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Food Drug Cosmetic Law JOURNAL

Additional Papers Presented at the 13th Annual Educational Conference of The Food and Drug Law Institute, Inc., and The Food and Drug Administration

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

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

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FOOD DRUG COSMETIC LAW JOURNAL

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REPORTS

TO THE READER

1969 FDLI-FDA Conference.—The following are additional papers presented at the 13th Annual Joint Educational Conference of the Food and Drug Law Institute, Inc. and FDA. Concluding articles from the Conference will be presented in the March issue of the JOURNAL.

E. M. Foster, Director of the Food Research Institute at the University of Wisconsin, gives some of the highlights from the report of the Salmonella Committee of The National Academy of Sciences. His article, which begins on page 60, is entitled "An Evaluation of the Salmonella Problem."

Joseph C. Olson, Jr., in "National Center for Microbiological Analysis," tells of the circumstances that led FDA to establish a center to combat, on a large scale, the health hazards presented by microbial contamination of our foods. The article begins on page 65. Dr. Olson is Director of the Division of Microbiology for FDA's Bureau of Science.

L. W. Hazleton discusses "Other Considerations in Foods and Food Additives" in his article beginning on page 70. Mr. Hazleton contends that progress toward solving the problems relating to food additives should include educational programs. Mr. Hazleton is Director for Life Sciences of the TRW Systems Group, Hazleton Laboratories.

"Food Standards," by *Keith H. Lewis,* presents the author's explanation of the time required to establish or amend food standards. Dr. Lewis invites those concerned with food standards to offer their suggestions for shortening the procedure. Dr. Lewis, whose article begins on page 74, is Director of the Bureau of Science, FDA.

Beginning on page 78, *Robert W. Elkas,* Manager of Pharmaceutical Quality Control & Services for Lederle Laboratories, discusses "Revised Good Manufacturing Practice Regulations." Dr. Elkas says that manufacturers believe they could be subjected to "unnecessary hardships" if the regulations are interpreted unreasonably.

Ira I. Somers discusses the White House Conference on Food, Nutrition and Health from the canning industry's point of view in "Additives, Standards, and Nutritional Contributions of Foods," beginning on page 83. Mr. Somers says that the proposals must be evaluated to insure that they will not represent change for change's sake. Mr. Somers is Director of Research Laboratories for the National Canners Association.

Warren E. Whyte, Senior Attorney for Abbott Laboratories, presents his opinion of the "Effectiveness of the NAS-NRC Drug Effectiveness Review," beginning on page 91. Mr. Whyte poses the question of whether FDA's method of implementation is in the best interests of the public.

Beginning on page 101, *Irwin B. Berch* explains that the purpose of "FDA's Intensified Drug Inspection Program" is to insure that the benefits accrued through research are transmitted to the patient without diminution in quality. Mr. Berch is Director of FDA's Philadelphia District.

"Revised Good Manufacturing Practice Regulations," by *Robert W. Jennings,* presents the Government's view of the proposed revisions, beginning on page 107. Mr. Jennings, who is associated with FDA's Bureau of Compliance, contends that abandonment to token improvements will not result in a measurably better drug supply.

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Food·Drug·Cosmetic Law
Journal

An Evaluation of the Salmonella Problem

By E. M. FOSTER

Mr. Foster Is Director of the Food Research Institute of the University of Wisconsin.

THE REPORT OF THE SALMONELLA COMMITTEE of the National Academy of Sciences is difficult to highlight in a brief report, but I have been asked to do so by Mr. Franklin Depew. This 207-page report, which took almost eighteen months to produce, was published last June as NAS Publication No. 1683. I will emphasize four specific areas: (1) the seriousness of the problem; (2) control measures by industry and the regulatory agencies; (3) needs for education and training; and (4) needs for research.

Seriousness of the Problem

It is common knowledge that some 20,000 Salmonella isolations from humans are reported each year to The National Communicable Disease Center, but this figure tells us very little about the actual incidence of disease. In the first place, relatively few cases of Salmonella gastroenteritis ever are seen by a physician. Only a fraction of these are hospitalized, and a still smaller number is submitted to laboratory examination, which is a necessary step in diagnosis. Even when the case is clearly diagnosed and a culture is isolated, the information may never complete the tortuous path from physician to State Health Department to the Communicable Disease Center (NCDC).

Reporting practices vary widely among the states. In 1967, for example, the top ten states with 44% of the country's population accounted for 60% of the isolations reported to NCDC. This represents one isolation per 7500 people in those states. By contrast, the bottom ten states with 4% of the country's population reported only 1% of the isolations, a figure equivalent to one isolation per 40,000 people. One may well question if the incidence of salmonellosis in the latter ten states actually is only one-fourth of the national average.

Taking these and other considerations into account, The Salmonella Committee concluded that 2,000,000 cases per year is a reasonable estimate. This figure was arrived at by extrapolation from the results of several intensive epidemiological investigations conducted by NCDC personnel.

Measuring the economic impact of salmonellosis is even more difficult than estimating its incidence. Without detailing our reasons, the Salmonella Committee concluded that salmonellosis costs the American economy at least $300,000,000 per year.

Thus, the sizeable economic impact plus the human suffering associated with salmonellosis combine to make this disease one of the more important microbiological problems facing our people today.

Controls

In view of the great number of potential vehicles of the Salmonella organism one may wonder if there is any hope of avoiding infection. At one time or another outbreaks of salmonellosis in humans have been traced to a wide variety of raw and processed foodstuffs, water, pharmaceutical preparations, pets and human carriers. Even soil was incriminated as the probable vehicle in one incident.

For the past four years special attention has been paid to the elimination of salmonellae from processed foods and pharmaceutical preparations. Extensive testing programs have been undertaken both by manufacturers and by the FDA. Any product found to contain salmonellae has been withheld or recalled from the market. Needless to say, the food processing industry now is well aware of the Salmonella problem.

Yet if one wants to reduce the incidence of salmonellosis in humans, it is clear that processed foods (excepting egg products) are not the place to start. During the period 1962-1968, NCDC personnel studied 138 outbreaks of food-borne salmonellosis with 15,761 cases

in which the specific food vehicle could be identified. 71% of the outbreaks and 77% of the cases were traced to meat, poultry and egg products. A very high proportion of the outbreaks were associated with faulty food handling practices in commercial food service establishments and institutions.

Yet in spite of these statistics, the Committee was well aware that processed foods and ingredients such as dried eggs, dried milk, inactive dry yeast, carmine red, coconut and possibly a few other items have, indeed, been associated with outbreaks of human salmonellosis. Moreover, compounded foods containing these ingredients, such as milk chocolate, pink summer candy coatings, egg noodles, and others have on occasion been found contaminated with salmonellae. Whether these compounded foods have ever served as vehicles of infection though is not recorded.

Up to now the presence of salmonellae in a food or drug product has been regarded as adulteration within the terms of the Food, Drug and Cosmetics Act. There can be no serious argument with this concept. If the organism is present it is potentially harmful and that is that. But unfortunately, the law does not tell us how to decide if it is absent. We know that contamination does not occur uniformly in a food product; moreover, we know that very small numbers, even less than 1 per gram, are potentially dangerous, especially if there is opportunity for them to multiply before the food is consumed. Therefore, the tendency has been to test larger and larger samples in an effort to be sure that salmonellae are absent. The problem is when to quit and decide that the product is not contaminated.

The Salmonella Committee considered this question at great length, both in terms of the manufacturer's problems, and of the protection of the consumer's health. We agreed that a Salmonella organism is potentially more dangerous in a product that offers an opportunity for growth before consumption by a highly susceptible individual (instant nonfat dry milk for infant feeding, for example) than it is in a product which does not permit growth and which is normally consumed by an older person (milk chocolate). Morever, a Salmonella organism is potentially more dangerous in a food that is ready to eat than it is in a food that is cooked during processing or before serving in the home.

The Salmonella Committee recommended that a food classification system be established to reflect the relative degree of hazard

based on considerations such as those just mentioned. We further proposed that foods in the more susceptible categories be tested more rigorously than those in the less sensitive categories. Thus, according to our recommendation, the sampling and testing protocol would give assurance with 95% confidence that the contamination level was less than one organism per 500 grams, or a little over a pound. Similar assurance would be achieved for less sensitive products, but with a smaller sample.

It should be emphasized that the Committee did not recommend a tolerance for Salmonella in foods. It recommended a sampling plan which, if followed, would give reasonable assurance that the level of contamination, if any, would be below a defined limit, such limit being related to the potential hazard of the product. Thus, in essence, the Committee defined zero. Both industry and the regulatory agencies need this definition.

The appropriate Federal agencies have recognized the merit of a system such as I have described, and have asked the Food Research Institute to develop a scheme that is generally acceptable. We have assembled a small group representing both industry and governmental agencies to consider how best to do the job. It will not be easy, but the need is clear, and I have hopes that we can make some worthwhile progress in the near future.

Education and Training

I am convinced, and I believe the Committee agrees with me, that a major part of the salmonellosis in humans is a direct result of faulty food handling practices and inadequate personal hygiene. If one examines the record, he will find outbreak after outbreak traced to roast fowl, cooked meat dishes, poultry salads, and the like. Salmonellae present in the raw materials should be killed during cooking; hence it must be concluded that foods are often recontaminated after cooking, both in the home and in commercial food service establishments.

Of course it could be said that extreme care in handling would not be necessary if the raw products were not contaminated in the first place. To a degree this is true, but the facts are that we shall continue to have Salmonella contaminated raw animal products in our food supply for some time to come. No doubt the situation could

be improved by better handling practices during slaughter and processing, but as long as infected animals are sent to market, we shall have contaminated products in our food supply.

The ultimate solution goes back to the farm, but to eliminate Salmonella from our domestic animals will require revolutionary changes in husbandry practices. In the meantime, what can we do to reduce the incidence of salmonellosis in humans?

The Salmonella Committee foresaw the need for a massive educational campaign directed at everyone in the food supply chain including the farmer, the processor, the distributor, the food service operator, and the housewife. Each segment in the chain needs to be told what to do to minimize the Salmonella hazard while the animal or the product is in his hands. Accidents still will happen, but an understanding of the problem should reduce the frequency of disease.

Research Needs

There is nothing mysterious or sinister about the salmonellae. They rarely kill anybody; in fact, the vast majority of cases are relatively mild and uncomplicated. Perhaps this is why we have been willing to live with them as we do, paying the price we pay and hoping the next victim is somebody else. We already know how to improve our chances; we could help matters a great deal if we merely insisted on sanitary food handling all along the line.

But to make substantial progress toward ultimate control we must learn a great deal more about salmonellosis both in man and animals. To devise control measures we must find out how animals become infected, where the organisms exist in the body, and how they are spread from one animal to another. Likewise, we need to know more about the disease in man, conditions leading to infection, the size of the infectious dose, and possibilities for chemotherapy and immunization. These are but a few of the research needs foreseen by the Salmonella Committee. The Committee's list is by no means complete; it merely includes a few areas of obvious need.

It has not been possible in this brief time period to cover all the highlights of the Salmonella Committee's report. I have not even mentioned problems relating to the control of Salmonella infections in hospitals and on farms. If you are interested in more information perhaps you should read the report. **[The End]**

National Center for Microbiological Analysis

By JOSEPH C. OLSON, JR.

Dr. Olson Is the Director of the Division of Microbiology for the FDA's Bureau of Science.

THE GREAT ACCELERATION IN THE DEVELOPMENT and application of new technologies in the food industry during recent years has required a reorientation towards surveillance activities relative to the microbiology of foods. Large quantities of convenience foods, many of them new, are now being mass produced. Many of these, which require only defrosting, rehydrating or warming prior to serving, are used daily by the nation's homemakers, the airlines, and other types of commercial food services. Because of the mass production techniques used by manufacturers coupled with our rapid transportation capability, there is a grave risk that if food becomes contaminated at any point before it reaches the consumer, thousands of people could be endangered. Food hazards resulting from lack of adequate "process assurance" safeguards have occurred, and continue to occur, as evidenced in numerous reports of epidemiological investigations of food-borne disease outbreaks.

We do not tolerate disease-producing organisms in foods. Factory inspections with bacteriological tests are an important method of checking on the adequacy of manufacturing practices, particularly in factories producing food that may be consumed without further heat treatment, or following a warming process only. In addition, efforts will be directed toward ready-to-eat foods prepared for institutional use, interstate carriers, restaurants, and similar mass feeding operations.

In areas other than food, health hazards are also present. Expanding scientific information and better reporting continue to uncover important hazards, real and potential, from microbial contamination of drugs and cosmetics. In the latter part of fiscal year 1968, and

again in early fiscal year 1969, topical lotions were implicated in serious infections of hospital patients. Again, centralized production facilities and rapid dissemination by the American transportation system carried such products to all parts of the nation.

In setting up the National Center for Microbiological Analysis (NCMA), The Food and Drug Administration (FDA) hopes to fill in the gaps that presently exist in the attack on these problems. The Center will examine large numbers of samples rapidly and efficiently, thus permitting us to accumulate data on any commodity in a short period of time. By using effective surveillance procedures, we hope to go a long way toward preventing illness, instead of reporting contamination or correcting it after it happens. FDA recognizes that it cannot do the job alone. It is hoped that with the information provided by the Center, plus other resources such as industry self-certification, planned inspections, state and federal programs, etc., we can arm the many government and private institutions of this country with the kinds of information that will lend direction to their efforts. Within FDA, the Center will assist greatly in identifying for our seventeen district offices the foods and drugs which currently pose the greatest threat, thus resulting in a better utilization of our manpower.

The Center, under the supervision of the Division of Microbiology, will conceive, plan and execute programs whereby it:

1. Tests large numbers of food, drug and cosmetic samples obtained in planned regulatory, surveillance, market product survey, and self-certification programs;
2. Assists in the development of simple, rapid screening methods for the analysis of such samples;
3. Adapts the analytical methods, where feasible, to assembly line, mechanized, or automated systems;
4. Develops a high degree of expertise and adequate facilities for sterility testing of parenteral drugs; and
5. Conducts examinations for specific pathogenic microorganisms or their toxic products.

Program Objectives

The program objectives of the Administration for the coming five years are to materially reduce microbial contamination in both domestic and import food products, and to ensure that no batch of marketed drugs will fail to meet compendia standards. It is imperative that FDA increase its ability to analyze large numbers of samples rapidly and efficiently to determine if these objectives are attained.

At present, sample collections often exceed the analytical capability of the district laboratories. When a backlog of samples develops, the overflow is shipped to the Division of Microbiology. As presently organized, the districts will not be able to examine the volume of samples anticipated in coming years. The examination of essentially routine samples by the Division of Microbiology Division hampers research programs, and it cannot take on a larger load.

In recognition of these problems, a number of discussions were held over the past two years relative to the feasibility of conducting certain microbiological examinations on a centralized basis. Staff papers were prepared which considered various facets of the general problem of attaining the microbiological analytical capability required for meeting program objectives. The result of these discussions was a decision by the Office of the Commissioner to institute a pilot study to be conducted within the laboratory facilities of the Minneapolis District.

The decision to proceed with a pilot study was reached in mid-August, and limited funding became available on September 1, 1968. In view of the fiscal year 1969 employment restrictions, the study was to be implemented utilizing existing personnel resources. It was agreed that:

1. There would be no physical alterations to the Minneapolis district office (MIN-DO) building;
2. Personnel would be detailed from Washington and from various district offices;
3. MIN-DO would provide the administrative-clerical support and would exercise control over the shared facilities; and
4. The Division of Microbiology would be fully responsible for the analytical program, and the center would provide microbiological analytical support to MIN-DO.

Center Operations

By September 15, 1968, arrangements had been completed for personnel to report on detail to Minneapolis, requisitions for equipment and supplies had been submitted for processing, sampling instructions had been transmitted to the districts, and preliminary discussions had been held concerning data retrieval.

The sampling schedule called for deliveries that would allow analytical work to begin on October 1. The majority of the personnel reported between September 15 and September 23 for the purpose of preparing media, stains, and reagents and making equipment operational.

Analytical Work

Product	*Samples Requested*	*Samples Received and Examined*
Frozen Pies	80	70
Frozen C-P Shrimp	20	20
Egg Noodles	24	22
Gelatin	22	12
Hi-Protein	20	20

For three products, the districts could not obtain the total number of samples requested because the firms had gone out of business or were not producing during this particular period.

It may be noted that each sample consisted of 10 subdivisions; therefore, within a two-month period of analytical work, the Center conducted microbiological examinations of 1,440 units. In addition, seventy-five subdivisions of cheese were examined for staphylococcal content, fifty subdivisions of gelatin were examined for Salmonella, coliform, and total aerobic count, and approximately 1,000 subdivisions of various products were examined for MIN-DO. By the use of team-approach and the application of assembly-line techniques, the Center examined some 2,500 subdivisions. This was accomplished by ten at-the-bench microbiologists. The attainment was achieved under less than ideal conditions since there was a shortage of incubator space, and there were inadequate facilities for dishwashing and media preparation. The work could have been increased had the sample flow been uniform. We estimate the output to have been four to five times the capacity of a five-man district laboratory.

In our opinion, the pilot program was very successful, and amply demonstrated that a Center is a practical way of examining large numbers of samples within a short period of time. It is evident that a Center can examine a larger number of samples than can any present laboratory within the organization. The analytical data garnered from the operation would have taken months under the present laboratory system, and would have been virtually impossible to achieve without diminution of regular district examinations.

The pilot program covered a wide range of microbiological analyses, including sterility, aerobic plate count, coliforms, E. coli, staphylococci, C. perfringens, C. botulinum, staphylococcal enterotoxins, and antibiotic residues. A capability to perform a diversity of analyses is essential for a Center that is to supplement the work of the individual district laboratories in carrying out a national program in microbiology.

Examination of the product survey samples indicated a need for follow-up on certain firms. We understand that the districts concerned instituted appropriate actions. Analytical work also led to the discovery of violative imports, Salmonella in an egg-breaking plant, and Salmonella in one sample of instantized nonfat dry milk.

Current Progress

Programs designed especially for NCMA were not completed for implementation during the first quarter of fiscal year 1970. Training of five new employees was accomplished, and the Center examined samples from two districts totalling 1,300 units in 127 food samples.

The programs suggested for the remainder of fiscal year 1970 place top priority on dangers to the health of the consumer. In addition to handling the microbiological workload for the Minneapolis district (estimated at 400 samples—5,000 analytical units), the Center expects to examine a maximum of 300-350 samples containing a total of 4,000 analytical units. In some instances, each unit will undergo examination for several types of microorganisms. These examinations will include determination of the incidence of C. botulinum in cold smoked fish, potentially toxigenic staphylococci in cheese, and Salmonella in high-risk dry mixes (such as those containing eggs, yeast, milk, or dried milk products).

Current thinking for fiscal year 1971 is that the Center will examine some 13,000 analytical units (approximately 1,300 samples) with continued emphasis on products in the "high-risk" category. This will include ready-to-eat foods of the types prepared by commissaries for institutional use, interstate carriers, restaurants and similar mass-feeding operations. The problems involved in shipping these latter products (refrigerated items) will be worked out during this fiscal year.

A microbiological analytical center is a practical and economical way of examining large numbers of microbiological samples without materially affecting present district functions or impairing the research studies of the other units within the Division of Microbiology. The Center will make it possible to implement a national program in microbiology, and will supplement the district laboratories. These latter will still remain essential for such things as the handling of special samples, food poisoning investigations, participation in microbiologist-inspector teams to evaluate factory conditions, and source of advice to the District Director on microbiological problems.

[The End]

Other Considerations in Foods and Food Additives

By L. W. HAZLETON

Mr. Hazleton Is Director for Life Sciences for the TRW Systems Group, Hazleton Laboratories, Falls Church, Virginia.

AT THIS MOMENT IN HISTORY it is difficult to prepare a presentation under the broad topic of "other considerations" pertaining to food additives. In the broadest sense, food additives include, not only those chemicals which may be used deliberately, but also those materials which become a part of food from environmental sources, such as pesticide residues.

Preparation for a public presentation today seems to involve reading the daily newspapers, magazines, the *Congressional Record,* and the trade journals. Too often this is considered sufficient background for public utterances. Instead we should go first to a review of published scientific literature and, when possible, to the carefully prepared research information and other data in food additive petitions, color additive petitions, new drug applications, and other formal submissions required for regulatory purposes. It would also be desirable to study the authoritative reviews of the World Health Organization Expert Committees, the National Academy of Sciences reports, and other special or ad hoc advisory committee reports. This course, however, does not provide for "instant science," and is apt to be short-cut by reading policy statements or *Federal Register* proposals.

This is a significant period in the history of food additives, because never before in history has a nation been in such a basically favorable position to provide adequate food for its total population. Time does not permit a review of the contributions which food additives and pesticides have made toward this adequacy of food supply. These facts are, however, well known and well documented; without the additives and pesticides our food supply picture would be entirely different, if not actually dismal.

Note that the emphasis has been on the *ability* to supply food. That we have hunger and malnutrition in this country is also well established. The correction of the economic and social problems involved in adequate nutrition has just been the subject of a four-day conference at the White House. While it is too soon to evaluate the results of that conference, it certainly is to be hoped that the emotional issues involved will not result in a reduction in the food producing, storage, and distribution advantages that food additives have provided.

Public Interest

Basically, of course, the most important "other consideration" with regard to food additives is the widespread public interest in this subject. It is regrettable that much of this new public interest has been aroused by, and is based on, inadequate and inaccurate information. This information appears in the public press and sometimes in the scientific press. It can be inadequate for many reasons, including structure or interpretation of results.

Both the scientific community and the general public become confused about the current administrative setup when the public press carries a policy statement on 2,4,5-trichlorophenol emanating from the office of the President's Scientific Advisor; announcements on the cyclamates and DDT from the Secretary of Health, Education, and Welfare; a statement by Dr. Mayer, the President's consultant on nutrition, advising the elimination of salt from baby foods six weeks before the White House conference; and a declaration by Dr. Egeberg, Assistant Secretary for Health and Scientific Affairs, that he is more worried about monosodium glutamate than the recently banned cyclamate sweeteners.

No one believes in the status quo in such an important aspect of our national health and economy as food additives. Fortunately, our nation has not been in a status quo position over the last several decades. There is, however, continuing room for both scientific and administrative improvement. It is encouraging to see Secretary Finch's support for the necessity of changing the so-called Delaney Clause in the Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act. It is also encouraging that sincere efforts are being made to revamp the Food and Drug Administration (FDA) into a more modern, effective administrative setup. Certainly, until this vital agency can develop a greater separation into scientific and legal responsibilities, less than satisfactory functioning will continue. I personally do not agree that the important division is between foods

and drugs. Both are part of our total environment, and the same scientific and legal principles apply to each. The Delaney Clause, perhaps more than anything else, demonstrates the futility of dictating scientific judgment by legislative fiat.

Both legally and administratively, the National Academy of Sciences-National Research Council has an advisory working relationship with FDA, as well as with other federal officials and agencies involved in the whole subject of food additives. Unfortunately, the administrative mechanism of this relationship is outmoded by its cumbersomeness. Under the present setup, literally months may go by before all of the background paper work can be accomplished even to set into motion an advisory study requested by the government agency from the National Academy of Sciences. This response time, I emphasize, is not in the performance by the Academy, but rather in initiation time. Following initiation, there may be room for criticism in the response time required, but this is not the initial delay in obtaining advisory responses.

Largely initiated by the monosodium glutamate subject, the whole "generally recognized as safe" (GRAS) list is being questioned at levels from consumer advisors through Congress. My sense of history tells me that these pressures for instant science will result in the expenditure of untold amounts of manpower and money that are not justified by the record. It is certainly true that this list should be under continuous, orderly review, and that any chemical on it should have its review accelerated any time there is a question as to its status. Hysteria and crash programs are not, however, going to solve legitimate questions concerning the GRAS list. Such a procedure as now seems imminent can only result in further chaos in regard to food additives. Is it worth the $30 million that publications say will be the first year's cost? Or $60 to $90 million for the same thing on pesticides? Money alone will not buy instant science.

Public Confidence

Perhaps the most serious "other consideration" regarding food additives during the last year or so is the shattering of public confidence in the adequacy and quality of our food supply. In a nation where, and at a time when, we are blessed with one of the best food supplies in the world, it is indeed unfortunate that irresponsible and ill-conceived publicity has resulted in shaking the confidence of the public. One can only hope that this, too, shall pass and that out of it will come a more streamlined and efficient educational program

which will help our public to understand their great good fortune in living where food is available and where the problem is only how to use it properly and distribute it more efficiently.

Perhaps the continued rational development and exploitation of food additives suffers most from the concept that instant science can be achieved through public clamor. Science, of course, is not the only aspect of our community life suffering from the demands for instant solutions. We have all criticized the slowness of regulatory activities and of the working of scientific and deliberative bodies. It is probably true that these processes could, and should, be speeded up. This is different, however, from thinking that the underlying life science research can be accelerated. While research toward this latter objective is continuously under way, it is important that adequate time be permitted for the careful development of the scientific evaluation and judgment necessary to reach valid conclusions. Our history during the last half-century suggests that our record has been good. Precipitous action, whether required by misguided law, or in response to public clamor, is not necessarily in the best interests of the public. Certainly a crusade in the guise of consumer protection which would undo the careful progress made during these years is unjustified.

Orderly Progress

In summary, it is to be hoped that the people here at this conference will, each in his own way, join other efforts to bring order rationally and logically out of the present food additive chaos. Specific activities are being undertaken toward this end by the Society of Toxicology, the National Research Council, the American Medical Association, and the President's Task Force on Science Policy, among others. Even Congress may join us in this effort! Representative Brademas of Indiana has introduced a bill "to authorize the United States Commissioner of Education to establish educational programs to encourage understanding of policies and support of activities designed to enhance environmental quality and maintain ecological balance." We would certainly expect such a program to be broad enough to include the classification of food additives, pesticides, and other chemicals in the environment as ecological factors.

We know that there are problems, that there always have been problems, and that there will be problems in the future. This is the time for a concerted endeavor toward correcting the problems that do exist, but perhaps more importantly, to mount a campaign in the consumer interest to educate the public on these subjects. **[The End]**

Food Standards

By KEITH H. LEWIS

Dr. Lewis Is the Director of FDA's Bureau of Science.

THE OPPORTUNITY TO DISCUSS FOOD STANDARDS is a privilege that I accept with some misgivings, because I can claim no special knowledge about the techniques of standards development or their legal implications. Nevertheless, the initiation and processing of food standards is an important function of the Bureau of Science which has concerned me from the time I was appointed Bureau Director a few months ago. My normal interest in this function has been sharpened by the probing questions that have been asked by the Administration, by industry, and others about the time required to establish or amend food standards.

The search for answers to these questions has required a thorough review of the entire process by the staff of the Division of Food Chemistry and Technology of the Bureau of Science. As a result, we have changed several practices and instituted new controls that should bring about substantial improvements. For example, when the Commissioner contemplates establishing or substantially amending a standard on his own initiative, all interested persons will be invited to offer information and suggestions before a formal proposal is published in the *Federal Register*. The invitation would be accomplished either by the Commissioner's publication in the *Federal Register* of a notice of intent, or by his use of press releases and other means to inform industry, consumer groups, institutions of learning, and others of his intent and needs. I sincerely hope that all those interested will participate by responding to such invitations.

We are experimenting with a suggestion from industry that some method of developing an early mutual understanding would be most helpful. We believe the new approach has the advantage of wider participation and development of better information as a basis for the formulation of proposals, and it should minimize the exceptions or objections to them after formal publication.

Similarly, when industry or other interested persons wish to establish or change a food standard, I urge that an early review and discussion of the petition be undertaken with our Food Standards Branch before a formal document is submitted. Those who have already taken advantage of this service will, I am sure, agree that the informal review usually reduces the time needed for processing.

You may be interested in knowing that a strict internal control system providing for frequent reporting to the Office of the Commissioner of the present status of each food standards project has been instituted. This system will permit us to check into any unusual delay and eliminate the cause for delay, if possible. If the delay results from lack of supporting data, or from some other cause within the scope of responsibility of the petitioner and cannot be promptly overcome, it may cause a petition to be denied. Such rejection would not prejudice reinstituting the petition at a later date, after the problems have been resolved. Any suggestions you may have on this feature will be welcome.

Processing a Proposal

Let us further consider the time taken for processing a petition. I agree that the time is sometimes too long. I am told that until a few years ago we routinely, and with few exceptions, provided thirty days for the filing of comments, but now we provide for sixty days. This has greatly extended the time for processing a proposal, but it was done because extensions of time for filing comments were so frequently requested.

Even the processing of an atypical food standards petition, one that is relatively simply and requires no great deal of research on our part, takes a considerable amount of time. For a full review by all agency echelons we must send all documents—in sequence—to four different buildings, where our various units are located.

I think you can readily see why a complicated and controversial proposal will require much more time and effort to process. I realize that to the petitioner the proposal may seem simple, and clearly in the interest of the consumer. Since he has invested time and money on research he is naturally impatient, but he must recognize that others may not immediately agree with his proposal, or for that matter, may oppose it.

Let us now consider the other side of the coin. What delays are sometimes caused by the petitioners or others outside of government? Of course one easily recognizes the problem of imperfectly

prepared petitions. This may be due to: (1) lack of reasonable grounds to properly support the proposal, with no readily convincing evidence that its adoption would promote honesty and fair dealing in the interest of consumers; or (2) an inadequate recognition of past regulatory history, such as a hearing record bearing on the proposal; or (3) a lack of provisions for proper label declarations; or (4) simply incomplete coverage. Another cause for delay is the last-minute submission of comments, or objections, or both. If they were sent in before the actual deadline, our staff could start tabulating and checking them early.

I am advised that the legal profession is intensively seeking a solution for the problem of delays caused by our hearing procedures.

Alleged Conservatism

We in FDA sometimes hear that we are overly conservative and sometimes oppose change or progress. Be assured that we, in fulfilling the Congressional mandate to amend or establish standards that promote honesty and fair dealing in the interest of consumers, are vitally interested, as you are, to establish a standard or promulgate an amendment if it benefits consumers. I shall be interested in hearing the full details of any instance of undue conservatism.

However, I believe you will agree with me that for a standard to be meaningful, it should not be changed solely to serve the economic advantage of a manufacturer or ingredient supplier. Further, a petition that lacks adequate support may cause us to appear to be unduly conservative when, in fact, it may be that the petitioner has not given us all the available information that would support the changes he desires. If there is consumer benefit to be derived from a major change in the finished food, the manufacturer should not simply seek to hang onto the identity of a well-known and established food, but instead should give serious consideration to establishing a new identity or subidentity for the product under a new or modified name. Here, I believe being called "conservative" when we protect the integrity of a food—when we insist that any change, either in composition or labelling, should not work to the consumers' detriment—may well be considered a compliment. In other words, we are not convinced that "change" and "progress" are necessarily one and the same in every instance.

As you know, there is considerable interest, not only in protecting the nutrient levels of our foods, but also in improving them

where necessary. At present, nutrient enrichment or fortification is essentially optional. Should this condition continue? Should we provide for a rational nutrition improvement for more of the common foods? Have nutritional aspects played too minor a role in the formulation of food standards? Is the old philosophy of food standards, which is concerned primarily with the protection of the essential characteristics of our conventional foods, still adequate to insure a wholesome and nutritious food supply? Particularly, is it adequate in the light of radical changes in eating habits, the use of food extenders, and the potential for application of new processes and technology, as well as the development of new foods? Would new legislation help? I welcome your suggestions here as well.

How many of you have been concerned about FDA's recent interest and activity with respect to microbiological standards for foods? Dr. Olson has adequately covered this subject, and I can only add my voice to urge that public health agencies and industry strive together to develop meaningful microbiological specifications and microbiological limits that will assure the safety of processed perishable products such as frozen or dried foods, precooked frozen foods of a moist neutral nature, and precooked chilled foods. Should microbiological criteria be incorporated as a mandatory requirement of an identity standard? I welcome your thoughts on this matter too. I sincerely believe that the reputable manufacturers of foods have as much at stake in maintaining a dynamic food standards program and a meaningful enforcement program as do consumers, for both suffer from the careless or shady food manufacturers. Sound, equitable rules, and an even-handed enforcement program can only benefit all concerned.

Cooperation for Progress

Finally, I assure you that if you have need for a new standard, or an amendment to an existing one, which will truly promote honesty and fair dealing in the interest of consumers, we are sympathetic to that need. You will receive all of our available cooperation. In turn, I ask that when you receive a request from the Commissioner to assist him in establishing a new standard or amending an existing one, which is also for the purpose of promoting honesty and fair dealing in the interest of consumers, that you, too, extend all of your available cooperation. We all have stockholders —200-plus million of them.

My staff and I shall be happy to discuss, now or later, any food standards problems or questions you may have. **[The End]**

Revised Good Manufacturing Practice Regulations

By ROBERT W. ELKAS

Dr. Elkas Is Manager of Pharmaceutical Quality Control & Services for Lederle Laboratories.

A FITTING CAPTION FOR THE PROPOSED REVISION in the Good Manufacturing Practice Regulations for drugs (GMPs) might well be the old Army Air Force slogan "The difficult we do immediately. The impossible takes a little longer." For over a quarter of a century, experts on the manufacture and evaluation of drug products, both in industry and government, have strived to create what might be called a total quality control system. It has been a unique challenge, fraught with a myriad of perplexing and complicated obstacles, but we are now on the threshold of that goal. The proposed GMPs might be looked upon as an outline of a quality control system, and thus represent a standard framework on which all sizes and types of drug manufacturers can build. To be sure, the subject is a complicated one, but nevertheless, the question might well be asked: "Why did it take so long?"

The philosophers tell us that the test or standard of judgment concerning the excellence of anything, whether structure or function, is determined by a study of the natural or normal development of that thing, and that a criterion is reached by carefully making explicit the implicit tendencies of any function. In this respect, the culmination of the Revised GMPs is to be hailed as a testimonial to the persistence and perseverance of a whole generation of dedicated scientists within the drug industry and the Food and Drug Admin-

istration (FDA). While the sheer love of excellence has given us something in common, the really motivating force that has led to this highest form of collaboration is a deep, basic common concern for that individual at the end of the line—the patient!

Since the end of World War II, each passing year has seen the introduction of new and more intricate drugs, methods, and machines. Concurrent with these changes, the field of medical knowledge has expanded and advanced even more rapidly. In fact, each advance in one area has stimulated, in turn, an advance in the other. As a result, we have in the pharmaceutical field today a degree of sophistication not to be found in most other industries, and the very nature of medicinals compels a degree of control surpassing that associated with most other industries. It is not surprising, then, that there is an abundance of governmental regulations pertaining to drug products.

The responsibility of the drug manufacturer is not only extensive and exacting; it includes the heavy burden of being held accountable for adherence to GMPs and such other standards as a firm may employ. That is, he is accountable for unauthorized errors in judgment or performance committed by his employees. Added to this is the varying degree of intensity applied in the enforcement of drug laws and regulations. While some of the regulations are directed at the end product itself, other regulations are directed at what the manufacturer does or fails to do. The drug regulatory official in government, mindful of the relative importance and applicability of these numerous regulations, must constantly seek an effective balance between his enforcement activities and his activities in the area of educational and voluntary compliance programs for industry. I allude, of course, to the oft-used expressions, "letter of the law" and "spirit of the law," and their respective orders of precedence in the areas of compliance and enforcement. The FDA information and educational programs, with their conferences, seminars, and workshops, have been extremely helpful and effective in achieving our common goal. The two-way communication they foster has been invaluable in solving many of our mutual problems.

Scope of the Regulations

Basically, government drug regulations cover three stages of industry activities, namely: (1) animal toxicity testing and human

clinical studies on new products prior to introduction (referred to generally as safety and efficacy); (2) manufacturing and packaging operations (standard operating procedures); and (3) finished dosage form evaluation (conformance of distributed products to compendial or other established analytical specifications). The second of these, the regulations concerning drug manufacturing and packaging operations, is the subject of our discussion today.

The Revised GMPs reflect a clarification of the initial regulations issued in 1963, the general aim being toward greater specificity. They also include several proposed features which have been added for the first time. Some of these newly added features would have especially far-reaching effects on manufacturers, and I should like to confine my comments to these few controversial regulations.

The proposed broadening of the GMP regulations to apply to the manufacture of raw material components as well as to finished pharmaceutical dosage forms is considered by manufacturers to be impracticable and unnecessary. While the regulations could be applied meaningfully to finished dosage forms, manufacturers believe that they would not be applicable, within reason, to components.

The proposed addition to the GMP regulations of microbial purity requirements for components raises questions in the minds of manufacturers as to interpretation, both of scope and extent of sampling and degree of testing. Manufacturers believe that they could be subjected to unnecessary hardships if unreasonable interpretations were made of such a regulation, especially with regard to the kinds and levels of micro-organisms that would be considered objectionable for the various intended uses of the components.

The proposed addition to the GMP regulations of biological availability testing presents a question of applicability and feasibility. Manufacturers believe that time-consuming and costly tests could be unnecessarily imposed if such a regulation were interpreted literally, particularly in view of the impreciseness of the term "bio-availability."

The proposed addition to the GMP regulations of expiration dating of all products presents a serious problem to most manufacturers in that there is an open question on the need for dating all products, and in any event it will take time (estimated at a minimum

of two years) to acquire the necessary data to make this possible for all of those products for which expiration dating would be desirable.

Interpretation

Undoubtedly, the biggest concern manufacturers have with regard to the Revised GMPs, in general, is the age-old question of interpretation. As mentioned previously, there is not, and there cannot be, any compromise when it comes to the patient's best interests. The matter of critical importance before us, those of us in industry and those of us in government, once we have the revised regulations, is how we interpret them. The French essayist, Montaigne, is reputed to have once said, in exasperation, "There's more ado to interpret interpretations, than to interpret things: and more books upon books, than upon any other subject." If that observation was true in the sixteenth century, it's just as true today. At any rate, I would venture to guess that the sentiment is no less real today than it ever was. Indeed, the scholarly pursuit of interpretation serves as the cornerstone of at least one lofty profession, and its ramifications are far-reaching.

If there is anything more unforgivable than adding to the tomes on interpretation of laws and regulations, it is probably that of second-guessing the law—by a layman, no less! Yet, that is what I would venture to do at this point in our discussion, in full humility, and with your forbearance, I hope. As a long-time student of drug product standardization and drug law compliance, it appears to me that the underlying objective of the Revised Good Manufacturing Practice Regulations is to bridge more effectively the regulatory gap between the first and third stages of industry activities which I mentioned earlier, namely, the safety-efficacy requirements and the compendial analytical conformance requirements. Both of these areas of drug industry activity are relatively narrow and have already been standardized to a degree which leaves the need for only minimal additional control. On the other hand, the second, or in-between, phase of drug industry activities, that of manufacturing and packaging, represents a vast field in which extreme conditions and practices have existed for a long time.

Total Control of Quality

In short, the Revised Good Manufacturing Practice Regulations will have commendably taken a leaf from the "book" written earlier by the Pharmaceutical Manufacturers Association (PMA), in which the concept was laid down that excellence in drugs may be achieved only by embracing a system of total control. As the PMA has so aptly stated in the introduction to its *General Principles of Total Control of Quality in the Drug Industry,* "Total control of quality as it applies to the drug industry is the organized effort within an entire establishment to design, produce, maintain, and assure the specified quality in each unit of product distributed." Time does not permit me to elaborate on this brief but profound statement. I would like, however, to address my remaining comments to one of the several basic tenets constituting the PMA's position on Total Control of Quality, namely, that dealing with personnel. The reference to personnel concludes with the following observation: "Total control of quality can be achieved consistently only through quality-mindedness in each employee and an understanding among all personnel of the part their performance contributes toward product quality."

To be sure, rigid control of materials, machines, and methods is of utmost importance in the production of drug products of high quality. But the real key to success in the manufacture of consistently reliable drug products is people—qualified, competent, honest, intelligent, and experienced employees, working together and with the right attitude in an atmosphere of conscientious dedication, and led by a management which insists on excellence. In my opinion, the quality of any drug product on the market will, in both obvious and subtle ways, reflect unmistakably the character of the company whose name is identified with it. Perhaps it was a similar sentiment which Oliver Wendell Holmes sought to convey when he said:

One-story intellects, two-story intellects, three-story intellects with skylights.

All fact-collectors—are one-story men.

Two-story men compare, reason, generalize—.

Three-story men idealize, imagine, predict; their best illumination comes from above, through the skylight.

[The End]

Additives, Standards, and Nutritional Contributions of Foods

By IRA I. SOMERS

Dr. Somers Is Director of Research Laboratories for the National Canners Association, Washington, D. C.

AT THE WHITE HOUSE CONFERENCE on Food, Nutrition and Health, which I attended in December, the subjects of additives, standards, and nutritional contributions of foods received extensive review. While it is too early to assess the results of the Conference, a lot was said which concerned the industry I represent.

Many of the proposals appear to be good, and are worth further consideration. On the other hand, a pessimistic reading of some of the Conference recommendations might lead one to conclude that we should scrap everything that has made the food industry what it is today and start over. Hopefully, this will not be the case. Some of these questionable proposals do, however, tear at the foundations for the use of additives, food standards, and provision of adequate nutrition since the passage of the 1938 Food, Drug and Cosmetic Act.

I believe the recommendations of the Conference must be carefully evaluated by all concerned before anyone races off to begin their implementation. We must be certain that they will really benefit the consumer and not just represent change for change's sake. Let me assure you that industry will spend considerable time assessing the proposals, and hopes to be invited as participants on some of the review committees recommended by the panels for further study of the issues.

Food Additives

At the beginning of a discussion on food additives, it is important to emphasize that food manufacturers do not use additives without a good reason. Adding ingredients for addition's sake just is not done, because costs alone would advise against it. Where there have been good reasons for it, however, industry, using the proper channels and advice, has gone ahead. This approach has given the American homemaker the greatest choices in any country of the world for providing members of her family with a wide variety of nutritious and tasty foods.

Referring to additives, a TV show held in connection with the White House Conference suggested in part, "Remember the day when you could taste food fresh-off-the-farm? A staggering amount of it is [now] camouflaged to make it look fresher, seem tastier, and smell better—everything from the meat and potatoes we eat to the corn that comes out of the fields in Iowa." Many well-meaning, but misinformed, press and news media representatives have gone along with those who believe that anything done to food after it leaves the field cheats the consumer. Unfortunately, our communications have broken down, and all of us here have an educational job to do. Certainly it would be unrealistic to eliminate additives from foods merely because a few people do not understand their necessity or desirability.

While the total number of additives used in the broad field of food is large, the number used in any one product is relatively small. Industry is basically conservative and depends heavily for advice on the recognized authorities, both scientific and regulatory, before going ahead with new additives or before changing the pattern of using those already employed. Doing otherwise would be detrimental to the company's economic survival for several reasons. The best interests of the consumer would not be served if there were no stability in the practice of using additives, and industry's survival depends on consumers' good will. With every change in formulation comes a change in labeling, and label changes are costly. Also, an amendment to a standard of identity may be required for standardized items. Making changes based on questionable and qualitative scientific data, or as the result of pressure groups—as has been suggested by some—would keep industry in constant turmoil and be a disservice to the consumer. There are too many self-appointed advisers in this area who do not know, or do not appreciate, the facts.

The decision to use an additive is a serious matter to any manufacturer, and is made only after the management has assessed all reliable facts associated with its value and safety. Thus, it is obvious that once the use of an additive begins, industry is likely to continue its use as long as the reason for its use remains. Even so, industry does not operate in a vacuum and is constantly alert to any questions raised about the validity of the evaluations which established the safety of the additive, or to test-results which might raise some doubt as to the desirability of its continued use. The concern of industry is naturally very sincere because to have an ingredient delisted when it is in wide-spread use can have a devastating effect. The delisting of cyclamates is a case in point. The economic loss from this act will be a serious, if not a crippling setback, to many companies. Some have asked why industry continued to use cyclamates when questions were raised about its acceptability a year ago. The reasons are those already expressed. The industry was concerned, but was reassured when limits were set last April by the Food and Drug Administration (FDA) in its proposal. It is well known that diabetics and obese individuals do need low calorie foods. These cyclamate-containing products served this purpose very well, so much so that they allowed these people a variety of choices, as compared to the lack of variety without artificially sweetened foods.

I will cite an example of a functional additive used in the canning industry. A few years ago, the tuna standard was amended to permit the addition of the optional ingredient sodium acid pyrophosphate for the prevention of struvite crystals. These crystals may form in the product in storage, and while they are not harmful, they are aesthetically objectionable and have resulted in many misunderstandings by consumers. The addition of the pyrophosphate has almost completely eliminated these complaints. In this case, the cost to industry is not great, but the advantages to the consumer are considerable.

Bread provides a good example of the value of additives for product-keeping quality. In the United States a person buys a loaf of bread, and it will keep for several days in the home without spoilage. Where no additives are present, there is considerable loss due to mold growth.

At the White House Conference, much was said about fortification of the basic food items to improve their nutritional properties.

In fact, one of the recommendations was that:

"The Secretary of HEW should, within 90 days after this report is submitted to the President, make public a list of important, unfortified standardized and unstandardized foods that should promptly be fortified by industry on a voluntary basis with specific nutrients at significant levels in order to launch an immediate attack on malnutrition in this country."

This fortification would, of course, be done with additives. We could go on with many such examples, but these should suffice to prove my point that additives do serve some useful purposes for both the consumer and the industry. It would be folly to adopt the view that taste and other non-nutritional characteristics are unimportant. Also, using additives only for nutritionally related purposes, as some have suggested, would be to return to the past.

Certainly, additives are needed to retain the standard of living to which we are all accustomed, but with the use of additives must go the responsibility of seeing that they are used properly. This responsibility rests with three groups: (1) the suppliers of the additives whose job it is to provide the data on use and safety; (2) the regulatory agencies with their scientific staff who evaluate the data and need; and (3) the industry which, based on the advice of the other two, use the additives. All three must accept this responsibility and, in so doing, make every effort to see that additives are properly used. They must also organize a campaign to educate the consumer in the view that the use of additives is not harmful, but is actually helpful and makes a substantial contribution to the luxury and well being of daily life. Without the services performed by the food industry with the help of additives, the average homemaker, to get comparable results, would have to spend considerably more time in the kitchen mixing, whipping, stirring and fixing, ending up with much less time for the many other things with which she occupies herself in this busy world.

Unfortunately, the question of using additives has entered the political arena. Scientists thus find themselves caught up in environments normally unfamiliar to them, some on one side of an issue and some on the other. Perhaps it is time to draft guidelines for scientists to use under such circumstances to make sure that their data are kept in perspective and are properly used. Science does not separate itself into two camps, and it is difficult to explain this to the nonscientific mind. To me, this is one of the real challenges ahead for the scientific community.

Food Standards

Much was said about food standards at the White House Conference. The panel on new foods spent considerable time reviewing the problems of traditional foods, and recommended that generally, there should be two types of standards for foods—standards of characterization and standards of nutritional quality.

The proposal suggested liberalization of the recipe approach to standards, and in some respects went far beyond this. Others present, knowing the history of standards, suggested that we should not go too far, too fast in revising and simplifying existing standards, or chaos might result. The panel suggested that "A standard of characterization for food must protect the consumer's reasonable expectations and provide maximum flexibility and incentive for marketing of new variations and new foods to the public." Considerable concern was expressed that the present procedure for amending standards or obtaining new standards had "a deadening effect on food technology" which encouraged industry to avoid promulgation of standards. It was proposed that standards of characterization would specify the characterizing properties or ingredients of the food, and perhaps establish a minimum level for them, but should not specify other ingredients that may properly be used either specifically by the chemical name, or generally by broad functional classes. It went on to say that any functional ingredient that is the subject of a food additive regulation, or of a prior sanction, or that is generally recognized as safe (GRAS), should be promptly available under any standard of characterization, as long as the standard did not preclude the use of such ingredients. Further, the panel said, a standard of characterization should be used solely for purposes of regulating the type of product for which a given name may be used, and not to preclude or hinder the marketing of new variations or new foods that are truthfully labeled.

Having had much to do with standards-making procedures for the past several years, I await the final report of that committee with considerable interest. We have often suggested that the "breaded shrimp" type of standard might be a desirable approach. If the proposal results in standards of this sort, we will be interested to see how they are implemented. If the report goes much further than this, one will wonder whether there is need for anything more than the basic Food and Drug Act which prevents adulteration as well as deception of the consumer.

The standard of nutritional quality proposed by the new foods panel suggests that there be minimum nutritional qualities assured for foods used by the public as a significant part of the diet. As recommended, a standard of nutritional quality for a food or class of foods would specify a minimum and maximum value for nutritional properties which are significant to consumers in relation to the use of the product or class of products in the daily diet. It was suggested that such nutritional properties should include, but not be limited to, vitamins, minerals, proteins, fatty acids, sodium, and calories, and that no safe ingredient be excluded from a food on the grounds that its nutritional usefulness is not proved. Also, specific claims of usefulness should be prohibited until supported by sound scientific evidence.

Products covered by this standard, according to the panel, should show on the label the nutritional properties within numerical ranges that are no broader than they are meaningful from a nutritional standpoint. Reference was also made to "a declaration of the amount of any characterizing ingredients" and "information about nutritional properties." Proposals such as these will need careful consideration to make sure that products do not end up in the advertising numbers game to win the affection of the consumer.

At the final plenary session, Congresswoman Katherine May referred to labeling in this way: "Product labeling is important. The consumer is not better protected because there is a mass of information on every package. The more that there is, the less readable it may be. But it is very important the foods be labeled meaningfully. . . ."

The canning industry has been active in the support of FDA standards since provisions for standards development was made by the Food, Drug and Cosmetic Act of 1938. Most of the nonformulated canned foods are standardized. We have always believed that there is an advantage to standards, but we do recognize that there are some problems. Standards have the advantage of making certain that all products sold under a specific and legal name comply with the compositional requirements of the standard. Also, when standards of quality exist, there is assurance to the consumer, and to industry in general, that all products will be kept up to that basic requirement Standards also eliminate the opportunity for some who might be so inclined to produce a product of lesser quality and sell it under the name of the standardized item.

While the canning industry has long supported the development of food and drug standards, we do find that in spite of the Hale Amendment, the standards-making procedure is still said to be cumbersome and complex, due, I believe, to faults of both the system and of those making proposals concerning the standards. The procedure has no built-in stimuli, with the result that an industry proposal may reside with the Food and Drug Administration indefinitely if the government believes that there is a lack of justification for its immediate publication.

In the case of a permit to pack a product which deviates from the standard, the packer must apply for this special permit and market an experimental pack in a specific area. All ramifications of the labeling must be worked out in advance, and even after the experimental permit is granted, the packer still must go through a somewhat slow and cumbersome standards-making procedure before he can put the product out for general distribution. The lack of confidentiality in this procedure allows a packer's competitors to catch up with him quickly once his application has been filed, and, in some respects, defeats part of the marketing advantage he hopes to realize with a new product.

Industry's faults in the standards procedure are largely those of failing to make proper presentations to the FDA, or failing to provide adequate information to justify the proposal. These faults result in reviews upon reviews, preparation of new proposals, and sometimes general frustration over minor and sometimes inconsequential points before the new standard, or an amendment to an old one, becomes a reality. In suggesting changes, however, we should not lose sight of the fact that important rights of interest are at stake, and there is no substitute for procedural protection from arbitrary action.

One of the advantages that industry saw in standards in the past was the fact that they did not require label declaration of all ingredients. This pattern has changed in recent years, and some of the suggestions from the White House Conference would require listing of all ingredients. If we go this complete route, some might question the need for new standards or for any standards at all. Our industry has not considered this point, but it could very well arise. Up to now, however, we have strongly supported the promulgation of standards for nonformulated food products, and we do not visualize that the experts in this field will be out of work in the foreseeable future.

It is true that many standards have been on the books for a number of years, and it may be time to re-evaluate these to see whether or not they are serving the best interests of consumers and industry. Such a review might be precipitated by the Codex Alimentarius standards as they come along, because sooner or later, the United States will have to decide whether or not this nation can accept international standards such as the Codex Standards.

The canning industry stands ready to work with FDA and others on the review of standards, or on any other standards matters.

Nutrition Considerations

The need for better nutrition was a central theme running through all the panel discussions at the White House Conference, and there is no question in my mind that industry must take its place in providing consumers with adequate nutrition. For this reason, we will be interested in the final recommendations of the White House Conference. Just last week, we authorized a program within our own laboratories to spot-check the data on nutrition presently available in our files to make sure that it is applicable to the products as presently packed.

While canned foods are good sources of nutrients, as evidenced from our own research and that of others, we do see some potentials for enrichment to increase nutrition for the consumer. For example, the Food and Drug Administration has generally ruled in the past that a product which is a good source of a nutrient should not be further enriched with that same nutrient. An illustration would be the addition of Vitamin C to tomato juice. Perhaps the White House Conference will suggest some modification in this philosophy. At this time, I am not prepared to say what our industry reaction might be, except that we will look into the matter of nutrition very carefully and help wherever possible to provide the consumer with the best and most nutritious foods.

Conclusion

It has been a pleasure to be with you. Perhaps I have done more to raise questions than I have to provide answers. However, in the field of food technology, which I represent, each day seems to bring even more questions, while we are still attempting to supply answers to those of yesterday. **[The End]**

Effectiveness of the NAS-NRC Drug Effectiveness Review

By WARREN E. WHYTE

Mr. Whyte Is Senior Attorney for Abbott Laboratories.

THE REVIEW OF THE EFFECTIVENESS of all drugs which received New Drug Applications (NDAs) between 1938 and 1962 was indeed a monumental and significant scientific accomplishment of the National Academy of Sciences-National Research Council (NAS-NRC). This work deserves to be recognized for many years to come as an outstanding achievement in the very difficult process of evaluating the effectiveness of drugs. I say it should be so recognized because it now begins to appear that the implementation of this study is degenerating into an extremely acrimonious controversy between the Food and Drug Administration (FDA) and the pharmaceutical industry. The significant achievements and the high scientific purpose of the study are beginning to be lost in this atmosphere of contention.

Although only relatively few of the study reports have been released to date, with more than 2,000 yet to come, already five major pharmaceutical manufacturers have found it necessary to resort to the federal courts to seek relief against what they believe to be an illegal implementation of the study. Moreover, on November 4, the major pharmaceutical manufacturers of the country, through our trade association—the Pharmaceutical Manufacturers Association (PMA)—found it necessary to file suit against the FDA concerning the *Federal Register* order of September 19. This regulation, which I shall discuss in a few minutes, is clearly a direct result of the implementation of the NAS study. The concern, however, is not only with the six lawsuits already filed, but with the many more that are bound to be engendered if FDA's implementation of the drug effectiveness

study continues on its present course. I am personally aware of several other pharmaceutical companies who are either seriously contemplating legal action, or who have already decided to file suit against FDA, if proposed implementations on particular drugs become final orders. When we realize that only a small portion of the reports have been released to date, we can well imagine the tremendous amount of litigation and controversy that may be expected if implementation continues in the present manner.

I would like to review briefly the scope of the NAS review and some of the litigation that has already begun. Then, more importantly, I would like to pose the question of whether this litigious course is in the best interest of the public, the medical profession, the FDA and the pharmaceutical industry. Or is there some better way to implement the findings of the NAS panels to the benefit of all?

As we all know, FDA has interpreted the effectiveness provisions of the 1962 Drug Amendments to require not only "substantial evidence" of effectiveness for all new drugs marketed since 1962, but also to require a review of the effectiveness of all drugs NDAed between 1938 and 1962. FDA also has concluded that all antibiotics subject to certification prior to 1962 must be reviewed for effectiveness, although these drugs have been batch-certified as being effective by FDA ever since their initial marketing. FDA determined that it could not internally perform this monumental task, and in 1966 entered into a contract with the NAS-NRC whereby that organization would evaluate the estimated 4,000 drug formulations that had been NDAed during these years.

Scope of the NAS Review

The effectiveness evaluations were performed by twenty-seven panels, with six members each. Individual drugs were assigned to the various panels on the basis of therapeutic groupings. The members of the panels were selected by the Policy Advisory Committee of the study in consultation with the chairmen of the individual panels. The panels were instructed to make the following judgments on the indications set forth for a drug in its labeling—effective; probably effective; possibly effective; or ineffective. Explanations of those elusive terms will be found in the "Guidelines for the Drug Efficacy Study," which was adopted prior to the commencement of the study. The panels were to base their judgements on factual information available in the scientific literature; factual information

available from FDA, the manufacturer or other sources; or on the experience and informed judgment of the members of the panel. The drug manufacturers were requested to submit pertinent information and literature references on their products for the information of the panels. In all, 237 firms submitted material on 2,824 drug preparations. Most of the drugs were prescription, but about 15% were over-the-counter (OTC) products. Two-thirds of the preparations were single-entity drugs. The remainder were combinations.

The majority of the work of the Drug Efficacy Study was completed by the end of 1968. Reports on 2,800 plus drugs have now been submitted to the FDA.

Although there was one prior lawsuit, litigation in connection with the effectiveness review really began to flourish when FDA began implementing the reports on antibiotic combinations. FDA announced that it was removing seventy-eight such products from the market. Some manufacturers disagreed. The first suit involved Upjohn and its products Panalba and six other antibiotic combinations.

The *Upjohn* Case

On May 15, 1969, FDA took the position in a *Federal Register* publication that it could remove Upjohn's products from the market, repeal the regulations under which they were certified, refuse to certify any additional batches, and revoke the certificates of batches previously certified, *before* it held a hearing concerning such actions. Upjohn filed suit in the Western District of Michigan for declaratory judgment and an injunction to restrain FDA from taking such actions before giving Upjohn a hearing. As FDA's order would have become final before the court had an opportunity to hear and decide the case, the court issued a temporary restraining order against FDA pending its decision.

FDA questioned the jurisdiction of the court, venue in the Western District of Michigan, the timeliness of the suit, and ripeness. The court, in its fifty-six-page opinion, disposed of those arguments without too much difficulty. It devoted the major part of its opinion to the questions of what statutory and equitable relief was available to Upjohn. The court concluded that Upjohn was not entitled to a hearing as a matter of right on its objections to the FDA order. Judge Kent opined that such a hearing is required only when "reasonable grounds" have been demonstrated and that FDA, under the

statute, must make that determination, at least initially. The district court also concluded that Upjohn was not entitled to a mandatory stay of enforcement of FDA's order under the provisions of Section 507.

However, Judge Kent held that although Upjohn was not entitled to a hearing as a matter of right and to a mandatory stay under Section 507, that did not mean that it was not entitled to relief under the general principles of equity, the Administrative Procedures Act, and the Declaratory Judgment Act. The Judge stated that the situation appeared to be the perfect example of the "life and death power given by the Act to the executive officials" which the Supreme Court had indicated in *Abbott v. Gardner*,[1] and which caused great concern among the members of Congress. He stated that the position taken by the Commissioner, and the requirements made by the Commissioner of Upjohn, did not appear to be in accord with the spirit of the review provisions set forth in Section 507(f).

The court stated that "The specter of the heavy bureaucratic hand is heightened considerably when all of the surrounding circumstances are fully grasped." The Commissioner and the NAS were not acting upon the basis of any vital newly-discovered information. There was no finding by the Commissioner that the plaintiff's drugs presented an imminent hazard to the public health. In fact, Panalba has been legally certified by FDA since 1956 as being both safe and effective.

The judge noted that prior to May 1 of this year, Upjohn had been led by FDA to believe that it would be afforded an opportunity to present its evidence at a formal evidentiary hearing. On May 1, Upjohn was informed that no such hearing would be held prior to the removal of its products from the market. All this was done despite the fact that Upjohn had indicated a willingness to subject the products to controlled clinical tests, if afforded sufficient time and an opportunity to do so.

Judge Kent concluded that "the Court finds it impossible to believe Congress ever intended that the drastic action here taken would be taken in the manner in which the Commissioner has proceeded." Rather, "the Commissioner should proceed with all due care and caution and extend to all interested parties a full opportunity to

[1] *Abbott Laboratories v. John W. Gardner, HEW Secretary,* 387 U. S. 136 (1967).

develop and present pertinent information relative to the safety and efficacy of drugs which have been on the market for many years and have been generally and widely prescribed by the medical profession."

The Court then enjoined the Commissioner and the Secretary of HEW from enforcing the order until thirty days after the date on which the Commissioner made a decision as to whether Upjohn would be given a hearing. On September 19, FDA denied a hearing to Upjohn. Upjohn appealed this refusal to the U. S. Court of Appeals for the Sixth Circuit. The case was argued in Cincinnati recently. Thus, we can expect an appellate court opinion on some of the important issues facing us within a few months. I would think that there is a distinct possibility, however, that one of the parties will attempt to seek review by the Supreme Court.

Other Significant Cases

A similar case was filed by American Home Products against FDA involving FDA's attempt to withdraw penicillin-streptomycin and penicillin-sulfa combinations from the market. Judge Latchum in the U. S. District Court in Delaware reached basically the same conclusions as did Judge Kent in Michigan. He also enjoined FDA. The Delaware court stated that the NAS conclusions that these drugs were "ineffective as fixed combinations" was in reality a determination of relative effectiveness as compared to other drugs. He concluded that American Home's objections appeared to raise reasonable grounds for a hearing. He also agreed with the Michigan court that the statute does not require a drug manufacturer to have conducted well-controlled clinical tests *on a continuing basis* since the drugs in question were first certified. He noted that FDA has never demanded such tests of the plaintiff until its order attempting to remove the drugs from the market.

Time does not allow discussion of the other lawsuits that have resulted from FDA's orders implementing the NAS study. The PMA suit against the Commissioner and the Secretary of HEW deserves comment, however. This suit was filed in the U. S. District Court in Delaware seeking a declaratory judgment and an injunction against the enforcement of the regulations published in the *Federal Register* of September 19. Basically, these regulations set forth what we believe to be an extremely narrow and strict test as to what constitutes an adequate and well-controlled clinical study, and excludes as irrelevant any other clinical tests and documented clinical

experience for determining the existence of substantial evidence of the effectiveness of a drug. These regulations, which were adopted without any notice or opportunity for comment, apply these new standards retroactively so as to place in jeopardy the continued marketing of thousands of drug products introduced before 1962 with FDA approval. Further, the regulations provide that when FDA proposes to remove a drug from the market on the ground of lack of substantial evidence of effectiveness, the manufacturer is entitled to a hearing only if he presents all his evidence to the Commissioner before the hearing and convinces the Commissioner that the effectiveness of the drug is supported by adequate and well-controlled clinical investigations of the kind described in the regulations.

The September 19 regulation, if literally applied, would make it virtually impossible for any drugs to be supported by substantial evidence of effectiveness. This is particularly true of the pre-1962 drugs. They would also make it virtually impossible for any drug manufacturer to obtain a hearing from the FDA. Thus, as we see it, the regulation is in reality an arrogation by the FDA unto itself of complete unilateral power to decide whether substantial evidence of effectiveness exists and whether FDA shall give us a hearing on that question.

PMA's Position

It is our position that the Congress in 1962 never intended the type of tests set forth in the regulation to be applied to pre-1962 drugs. The very concept of substantial evidence, as we understand it, was designed to reflect and accommodate the fact that clinical experts often disagree as to the effectiveness of a drug. The Congressional standard was designed to insure that any drug believed by a respectable number of experts to be effective could be marketed, even if the view of a majority of experts was that the drug was not effective. In the PMA brief for the Delaware court, the legislative history is quoted at length to support our understanding of Congress' intent in adopting the substantial evidence test.

We believe that it is also clear that the NAS panels did not apply such rigid standards as to what constitutes substantial evidence. That the NAS panels relied, to a great extent, on personal experience and opinions is apparent from a reading of the Drug Efficacy Study report and from statements by those physicians intimately connected with the NAS review, such as Doctors Cannan and Lasagna.

Further, we believe that the FDA, in its administrative interpretations of the substantial evidence test, did not, until just recently, understand it to mean the very strict and narrow definitions set forth in the September 19 regulation. For example, the prescription drug advertisement regulations state that claims may be made for drugs in commercial use on October 9, 1962 "for which there exists substantial clinical experience, adequately documented in medical literature or by other data. . . ." This provision is still in effect. Also, the pharmaceutical industry was assured by top FDA officials in 1963 and 1964 that well-documented clinical experience would be considered by FDA as sufficient to establish effectiveness for drugs approved prior to 1962. An affidavit attesting to those assurances has been filed in the Delaware lawsuit.

The FDA implementation of the NAS effectiveness study, then, has already engendered serious controversies between FDA and industry. Is all this contention really necessary?

Is it in the best interest of the public, the industry and the FDA to have to thrash out the implementation of these scientific reports by resorting to extensive litigation? I think not. I think that there are at least two possible ways to resolve the differences of opinion between the FDA and the pharmaceutical manufacturers on these scientific and medical questions without the necessity for resorting to the federal courts.

First, let us examine what the NAS study reports actually constitute. In my view, they are *opinions* rendered by groups of eminent scientists on the effectiveness or ineffectiveness of drugs. Although, because of the basically secretive manner in which the NAS review was conducted, we do not know very much as to how the panels proceeded, it does appear fairly clear that each member of the panels could not possibly have reviewed the New Drug Applications, the clinical studies, and the literature on each of the many drugs before each panel. On an average, each panel would have had approximately 150 drugs assigned to it. Dr. Lasagna makes this quite clear in his affidavit when he states that his panel would participate in a general discussion of each drug, but all members did not necessarily review all of the material and studies available on each drug. Dr. Lasagna states that personal opinion and experience often became a part of the evidence used for a panel decision.

Dr. Lasagna also states that "the findings of the NAS-NRC panels should not be regarded as final, conclusive, or irrevocable scientific determinations, decisions, or recommendations."

The NAS reports in reality, then, are only the opinions of a very small group of scientists. While we are grateful to have these highly educated opinions, we must realize that medicine is more of an art than a science, and that there are substantial differences of opinions among physicians as to the efficacy of various drugs. When FDA attempts to remove a drug from the market on the basis of an NAS report, I think FDA should recognize that other scientists and physicians may, in all good faith, disagree with NAS's and FDA's evaluation of the drug. I do not think that FDA should attempt to resolve such differences by demanding that a drug be removed from the market within forty days, and by making it quite clear that no hearing will be granted to examine the correctness of such an action.

Possible Solutions

I would suggest that the better procedure would be for FDA to grant a hearing to a drug manufacturer, where there appears to be a sincere contention that others may not share the opinions of the NAS panel or the FDA.

I do not think that the objections that I have seen to several of the FDA orders are frivolous or without any scientific merit. Why not resolve these differences of scientific opinion at a full and fair hearing? Without going into the arguments as to who must bear the burden of proof, a hearing would most likely give both parties an opportunity to expose to the light of day their opinions as to the effectiveness of a drug and the evidence on which they base such opinions. By confrontation and cross-examination, the differences of opinion among our scientists on these admittedly difficult questions would be fully tested. I think we would end up a lot closer to the ultimate scientific truth as to the effectiveness of a drug.

Actually, I don't think that we would have too many hearings on drug effectiveness. Experience has shown that often when an FDA hearing is contemplated, one party or the other, after preparing for the hearing and examining his evidence, will conclude that he cannot produce substantial evidence of record to support his position and the matter is settled without a hearing. However, if the FDA and the manufacturer cannot reach such an understanding, then

I think a full hearing is in the best interest of all. Further, I suspect that after a hearing, and a review of the record, one party or the other would conclude that they could not prevail in a resort to judicial review, and we would not see too many appeals to the courts. I think the granting of such hearings would be definitely preferable to the present situation where we have the FDA and industry confronting each other in the federal courts over the bare legal issues as to what showing a manufacturer must make in order to obtain a hearing.

Further, I think FDA should seriously contemplate the administrative fairness of its present course of action in attempting to remove drugs from the market within forty days before it even rules on the objections and a request for a hearing. Two federal courts now have concluded that they should resort to the extraordinary remedy of enjoining the Commissioner from taking such final action until a decision has been made on the hearing request and the manufacturer has had sufficient time to appeal the refusal pursuant to the statutory scheme. Faced with these judicial decisions, should FDA continue to demand of other manufacturers that their drugs be taken off the market within forty days and thus force one manufacturer after another to resort to lawsuits to prevent such actions from becoming final? I would suggest, as an alternative, that when a manufacturer files objections and a request for hearing, if FDA does not see fit to grant a hearing voluntarily, that it hold its final action in abeyance until the litigation already underway on these questions has been concluded. We will most likely learn from the *Upjohn* and *PMA* cases whether FDA has the statutory authority to summarily remove drugs from the market. I see nothing to be gained by FDA and other manufacturers litigating the same questions in federal courts all over the country.

Another possible method for resolving these effectiveness controversies is exemplified by a situation in which my company was involved. One of the earliest NAS reports opined that an inhalation therapy drug, marketed by Abbott, was ineffective. Although this was not a major product, it was one that we firmly believed to be effective and useful, and there were a substantial number of practitioners who were very devoted to the use of the drug. We notified

FDA of our sincere belief as to the effectiveness of the drug, and that we would vigorously oppose any premature attempt to withdraw approval of the NDA. Although there were many years of successful clinical experience with the drug, we requested time to conduct up-to-date clinical studies to prove its effectiveness. FDA took no action while the clinical studies were being conducted. As a result of extensive, controlled clinical studies, it began to appear that we could not prove that the drug was any more effective for its intended purpose than saline or water. Although the studies were not finished, when this became apparent, we notified the FDA, voluntarily withdrew our NDA and immediately ceased marketing the product.

Thus, by allowing us sufficient time to set up and conduct the always difficult controlled clinical studies, and by allowing sufficient time for those studies to become meaningful, FDA was able to avoid the distinct possibility of litigation over the withdrawal of the NDA. All of this occurred within the space of a year, a much shorter time than it would have taken to conduct litigation. In like manner, I would hope that if those clinical studies had shown that the drug was effective, that FDA would have withdrawn their proposal to revoke the NDA.

Evaluation Needed

In conclusion, the extensive work of the NAS in the Drug Efficacy Study was a major scientific accomplishment in the always difficult area of evaluating the effectiveness of drugs. We should be implementing this endeavor by quickly removing from the market those drugs on which there is agreement that they are not effective. On the other hand, I believe we should be willing to submit to a hearing those scientific controversies where there is a genuine difference of opinion as to the effectiveness of a drug. I would suggest, then, that we should all take another long hard look at the road we are presently following to see if the positions of the FDA and of the pharmaceutical industry are really in the best interests of all concerned in our attempts to implement the outstanding work of the NAS Drug Efficacy Study. **[The End]**

FDA's Intensified Drug Inspection Program

By IRWIN B. BERCH

Mr. Berch Is Director of the Philadelphia District, FDA.

THE OBLIGATION OF EXCELLENCE, the theme of today's meeting, is particularly fitting to discuss efforts of the pharmaceutical industry to improve the quality of products which play an important role in the health and well-being of today's consumers. The continued theoretical and applied research leading to development of pharmaceutical agents is a true reflection of creative endeavor. This morning I shall discuss steps that we in government are taking to insure that the benefits accrued through research are transmitted to the patient without diminution in quality. The Intensified Drug Inspection Program, or IDIP, was designed to correct conditions which have detracted from the excellence of some products. Recently, the IDIP approach has been studied with renewed interest by the food industry in connection with pending legislation, because it appears to offer a meaningful solution to consumer protection problems without the high costs of continuous inspection.

At present, the IDIP is one of the major workloads carried out by our field staff, requiring about one-third of our available inspection manpower during the past year. Passage of the Kefauver-Harris Amendment in 1962 established the legal requirement that failure to manufacture drugs in accordance with Current Good Manufacturing Practices (GMPs) would deem them to be adulterated. Regulations were adopted in 1963 defining Current GMPs; a proposed revision of this regulation has recently been published, and comment by the affected industry is currently under review.

Despite passage of the Amendment, there was mounting concern over the continued failure by many drug manufacturers to comply with the new requirements, and over the continued presence on the market of subpotent and otherwise improperly compounded drug preparations. Drug recalls continued to increase. Several alternative enforcement solutions were considered and evaluated, including continuous inspection, licensing of manufacturers, and extending batch certification authority to all potent or life-saving prescription drugs. Because of cost considerations, as well as the need to seek new statutory authority to implement such programs, we adopted another alternative, the intensified inspection. This was made possible only by reexamining all of our priorities and reprogramming the necessary resources to carry out this work.

Initiating the Program

The IDIP program was instituted July 1, 1968 with the avowed objective of bringing firms into compliance or taking the necessary regulatory steps to keep the firm's products from reaching the patient. The IDIP concept envisions that a qualified inspector, or inspection team, will remain with a drug manufacturing firm long enough to thoroughly evaluate the firm's operations, to pinpoint deviations that may exist, and to monitor corrective action until there is reasonable assurance that the firm is operating in compliance with Current GMP Regulations. Constructive suggestions for resolving problems are offered by the inspector, but the firm itself must bear responsibility for decisions leading to corrective action. If the firm is unwilling or unable to comply within a reasonable period of time, the inspector is required to document the shortcomings as a basis for initiating regulatory action. The program presently extends coverage to all manufacturers of prescription drugs in dosage form, and to related firms who provide contract services such as laboratory analyses, custom packaging and labeling, custom grinding, etc.

The new intensified inspection has resulted in several changes from the traditional FDA approach. Because the program is designed to secure compliance by all available means, greater emphasis has been placed on voluntary compliance techniques. These are more flexible, and each of our field districts has explored new and innovative ap-

proaches to meet and deal with compliance problems. Some of our districts have concluded that weaknesses exist in management planning, and they have offered to review the firm's Current GMP policies and operating procedures for the purpose of recommending changes designed to minimize the risk of releasing defective products.

By far, the most significant change in our voluntary efforts has been in the field of communication. This begins with a pre-IDIP conference in which the District Director meets with top management of the firm involved and discusses the forthcoming inspection, procedures to be employed, channels of communication to be utilized, reporting methods, and scheduling details. In addition, most of our districts regularly hold interim conferences with the firm's management as problems arise, and some districts schedule post-IDIP conferences to review progress achieved and to make long-term recommendations for continued improvement. Some of our districts have conducted in-plant seminars at the beginning of the IDIP to acquaint supervisory personnel with the nature and objectives of the inspection. These seminars are an extension of our Current GMP workshops and regional seminars, and provide an opportunity for operating personnel to become better acquainted with the inspectors and the current rules under which they operate. Some firms have reciprocated by presenting seminars or briefings to FDA personnel to acquaint them with duties and responsibilities of major operating units, the manner in which the quality control unit functions, and the firm's own zero-defects program. Needless to say, the rapport established can go a long way toward promoting mutual understanding and voluntary compliance.

Program Objectives

Once the inspection has started, communicating our findings is essential to the success of the operation. Wherever possible, problems are immediately called to management's attention during the course of the inspection to bring about immediate voluntary compliance. A written report of observations by the inspector is given to the firm, and the district office periodically furnishes management with a list of any items which are deemed to constitute significant deviations from Current GMP Regulations. Part of the IDIP is devoted to

acquainting industry with inspection techniques we employ and encouraging them to engage in self-regulatory and self-inspection programs.

In carrying out our inspection responsibilities we all recognize that the use of terms such as "adequate" and "suitable" in the regulations can lead to differences in subjective interpretation. This problem has been extensively discussed within FDA between our headquarters and field personnel. As a result, guidance has been provided to all of our district personnel to insure that uniform interpretation is made in classifying findings as significant deviations from Current GMP requirements. This guidance has been incorporated into training programs for field personnel, both inspectors and field scientists, who also participate in evaluation of analytical and microbiological aspects of the inspection.

In seeking to promote excellence in the pharmaceutical industry and the products which they produce, we must rely upon the excellence of the people assigned to carry out the inspection aspects of the IDIP program. In furthering this objective, our field districts have materially increased the advanced training of our personnel, with special emphasis on subjects such as statistical quality control, drug technology developments, newer laboratory instrumentation, and employee motivation. To provide for continued improvements in program management, our Philadelphia District has established a new academic curriculum, a Master of Science program with specialization in Pharmaceutical Quality Assurance Management. This special interdisciplinary program was set up at Temple University by our Science Advisor, Dr. Murray Tuckerman of the pharmacy school, and two initial enrollees are currently undergoing a year's training in the Departments of Pharmacy, Medicine, Law and Business. Next year, this program will be open to both industry and government representatives, and should help furnish program managers who are urgently needed by both groups. We hope that similar courses will be established by other universities.

In carrying out our IDIP, we have not overlooked the role which can be played by state officials. The program is actively supported at the state and local level. However, very few of the states have sufficient manpower or resources to participate in the longer inspec-

tions envisioned by the IDIP. Instead, each of our districts and their state counterparts have determined the areas for best utilization of state input. Most states presently receive copies of post-inspection letters listing significant deviations from the Current GMP regulations. Some state officials are participating in pre-IDIP or interim conferences with plant officials. In the Philadelphia District, we have found these joint efforts to be very helpful in securing desired compliance, particularly for firms whose activities are concentrated within a given state, even though federal jurisdiction also exists.

Preventive Activities

To date, a total of 228 inspections have been initiated, and 106 of them have been terminated as being in compliance. Legal actions have been instituted against two firms. A total of twenty-five inspections of commercial testing laboratories have been initiated, with eleven of them terminated as being in compliance. This does not tell the whole story. We have seen a marked shift in emphasis toward preventive steps designed to minimize the risk of producing violative products, rather than to rely on the laboratory to catch errors before products leave the plant. Many firms have made significant and costly improvements in facilities and personnel, and some marginal operators have become convinced that they cannot comply with the regulations and have discontinued manufacturing operations. From a statutory point of view, there are two parameters of significance in evaluating progress under the program: one deals with the manufacture of drugs under conditions defined as Current Good Manufacturing Practice, and the other deals with the ability of finished products to meet established or claimed standards of acceptable quality.

To evaluate changes in the condition of an establishment, we have an experimental program underway—the Plant Evaluator, or PEV System, suggested to us by a management consultant firm. This system is designed to make industry-wide measurements of important elements at the start and finish of the inspections. Preliminary data indicates a very significant trend toward improved compliance. Although data on a nationwide basis on finished product examination is not yet available, the Philadelphia District has made an extensive

review of its data for the first year of IDIP operation. Surveillance samples were collected and examined from 20% of all batches produced. Results of analysis indicate a very significant improvement, with a 46% decrease in the batch defect rate. In addition, the fiscal year 1969 showed a reversal in the upward trend of nationwide drug recalls, with 699 recalls of defective drugs for human use compared with 722 the previous year.

Evaluation

We believe the Intensified Drug Inspection Program is working well, although budgetary restrictions will not permit completion of the program within the two-year period originally projected. In general, the program has been favorably received by industry. The industry representative on today's panel can provide a better insight on this reaction. We do not view our program accomplishments with complacency. Technological developments, changes in compendial requirements, and new and better understanding of factors affecting biological availability all add to the problems of industry and government, and the quest for excellence must continue. **[The End]**

SECRETARY'S COMMISSION WARNS OF PESTICIDE DANGERS

In its final report, the Secretary's Commission on Pesticides and Their Relationship to Environmental Health has recommended a drastic reduction in the use of pesticides. The commission warned that pesticides may reduce the ability of plants to produce oxygen. The comprehensive report stressed the need for more knowledge of the hazards associated with pesticide usage. Dr. Emil M. Mrak, former chancellor of the University of California at Davis, is the chairman of the commission.

Secretary of Health, Education, and Welfare Robert H. Finch said that certain measures would be taken to implement the recommendations in the commission's report. A clearinghouse for pesticides and a permanent Pesticides Advisory Committee will be established. An HEW task force will be appointed to improve program operations. In addition, a new interagency agreement will be negotiated to establish operational authority. Other action will be aimed at improving industry testing to detect hazardous effects of pesticides.

Secretary Finch said that HEW must have clearly defined authority to intervene against registered uses of pesticides deemed to be hazardous to the health of man or other living organisms.

Revised Good Manufacturing Practice Regulations

By ROBERT W. JENNINGS

Robert W. Jennings Is Associated with the Bureau of Compliance, FDA.

THE THEME OF THIS CONFERENCE is "the obligation of excellence." To meet this obligation, it is appropriate that we attempt to improve our participation in the rapidly changing world of manufacture, processing, packing or holding of drugs that are essential to good medical care. Both the Government and the pharmaceutical industry are responsible to the large population that comprises the deserving people of our country.

The revised good manufacturing practice regulations that will be discussed in this drug workshop are not in themselves entirely new, and represent many hours of conferences and hard work by numerous persons. They encompass many currently accepted aspects of manufacturing practices that were initiated, developed and polished over a number of years by frank discussions between Food and Drug Administration (FDA) manufacturing control groups reviewing new drug applications, and industry representatives visiting Washington in support of applications submitted by their firms. Neither should we forget industry conferences, cooperative workshops, or helpful hints of Food and Drug Inspectors during establishment inspection. These conferences or discussions were held between individuals known to be soundly educated and experienced in the varied fields of drug manufacture. Through such direct communication, many have contributed a wide range of ideas toward good drug manufacturing practice.

The revisions now proposed with respect to drug manufacturing practices are merely another step to strengthen and make more

specific what might be termed "minimum standards" for drug production. I say this knowing that there are members of industry who go beyond the present regulations pertaining to current good manufacturing practices, and who will meet or surpass those now proposed.

I can recall an instance many years ago when I was a Food and Drug Inspector, routinely visiting drug manufacturers, both large and small. In one instance, a drug manufacturer who distributed a product prescribed for heart patients was supplying drug outlets with a tablet nine to ten times more potent than the label indicated. His primary mistake, if one can regard it as such, was the absence of both raw material and finished product assay. The philosophy, of course, was that double checking of component weighings and other aspects of manufacturing procedures would produce a drug of adequate quality. That was many years ago; except for underground operations, this type of drug manufacture is rarely encountered. Obviously, the firm, no longer in existence, did not believe in the "obligation of excellence."

If we are to take the theme of this conference to heart, we can agree upon the principle that a drug manufacturer or distributor should assure that his products are safe and effective before they are permitted distribution. Without these characteristics, they cannot provide the miraculous and sometimes life-saving recoveries attributable to modern medicine. With such agreement, there is established a common ground upon which all of us can meet. Hence, I believe that this Drug Workshop will be successful.

The proposed regulations deserve, and are receiving, close review by all persons affected by or interested in them. The Food and Drug Administration has received comments and criticisms from individuals, trade groups and drug manufacturers. These communications are welcome, and certainly there is a need to discuss major points of interest when a document of this importance is to be promulgated. When both the pharmaceutical industry and the FDA, as a regulatory agency, know and understand each other's problems, a meaningful and acceptable regulation can be written in final form. It is said that FDA has the responsibility to assure the safety and effectiveness of the drugs supplied to the people of our nation. However, it is equally important and incumbent upon the pharmaceutical manufacturers and distributors to consider the interest of consumer protection and establish for themselves excellence in their chosen business.

Internal Problems

To indicate that FDA has taken time and effort to prepare a proposal that is intended to provide workable guidelines for drug manufacture, processing, packing and holding of such articles, I would like to invite you to hear of some of our internal problems in devising modifications that seemed, at least at the time, suitable to the document we are discussing. For instance, in the definition of "materials approval unit" (Sec. 133.1(d)(7)) the words "packaging components" were substituted for the word "container" to broaden the burden of responsibility of the materials approval unit. Under laboratory controls (retention of records, Sec. 133.11(h)) the phrase "except for stability data as provided for by Sec. 133.13(f)" was added to remove conflict between this paragraph and the newly devised Sec. 133.13(f) which provides for retention of records of expiration dates for periods assigned to batches of drugs. Careful consideration was given to definitions for terms such as "component," "batch," "lot," "active ingredient" and "strength." There are added general requirements for raw material control, including examination of shipping containers for damage, as well as additional tests, all of which were steps intended to add clarification, strength and specificity to the regulations being discussed.

Let me assure you that FDA is fully aware, from comments received as well as from publications concerned with the proposed revisions of the regulations, that the regulations do contain controversial aspects, such as expiration dating on drug labels and the issue of biological availability as it pertains to a drug. Some of these may well deserve additional conferences between those affected and FDA. We know that the drug manufacturers, practicing physicians, pharmacists and raw material suppliers, as well as others, are vitally interested in these regulations. This is understandable, because once they are promulgated, both FDA and industry must live with them. Let us consider cooperation, discussion, and most importantly, understanding, with respect to the more important provisions of the proposal.

Many years ago, I discovered that one of the large manufacturers of drugs had, through their Technical Director, established an outline of pharmaceutical control. In scanning it the other day, I noted that, basically, it differed little from the goals intended by the current subject regulations and proposed revisions. They had established

criteria for formulations of control, developed an organization establishing a Chief of Control, laboratory and product departments. In their methods of operation were included production facilities of control for raw materials, production orders, material tickets, bulk release instructions, batch size information, and packaging and labeling instructions, all with detailed descriptions and directions. The firm had not ignored laboratory facilities of control with respect to either equipment, raw materials, finished products, samples, records, assay methods, label control or stability.

Flexible Standards

As the years have passed, this firm and others have modified, corrected, improved, refined and developed far more sophisticated procedures. However, have we advanced so far that we can live with complacency and ignore progress and new challenges in a rapidly changing, advancing struggle to produce better new and old drugs for the protection of public health? I doubt it. I have enough faith in our Government and the pharmaceutical industry that serves this nation to believe that the desire of both is to establish flexible drug manufacturing practices that will revise and strengthen those that are now employed. In fact, the current good manufacturing practice regulations proposed in early 1963 encountered comment and discussions reminiscent of today—but none reflected a lack of desire to produce reliable drugs.

Basically, the reason for the currently proposed revisions is to respond to a constant responsibility to the drug consumer and to the protection of public health by offering additional guides for drug manufacturers and distributors to observe in current good manufacturing practice. The proposed criteria essentially follow an updating of the same basic pattern established by the previously mentioned pharmaceutical firm of fifteen years ago.

Very briefly, the proposed document is concerned with:

(1) Buildings and equipment, including laboratory and storage facilities, suitable to provide for adequate sanitary manufacturing and storage necessary to production of quality drugs.

(2) Personnel responsible for manufacture and control of the drug, and a flexible requirement that such persons are adequate in number and have backgrounds and capabilities that assure that their particular jobs are understood and hence well done.

(3) Raw materials used in the manufacturing and processing of the drugs, and steps that should be taken to assure controlled release and protection.

(4) Master-formula and batch production records adequate to establish a history of manufacture, as well as records which, hopefully, will prevent in-plant errors and offer a chance for prompt investigation and discontinuance of manufacture in the event of emergencies.

(5) Production and control procedures to provide for protection of the integrity of the drug.

(6) Testing, handling and storing of product containers, as well as controls for packaging and labeling operations.

(7) Laboratory controls to be employed, including sample requirements.

(8) Provision for finished-goods warehouse control distribution records.

(9) Stability to ensure the integrity of the product at time of use—components, composition, physical characteristics, and the use of related conditions of storage on the drug label are not ignored.

With respect to the stability requirements as proposed in the regulations, much attention has been given expiration dating, rate of drug absorption and the biological availability of a drug product. Aging processes, whether they take place in the manufacturers' warehouses, distribution points, consigneees' storage facilities or pharmacists' prescription shelves, influence the quality of any drug product. Does a passable assay for potency reflect an absence of other changes, after aging? If found to be true in one instance, what is the potential that the same drug, manufactured by a different firm, using other inactive ingredients or employing a modified though acceptable method of manufacture, follows the same aging pattern? What about methodology? Many comments we have received deserve serious consideration.

At the moment, the revisions propose that stability be determined in relation to specifications necessary to assure reasonably uniform rates of absorption and biological availability during the dating period. Labeling is to bear an expiration period for solutions or suspensions prepared from products marketed in dry form. An expiration date must assure integrity of the drug until that date, but only if related conditions of storage are met.

As we, the Government and pharmaceutical industry, react to our continuing "obligation to excellence," expiration dating for all drugs will someday be with us, and I am sure we will not find it too difficult to survive when that time comes. Expiration dating for all drugs is not only a challenge, but a commendable goal to attain. Man finally reached the moon; some day expiration dating of all drugs will become a reality. It can be done, and will provide a satisfying pride in achievement when accomplished. Neither Government nor the pharmaceutical industry can ignore its need. The FDA is willing to listen to and cooperate in resolving problems associated with specific drugs or groups of drugs. Resolutions can be found.

What the FDA has proposed strengthens guidelines for drug manufacturers and distributors to observe in current good manufacturing practice. These criteria can be properly implemented by cooperation in the context of the law, regulation and good business administration.

It is my belief that industry is interested in: (1) protection of public health, (2) assurance of good drug quality, (3) assurance to the consumer that their drug is as claimed with respect to both potency and usage, (4) establishing and maintaining prestige with the consumer and members of their own industry, and (5) operating within the laws applicable to their business.

I am not a lawyer and have offered no opinions concerning legal merits or controversy on the proposed regulations. I am sure there are able lawyers in both Government and industry who can resolve problems of this nature. I stand firmly behind my conviction that both FDA and the pharmaceutical industry have a responsibility to the drug consumer that can only be attained by the marketing of good pharmaceuticals. FDA and pharmaceutical industry cooperation and mutual respect are important keys to fulfilling this aspect of duty to serve the interests of public health.

Controversy, conferences, discussion, problems placed face up on the table—yes. But for the FDA or the pharmaceutical industry to fail to cooperate and seek constructive resolutions which will result in promulgation of improved drug manufacturing practice regulations, with which we both can live—no. Abandonment to token improvements will not result in a measurably better drug supply. It can only reflect lack of a contribution toward our "obligation of excellence."

[The End]

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