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Food Drug Cosmetic Law JOURNAL

Papers Presented at the 17th Annual Educational Conference of the Food and Drug Law Institute, Inc., and the Food and Drug Administration

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PUBLISHED IN ASSOCIATION WITH THE FOOD AND DRUG LAW INSTITUTE, INC.

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

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Remarks

By CHARLES C. EDWARDS

Dr. Edwards Is Assistant Secretary for Health, U. S. Department of Health, Education, and Welfare.

LIKE SO MANY OF YOU HERE THIS EVENING, I had the good fortune to know Laurence Wood both as a friend and as a valued and respected advisor during a time when the Food and Drug Administration (FDA) and the Food and Drug Law Institute (FDLI) were undergoing significant change and unprecedented growth. The FDLI became—and continues to be—an invaluable avenue for communication and education among all of us in government and industry who share a responsibility for the health and welfare of the American people.

I know of no one who had a clearer or more constructive sense of this shared responsibility than Laurence Wood. It is in no small way thanks to his wisdom and leadership that we have moved into a new era, not just in the application of food and drug law, but in the broader effort to serve the interests of the people of this country. His vision was clear, and it is being realized.

I think this is the fifth year I have had the opportunity to speak to the FDLI, and I am beginning to feel like a permanent fixture. I well remember those earlier years, particularly in 1969, when Billie Goodrich and Sam Fine led me by the hand through a process of learning, not just about the workings of the FDA, but about the valuable contribution that the FDLI would and could make toward dealing with the increasingly complex task of regulation.

Undoubtedly, there have been a great many changes over the past five years, changes that I believe have made the FDA a more effective agency for the protection of the American consumer. While I miss the day-to-day association that I enjoyed as Commissioner, I have the fullest confidence in the leadership and staff of the FDA and am assured that it is one of the best managed health agencies in the Department of Health, Education, and Welfare and certainly the best managed regulatory agency in the federal government.

Despite the turn that my own career has taken, I regard my association with the Agency, its staff and with the many people outside FDA who are helping to carry out its mission, as among the most satisfying and challenging I have ever known.

My sense of satisfaction comes from having had a hand in guiding a program that has so clearly made a significant contribution to the field of consumer protection. But my tenure as Commissioner was challenging, I think, chiefly because we witnessed, perhaps, the arrival of the period of public accountability that has touched virtually every sector of American life and all of our institutions, public and private.

The American System of Health Care

Currently in progress is a major national assessment of the function and performance of commerce and industry, education, the judicial system, and public service activities of all kinds—government among them. In the case of government, this assessment is perhaps long overdue. It is equally obvious to me that the American system of health care cannot and should not be exempt from an obligation to account for its accomplishments, and its shortcomings in meeting the health needs of the American people—an obligation that certainly has not always been recognized and accepted.

I am today perhaps more broadly aware of the ramifications of accountability in the health field than I once was, if for no other reason than that my responsibilities themselves have broadened. However, I think all of us who are or have been directly involved in the work of the FDA—whether within the Agency or outside it—sense very keenly the impact of the public's demand for responsible performance in consumer health protection.

I think we are all well aware of the substantial impact that increased public accountability has had in the field of consumer protection, and especially on the work of the FDA.

With sometimes little awareness of the complex scientific, economic, managerial, and political problems that might be involved, the American people insist—as they have every right to do—that the products on which their health depends be as safe, wholesome, dependable, effective and trustworthy as possible.

Of course, those who have the increasingly complex task of providing the public with this kind of assurance, the FDA on the government side and the regulated industries on the private side, cannot evade the hard scientific and technical problems that have to be faced if the public's desires are to be met. On the contrary, in my judgment they are among the most difficult problems we face.

Need for FDA Expertise

With the increasing sophistication and complexity of science and technology in the pharmaceutical and food industries, it is absolutely essential that the responsible regulatory agency be in a position to apply the same level of expertise. For if the FDA were to lack the capability to investigate and evaluate on a par with the industries it regulates, it would simply be unable to provide effective service either to the consuming public or to the regulated industries.

As I think you know, the need to muster an outstanding scientific capability is one of the most formidable problems facing the federal government and particularly the Food and Drug Administration. I am sure you also know that it is both unrealistic and unnecessary to expect the FDA to acquire unto itself all the scientific and technical resources needed to carry out its responsibilities. These resources need not be part and parcel of the FDA, not as long as they are available to the Agency on an *ad hoc* or continuing basis.

Collaboration Between Agencies

However, I think we have an important opportunity to tap needed scientific and technical capabilities that go beyond the use of outside advisors and resources. It seems to me that we in government, and especially the health component of the Department of Health, Education and Welfare, are going to have to make far more effective use of the substantial capabilities that exist within our own house.

Plainly the NIH and the Center for Disease Control are capable of providing valuable assistance to the Food and Drug Administration, and we intend to pursue this objective to the fullest possible extent. By the same token, other health agencies in the Department—the new Alcoholism and Drug Abuse Agency, the National Center for Health Statistics, the Bureau of Quality Assurance, and a number of others —can and should work collaboratively with FDA where their functions and missions obviously merge, and even overlap.

I have felt for some time that the federal government has lacked a coherent set of strategies—including a strategy for consumer health protection—that could help make the most effective use of federal resources wherever they happen to be located organizationally.

I might just say parenthetically that we in government are accountable for the management of billions of dollars worth of public resources in the health field alone. I personally place the very highest priority on the goal of making the most effective use of these resources, something I fear we have done poorly in the past.

Making Use of Existing Resources

I happen to believe that, rather than add substantially to the catalog of federal health programs and projects, we should be seeking ways to make more effective use of the resources we already have. That means putting the emphasis on sound management, not on poorly planned and often unnecessary growth.

However, the central point is that we in government are being called on as never before to meet the legitimate demands and expectations of the American people, not just by some kind of unplanned and uncoordinated reaction to the shifting currents of public sentiment, but through an enlightened stewardship of the public trust. In my judgment, nothing less is demanded of industry.

On the whole, I happen to believe that the industries that are subject to regulation by the Food and Drug Administration are doing a steadily more effective job of providing the consuming public with an array of products which they can buy and use with confidence. Partly because of improved regulation and partly because of their own sense of responsibility, the great majority of food and drug firms are making substantial efforts to produce and market products that have

a useful and necessary place in the American economy and are of generally high quality.

Certainly there is room for improvement, just as there is room for improvement in the regulatory system. But I must say that the goal of improvement is not served when some individuals suggest, for example, that drug recalls are of little importance and have little meaning to the consuming public or that nutrition labeling will deprive Americans of some kinds of especially wholesome and nutritious foods.

Weakened FDA Ill-Serves Industry and Public

Let me just suggest that, to the extent these allegations may mislead the public and possibly hamper the FDA in the discharge of its responsibilities, they constitute a disservice both to the public and to industry. For if I have not made it clear before, let me say now that an FDA weakened in its ability to provide sound and responsible regulation ill-serves both the public and industry.

FDA on Solid Regulatory Path

All of us, I am sure, recognize that there will continue to be profound changes in the sciences and technologies that contribute to food and drug development. Certainly there will have to be corresponding changes in the process of regulation and the technical and scientific base on which it rests. But I do not foresee a turning back from our present path. Industry, it seems to me, is on considerably more solid ground in trying to gauge what requirements regulation will make. The FDA likewise is in a substantially better position to develop and carry out rational and orderly regulatory programs.

And what is most important is that the public's requirements for safe and effective products, honestly presented and confidently used, is being served more effectively than ever before.

In this less than perfect world, we have moved a long way toward a goal that both industry and government share. **[The End]**

Communication as the Basis of Regulation

By ALEXANDER M. SCHMIDT

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

IT IS A DISTINCT PRIVILEGE FOR ME to take part in this Seventeenth Annual Educational Conference sponsored by the Food and Drug Administration and the Food and Drug Law Institute. From all I have been told, it is clear that this now traditional event has won both the respect and the affectionate regard of responsible leaders in the Food and Drug Administration (FDA) and industry alike.

Many here are veterans to this conference while I am, of course, a rookie. This being the case, I will begin by taking just a moment to introduce myself.

When I first came back to Washington earlier this year, and the word began to get around about my new job, I was impressed with all the solicitude. It was only later that I learned that the new people I was meeting were solicitous because they thought I didn't know what I was getting into; and my old friends were solicitous because they thought I had suffered some mental deterioration.

I tried valiantly to explain that I was neither innocent nor crazy, but everybody reacted with the same question: "Well, then, why on earth did you take such a job?"

The explanation is not really all that difficult. In the first place, I was not unaware that the FDA Commissioner occupies a very hot seat. If he does his job properly, he is unlikely to win universal popularity. Neither was it a secret to me that FDA occupies a no man's land between those who fear almost any regulation, and those who

constantly demand more. Both sides freely press their case, frequently in public.

Congress naturally feels the same pressures we do, and reacts with a growing array of regulatory laws. However, laws need men and money to enforce them; so, FDA must compete for both, against other equally serious national priorities.

Taken together, all of this inevitably results in competition, conflict and criticism. This, in turn, makes news; so the media—professional, industrial and lay—reflect the whole confusing story in lively fashion.

If one stopped here, the FDA job might indeed look like a loser. But there is a positive side to the job, which begins with the fact that in our technologic society, there are certain protections that the public simply must have and cannot provide for itself.

The consumer-activist can help articulate the need; the press can reflect the public view; the Congress can respond with laws; responsible industry can cooperate; and the Administration can—as this one has—act with allocations of money and manpower to provide the means to implement programs.

But somebody has to put it all together and make it work. It may be trite, but it is true to say that if we did not have an FDA, somebody would have to invent one.

So, it was easy to decide that the job is challenging, necessary and useful. But, even so, the question still remained, "Why me?"

It helped to begin by asking myself, "What's the worst thing that could possibly happen?" And since capital punishment is unpopular these days, I found I could go on to more serious considerations.

Essentials of a Successful FDA

The most important of these involved a look at the essentials of a successful FDA.

They are not hard to figure out, and I am far from the first to do so. The bases for an active and responsible regulatory agency such as FDA include good science backing a sane regulatory philosophy, sound management, and effective law enforcement. I determined that

philosophically I was attuned to what was going on in the agency, and that by training and inclination I could hope to contribute to it.

After six months on the job, I have no reason to change my mind, although I now rate the job as an even more serious and exhausting challenge than anticipated.

Those nights I suddenly sit bolt upright in bed, I am comforted by the fact that I used to do the same thing when I was Dean of the University of Illinois Medical School in Chicago—I have learned to live with a little challenge.

It is even greater comfort to know that I do not have to face this challenge without help. I did not have to start from scratch. For FDA today is a well-functioning agency with authority and an excellent staff that knows where it wants to go and how to get there.

One of the most important inducements for me to accept this job was the strong support the Agency obviously has within the Administration and Congress. A more than doubled budget in the past four years is rather substantial proof of this, as is the increased number of positions allotted.

But I am sure that what you want to know is, "Now that I have got the job, what am I going to do with it?"

To start with, I operate from the premise that FDA is a scientifically oriented regulatory agency with a single mandate: consumer protection.

A Mandate for Consumer Protection

To serve this mandate properly, the FDA must continue to broaden its base of expertise and advice upon which major regulatory programs are built. This expertise and this advice must be brought to bear across the boundaries of bureaucracy and across the barriers which separate the public and private sectors.

I consider it foolish to imagine that rational and effective regulations can come from an FDA isolated from those it regulates. Those regulated have important views as well as expertise, and they must be heard.

At the same time, the consumer must be heard. He must know why and how and *if* we are acting in his best interest. And if he is to know, the consumer must have the same opportunity as industry to participate in regulatory decision making.

In support of this view, I accept as a priority our efforts, now underway, to set specific guidelines for an "open door" policy, under the Freedom of Information Act.

In talking about the need for outside advisors, in committing the Agency to consultation with industry and consumers, and in fostering an "open door" policy in general, I am, of course, talking about communication.

Communication—A Major FDA Theme

Communication, really, is the major theme I want to follow here today. I am delighted that the same theme runs through so many of the workshops for the convention.

Webster defines communication quite simply as the "interchange of thoughts or opinions." But in practice, we too often make communication sound far more complicated. While I admire the practice of communicating, I find unpleasant the jargon we use in describing it.

For example, we in government often say "data exchange" when we mean communication with physicians or other scientists; we reduce the term to "public information" when we mean communication with consumers; we call it "liaison" when we communicate with other government agencies; and—God forgive us—we usually refer to communications with industry as "a dialogue."

But whether what we do involves an exchange of data upon which to judge a new drug application or to develop drug labeling; whether we hold a press conference to explain nitrite uses in processed meats, or to issue a new regulatory proposal for bottled water, or even to participate in a convention such as this one—what we are seeking to do is to communicate.

Only when we fail to communicate with a desired effect do adversary terms like "compliance, enforcement and prosecution" come into play.

Advisory Committees as a Method of Communication

As I have indicated, I am a strong advocate of advisory committees as a method of communication. And I am pleased today to report our progress with a program which was still in the planning stage when presented to you last year. Today, the FDA has fourteen standing advisory committees attached to the drug review process. This

number will increase to 18 by July. This compares to only one such committee existing in 1970.

These committees insure FDA constant access to highly qualified and independent experts in every major drug category. The result should be apparent in better decisions in behalf of safer and more effective drugs, and a more efficient and effective monitoring of our processing of IND's and NDA's.

Out of this improved communication with outside scientific expertise will come another major benefit—improved drug labeling. In turn, drug labeling is at once the heart of FDA's communication efforts with the medical community and one of our best hopes for contributing to a better health care system.

A Drug Compendium

I see a pressing need to make more readily available, for physician reference, the labeling information now existing on all legally marketed prescription drugs. We are now talking seriously about the publication of a drug compendium. I recognize that in addition to its sponsorship, there are other important details to be resolved, not the least of which is the needed financial support. Other issues include such matters as format and presentation, and the sheer management of such a mass of information. But these are details that should not prove insurmountable if reasonable men attend them. Our overriding consideration must be, and is, the validity of the concept and the urgency of the need for a compendium.

I can think of no single accomplishment that would contribute more to communications with the medical profession on matters which directly affect the quality of their practice. However, our obligation to share the accumulated knowledge we have gained about drugs and drug use extends beyond the professional user to the ultimate beneficiary—the consumer.

I sense that some in the pharmaceutical industry, and many in medical practice feel uncomfortable with some of the things I have said and done in behalf of patient information during the past half year. To be explicit about it, what I have said is no more or less than to argue the right of each patient to understand his options, and to give or withhold consent whenever he is asked to accept a significant risk engendered by drugs or any other mode of diagnosis or therapy.

Patient Package Insert

Since I have been Commissioner, the FDA has required patient package inserts for two newly approved forms of chemical contraception. This continues our practice since 1970, of requiring patient brochures for oral contraceptives. I believe the time has come to consider similar brochures for other classes of drugs. A good patient package insert may be an excellent means of communicating to the patient information which will improve patient compliance to chronic medication, increase the patient's ability to recognize or cope with adverse effects, and ultimately improve the patient-doctor relationship.

There is much to be explored before we have the final answers on this issue. But the subject is worthy of continued study, and you will be hearing more about it.

Benefit-Risk Decisions

I spoke a moment ago about benefit and risk. If anything ever needed to be clarified and better communicated, this subject qualifies. The same consumer who lives willingly with benefit-risk decisions every time he crosses the street or catches an airplane, somehow expects—and often thinks he is getting—absolute safety in food and drugs. Even Congress is tempted to reflect this public view in legislation, requiring us to make certain types of benefit-risk decisions. At the other end of the spectrum, the physician wishes the FDA would leave benefit-risk decisions concerning drugs to his judgment; and industry, no matter how things turn out, argues that we take too long and demand entirely too much data.

In the midst of this clamor stands the FDA and its scientific advisors. Now, I'm not trying to evoke your tears of sympathy. The middle is usually the proper place for the FDA. The important thing is, that in the coming months and years through much more effective communication, we must achieve the kind of understanding that will lead to a consensus concerning the need for, and appropriateness of certain kinds of benefit-risk decisions to be made in, among others, the food area. Probably the laws, our regulations, industry practices and consumer behavior will all have to reflect a new and wise consensus, hopefully based on rationally interpreted and soundly derived data.

In regard to this general area, I might cite one problem that puzzles me. This concerns the present clumsy process for removal from the market of those drugs that have been judged ineffective. Except when an "imminent health hazard" can be demonstrated, the present procedure is too costly in both time and money for all concerned.

This situation seems to me somewhat of a perversion of the basic principles of benefit-risk matters, since the drug firm that resists removal of a drug and continues to market the ineffective product during the long, drawn out dispute, assumes all the benefits while the physician and his patients assume all the risks.

In the long run, I fail to see how industry, the FDA, the physician or the public can profit from this situation. It calls for correction, and I personally feel that we must try to find a more effective and efficient means of accomplishing this often too-difficult task.

Increase Legislative Action

Let me turn from benefit and risk decisions to legislative matters. Medical devices is one area in which I see an FDA requirement for basic new authority. Food plant registration, and ingredient labeling for standardized foods are areas in which existing authorities need strengthening. We anticipate early and favorable Congressional action in all three areas.

In the meantime, I have found that generally, the FDA has a strong and good legislative base. Even in the matter of medical devices, the FDA is not powerless within existing law.

We are now two years along with a successful effort to inventory and classify these essential tools of medicine. In addition, labeling requirements for diagnostic products will be made effective in March and the development of product class standards for diagnostic products is proceeding with good help from industry. We are now moving to merge certain scattered activities within the Agency, and will create a new Bureau of Medical Devices and Diagnostic Products. This will provide a needed focal point for these various activities. The entire medical device program can be described as an attempt to communicate with industry and with the professional or technical consumer, first, to insure that dependable products are available, and then, to insure their proper use.

There are other good examples of FDA programs that are based even more directly on a foundation of communications. Our recent

drug pricing statement is intended to insure that full and honest information about drug pricing is available to consumers. As many of you know, the drug pricing statement is essentially a clarification of a long-held FDA position in regard to advertising.

Peter's Preambles

In contrast to that, our expository introductions to final orders, or "Peter's Preambles"—so-called in honor of their chief architect, Peter Hutt—are a significant change from past position. Peter's Preambles underscore our new determination to use the *Federal Register* as a means of communication and consultation rather than simply as a depository for FDA decisions. I am sincerely committed to the publication of FDA proposals that are *in fact* proposals, designed to stimulate a maximum response to our suggestions.

I predict that in the months ahead you will be seeing more *Federal Register* statements such as the recent asbestos and the drained weight documents. Both of these ask for information and invite comment to help determine the best course of regulatory action.

You will be seeing more examples that will be like the new flavoring regulation which, in ten months, went from proposal to final order to revised proposal to revised final order.

Some may argue that such activity projects the image of a wishy-washy agency. I do not agree. I am far more concerned with promulgating the best regulations we can, following the fullest public input, than I am with bureaucratic imagery.

Another recent example of what I consider a wise action, after informative communication, is the textured protein document. On the basis of better information and new advances in technology, we have decided that an entirely new proposal is in order. We will, therefore, start anew with this regulation.

In all we do, my goal is to be certain that industry and consumer alike will have full opportunity to react to every *Federal Register* proposal, and that they can, with sound argument and solid science, affect the direction and shape of our regulations.

Codification of FDA Procedures

One of the most ambitious projects which will foster good communication has taken form in Peter Hutt's office. He is overseeing a truly massive and unique codification of all FDA procedures. The first section is now under review by our Policy Committee. When completed, we will have produced a "how-to" guide on every possible procedure from the establishment and conduct of advisory committees to the filing of citizen petitions, to dissemination of draft regulations. I believe that this will be a very significant document, and when published, will be concrete proof of our commitment to an open Agency. We think that that approach is the only way to go and I might suggest that the concept applies not only to our business at FDA but to yours as well.

As a last major point, I would emphasize my personal commitment as FDA Commissioner to those ongoing programs: the OTC review, the food safety initiatives, and the food labeling program. All are perfect examples of my thesis that communications is what the FDA is all about, and all provide important clues for those of you who are looking for trends and priorities in the current FDA approach.

The OTC review is testing—with every promise of success—the monograph approach to regulation. It is demonstrating the feasibility, the efficiency, and the sheer necessity of regulation by product classes instead of by isolated product actions.

This procedural concept is being applied—or soon will be—in five other ongoing programs:

—The GRAS review
—Medical devices
—Old drug regulation
—Safety and efficacy review of biologics, and
—Last, but far from least, the vitamin-mineral definitions.

Food Safety

Present food safety initiatives include new emphasis on such programs as basic sanitation, new techniques for process inspection, review of food additives, and surveys for mycotoxin residues. Each of these efforts is designed to help us regulate effectively in the face of—forgive the term—a mushrooming growth of new foods and new food processes.

Under the twin pressures of population growth and the necessary search for new ways to stretch the natural food supply, the problems of toxicity and tolerances will increase. Maintenance of nutritive status will demand continuing vigilance. The plain fact is that we are fast approaching the time when the consumer must face some kind of benefit-to-risk decisions about the foods he eats.

And, finally, food labeling in all its many facets gives testimony for all who will listen to the new directions we are taking. Here, as in no other FDA activity, the communications theme predominates.

As industry moves from natural to fabricated foods, the consumer will find less value in ingredient labeling, and will look as never before for the kind of information to be given by nutritional labeling and quality guidelines. He will learn to read information panels, and learn about the identification of imitation products, common and usual names and the listing of incidental additives. He will become familar with dietary supplement definitions based on the U. S. Recommended Dietary Allowances (RDA).

The FDA has carried the ball in developing sound programs to guide industry in communicating this kind of information to the consumer. As a result, more than 20 separate orders now constitute our food labeling initiatives. The program looks good on paper. But the final test will come when industry has provided the new information, and consumers have learned to use it.

Responsibility to Teach the Consumer

Teaching the consumer is a joint responsibility involving FDA and the food industry, and there is cause for optimism. In very significant ways, the food industry is demonstrating a willingness to accept its part of this responsibility. The FDA will accept its share, as well. Early next spring the Agency, with professional help, will launch the first part of a nationwide campaign of consumer education on the uses and the usefulness of the new labeling.

The food labeling program is among the most important priorities on my personal list. Within the years immediately ahead, we will devote whatever resources are possible to make this program work. We invite an equal commitment from industry.

And now, in conclusion, this comment:

When Doctor Edwards came to FDA, his charge, as he saw it, was to get the Agency moving. And he did that very well.

My charge, as I see it today, is to keep the Agency moving, to continue the development of new regulatory concepts and to consolidate and build upon solid foundations that have been laid.

Through the conversion of concepts into program realities, the next few years should be even more important than the past four to our single goal of consumer health and safety. I believe communication is the major ingredient of such progress.

Finally, I believe that progress of any sort is an uneven process. It usually lurches along in bumps and surges. If this is so, then none of us concerned with food, drug and cosmetic regulation can reasonably expect the road ahead to be always straight and smooth. But the road is there. And it is passable. New and better signals are being installed along the way. But the driving is up to us—all of us.

[The End]

U. S. DEPARTMENT OF AGRICULTURE APPROVAL DID NOT PREEMPT STATE REGULATION

Approval of the labeling of "All American Fun-Links" as frankfurters by the U. S. Department of Agriculture did not preempt regulation of the product by the state of New York, according to the U. S. District Court. The product was, despite the approval, misbranded under both the New York Statutes and regulations and the identical federal Wholesome Meat Act and related regulations. According to an official of the Department of Agriculture, the Department approved the "Fun-Links" labeling because it agreed with the view of a White House Conference on Food, Nutrition, and Health that consumers are reluctant to purchase products labeled "imitation" even though they are nutritious. That view did not justify the Department's disregard of the Wholesome Meat Act, said the court, and, by the provisions of that Act, a state may enforce its own laws that are consistent with the Act. Consequently, the court refused to issue an injunction against enforcement of a state ban on the sale of the product.

Swift & Company, Inc. v. Frank Walkley, Commissioner of Agriculture and Markets of the State of New York

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Federal/State Concurrent Regulations

By FRANK E. FISHER

Mr. Fisher Is the Director of the Bureau of Food and Drugs, Indiana State Board of Health.

I APPRECIATE THE OPPORTUNITY to represent the Association of Food and Drug Officials of the United States (AFDOUS) in discussing our position on the subject "Federal/State Concurrent Regulations."

AFDOUS is a national organization of local, state and federal food and drug law enforcement officials, scientists, associated industry administrators and researchers dedicated to the promotion of consumer protection through workable laws equitably and vigorously enforced. The Association is a nonprofit corporation. As stated in our constitution, the objectives and purposes of the corporation are to:

(1) Promote and foster uniformity of laws affecting foods, drugs, cosmetics and devices;

(2) Encourage and promote enforcement of said laws;

(3) Encourage and support programs which will contribute to consumer protection consistent with the broad purpose of said laws;

(4) Assist members in their technical work and development;

(5) Cooperate with other professional groups in advancing consumer protection under the laws;

(6) Disseminate information and ideas relating to food and drug law enforcement and administration;

(7) Encourage and promote cooperative enforcement programs with federal agencies and between related enforcement agencies within each state.

History of AFDOUS

AFDOUS had its beginning in 1897 and held its first conference in Detroit, Michigan. It should be noted that at that time, no food and drug legislation existed at the federal level, and there was little or no uniformity in existing state legislation. In the report of the proceedings of our 10th Annual Convention, the following statement appears:

"With the single exception of Indiana, no state has specific laws governing the sanitation of all food-producing establishments. Many states have laws for dairies, bakeries and slaughterhouses, but Indiana seems to be the only one with a general law."

From 1897 to 1906, the Association actively supported and worked for passage of the proposed legislation for a federal food and drug law. On November 16, 1905, the Association, together with the Consumers League, the American Medical Association, and the National Federation of Women's Clubs, presented a statement to President Theodore Roosevelt asking for a message to Congress in behalf of the pure food bill, then pending in the Congress. In part, the statement asserted,

"* * * that the interstate commerce in adulterated, misbranded, and imitated foods and drugs is of such a character that it cannot be properly controlled by state legislation alone, and that a federal law, fair to all interests and with full protection to the consumer, is needed to supplement the state laws in order to require all food and drug products intended for interstate commerce to be truthfully labeled, and to be labeled to show whenever any adulteration has been added or practiced in the preparation."

The statement concluded,

"* * * the committee respectfully petitions the President to recommend the passage of a law to control the interstate shipment of adulterated and misbranded foods and drugs in his coming Message to Congress."

The bill did pass and again, reading from the report of our 10th Annual Convention, the following resolution appears,

"Resolved, That this Association rejoices that its ten years of persistent efforts to secure the passage of a National Pure Food Law have been crowned with success by the enactment by the Fifty-Ninth Congress of such a law, and the thanks of this Association to that Congress are hereby recorded for that legislation. We pledge this Association to continued efforts to secure further legislation as may be found necessary to strengthen the effectiveness of that law in accomplishing the purposes for which its enactment has been urged."

Uniform Food, Drug and Cosmetic Act

AFDOUS was active in the support of the Federal Food and Drug Act of 1906 and the state laws adopted during that period. We strongly urged that state food and drug laws be made uniform

with the federal act and we also supported the adoption of the Federal Food, Drug and Cosmetic Act in 1938. A committee of AFDOUS then drafted the Uniform Food, Drug and Cosmetic Act which has been adopted by many states and which has been kept modern by committees of the Association. We again urged all member states to adopt the uniform act and, at present, 41 states have done so. We still have hopes for the other 9. The uniform bill carries the same provision for the adoption of regulations and definitions and standards of identity as the federal act and most states with the uniform act make an effort to keep their regulations and food standards uniform with federal regulations and standards. Seven states have provided for automatic adoption of federal regulations under the Food, Drug and Cosmetic Act.

In Indiana, our Deputy Attorney General has stated,

"The authority to adopt a document by reference within a rule is limited to that specific document in existence at the time the rule is being promulgated. If the referenced document is thereafter revised or changed, these changes are not valid insofar as the basic regulation is concerned. To consider said changes as a part of the original regulation would, in the opinion of our counsel, be considered an improper delegation of legislative power and the rights of due process would be abrogated."

Many other states have stated similar positions.

"Concurrent" Defined

If you have examined your program, you will notice that the moderator of this panel and the other two panel members are attorneys, each distinguished in his particular field. This reminds me of the layman who went on a fishing trip with three attorneys. After they had rowed the boat out to the middle of the lake, one attorney discovered that he had left his fishing pole on the bank. He stepped out of the boat, walked across the water, picked up his pole and returned to the boat. In a few moments, the second attorney discovered that he had left his bait can on the bank. He also stepped out of the boat, walked across the water, picked up the bait and returned to the boat. The layman then discovered that he had forgotten his pipe tobacco. Not to be outdone, he also stepped over the side of the boat, but immediately sank to the bottom of the lake. The third attorney looked at his two companions and said, "Do you suppose we should have told him where the rocks are?"

In order to be sure that I have stepped out on a rock, I consulted Webster's New International Dictionary for a precise definition

of the word "concurrent". Among the several definitions, the ones most pertinent to today's discussion seem to be.

"Joint and equal in authority; taking cognizance of, or having authority over, the same subject matter; operating on the same object; as concurrent jurisdiction of courts; operating simultaneously; as concurrent sentences."

Webster further defined concurrent powers as "political powers exercised independently in the same field of legislation by both federal and state governments." The rationale of including a representative of AFDOUS on this program immediately becomes apparent.

The Federal Food, Drug and Cosmetic Act and the food and drug laws of the various states meet all the criteria mentioned above and it is apparent that the several states and the federal government have concurrent powers in the field of food and drug legislation.

Problems of State Level Food and Drug Enforcement

I have discussed the history of federal and state food and drug laws in order to make the following observations. Food and drug enforcement at the state level always has, and probably always will, have certain obstacles to overcome. *First*, there will always be a shortage of funds for enforcement. Therefore, state monies can be used to the best advantage by employing qualified personnel to do the field work and laboratory analyses without having to use portions of it for setting up independent standards. Much of this work has already been done on a federal level and can be used by states if their laws are uniform with the federal act.

Second, state enforcement officials will always encounter the problem of legal interpretation of their acts in local courts. Most state regulatory agencies are without legal talent on their staffs. Therefore, lay administrative personnel must prepare and evaluate the evidence, draft the necessary legal papers and present the case to the county prosecuting attorney who, in most cases, is their legal representative in the case. Food and drug laws are unfamiliar to them and, in many cases, it is difficult for them to grasp the significance of the violations presented. It is a well-known fact that judges are prone to rely on precedence and interpetations laid down by other courts, especially the higher courts. In the states having the Uniform Food, Drug and Cosmetic Act, state and county judges can and, in many cases do, use federal court interpretations in deciding state cases.

Third, it is difficult and sometimes impossible for state enforcement authorities to provide expert testimony in presenting cases.

It is certainly advantageous for the state to have uniform legislation since when uniform legislation is being enforced, the assistance of the Food and Drug Administration (FDA) is always available.

Fourth, even though food and drug legislation is designed to protect the consumer and promote fair dealing, it also has an obligation to the manufacturer or dealer in these commodities. A New York manufacturer whose products meet New York state requirements has every reason to expect that his product will be accepted in any other state and in interstate commerce. This is only fair, but it will not be the case if states have varying requirements and restrictions which act as trade barriers between states. In Indiana, we receive many requests from out-of-state manufacturers and wholesale distributors of foods, drugs, devices, and cosmetics for information regarding state regulations. Since we have uniform legislation, we can tell them that if their product meets the requirements of the federal act, it will automatically meet Indiana requirements. Similarly, we can tell our own manufacturers and wholesalers that their products will probably comply with the federal act if they meet the requirements of our Indiana law.

Finally, uniform legislation makes it possible to coordinate state enforcement efforts with those of the Food and Drug Administration. I am sure that you are aware that many states are operating under work-sharing agreements with FDA and that frequent planning meetings are held between our groups. Our total efforts are directed in such a manner that our field forces supplement each other. Laboratory results are exchanged and other information is shared with the result that a great deal of duplication of effort has been eliminated.

Case Against Federal Preemption

If this sounds as if I am making a case for federal preemption, you are wrong, and I have led you down the primrose path. In stating my case against preemption, I would like to make the following points.

First, the states have for many years provided much of the impetus for food and drug legislation. Through AFDOUS, the states have promoted uniformity in both laws and regulations. The present system, while certainly not perfect, is working reasonably well.

Second, in much of the recent federal preemptive legislation, the enforcing agency has found that it is necessary to enlist the aid

of state agencies for proper enforcement. In many instances states are expected to provide the enforcement at no cost to the federal government. When pinned down, these agencies will admit, albeit reluctantly, that without massive state assistance they would be unable to effectively enforce the statutes they are required to administer.

Third, state legislators are becoming more and more reluctant to appropriate state funds to enforce federal laws and regulations. This reluctance also extends to state laws which are required to be equal to or identical with federal legislation. This is particularly true in states where pioneer legislation was enacted which later became the subject of a federal law. This reluctance is even more understandable when you consider that the states for many years have been quite active, individually and collectively, in developing and enforcing fairly uniform regulations.

Fourth, it is readily understandable that state officials are not eager to enforce regulations in which they had no input. They are reluctant to merely "rubber stamp" federal dictates, particularly if they feel that in the drafting of the regulation or standard their views received little or no consideration. I believe that you will agree that states have followed federal laws and regulations—not 100 per cent—but in most instances they have cooperated in enforcing programs which they felt were legal and needed.

Fifth, states are capable of adopting uniform regulations and indeed have done so. Even though an occasional maverick raises his head, on the whole the record is good. An outstanding example of what can be accomplished by a cooperative state effort with assistance from, rather than domination by, the federal establishment is the Interstate Milk Shippers Program. From its beginning over 23 years ago, when 26 states met to develop rules mutually acceptable to both shipping and receiving areas for the interstate shipment of high quality dairy products, the program has grown in size and stature until participation in recent conferences has been by representatives from as many as 46 states, Canada, and Puerto Rico. The fruits of the program, respected sanitation compliance and enforcement ratings, are not only used by most states as a basis for the acceptance of fluid milk supplies from distant shipping areas, but are also used to determine the acceptability of such products for use in military establishments, federal hospitals, and on interstate carriers.

Even though tremendous progress has been made in recent years in the free flow of products across state lines without the necessity of duplicate inspections, admittedly there are still a few areas which do not subscribe to the philosophy of inspection reciprocity. With the continued assistance of the U. S. Food and Drug Administration, however, the National Conference on Interstate Milk Shipments is confident that these artificial trade barriers will also dissipate.

National Conference on Weights and Measures Officials

You are undoubtedly familiar with the activities of the National Conference on Weights and Measures Officials in developing and enforcing uniform net quantity regulations for consumer products, as well as Handbook 44 covering the specifications, tolerances, and other technical requirements for commercial weighing and measuring devices and individual handbooks covering the testing of packages, LPG, farm milk tanks, aerosol containers, etc.

The decisions of the National Conference on Weights and Measures Officials are purely recommendatory. A code of specifications and tolerances on a scale, for example, can have no effect in any state until it is promulgated or enacted by competent authority in that state. However, the reputation of the conference for making only reasonable and proper recommendations is so well established that they are automatically adopted by the states under the provision of adopting these by reference.

In conclusion, I believe that federal preemption in the area of food and drug laws and regulations is both unnecessary and unwise. I would be the first to admit that our present situation is not perfect and certainly we all have a vital interest in solving the problems which do exist. But the present system has served the public well. It is also my firm belief that federal preemption would tend to create many more problems than it would solve.

Charles Wilson, Secretary of Defense during the Eisenhower Administration, once created quite an uproar when he made the statement, "What is good for our country is good for General Motors and vice versa." No one argued with the first part of his statement but his "vice versa" brought down the wrath of many on his head. I would suggest that you not be caught with your vice versa showing.

[The End]

An Industry Overview of BVM Activities

By A. M. McVIE

Mr. McVie Is the President of the Animal Health Institute.

ON BEHALF OF THE ANIMAL HEALTH INSTITUTE (AHI) and its fifty-nine member companies, I wish to thank the Food and Drug Law Institute (FDLI) and the U. S. Food and Drug Administration (FDA) for extending to me the gracious invitation to speak before you today. I take particular pleasure in discussing with you an industry overview of BVM activities.

What I will say is, I believe, positive, and hopefully, constructive. In these times of skepticism and torturous introspection in virtually all sectors of our society, it is increasingly evident that the animal drug industry, its federal regulators and the American public, must come together for the common good of all. This meeting is one such example.

The foundation of this dynamic and growing animal drug industry is science, and science demands constant dialogue. This is also true with those regulatory aspects of our industry. To expand one side of the equation and deny the other side its needs in order to maintain the equilibrium, is to ultimately destroy the solution—the benefit. My presentation today is dedicated to the furtherance of cooperation among those of us here today and those we represent.

This past year has seen the emergence of several major issues that, when resolved, promise to profoundly affect the animal drug industry for decades. Antibacterial research, standardization of assay methodology, environmental impact analysis . . . are good examples, and they all need and deserve cooperative interchange essential to meaningful resolution.

In keeping with the concept of "overview," allow me to briefly discuss these three major issues I just mentioned, and how we intend to face them with the Food and Drug Administration and its Bureau of Veterinary Medicine.

I will be followed immediately by Dr. Richard Lehmann and Dr. Jane Robens, who will discuss "Criteria for Acceptable Methods to Detect Residues." To me this title elicits one word, "Delaney." Few drug issues in recent memory have received the broad-spectrum attention the Delaney Clause has received. The fact that the Delaney Clause has been the emotional "whipping boy" of the animal pharmaceutical world has, I believe, impeded our progress to resolve the scientific issues behind the language of the law.

These scientific issues crowd up against the very frontiers of our technology. They must be addressed . . . and addressed now! We in industry realize this need and have devoted considerable attention both to a review of the existing technology and its long-term implications for our society. The FDA's July 19 *Federal Register* proposal, "Compounds Used in Food-Producing Animals," in particular, has enormous long-term implications for industry and society.

Technical Assistance to the FDA

In a recent letter to FDA Commissioner Schmidt, AHI offered its technical assistance to the Agency in its review of questions raised by the July 19 proposal. In the letter we stated that "When published as a final document (the current proposal), could have greater impact on the animal drug industry than any other regulatory document issued in years . . ." On this issue especially, the dialogue I spoke of earlier is *essential*. The AHI has initiated such an interchange by first, and formally, submitting a highly technical document to FDA which offers both general comments and some 36 specific recommendations to the proposed regulation.

In response to our offer-of-assistance letter, the FDA, it is heartening to report, views AHI's participation as "highly desirable and (we) will see to it that your group is invited to present its views before responsible officials of the Agency at an appropriate time." Once an initial group of scientists and biostatisticians have prepared a special report on certain technical considerations, FDA has informed the Institute that it will then begin further critique of the

proposal. "It is at this point," AHI has been advised, that our "additional views would be welcome."

As our lengthy proposal comments suggest, the initial document is far from perfect. But it is a start, and that in itself is extremely significant. Further, we have been assured that a highly technical issue fraught with emotional overtones through its close association to the Delaney Clause, will be carefully and scientifically reviewed. The July 19 proposal and its final order will take time to resolve, but we of the AHI are ready to assist in every way possible to see that a fair and objective decision is rendered.

Antibacterial Research

The concept of time is also vital to the next issue, . . . antibacterials in feeds. These valuable production tools are essential to modern meat production. Without proper medication today's high concentrations of livestock and poultry would face the increased risk of yesteryear's disease rates.

Confinement rearing now assures American consumers the quantity and quality of protein they want, provided a free market environment exists. To question the role of antibacterials in feeds to agriculture and their safety to man is the highest test of the reasonableness of the equation known as "benefit-to-risk."

Yet it is industry's belief that from BVM's review of low-level antibacterials in feeds will come positive answers that will serve to further public confidence in our ability to market safe and effective animal drug products. Our contention remains: There is not one shred of documented evidence that antibacterials used in feed present a hazard to the animal or human population. Yet definitive scientific proof is required, and so again, as with the assay methodology issue, we will cooperate to our fullest in responding responsibly to the questions raised by the FDA antibiotics task force.

To meet its responsibilities in answering all questions completely, the AHI has implemented the largest single cooperative research program in its 34-year history. The magnitude of our earlier penicillin-streptomycin study program is totally eclipsed by this current effort. AHI's basic organizational unit in dealing with the antibacterials issue is the Antibacterials Research Criteria (ARC) task force. The ARC was formed following the February 1972 publication

of the FDA's proposed statement of policy on antibiotics used in feeds. For the past year and one-half the ARC has worked diligently to provide guidance to the industry. AHI's finest scientific protocols today form the basis from which the required studies proceed.

On April 20 this year the FDA published its long-awaited final order. AHI was ready. Under a previously approved plan, the ARC divided into subgroups, each responsible for organizing a cooperative research program for human and animal safety aspects of a particular antibacterial drug category. FDA's first-round studies will involve research in so-called "target drugs," those antibacterials used in humans as well as animals. The five target drug classes are tetracyclines, streptomycin, dihydrostreptomycin, penicillin and sulfonamides. Efficacy requirements will be handled separately by member companies.

The subgroup research projects are either now under way or are in the final organizational stages. As you may know, the research data involving the five "target drug classes" and their relationship to the salmonella organism, are due on April 20, 1974. A deadline of April 20, 1975, has been set for completion of the remaining research, which involves antibacterial effects on other microorganisms and on product efficacy. For example, work on the bacitracin class of "non-target" drugs is proceeding nicely and should meet the 1975 deadline with little difficulty.

AHI's Cooperative Research Projects

At this point I would like to emphasize that in labeling our various research projects "cooperative," we mean just that. Non-AHI members are welcome to join us at any point in our efforts to resolve these highly technical questions. Additional expertise is always welcome. Some nonmember manufacturers have already accepted our invitation and are participating in ARC subgroup activities.

The interchange between BVM and AHI scientists during this long and arduous technical exercise has been good. True, there are differences of opinion on certain issues. But again, we remain confident that once the data begins to come in, these "grey areas" will be resolved. As with research on assay methodology, one must remember that we are operating in a scientific area for which little technology is available. Our scientists have in many ways started "from the ground up."

Argument for Meaningful Research

We cannot fault the need for conducting research to answer questions concerning the risk side of the human equation. We're all in the same boat. It is a question of *"meaningful research."* Much philosophical as well as scientific discussion has occurred on "meaningful research," and I don't pretend to have a concrete axiom for society to follow.

However, I do think it important that we define the "benefit" side of our so-called equation as well as we have defined the "risk" side. This has not been done satisfactorily, in my estimation. To shift into what I call "defensive research," to substantiate products that have benefitted society tremendously without any documented health hazard whatsoever, is a practice that can have considerable long- and short-term negative ramifications for industry and ultimately, the public it serves.

At a time when we have an energy crisis, when we have extremely competitive world markets for American products, and when we have many other similar demands for solving problems by innovation that can only come about from productive Research and Development (R&D), any R&D effort diverted to investigation of unsubstantiated charges is an irretrievable loss of valuable resources and plainly not in the best public interest.

The public and the regulatory agencies we work with simply *must* understand that every dollar spent in defensive research is a dollar diverted from the more important pursuit of progress. Further, even if corporate profits were as large as the government budget, the availability of well-trained scientists has severe limitations.

Effects of Defensive Research

Gone are the days when one brilliant scientist would reappear after months of seclusion to announce a major technical breakthrough. Research programs require teams of specialists, many of them extremely difficult to obtain. Let me digress for a moment and speak not as the president of the Animal Health Institute, but rather as a corporate official of Eli Lilly and Company. Our Research and Development efforts for a new and exciting antibiotic that we hope will ultimately be cleared for use exclusively in animal agriculture . . . has been slowed almost to a standstill.

Why? Because of the need to focus the efforts of several of our key research scientists toward the question raised by the FDA in response to the recommendations of the antibacterials task force. This work, which also ties up laboratory facilities and consumes R&D monies, will in our view add very little, if any, new useful scientific knowledge to the technology.

Contrary to the prevailing attitude in certain anti-industry circles, we at Eli Lilly or any other company do not have unlimited resources to tap for costly research projects. R&D funding takes an industry average of 10 to 15 cents from every sales dollar. Research expenditures are rising at a 12 percent annual clip, compared to a nine percent sales growth. Research moving in high gear is our best weapon in combatting the principle of diminishing return, not just for profit, but for progress, the kind of progress that benefits us all.

Environmental Impact Statements

I will now turn to the third major issue confronting the animal drug industry—FDA's exercise of its statutory responsibilities under NEPA, the National Environmental Policy Act, which Congress enacted in 1969 with the admirable goal of preserving, protecting, restoring and improving our surroundings. By now everyone has heard of Environmental Impact Statements (E-I-S), those documents which all federal agencies must issue whenever their proposed actions have a "significant" impact upon our environment. That word "significant" is enclosed in quotation marks because it seems to be the key. I suspect that our descendants will be debating its meaning a hundred years from today.

FDA has long been in the business of protecting the public from harmful foods and drugs, and I believe environmental protection has also entered into the Agency's considerations for many years. But now there is this broad-gauge statute that says *every* federal agency must get into the act, and must do so under a series of rigid guidelines that are designed to cover every eventuality. The Council on Environmental Quality insists that each department and agency, including FDA, must propound elaborate procedures to comply with NEPA.

Right now our industry—as well as the food and human drug industries—is anxiously awaiting FDA's third major effort to fit its own types of "actions" into this cumbersome, legalistic framework. The first FDA pronouncement was its "Proposed Preparation

Procedures," published in the *Federal Register* in July 1972, with 60 days for comment. The Animal Health Institute formed a special task force to prepare AHI comments on that proposal, comments which were submitted two months later. We expressed our concern over the FDA proposal's failure to protect trade secrets; we suggested that there would be extensive duplications of effort, both by industry and governmental agencies, wasting time, money and manpower; and—perhaps most importantly—we urged that groupings of similar products should be allowed where their "environmental impact" would be of the same character and magnitude.

Just one year ago, an AHI delegation met informally with representatives of FDA in an effort to clarify our written comments. Later we developed groupings of animal health products which might be covered by blanket environmental impact statements, and we suggested that certain classes of products might be excluded from the E-I-S requirements entirely because their administration to animals could not conceivably affect the environment significantly.

Last March 15, FDA published its "final" version of E-I-S preparation procedures. This document was distressing to us, frankly, because it appeared that all of our efforts had been lost in the shuffle or simply ignored.

I won't pretend I know what then transpired out at Parklawn, but suddenly, FDA seemed to be taking another look at the whole environmental impact situation. It was as if someone at the top had suddenly recognized that a paperwork monster was being created. We had another meeting with FDA officials, and more AHI suggestions were developed.

FDA's Revised E-I-S Proposal

Now, prompted by revised requirements and guidelines issued by the Council on Environmental Quality, FDA is about to publish a revised proposal. Until we've had a chance to analyze the nuts and bolts of the new document, of course we don't know whether it's an improvement over the previous ones. It remains our conviction, however, that unless FDA realistically and efficiently addresses the key issues set forth in the Act, redundant, bureaucratic paper shuffling will result, and the entire effort will be negated. Society, including all of its sectors, is the ultimate loser.

On behalf of the Animal Health Institute, let me again express my thanks to the FDLI and the FDA for allowing us to present an industry overview of BVM activities. The coming year will be a busy one for all of us, and so it is important now for us to take the time to make a candid appraisal of current attitudes and trends. With the foundation of understanding and encouragement that increased communications and cooperation brings to our deliberations, the major issues I have just outlined stand a far better chance of meaningful resolution in the coming year.

Science, gentlemen, is our lifeblood. How we expend our resources of manpower and funds in harnessing the unknown depends on our understanding of its interrelated impact on all aspects of society. To divert industry's research energies without proper substantiation, we believe, is a serious mistake, not simply because it can impede development of new products, but also because it creates a dangerous drain on existing resources.

We look to the new year with the hope that industry and government alike will gain increased awareness of our responsibilities not just to institutions and dollars, but to the people. One thing is certain. We must all share that responsibility if we are to succeed.

[The End]

SELENIUM APPROVED AS ADDITIVE IN POULTRY AND SWINE FEED

Selenium has been approved for use as a food additive in the feed of chickens, turkeys, and swine. After reviewing comments received on its proposal, the Food and Drug Administration has determined that no significant issues were raised and, therefore, the order will become final February 7, 1974. The amended regulation (21 CFR 121.325) allows selenium to be added to the feed of chickens of up to sixteen weeks of age, to the feed of swine in amounts up to 0.1 p.p.m., and to the feed of turkeys in amounts up to 0.2 p.p.m. The FDA cited studies showing that these amounts are beneficial to the growth and maintenance of the animals and are not deleterious to humans when the meat from the animals is consumed. A statement entitled "Final Environmental Impact Statement—Selenium in Animal Feeds" has been issued by the FDA. It may be obtained from the Office of the Assistant Commissioner for Public Affairs, Rm. 15B-42, or from the Office of the Hearing Clerk, Rm. 6-86, 5600 Fishers Lane, Rockville, Md.

Criteria for Acceptable Methods to Detect Drug Residues

By RICHARD P. LEHMANN

Dr. Lehmann Is the Director of the Division of Nutritional Sciences, Bureau of Veterinary Medicine, Food and Drug Administration.

ON JULY 19, 1973, WE PUBLISHED IN THE *FEDERAL REGISTER* a proposal to establish a scientific basis for determining the sensitivity of an analytical method for drug residues when that drug is considered to be a carcinogen or a suspect carcinogen and, therefore, is required to have *no* residue in the tissue following its use under the Delaney Amendment.

As most of you know, *no* residue or *zero* tolerances are scientifically unacceptable. Some years ago, the National Academy of Sciences/National Research Council concluded that *zero* tolerances for pesticides should be replaced with *negligible* tolerances. This can be done for those drugs not required to have a *zero* tolerance or *no* residue because they are considered carcinogens. But *zero* or *no* is always subject to redefinition based upon the sensitivity of the analytical method. You are all familiar with the history of no residue for DES. As a result, there has not been an adequate basis for us to assure firms that a certain analytical sensitivity was sufficient for a particular drug.

In the past, scientists working for the Food and Drug Administration (FDA) reviewed data and established required analytical methods—both biological assays and chemical analyses—for the hormonal agents. They believed the results of this work assured the Agency that there was *no* residue based upon the evidence that there was no physiological response. DES was considered to be more or less the model, and other judgments were usually compared or related to the DES decision. This was based on the fact that Congress knew

that 2 ppb was the recognized sensitivity of the analytical method for DES when they passed the so-called Stilbestrol Amendment to allow the use of DES in cattle and sheep feed.

With our recent DES decisions, we have gone beyond the physiological response levels. We are now measuring quantities with radioactive tracer studies, chemical analytical methods, and are talking about using the radioimmuno assays which will go far below what can be shown to evoke a gross physiological response. With the availability of the new analytical techniques, it became apparent that FDA and sponsoring firms were constantly subject to attack for the approval or marketing of these products on the basis of no residue whenever a more sensitive method was developed which would show some below the sensitivity of the approved method.

Exogenous and Endogenous Substances

Therefore, on July 19 we proposed a new scientific rationale for establishing the sensitivity of an analytical method required for exogenous and endogenous hormonal agents that could be used in food-producing animals. We recognized the need for this distinction between exogenous and endogenous substances. An attempt to exclude any endogenous hormone residues from the diet would actually require, in all likelihood, a discontinuance of eating meat from animals. Also, the exclusion of all estrogenic substances would, for example, exclude the consumption of other natural foods which had been shown to contain rather high levels of estrogens.

The document proposes a system for establishing the required sensitivity of a method to detect residues which have been shown to exist, and to determine when such drugs have been metabolized or excreted and are no longer detectable in the edible portions of the animals through properly conducted metabolism studies. We also propose that such residue determinations should be made on the food at the time it reaches the consumer, and if it is normally not consumed without cooking, what the amount of such residue is at the time of actual consumption. Our past concern has been with residues in food animals at the time of slaughter. We know that certain products are degraded in the process of aging and storing of meat, and that certain other drugs degrade through time and temperature exposure. We believe that these variations should be taken into account in calculating residues.

Use of Mantel-Bryan Procedure

Perhaps the most controversial section of the proposal is the attempt to project a virtually safe level below the levels which can be demonstrated on a biological response basis. In other words, due to the extrapolation that will always be necessary between experimental animals and man, a margin of safety in addition to that which can be shown through tests in laboratory animals will have to be required. This margin of safety can be projected on an arbitrary figure such as 5,000 or 10,000; or it can be attempted by using mathematical-statistical projections. In the document, we have attempted to use the rather well-known "Mantel-Bryan" procedure for doing just this. However, we believe that the projection should be based on biological response data combined with mathematical-statistical projection rather than on a mathematical projection alone. As many of you know, this has evoked a great deal of discussion and comment. We are going to attempt to coordinate the opinions of the biometricians with the views of the chemists, pathologists, and other scientists and try to determine what we believe will be the rate of exposure which may result from the establishment of an adequately sensitive method.

Margin of Safety as an Ethical Question

The rate of exposure or margin of safety is not, I suggest, a scientific question but rather a sociological or an ethical question. Even the most rabid critics will, I think, agree that there is no such thing as *absolute* safety. Therefore, some calculated determination has to be made as to what level of risk the public is willing to accept in exchange for the benefits that can be gained if the product is to be used. This document also attempts to present how we will evaluate the relative toxicity of various compounds, especially in regard to their carcinogenic potential. Even though the document states that the standards for determining the carcinogenicity will be those that were adopted some years ago by the Agency, it is our intention to assemble a group of experts and attempt to redefine the proper models and procedures for determining carcinogenicity.

The document also makes some distinction in regard to products that are used only for treatment of a few animals as compared to the exposure of large numbers of animals for long periods of time

when substances are used for growth promotion, disease prevention, or control.

As far as the endogenous substances are concerned, what we have said is that they do not need to be tested for carcinogenicity if they truly are endogenous and present in the tissues normally. All we are suggesting be required in this case is that the level of endogenous substances such as estrogens, progesterone, testosterone, in the tissue at the approved time following the use of such products, either in feed or as implants, be no higher than the normal level in animals that have not been treated. Since we recognize that these levels may fluctuate during different stages of the animal's life and sexual cycle, determinations will have to be made as to what is the normal level. Only endogenous compounds which exceed this normal level will be considered to be the result of animal treatment or feeding.

Nature of Analytical Methods

Up until this time I have not spoken about analytical methods, which is the primary purpose of the document. However, these previous statements, I think, are an indication of what would be required for any analytical method. It is still our intention that such an analytical method be practical so that it can be used for surveillance purposes. That basically means that it can be run by laboratories across the country, not just highly specialized laboratories; that the time involved in assaying is not excessive; and that its reliability is sufficiently accurate that it can be confidently used for surveillance programs. This, of course, is easy to say and not as easy to achieve, but we believe that there are new techniques on the horizon which may be utilized for these purposes. If the required sensitivity is not, in fact, in the realm of only a few parts per trillion we believe that such analytical methods can be developed and utilized. **[The End]**

Criteria for Acceptable Methods to Detect Drug Residues

By JANE F. ROBENS

Dr. Robens Is the Assistant Director of Drug Regulatory Affairs at Hoffmann-La Roche Inc.

I WAS PLEASED WITH THE OVERALL OUTLOOK and philosophy on drug residues expressed by FDA in the proposed July 19, 1973 regulations on Compounds Used in Food Producing Animals. It indicated to me an attempt at working to establish a scientific basis for determining the sensitivity of the analytical methods required by the Delaney Clause for the so-called "zero residues" for carcinogens and suspect carcinogens which may become components of human food. I believe this proposal was a realistic effort to remedy an otherwise completely unscientific situation wherein the presence or absence of residues is assessed by methods of continually increasing sensitivity almost to the molecular level.

Assay Sensitivity—July 19 Regulations

I do want to emphasize that I am confining my remarks on the criteria for acceptable assay methods to the criteria for determining the assay method sensitivity which will protect the public health and not the virtues of mass spectrometry v. gas-liquid chromatography, etc. The latter is properly the subject of a workshop for chemists.

I want to restate some of the assumptions concerning assay sensitivity made in the July 19 regulations which I believe are commendable.

(1) The projection of the margin of safety should be based on the biological response data combined with a mathematical projection rather than on the latter alone.

(2) Residue determination should be made on food at the time it reaches the consumer.

(3) The projected uses of the drug and the site of drug accumulation in the animal are factors influencing the projected rate of exposure of the population.

I am particularly happy that Dr. Lehmann stated that the public should consider the level of risk they are willing to accept in exchange for the benefit gained from use of the product; that is, no chemical is absolutely safe. The regulations also recognized that food animals have endogenous hormones and that all meat contains some levels of these hormones.

Sensitivity of the Assay Method

In these proposed regulations to determine the required sensitivity of the assay method, there were a few points FDA failed to include and there are a few points that I, knowing the problems which industry faces in obtaining approval of any drug, particularly a drug for food-producing animals, would like to change.

Metabolism and residue studies should be required to determine the *major* metabolites only, not every one which can possibly be identified. Studies should be required only for those compounds or metabolites which are of toxicological concern; for instance, the effect of the administration of compounds related to endogenous compounds should not need to be determined unless the related compounds are of toxicological concern.

Degradation studies of a compound in meat should not be mandatory unless there is evidence to indicate that degradation products may be more toxic than the parent compound. I do realize that this requirement was added to the regulations to provide a basis for establishing a withdrawal period on the residue which is actually present in the food which the consumer eats.

The requirement for routine carcinogenicity testing for compounds for which *a priori* knowledge is incomplete should be deleted as the requirement makes the unwarranted assumption that all such compounds are possible carcinogens.

The classification of a compound as a carcinogen is particularly important since the required sensitivity of the assay method and thus,

the length of the withdrawal period increases so greatly as a result of this decision. A compound should not necessarily be classed as a carcinogen where data are available to indicate that the increase in tumor incidence is simply a reflection of the physiological effect of the compound at doses far in excess of those which might be consumed as residues. Not every increase in tumor incidence is a sufficient basis for classification of a compound as a carcinogen. If reasonable interpretation of the total biological information available indicates that the increase in tumor incidence is only reflective of the indirect physiological or toxicological nature of the compound, the compound should not necessarily be labeled a carcinogen. Where human biological effect data is available or can be obtained in an appropriate manner, this information should be used in assessing the effects of possible residues in human foods.

Carcinogenicity Studies—Initiation and Evaluation

I could outline all of the factors that one should consider in initiating and evaluating carcinogenicity studies—housing of laboratory animals, drug stability in feed, purity of the compound, sex of the animals, etc., but these factors are well-known and are the subject of limitless review. Let me just emphasize a few which I believe have been often overlooked.

Knowledge of metabolic pathways for the chemical to be studied should be a factor in the selection of species for carcinogenic testing, and an essential element in the interpretation of results. Positive results obtained in a species in which the metabolism of the chemical is quite dissimilar from that of man should be considered as inconclusive and, if negative data are found in a more appropriate species, inconsequential.

In long-term animal studies designed to evaluate the carcinogenic potential of a food additive, the maximum dosage level should not exceed the physiological capacity of the animal to metabolize and/or eliminate the dose of the substance in a fashion consistent with that observed at lower dosages. High doses may result in changes in dose-dependent plasma half-life and quantitative changes in metabolism and excretion.

The proposed regulations refer to the report of the FDA Panel on Carcinogenesis published in *Toxicology and Applied Pharmacology*† as the guidelines for conducting carcinogenicity studies. There is one recommendation in this report which demands careful reconsideration, that is, Number 7 which states that testing should be done with several doses including one likely to yield a maximum tumor incidence. Such a level could certainly result in a change in the elimination and metabolism patterns from that observed at lower levels nearer the anticipated animal and human exposure levels. I certainly agree that the test levels should include a level producing some toxic effect but I fail to understand why any higher levels are necessary. The mathematical model proposed to calculate the virtually safe human dose, that is, the Mantel-Bryan method, allows extrapolation from any level used.

Since effects obtained by one mode of administration are not always applicable to those obtained by others, substances which will become components of food should be tested by admixture of the material in the diet of test animals rather than by oral gavage or some other method.

Results of Carcinogenic Studies

The results of carcinogenic studies should be amenable to duplication in a second laboratory. Isolated reports of carcinogenicity, particularly where a well-defined dose response curve is lacking, should be viewed with scientific skepticism, and judgment withheld on the significance of the study until the data are confirmed.

You will note there is one point that I did not mention in discussing carcinogenicity studies, that is, the effect of good experimentation v. bad experimentation on the projected safe level. Quite a few heated comments have been generated over this topic. I believe FDA should end all controversy about rewarding good and penalizing bad experimentation or vice versa, quickly, by simply refusing to accept poor studies.

Since the Mantel-Bryan model is untested in practice, even though I realize it was proposed over ten years ago, FDA must be

† Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides. *Toxicology and Applied Pharmacology* 20, 419-438. (1971)

flexible and be free to adopt other conservatively acceptable mathematical models if necessary or desirable. I want to point out that the procedures for establishing assay sensitivity do not establish population exposure levels. The latter will be below the assay sensitivity, since individual animal variation requires that the withdrawal period be established to include those animals who excrete residues more slowly.

The assumptions going into the Mantel-Bryan model should be the subject of full and careful consideration. Do we really know if a virtually safe dose of one in one hundred million is a realistic criteria? Any regulations setting forth criteria for an acceptable assay method must contain the necessary flexibility to assure that no new product of worth is denied approval while at the same time maintain the integrity of the food supply, that is, regulations should not impede assessment of the optimum benefit risk ration of additives.

[The End]

SPECIAL PACKAGING REGULATIONS PROPOSED

Regulations designed to expedite the handling of supplemental new drug applications to cover changes made in packaging and labeling by poison prevention packaging standards have been proposed by the Food and Drug Administration. The proposed changes establish procedures for handling the supplemental applications and specify that such applications are required only if the change in packaging could affect the purity or effectiveness of the drug. No supplemental application for approval would be required if the changed closure would not come into contact with the drug product. Modified closures that would contact the drug could be used in advance of approval provided that materials identical to those in the original closure are used in the new design and that required supporting data is submitted in the supplemental application. If different materials are to be used, the supplemental application would have to be approved before the closure could be used. Additions to labeling as required by the Poison Preventive Packaging Act would not require prior approval.

The Relationship of Research and Regulatory Programs of the Bureau of Veterinary Medicine

By NICHOLAS H. BOOTH

Dr. Booth Is the Director of the Division of Veterinary Medicine, Food and Drug Administration.

IN DISCUSSING THE INTRA- AND EXTRAMURAL RESEARCH FUNCTIONS of the Bureau of Veterinary Medicine (BVM), I will describe and emphasize a few of these activities with respect to how they assist the Bureau, as well as the Food and Drug Administration (FDA), in the fulfillment of its regulatory responsibilities. Inasmuch as FDA is a regulatory agency and its principal function is to see that laws are complied with, in accordance with those proclaimed by the United States Congress, the Agency cannot properly execute its regulatory duties without the availability of high quality scientific data. This point has been emphasized many times. Dr. Frederick W. Wolff of the FDA Bureau of Drugs stated, "The basis for regulatory action is both the scholarly interpretation of existing data, and the development of new data." Consequently, our function in research within BVM is both the interpretation of existing data, which has been published, and the development or acquisition of new data. Without the benefit of solid scientific data as generated by research, FDA would be unable to properly assess the safety and efficacy of drug products and would be ineffective in taking appropriate regulatory action.

BVM Research Activities

The Division of Veterinary Medical Research, located at Beltsville, Maryland, has approximately 40 intramural research projects underway involving seven domestic animal species. Concurrent with the intramural activities in research, BVM has an extramural research contract program. Since our laboratory has manpower, equipment and space limitations, it is necessary to obtain assistance on the outside through contractual arrangements in a number of research areas.

The approximate percentage of time devoted to the various categories of research are as follows:

Drug Residues	50%
New Animal Drug Applications (NADA)	30%
Low Level Antibiotics	15%
Product Testing	5%
TOTAL	100%

Drug Residues

An excellent example of work involving drug residues is the surveillance studies involving the antibiotic preparations used in the treatment of bovine mastitis. Milk-out studies are made to determine whether or not residues persist in milk of normal animals and those experimentally infected. During the past seven years, the research laboratory at Beltsville has studied about 50 different intramammary infusion preparations that are used by the dairy industry in the treatment of mastitis. In approximately 33% of the products that have been evaluated, the milk-discard times were found to be in accordance with that described on the label. The remaining products tested left residues in the milk from 12 to 140 hours beyond the stated discard time; 96 hours is the maximum time allowed by FDA for the disappearance of drug residues following the use of intramammary infusion products. Data obtained in these studies enabled the necessary corrective or regulatory action to be taken against these products that were improperly labelled.

Also, in lactating dairy cattle, we have completed studies to determine the absorptive ability of the bovine uterus following parturition. Therapeutically, antibiotic and sulfonamide preparations were infused into the involuting uterus for the control and treatment of bacterial infections after calving. Blood, milk and urine were sampled to determine absorption patterns and how long residues may be

detected following the intrauterine infusion of these products. A manuscript of our findings has been submitted for publication in the *Journal of Dairy Science*.

Residues in Chickens and Eggs

Within the last year, a study of the tissue residue levels of Aroclor 1254 (a polychlorinated biphenyl or PCB) in chicken broilers and egg-laying birds was completed. Within the last few years, it has become readily apparent that Aroclors or PCB compounds are capable of entering the animal and human food chain. Because of the need to know more about the potential toxicity of the PCBs, a titration study involving Aroclor 1254 in feed from zero to 10 ppm was conducted for the entire life cycle of poultry. Broiler chicks received six levels of PCB in feed up to 8 weeks of age and tissue levels were determined; some of the birds were continued on these feeds through the egg-laying phase; tissue and egg concentrations for PCB were determined. Also, eggs from the various experimental groups were collected to determine if hatchability would be adversely affected. In addition, tissues from newly-hatched chicks were analyzed to determine the degree of transmission of PCB. At all of the levels of PCB fed in the study no adverse or toxic effects were observed. In particular, there were no adverse effects noted on the hatchability of eggs or on eggshell thickness. This was a significant and important finding because one of the most sensitive effects of PCB is its inhibitory effect upon hatchability of eggs. From this information, a tolerance level of 0.2 ppm was supported and recommended in animal feeds. From a regulatory aspect, this recommendation was of value in assisting FDA in the establishment of an interim tolerance level for PCBs in finished animal feeds which was published in the *Federal Register*, volume 38, pages 18096—18103, on July 6, 1973. Also, an extramural research contract is in progress to determine the tissue residue characteristics of PCBs in other food-producing animals.

Rapid Screening Methodology

The practicality of using rapid screening methodology prior to and at the time of slaughter for the detection of drug residues is presently under study within our laboratory. We are hopeful that the electrophoretic gel apparatus may be successfully adapted in the rapid detection of antimicrobial residues. An extramural contract with the University of Illinois has been of assistance in the develop-

ment of the electrophoretic procedure for the detection of drug residues. Although this procedure for the rapid screening of penicillin, oxytetracycline and dihydrostreptomycin looks feasible at the level of 1 ppm or less, further confirmation is necessary before reliance in the method can be established.

A recent accomplishment of our research laboratory of major significance has been the development of an analytical method to detect trace amounts of chloramphenicol in skeletal muscle, liver, kidney, serum, plasma and whole blood. The lower limit of sensitivity for chloramphenicol in skeletal muscle is 0.1 ppb. Studies in chickens, calves and swine have revealed that skeletal muscle may be the preferred tissue for screening field samples of chloramphenicol. The analytical method for chloramphenicol is presently in the validating stage by the United States Department of Agriculture (USDA) as well as laboratories in the Bureau of Foods and Bureau of Drugs. Once the method is validated, it will be published in *J. O. A. C.* and will be available to USDA for use in their meat inspection and monitoring program.

Another area we are devoting our efforts toward is the establishment of a radio-immunoassay (RIA) laboratory for the detection of tissue residues such as those that may occur from estradiol, testosterone and progesterone. The RIA method is a highly specific, reliable, accurate, reproducible and sensitive procedure capable of detecting levels of the sex hormones in amounts as low as a few picograms per milliliter or per gram (i.e., in parts per trillon). The RIA laboratory has only recently become operational and will spend most of this next year working with the estrogens and their metabolites.

New Animal Drug Applications (NADAs)

As pointed out previously, approximately 30% of the time the research division is involved in the review of NADAs in the determination of the safety and efficacy of a new drug. This service is provided following a request from the Division of Nutritional Sciences (DNS) and/or DNAD. Also, at the Veterinary Investigational New Drug (VIND) stage we are frequently consulted with respect to the experimental design of drug studies in the development of data for an NADA. This includes meetings with the administrative and scientific personnel of drug manufacturing firms.

The Division of Veterinary Medical Review (DVMR) also confers with us on matters pertaining to Drug Experience Reporting

(DER) as related to adverse drug reactions. DVMR may request that we conduct a research study paralleling the information received in an adverse drug reaction report. They may also ask to conduct toxicological studies involving chemical contaminants in animal feeds. As mentioned earlier, we completed a titration study this past year in the chicken involving Aroclor 1254.

Low Level Antibiotics

The research division is spending approximately 15% of its time in the study of the phenomenon related to the transfer of bacterial resistance due to exposure from antibiotics. A survey of infectious multiple drug resistance among *Salmonella* isolated from animals, in the U. S. was published (In *Applied Microbiology*, 21:358-362, 1971) about two years ago by some of the staff of our laboratory. Public health officials have a keen interest in the use of antibiotics in animals because the transfer of resistance from bacteria of animals to sensitive ones may possibly be a potential public or animal health hazard. Because of this interest and concern, an Antibiotic Task Force was selected in 1974 by FDA to study this matter. Dr. Gerald B. Guest will undoubtedly mention to you the progress being made regarding the implementation of the recommendations of the Antibiotic Task Force.

Work by the research division was recently published (In *Antimicrobial Agents and Chemotherapy*, 4: 277-280, September, 1973) showing the effect of racephenicol on antibiotic resistance. Racephenicol has been recommended for the treatment of fowl cholera by the addition of the drug to poultry feed at either 100 or 200 grams per ton. Of particular interest from an animal and human health aspect was the potentiality of the emergence of chloramphenicol resistance from feeding racephenicol to poultry. Our laboratory demonstrated that the incidence of enteric organisms resistant to chloramphenicol increased from less than 0.1% prior to treatment to more than 90% when chickens were fed racephenicol-supplemented feed at 50 or 140 grams per ton for 10 days. In addition, a concurrent increase in the incidence of organisms resistant to dihydrostreptomycin, oxytetracycline, ampicillin and sulfonamides occurred. These findings by our laboratory had a significant impact upon the decision of the manufacturer of racephenicol to the extent that they requested withdrawal of their pending NADA.

Extramural research studies are currently in progress to determine the effect of antibiotics upon the microbial ecology of the enteric

tract of animals and man. Information generated by these studies will be beneficial in determining and formulating regulatory policies regarding the use of low levels of antibiotics in animal rations. A substantial sum of extramural research funds were allocated to the low level antibiotics during 1972-73; for comparative purposes, expenditures for extramural research is given as follows:

Category	*Amount*	*Percent*
Low Level Antibiotics	$496,162	51.2
Drug Safety and Efficacy	268,283	27.6
Drug Residues	201,862	20.9
Animal Foods	3,300	0.3
Total	$969,607	100.0

Product Testing

Of the remaining time spent by our research staff, approximately 5% is spent on product testing. The principal function of this activity is related to the testing of products such as drug preparations and pet foods that may arise from consumer complaints properly filed through District Offices. It may also involve a follow-up from DERs submitted through the Division of Veterinary Medical Review (DVMR). Such things as efficacy and bioavailability checks on similar commercial products may be involved. Moreover, studies on the toxicity of the product may be necessary because of an adverse drug reaction. Another area involving product testing may be a request from DNS or DNAD relating two similar drug products at the NADA level where the drug withdrawal times are dissimilar. We check the withdrawal times in our laboratory to determine if the two products are comparable or if they are not comparable. These tests are then followed up by appropriate regulatory action.

Information was briefly provided which characterizes the type of research projects at the intramural and extramural levels of BVM. The percentage of time devoted to the research activities of the Bureau were also delineated. An attempt was made to relate the significance of these research activities to the regulatory functions of the Bureau and FDA. As aptly phrased by Dr. Frederick Wolff, we in research believe that, "The basis for regulatory action is both the scholarly interpretation of existing data, and the development of new data." **[The End]**

Use of Drugs in Feeds

By GERALD B. GUEST

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

THE TITLE OF THIS PARTICULAR PRESENTATION leaves room for quite a broad look at perhaps the most important method of administering drugs to the food animal today. Unlike the dosage form drugs, drugs given in feed make possible the treatment of larger groups of animals for longer periods than any other way of administering drugs. The benefits of a feed-use drug over the other types of administration are fairly obvious. It is for these obvious reasons that the practice of mixing drugs with animal feeds has gained much popularity over the past 25 years or so. Of course, along with the benefits gained with feed-use drugs, we also have created some problems or potential hazards, which are not as inherent in drugs given to animals by other routes of administration. Certainly a drug for intramuscular use will not be used with the frequency that a feed-use drug may be utilized. With this the circumstance, depending on the absorption from the gastrointestinal tract and other metabolic factors, it is reasonable to assume that chemical residues in meat, milk, or eggs have a potential for occurring in more animals from feed-use drugs than from dosage form drugs, simply because of numbers of animals reached on a continuous basis. I am sure each of you could cite exceptions, but generally speaking, I believe that this is a true statement.

Drug Use in Animal Feed

In addition to the potential for residues, we must consider, in the case of antibacterial drugs, the effect on the bacterial flora of

the recipient animal following long-term use, as is usually the case with a feed administered drug. What is the effect on the health of the animal? What does this do to treatability of clinical disease in those animals, should a disease occur? Is there an impact on the health of man?

Briefly now, the ease of getting a drug to large groups of animals over extended periods of time and, the occasional difficulties encountered in withdrawing feed-use drugs from food animals is justification, in my opinion, for stating that feed-use drugs are perhaps the most important and therefore one of the most critical issues facing the drug industry, the livestock industry, and regulatory agencies today.

Each of us can recall some very important issues and/or actions which have occurred with feed-use products in the very recent past. Diethylstilbestrol (DES), implementation of the Antibiotic Task Force recommendations, selenium, liquid supplements, and copper, just to name a few, are all subjects which have had an impact in some manner on many individuals involved in the animal and drug industries.

In the antibacterials-in-feeds area we have essentially completed the first phase of the requirements placed on drug sponsors. That phase, of course, is the submission of protocols for studies necessary in addressing the questions raised by the Task Force. Drug sponsors are presently involved in the studies, particularly the salmonella reservoir studies.

We have placed some rather stringent deadlines on the requirements for completion of studies. No phase, neither the human health, nor the animal health, nor the efficacy studies is more important than the other. The dates of April, 1974 for completion of some of the salmonella studies and April of 1975 for completion of all requirements will be upon us very soon. We plan to make some rather critical decisions on these drugs at that time.

We are encouraged that the drug industry is responding in a responsible fashion to the need for additional information. I believe that the long-range outcome of this program will allow for not only safe use of the products in animal production, but also more efficacious use at the same time.

Now, perhaps I can tell you what I see ahead, following completion of the Task Force implementation. I believe that some of the traditional antibacterial drugs will not measure up under the

usage patterns as we know them today. Those single or combination drug products which are shown to increase the salmonella reservoir and/or promote transferable drug resistance to drugs used in human medicine will be subject to restricted usage. In some cases use of the drug in feeds will be reserved for high-level, short-term use and only by the order of a veterinarian. Depending on the circumstances and the degree of the problem, other restrictions may be necessary. We view this approach as a mechanism to allow for continued availability of a product that may be useful for therapeutic purposes, while at the same time limiting the improper use of a product that has not met safety and/or efficacy standards at subtherapeutic levels.

Current Status of Selenium

Although this is a proposed food additive and not a drug, you may also be interested in the current status of selenium. The proposed food additive regulation and the proposed environmental impact statement were published in the *Federal Register* on April 27, 1973. Comments were received from 21 interested persons regarding the environmental impact statement. These 21 comments have been reviewed, evaluated and considered in a final statement which has been prepared by the Bureau of Veterinary Medicine. This document, which consists of some 240 pages, has not been released at this time. An announcement will be made in the *Federal Register* at the time of release. The proposed food additive regulation resulted in comments from 153 individuals. Of the 153, 73 opposed the regulation, 77 were in favor of the regulation, and 3 offered no opinion, only information or comment. These 153 comments are still in the process of being evaluated. It is difficult to say at this time when final disposition will be made of the proposed regulation.

Copper in Animal Feed

On September 14, 1973, a proposed restriction on the level of copper in animal feed appeared in the *Federal Register*. This proposal explained in some detail the concerns of the Agency and the questions raised by the Ad Hoc Committee on High Level Copper Swine Feeding Program. At the same time the document proposed limits on the amounts of copper to be added to livestock and poultry feeds. These levels are considered nutritive levels only and the levels proposed are based on information from the published literature. Many of the comments received on the proposal have concerned the

use of copper in poultry feed. Although the issue began as a drug for swine use, the poultry industry appears to be exhibiting perhaps more concern than the swine industry. Since several groups and individuals requested additional time to submit additional information in the way of comment on the proposal, the *Federal Register* of November 26, 1973, contained a document which extended the period for comment from November 12, 1973 to December 12, 1973. Certainly all the new information received will be carefully considered prior to final action on copper levels.

High-Level Short-Term Drug Use

I believe that, no doubt, the future holds continued emphasis on the use of animal drugs on a herd or flock basis, but with more sophisticated innovations in the patterns of use. With antibacterials we will see more drugs used at higher levels and for periods of time which are less than the life of the animal or bird. This approach is particularly indicated during stress periods and at other times during the early part of the animal's life. In addition to the high-level, short-term use of drugs, there will probably be an increased need for alternating drug products during an animal's time in the feedlot, so that a drug exhibiting a higher potential for residue or resistance enhancement might be used early in an animal's life, with a switch to another product in the finishing phases prior to slaughter.

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

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

New technology is making available new nutrient sources. Protein sources from petroleum by-products, wood molasses, and animal

waste are only a few. These things do not bear heavily on the topic of this talk, but they do raise questions regarding food additive considerations, which will be dealt with as time goes on.

Drug Residue Detection

I believe that we can all look forward to continuing refinement in drug residue detection techniques for meat, milk, and eggs. For some time now we have been talking in terms of parts per million and billion. We are now able to measure in parts per trillion. If I may quote Dr. Charles Edwards, former FDA Commissioner, "Time and technology in the field of residue detection have brought us to a point, where at times, it has outstripped our ability to interpret the meaning of such findings." In my opinion, we have probably abused the word "safety." We need to redefine the word in a more precise manner. We are all beginning to ask ourselves, "just how safe must something be?" Our *Federal Register* document of July 19, 1973, which had to do with setting the sensitivity of a method, is a first attempt at establishing a fixed sensitivity so that the rules on a drug residue might not change each time a new, more sensitive technique is demonstrated. I believe this document represents one of the most imaginative and innovative problem-solving approaches to come out of the FDA in a long time. It is a giant step forward in defining the limits of "safety."

Safety Demands

The trend toward more demands on efficacy and safety considerations will have, in my judgment, a beneficial effect on benefit-risk analysis. The more precisely we document the efficacy and the more thoroughly we pursue safety questions, the better position we are in to make true benefit-risk oriented decisions. It is not going to come overnight, but I believe that we will be able to quantify many of the ethical, sociological, philosophical, and moral arguments relative to safety.

Certainly use of any drug in the feed of food animals may come under very close scrutiny from time to time. Questions are continually being raised as science progresses and consumers become better educated and more concerned. These questions must be addressed and resolved as they occur. Each time the occasions arise, it is an excellent opportunity for all of us to recognize and fulfill our appropriate responsibilities to serve the needs of the consuming public.

[The End]

Use of Drugs in Feeds

By LEE H. BOYD

Mr. Boyd Is the Director of Feed Control and Nutrition, American Feed Manufacturers Association.

THE SUBJECT OF THIS PRESENTATION, shared with Dr. Guest of FDA, is indeed broad. For my part, I have chosen to reflect on some personal experience as a member of the feed industry itself and its trade association staff—and to share with you some concerns and questions generated by that experience.

In 1953—a little over twenty years ago, I joined the staff of a midwest feed manufacturing concern. The use of drugs at that mill at that time was confined to a single coccidiostat and two antibiotics. The coccidiostat was sulfaquinoxaline used at two levels —one pound per ton for prevention/control, and two pounds per ton for treatment. One antibiotic, penicillin, was used in poultry feeds for growth promotion and feed efficiency. The other antibiotic, a tetracycline, was used in swine feeds for the same purpose. In the next seven years, I witnessed the well-recognized surge in available animal drugs for various purposes, and medicated feed became the rule.

Use of Animal Drugs in Feeds

Hand in hand with the increased use of animal drugs in feeds came the intensification of animal production and the feeding of large numbers in confinement. I am not sure which came first—much the same as the long-standing debate about the chicken and the egg. It does seem obvious, however, that there must have been a need for the various drugs, or their development simply would not have taken place. Hence, the intensification of animal production could not

have continued and grown to what it is today without the protection and advantage provided by animal drugs.

While some may wish to debate the merits of animal drugs, I believe an impersonal, impartial review will reveal substantial, documented benefits to animal health and the economics of animal production. While the immediate and major benefits might seem to accrue to the animal producer, the advantage of these benefits ultimately accrues to that most important individual—the consumer.

I believe you will share my belief that healthy animals are a more desirable source of food. Those of you who join me in doing at least part of the family grocery shopping—and probably paying for all of it, will also share my concern for reasonable food prices. A lowered cost of production must ultimately be reflected in lowered cost to the consumer.

The feed industry does not develop drugs. This is the role of the animal drug industry. The feed industry is simply the means of conveying the drug product to the feeder in a usable and convenient form. Not always recognized is the fact that drugs in feeds are not in themselves a significant source of revenue to feed manufacturers. When feed is offered in "plain" and "medicated" versions, the differential in price is basically the drug cost. We are, in other words, providing a service on a cost basis. You might ask why on a cost basis? Shouldn't there be some return on investment, or profit? Profit is certainly warranted, but medicated feed developed as a service and competition has served to keep it just that and nothing more.

Benefits of Drugs in Feeds

Why then do we incorporate animal drugs in feeds? We and our customers, the animal producers—who are one and the same in many instances, recognize the benefits of protecting or improving animal health and the advantages of improved conversion of feed to food. It is the positive contribution to animal health and the contribution to economical production that stimulates and holds the attention of feed and animal producers. With both of us dependent upon the consumer of food, our interest in animal drugs is of necessity limited to the contributions these products can make to the economical production of wholesome food of animal origin. Any other interests on our part would be self-defeating.

As feed manufacturers, we appreciate the endeavors of the drug industry to provide appropriate drug products which have proven to be valuable production tools for animal producers. We also appreciate the vital third-party role played by the Food and Drug Administration in ascertaining the safety and efficacy of these products, particularly the safety aspect which neither we nor the animal producer is in a position to determine.

Over the years we have enjoyed good communications and cooperation with the Agency. As a result of this good working relationship, there has been mutual increased understanding and good progress in many areas of common interest. This is not to say, however, that we always see eye to eye or that the road has always been smooth—and that is to be expected. There will always be honest differences of opinion and interpretation.

Drug Controls

While we in the feed industry have had access in the past to a wide variety of drugs and have been able to secure in good part needed changes in the controls under which we operate, we are presently faced with a number of concerns. The supply of available drugs has been reduced and is threatened with substantial further reduction. Certain facets of controls over our use of drugs are in need of improvement and we are more or less continuously subjected —by existing or new law—to the threat of additional control burdens which are usually quite inappropriate. This set of facts gives rise to some thoughts and questions I would like to place before you.

We are concerned that clearance of animal drugs be on a sound and reasonable basis to insure continued development of needed or desirable products. We are concerned that the controls over the use of these drugs by feed manufacturers and feeders are appropriate and that the means used are capable of achieving the desired control in a realistic and efficient manner. We are concerned about the complexities of the Food, Drug and Cosmetic Act and the problems caused by imposing drug and food type provisions on feed. The same statement can be made with respect to other laws and the respective regulations. Above all else, we are concerned that the political climate is such to breed hesitancy in attempting to secure needed changes to laws—and, in some cases, regulations. For maximum efficiency of feed and food production, unnecessary restrictions

or burdens must be kept to an absolute minimum. We solicit your aid in helping to maintain a realistic climate.

With respect to determination of safety and efficacy of animal drugs, we believe questions must be relevant. We also believe all pertinent questions of fact must be answered. Equally important as the answers themselves is the possibility of review of these answers in proper perspective and climate. While critical review of safety and efficacy is important, so too is the attitude. While thorough review is important, so is the time factor. A positive attitude and reasonable time are most desirable. Everything new is not necessarily bad. The quality of review is not necessarily dependent on the time taken.

Clearance Procedure—Selenium

Let us look at the source of authority for overall control of animal drugs and medicated feeds—the Food, Drug and Cosmetic Act. At best, it seems to be patchwork. More often than not it is couched in negative language. It defines food and feed as synonymous —and that they are NOT. This makes feed subject to food and drug type considerations. Every new food or drug amendment may affect feeds! Is this a good base from which to operate? Have "we" provided through law the proper climate for a positive attitude and reasonable action? Do the actions of the public in general provide for a good climate?

Selenium can be used as an example. While selenium is a nutrient and *not* a drug, it has been subjected to much the same clearance procedure through the review of AFMA's Food Additive Petition for use in feed. Having authored that petition and followed it since submission in April of 1970, I have been exposed firsthand to an interesting and educational experience—both good and, frankly speaking, not so good. It is December 1973, and the Final Environmental Impact Statement is expected to be available this month. That means the regulation providing for use of selenium will be effective 30 days later—or sometime in January 1974, almost four years since *formal* submission. In my opinion, that time frame is the result of factors mentioned earlier.

Problems in Drug Clearance

On the good side was the cooperation of many members of the Agency staff who worked diligently in processing our petition—and

we do thank them for their efforts. On the not so good side and of grave concern is the time that transpired in the face of seriously affected poultry and livestock. More important, what are the reasons for this state of affairs? Have too many restrictions been placed upon the Agency to exercise judgment? Has time been equated with safety? Has the Agency been subjected to so much "pressure" that it cannot operate effectively? Has the feeling been fostered that anything new should be viewed as bad, or suspicious at best? Has the Agency been burdened to the extent that action on vital issues cannot be carried out in reasonable fashion? I do not know the answers to these questions, but obviously I have some suspicions. In business we make good progress only when we select good people and provide them with appropriate authority and responsibility—and then let them do their job. Certainly there is a need to be held accountable for actions—but this does not mean criticizing at every turn or expecting satisfaction from all the people all of the time.

While selenium was originally "clouded" with the contention it was a suspected carcinogen, it had—for all practical purposes—everything else going for it. It was an acknowledged essential nutritional element. It was demonstrated to be in short supply in the vast majority of feeding situations. There was a recognized body mechanism which resulted in excretion of selenium over and above needs. The difference between needed levels and toxic levels was comparable to a number of other nutritional elements. It had been in use in other countries for many years. The background information was basically developed through academic studies and the petition submitted by AFMA—neither of these "parties" having any vested interests. There was a growing body of evidence of importance to human health! Our petition enjoyed the support of practically everyone with knowledge of the subject—the only apparent exceptions being a limited number of individuals who pursued the contention it was a suspected carcinogen. Fortunately, this contention was ultimately laid to rest.

With respect to expressions for the general public on selenium, you are invited to read comments on file with the FDA Hearing Clerk. If you have never done this on any issue, it can be eye opening! It can also cause one to speculate on the reasons behind certain types of comments and what might be done to correct the situation.

A logical question would be how long would it take for approval of some substance not having all of selenium's pluses? How long for a comparable substance which at high levels over extended time in some specie might be classed a carcinogen?

Future of Animal Drugs and Medicated Feeds

The most pertinent question of all is—where are we headed with animal drugs and medicated feeds? I believe there is a need for all of us to be concerned. The various factors involved have created a prohibitive expense in keeping products on the market or clearing new products for the market. As a result, there now appears to be every reason to believe drug industry interests logically will be limited to drugs applicable to major health problems in major species. If it is a relatively minor health problem, or if the specie involved is not a major market, there simply may not be financial incentive to do the necessary work. This trend has and apparently will continue to create a bigger void in the protection of animal health and promotion of economical production. Is this what we, as consumers, want? I hesitate to think so.

What are the alternatives? Basically, we need to take a new, hard look at the controls exercised over animal drugs and medicated feeds, determine what changes are needed, and—if the political climate will in any way permit—work for those changes. It will have to be a team effort of no little magnitude. **[The End]**

COUGH, COLD, ALLERGY PRESCRIPTION DRUG LABELING DEFERRED

Prescription drugs for oral administration offered for relief of symptoms of cough, cold, or allergy have been added to the list of drugs which may remain on the market pending completion of scientific studies to determine effectiveness. The Food and Drug Administration said that its previously-issued interim guidelines for labeling of prescription drugs for cough and cold were premature since the close relationship of the issues involved in the over-the-counter drug review and the prescription drug review makes it essential that both types of products be subjected to new requirements at the same time.

Informative Labeling

By TAYLOR M. QUINN

Mr. Quinn Is the Director of the Division of Regulatory Guidance, Bureau of Foods, Food and Drug Administration.

I THINK ALL OF US ARE CONCERNED with seeing that foods bear informative labels. We don't always agree, however, on what constitutes informative labeling. The Food and Drug Administration (FDA), in an effort to resolve some of the differences and to lay out some ground rules to follow, has, in recent months, published some regulations in this area. I would like to discuss a few of these regulations.

The first of these regulations concerns common or usual names for non-standardized foods. Foods for which there are standards of identity, of course, have prescribed names and these names must be used on the labels of the foods. The names to be used on non-standardized foods have, over the years, mostly been decided by the sellers of the foods. These have in some instances been informative and in some instances not very informative and in some instances downright deceptive. In an effort to bring some order to this area, the Food and Drug Administration proposed in the *Federal Register* of June 22, 1972 a procedure for the establishment, by regulation, of common or usual names for non-standardized foods. After reviewing all of the comments received regarding this proposal, a final regulation was published on March 14, 1973. This regulation sets forth the general principles for establishing common or usual names.

These general principles stated that the common or usual name must accurately identify or describe in simple and as direct terms as possible the basic nature of the food or its characterizing properties or ingredients. The regulation also said that the name shall be uniform among all identical or similar products and may not

be confusingly similar to the name of any other food that is not reasonably covered under the same name. Each class or sub-class of food must be given its own name that states in clear terms what it is, in a way that distinguishes it from other foods. These general principles also provided that, where necessary to properly inform the consumer or to keep the consumer from being misled, the common or usual name would have to include the percentage of any characterizing ingredient or component, or a statement as to the presence or absence of a characterizing ingredient or component. The regulation also set forth the manner and size for such statements to insure that they would be set forth uniformly and prominently. The regulation also set forth the procedure for submitting petitions to establish such common or usual names.

Regulations Concerning Common or Usual Names

We have already published several final regulations following these principles, and proposed others. I am sure that in the near future we will be publishing a number of other such proposals, both on our own initiative and on petition from interested parties. The final regulations include common or usual names for seafood cocktails and diluted orange juice beverages, both of which require the declaration of the percentages of characterizing ingredients as part of the common or usual names of these products. Other final regulations provide for the use of a statement showing that fruit or vegetable flavored non-carbonated beverage products containing no fruit or vegetable juice, do in fact not contain any such juices. Also, that foods packaged for use in preparation of main dishes or dinners to which characterizing ingredients must be added, include in their names a statement as to how much of the characterizing ingredient must be added.

Regulation Concerning Flavorings

The second of these regulations concerns spice, flavorings, colorings and chemical preservatives. This was published as a proposal in January, 1973.

A large number of comments were received, and after considering these a final order was published in August of 1973. A number

of requests were received for reconsideration or modification of the August order and on October 5, 1973 further modification was proposed. Again many comments were received and recently another final order was published in this matter. Although this regulation covers several areas it was the flavoring provisions that caused most of the controversy and these are what I wish to talk about today.

This document, among other things, defines the terms "artificial flavor" and "natural flavor". It states that if a manufacturer or distributor wishes to designate the type of flavor in the food in any other way than through the statement of ingredients, he must inform the consumer as to the nature of its characterizing flavor in certain stated ways.

This document provides for five categories of labeling on the principal display panel of foods. For the vast majority of foods, however, which contain added flavor, but no characterizing food ingredient, only three of the labeling categories would apply.

In the first of these categories would be products whose characterizing flavor is all natural, and which is derived only from the product whose flavor is simulated. Such products would use only the name of the flavor with the name of the food. The second category would be foods whose characterizing flavor is still all natural but is partly derived from the product whose flavor is simulated and partly from other natural sources. Such products will be required to add the words "with other natural flavor." The third category is foods whose characterizing flavor is natural but is derived entirely from sources other than the product whose flavor is simulated or whose characterizing flavor is in part or wholly artificial. Such foods would be labeled "artificially flavored."

Categorizing Flavor Ingredient

Two additional labeling categories will exist for foods expected to contain a characterizing food ingredient, but which do not contain a sufficient amount of such food ingredient to independently characterize the food. If such foods contain a natural characterizing flavor derived solely from the product whose flavor is simulated, the name of the characterizing flavor must be followed by the word "flavored" and may be preceded by the word "natural". Such foods

which contain natural characterizing flavor both from the product simulated and other natural sources would be labeled in the same manner, but in addition the name of the food would have to be followed by the words "with other natural flavor".

You will note that I have repeatedly used the word "characterizing flavor" in these remarks. If the flavor is not characterizing, the regulation provides that, whether natural or artificial, it need only appear in the statement of ingredients.

I will have to agree with some of the comments that we received that said that the October 5 proposal was somewhat confusing and rather unwieldy. I believe that the final regulation is considerably simpler and easier to understand and at the same time prominently provides the information needed by the consumer to determine the source of the characterizing flavor of the food she or he is purchasing.

Food Label Information Panel

The last thing I would like to talk about is the food label information panel regulation. Previous regulations have already provided that the common or usual name of the product and the quantity of contents statement must appear on the principal display panel. This regulation provides that the ingredients statement, the manufacturer's name and address, and the nutritional information, if it appears on the label, must appear either on the principal display panel or on a specified information panel. It also provides for a minimum type size for this information. I believe that this regulation will make it much easier for the consumer to find all of the information that she needs or desires in purchasing a food product. We recognize, of course, that some exceptions to this regulation will be necessary for small packages and we recently published proposals in this area.

I would like to close by stating that all the regulations I have discussed today could really be summarized in one statement—tell it like it is. I think that this is what the consumer really desires and I hope that we will all work towards that end. **[The End]**

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