the National Institute for Neurological Diseases and Blindness.

Effects of pesticides on the conditioned avoidance reflex of rats.—Preliminary work to evaluate the blockade of a conditioned escape

response to electric shock in rats as a means of detecting early toxicity to the central nervous system has been negative. Ten pesticides of diverse structure and use have been screened using this method.

Potentiation between drugs and pesticides.—In a study of the possible potentiation of drugs and pesticides it was found that the tranquilizer Chlorpromazine increased the toxicity of each of the two organic phosphate insecticides Parathion and OMPA when given in combination with them. Additional experiments are in progress.

Metabolism of pesticides.—The disappearance of various anti-esterase carbamates from specific tissues of the experimental animal is being followed analytically through periodic sampling of selected tissues for component parts of the toxicant.

Acute toxicity.—The acute toxicity of most pesticide compounds submitted for tolerances is routinely being determined.

Subacute feeding tests.—Studies of the effects on dogs and rats of oral ingestion of pesticidal compounds for 90 days are a continuing phase of our pesticide research either to monitor industry or in support of chronic two-year studies. Compounds under test or on which work has recently been completed are: 4-nitrophenylarsonic acid, arsenosobenzene, arsanilic acid, sodium arsenite, sodium arsenate, 3-nitro-4-hydroxyphenylarsonic acid, 2,4-D diethanolamine salt, 2,4-D propylene glycol and 2,4,5-T (free acid).

Chronic feeding tests.—The following chronic feeding tests of pesticides are in progress or have recently been completed: 2,4-D (free acid) (rats and dogs), Aldrin (mice), Dieldrin (mice), Heptachlor (mice), Heptachlor epoxide (mice), arsanilic acid (mice), sodium arsenite (rats and dogs), sodium arsenate (rats and dogs) and 3-nitro-4-hydroxyphenylarsonic acid (rats).

TOXICOLOGICAL INVESTIGATION OF A PESTICIDE

During the past 20 years there has been an increase in research activity in toxicology. Traditional methods in pharmacology are changing and the experimental toxicologist is applying as a part of his procedures, newer methods in histochemistry, biochemistry, and radiochemistry in his attack on the problems of human and animal toxicology. With the introduction and application of these new methods, the science of toxicology is evolving from the status of empirical studies to that of a special and precise field of inquiry.

In the FDA recognition of advances in the science of toxicology encouraged the staff of the Division of Pharmacology to publish in

1959, a monograph entitled "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics." This monograph contains the methods and procedures recommended to the manufacturers of foods, drugs, cosmetics and pesticides for the evaluation of safety of products subject to the Food, Drug and Cosmetic Act. By these methods, it is possible to establish the "no-effect" level of a given compound based largely upon histopathological evidence.

Evaluation of "No-Effect" Level

In dealing with the safety of pesticide residues which remain in or on raw agricultural products, we begin with the proposition that it is self-evident that all pesticides are poisonous. They are compounds which are injurious to both animals and man at some dosage level but can be tolerated without effect at some lower dosage. The nature of the injury that may be produced in man from excessive amounts of a pesticide can be demonstrated by animal experimentation. In the methods now applied we devote our attention to defining the level of exposure that has no effect by measuring at different dose levels the injury caused in the experimental animal or the lack of it.

We recognize that one of the problems in the evaluation of the "no-effect" level in animal experiments is the variation of end points or measurements that must be used. In some instances, the end point has been taken as the level of intake which is within the ability of the body to excrete the substance so that no accumulation occurs. In another instance, it may be the effect on body weight or the relationship between organ weights and body weight. In still another, the effect upon an enzyme system has been the indicator. By and large, the level at which no histopathological changes have occurred has been the principal basis for defining the "no-effect" level.

The present system provides the pharmacologist with information about the injury, if any, that results from feeding different amounts of the chemical. It is desirable, however, that the investigator also learn the way in which that injury developed over the period that the feeding was going on. A good illustration is the injured liver, which we know can be adversely affected by several different mechanisms.

Problem of Combinations of Pesticides

We are concerned with the problem of combinations of pesticides. The combined effects of two or more insecticides ingested at the same

time, particularly if one increases the effect of the second, would not be determined by a study of each separately. We have required in petitions offered to show safety some evidence as to whether potentiation occurs.

It is well recognized that the extrapolation of information from animal experiments to physiological effects upon man leaves something to be desired. Research in this area is very much needed but has been most difficult to carry out. The greater part of information on man available with respect to pesticide injury comes from those cases of overdose or poisoning. Much needed are experiments and clinical evaluations in which biochemical, histochemical and radiochemical means are employed.

With the development of new analytical tools of exquisite sensitivity, it should be possible to detect transient reactions to poisons before these effects progress to permanent disability (injury). A general plan would be to determine the reaction of the pesticide under study at the cellular and subcellular level using the dog, the rat, and the miniature pig. Monkeys may also be included. The effects would be correlated with dosage. When the correlation becomes well-established for the first pesticide, others could be subjected to this same series of tests to determine if the reaction is similar to or varies from the established pattern. A procedure could be developed whereby the transient effects can be fitted into a pattern which will permit extrapolation of data on the basis of a histochemical "no-effect" level. The ultimate hope is to set up a protocol which will consume less time and be more precise in evaluating the adverse actions of a pesticide.

Final Step

After careful evaluation of all data, the final step would be studies in man. If the animal studies indicate that an acceptable tolerance for the pesticide under study is 10 p.p.m., for example, there is no reason to hesitate to administer to human volunteer subjects a level equivalent to, or even small multiples of the quantity represented by the residue. Subclinical degrees of response can be determined and correlated with the animal data. Eventually it may be possible to demonstrate which of the several species of animals respond similar to man so that meaningful extrapolation from animal to man is more secure.

A protocol of a research project to add to and improve our present procedures is presented below.

PROTOCOL

A group of 32 young purebred beagle dogs, 16 male and 16 female, individually housed and kept on routine diet fortified with L-cysteine, will be divided into four groups of eight animals each, a control group and three experimental groups. The latter three will be given graduated doses of the halogenated hydrocarbon or organophosphate compound under investigation.

Each one of the four groups will be subdivided into two groups of four, so that the following setup will prevail: I-A, I-B; II-A, II-B; III-A, III-B; IV-A, IV-B.

The following groups of tests will be performed at biweekly intervals for three months before the administration of the compound is started and at the end of the 1st, 2nd, and 4th weeks and monthly thereafter following initiation of the drug administration. The following tests will be performed on all animals: (daily) food and water intake, (daily) clinical observation and record thereof, (weekly) weight gain, WBC with differential, RBC, Hgb, Hmct, cell indices, reticulocyte count, platelet count (phase contrast), prothrombin time, silicone clotting time and drug level in blood.

The following tests will be performed on all animals in the various "A" subgroups: SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), glucose-6-phosphatase, total proteins and A/G ratio, protein electrophoresis, fasting blood sugar, serum iron and urinalysis.

The following tests will be performed on all animals in the various "B" subgroups: ISDH (isocitric dehydrogenase), alkaline phosphatase, total cholesterol and cholesterol esters, BUN, lactic dehydrogenase isosyme pattern, ornithine carbamyl transferase, urinary ascorbic acid level and radioisotope metabolic tracer studies.

When any of the above liver function tests become abnormal, liver biopsies will be performed from half (2) animals in each subgroup, the other serving as controls, and the following histochemical studies done:

Subgroup A.—glycogen (PAS or Bauer feulgen), glucose-6-phosphatase (chiquoine), mitochondria, phase contrast, H & E and liver homogenate drug incubation studies.

Subgroup B.—alkaline phosphatase (Gomori), non-specific liver esterase (bromoindoxyl acetate), microsomes and Golgi apparatus,

phase contrast, H & E and microsome (ultracentrifuge) drug incubation studies.

The first experiment, which will be a pilot study, will be terminated at six months, at which time all surviving animals will be autopsied.

Subsequent experiments will be accordingly modified and extended to other species, especially the miniature swine.

In the above experimental design, please notice that any one parameter is followed both in the blood and in the tissue within the same subgroup, for instance fasting blood sugar, glycogen and glucose-6-phosphotase in subgroup A, while alkaline phosphotase, cholesterol esters and non-specific (pseudo) esterase in subgroup B. This, it is hoped, will make interpretation of the results more comprehensible.

[The End]

BOTULISM OUTBREAK FROM SMOKED WHITEFISH

The FDA's Detroit district was informed by the Michigan Department of Agriculture Food and Standards Division, Lyle Littlefield, chief, that two deaths attributed to botulinus poisoning had occurred at Kalamazoo, Michigan on October 2. The report, dated the same day, said the deaths were attributed to smoked whitefish from an unidentified source. An investigation was begun to determine the facts.

Two deaths were reported in Knoxville, Tennessee on October 6, from botulinus poisoning attributed to "smoked whitefish chubs" shipped by a Grand Haven, Michigan firm.

These two reports have led to the disclosure of three other deaths not previously attributed to botulism. As of October 18, a total of seven deaths had been reported between September 30 and October 7. In addition, seven persons had been hospitalized and treated for botulism. All cases were in the Knoxville-Nashville, Tennessee area, except the two Kalamazoo deaths, and all cases in the area related to consumption of fish from one shipment from the Grand Haven plant.

Investigation by FDA concluded that this shipment went to 18 retail stores of one grocery chain—3 in Alabama, 1 in Kentucky and the remainder in Tennessee. At the first suggestion that the fish may have caused illness, the grocery chain ordered return of the product, took immediate action to stop sales and undertook to locate customers who had already purchased the item. The Grand Haven firm requested its distributors to destroy all stocks on October 7.

All FDA districts were alerted to notify all cooperating state and local officials and to request them to warn the public and to supervise destruction of any of the Grand Haven product located in their areas. FDA is continuing to conduct an intensive investigation into the cause of this botulism outbreak.

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