VOL. 32, NO. 1 JANUARY 1977

Food Drug Cosmetic Law JOURNAL

Additional Papers Presented at the 20th 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.

The FOOD DRUG COSMETIC LAW JOURNAL is published monthly by Commerce Clearing House, Inc. Subscription price: 1 year, $35; single copies, $3. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

January, 1977
Volume 32 • Number 1

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

FOOD DRUG COSMETIC LAW JOURNAL

Table of Contents . . . January, 1977

Volume 32 Number 1

FOOD DRUG COSMETIC LAW JOURNAL

Editorial Advisory Board

REPORTS

TO THE READER

Twentieth Annual Educational Conference of the FDLI and the FDA. The following papers were presented at the 20th Annual Educational Conference of the Food and Drug Law Institute and the Food and Drug Administration, which was held in Washington, D. C. on December 7th and 8th, 1976.

The impact of the Bureau of Veterinary Medicine on CGMP regulations because of its reliance on three sets of those regulations—pharmaceutical products, medicated premixes and medicated feeds is the subject of *John R. Markus'* article. Mr. Markus is acting chief chemist for the Bureau of Veterinary Medicine, Food and Drug Administration. His article "CGMP Regulations for Animal Drug Production" begins on page 5.

In the article beginning on page 9, "Informational Anemia or Informational Overload—What Consumers Want and Need to Know to be Protected," *Johanna T. Dwyer, D. Sc.* emphasizes the need of the public sector to adopt a vigorous approach in order to foster more healthful food consumption practices. While categorizing consumer interest in food nutrition, he also brings into focus confusion wrought by regulatory classifications. Dr. Dwyer is director of the Frances Stern Nutrition Center and Associate Professor for Tufts University Medical School and Harvard University.

"A Compliance Program and Enforcement Activities for Marketed Drugs" provides an approach to the current compliance program in relation to marketed drugs. This is the direct result of experience with the DESI Program and the influence of the *Hoffman-LaRoche v. Weinberger* case. Written by *T. E. Byers*, Associate Director for Compliance, Bureau of Drugs, Food and Drug Administration, the article begins on page 16.

"Individual Product Licensure," by *M. J. Schiffrin, Ph.D.* presents various policies regarding drugs as promulgated by the Food and Drug Administration. Dr. Schiffrin is Assistant Vice President of Hoffman-LaRoche, Inc. His article begins on page 21.

The article by *Gerald B. Guest, D.V.M.*, beginning on page 27, discusses the problems of bacterial drug resistance in animals as it relates to public health. Dr. Guest is Special Assistant to the Director, Bureau of Veterinary Medicine, Food and Drug Administration and his article is titled "Antibiotics in Animal Feeds: Current Status."

In "Section 514.111 of Title 21", *Ann B. Holt, D. V. M.* emphasizes the importance of careful review of Section 514.111 before designing protocols or initiating studies to support the efficacy of a new animal drug when developing a new product. Dr. Holt is Acting Director for the Division of Drugs for Ruminant Species, Bureau of Veterinary Medicine, Food and Drug Administration. The article begins on page 31.

Jacob E. Mosier, D. V. M. is the Head of the Department of Surgery and Medicine, College of Veterinary Medicine, Kansas State University. In "The Role of the Advisory Committee" he discusses the purpose of the advisory committee which has been

to render judgment as to the issues involved in antibacterials in animal foods based on presentations given, discussion generated by the presentation, and discussions generated by those making presentations with consultants and interested parties. The article begins on page 35.

Robert P. Giovacchini, Ph.D., Vice President of Corporate Product Integrity, the Gillette Company, states that the evaluation of safety of cosmetic ingredients could be achieved by developing a review program which follows the principles of scientific integrity and open reporting of scientific data and the rationale which lead to a particular determination. His article "The Cosmetic Ingredient Review Program" begins on page 40.

Martin Greif, Assistant to the Director of Division of Cosmetic Technology, Bureau of Foods, Food and Drug Administration, reviews some new approaches undertaken by the Food and Drug Administration to improve the Agency's cosmetic establishment inspection program. His article "Cosmetic Establishment Inspections—New Approaches" begins on page 44.

Vol. 32, No. 1 January, 1977

Food·Drug·Cosmetic Law
Journal

CGMP Regulations for Animal Drug Production

By JOHN R. MARKUS

Mr. Markus Is Acting Chief Chemist of the Bureau of Veterinary Medicine, Food and Drug Administration.

REGULATIONS expressing Current Good Manufacturing Practices (CGMPs) exist for drugs used in three (3) types of animal preparations, namely, finished pharmaceuticals, medicated premixes and medicated feeds. I could give a history of the whys, wherefores, etc. of each set, but I do not think that is necessary. You, the industry, and we the regulators know them very well and their value. We can infer that the CGMPs are quality control measures: measures that, if followed, will assure a quality product.

Very few of us realize, though, the impact the Bureau of Veterinary Medicine (BVM) has on CGMP regulations. Many of us are of the notion that the Bureau merely approves applications for new animal drugs or provides information to industry.

Animal Drug Area

The Bureau, however, in conjunction with the field operations of the Agency administers the Federal Food, Drug and Cosmetic Act and related regulations as promulgated in the animal drug area. The field units do the "leg work" conducting inspections. When violations occur or are uncovered, the field units recommend regulatory action to the Bureau for appropriate enforcement of the reg-

ulations. The Compliance Division of the Bureau reviews the recommendations. If the Division concurs in the action, they have recourse to regulatory letters, prosecution or injunction. Those actions prepared for litigation are forwarded through General Counsel.

Drug Dosage Products in Violation

An example of a recent regulatory action was an injunction based on CGMP violation secured against a firm in the Midwest. The firm was producing finished drug dosage products in violation of CGMP regulations.

In relation to the approval of new animal drug applications (NADAs), the applicant is required to attest to his conformance to the CGMP regulations as required by the Federal Food, Drug and Cosmetic Act and corresponding regulations. If, for any reasons, information that is related to the CGMPs and submitted by the applicant is not considered adequate, an inspection of the facilities and manufacturing procedures may be called for to verify conditions. Deviations from CGMP regulations may be the basis for disapproval of the pending NADA. The Bureau of Drugs (BD) also considers compliance in a similar manner in the review of human new drug applications.

CGMP Regulations

BVM relies on three sets of CGMP regulations—those for finished pharmaceutical products, medicated premixes and medicated feeds. Presently two of the three sets of regulations—finished pharmaceutical products and medicated feeds—are under revision or have been revised. These revisions have been necessitated because of the new trends in pharmaceutical and industrial technology and the general need for updating manufacturing operations. The revisions, which reflect practices considered implicit or desirable requirements, are in keeping with the context of the word "current." Such revisions will only make the regulations more meaningful.

No action has been contemplated, at present, on medicated premixes. The CGMP regulations for medicated feeds can easily be addressed. They were revised as proposals in the *Federal Register* of August 8, 1975. Following a long period of comments and revisions, the final order expressing the final revised version of the CGMPs was published in the *Federal Register* on November 30 of this year. The effective date of their implementation is December 30, 1976.

Medicated Feed Regulations

Some of the significant changes in the revised Medicated Feed Regulations are:

(1) A change in format. The first paragraph in each section describes the significance of the section; the second paragraph establishes the criteria.

(2) A system of "quality control" (based on inventory control) that best reflects the type of product.

(3) Changes in annual assay requirements on the final products. The new requirements are:

(a) Three samples for each medicated feed (subject to FD 1800 approval) containing a drug or drug combination used.

(b) At least one sample of medicated feed (not subject to FD 1800 approval) containing a drug or drug combination.

(NOTE: In case of the combination of drugs in either product, only one of the drugs need be subject to analysis each time, provided the drug tested is different from the one(s) previously tested.)

(4) Controls of possible drug carryover.

(5) Provisions that will in effect consider non-medicated feed (produced in the same plant as medicated feed) adulterated should non-adherence be found for the medicated feed.

The Food and Drug Administration (FDA) feels that the revised regulations more accurately reflect the practice and technology actually existing.

As for the umbrella CGMP regulations for finished pharmaceuticals proposed in the *Federal Register* on February 13 of this year, comments are still under review. We, in BVM, since we have an impact in this area, commented on the proposal and have submitted them to the BD, who have the prime responsibility for preparation of the final order.

Inspections of Firms

Since veterinary pharmaceutical products are produced in the same manner as human pharmaceutical products, we, in BVM, feel our ideas and concepts are compatible with that of the BD. With

minor exceptions in the proper areas, FDA's field investigators conduct their inspections of firms—both human and veterinary—under the same context of the CGMP regulations. Both BVM and BD compliance units advise each other of problems that are commonly encountered. The commonality of the regulations resulted in the addressing of the CGMPs for both human and veterinary drugs.

The big question I assume in your minds is "when will the final order be published?" The BD, which is responsible for the development and control of the issuance of the regulations, indicated the intention is to publish the final order "sometime" after the first of the next year. No firm date was given. Those of you who have read the Gold Sheet and other publications and who have made comments know the issues and areas of concern. At present, how the issues will be resolved is unknown but they will be one way or the other.

No matter what the outcome, there will be no let up in the enforcement or use of the CGMPs. Life still must go on! Product awareness and, most importantly, consumer protection still dictates adherence to these practices. **[The End]**

FDA PROHIBITS THEOPHYLLINE AS SINGLE-INGREDIENT OTC PRODUCT

Over-the-counter drug products containing theophylline as their single ingredient are subject to immediate regulatory action, the Food and Drug Administration has announced. The FDA's Panel on OTC Cold, Cough, Bronchodilator and Antiasthmatic Panel had recommended allowing theophylline to be made available as a single-ingredient OTC product, but subsequent data indicates that the suggested therapeutic dose may be toxic to some people. The additional data indicates that the safe and effective use of the substance requires careful dosage titration based on theophylline serum concentrations. There are remarkable differences in the rate at which theophylline is metabolized, according to the Panel's studies. The later study indicates that clinical titration should be based on measurement on theophylline serum levels, because serious toxic effects such as seizures and death can result from excessive serum concentrations without earlier signs of lesser toxicity.

The FDA is in the process of extensively reviewing the use of theophylline in OTC and prescription drug products, both as a single ingredient and in combination. The agency has recommended that, pending announcement of results of the view, there not be any proliferation of products containing the substance.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,793

Informational Anemia or Informational Overload— What Consumers Want and Need to Know to be Protected

By JOHANNA T. DWYER, D.Sc.

Dr. Dwyer Is Director of the Frances Stern Nutrition Center and Associate Professor of Tufts University Medical School and Harvard University.

The Need to Widen the Focus of Consumer Protection

THE QUESTION OF WHAT THE CONSUMER needs and wants to know in order to be protected is a good one. It widens the focus of consumer protection from one based solely on legalistic definitions and regulations to a broader emphasis on consumer knowledge and practical applications of this knowledge base. And, it forces us to remember that, while we are trying to *protect* consumers against false and misleading advertising and clear hazards resulting from unhygienic or otherwise harmful food supplies, we are also trying to *foster* healthful food consumption practices. This will involve encouraging consumers to demand the mix of foods which best meets their needs for nutrients. This is what nutrition education is all about. I was glad to read, in the latest *Forward Plan for Health,*[1] of an increasing emphasis on the part of the Department of Health, Education, and Welfare to foster more

[1] U. S. Department of Health, Education, and Welfare, Public Health Service. Forward Plan for Health FY 1978-82, U. S. Government Printing Office, Washington, D. C. 1976.

healthful food consumption practices. Obviously, this is not a task simply for health professionals, nutrition educators and dietitians to tackle.

All those whose activities have an impact on nutritional status, be they in the public, private or voluntary sectors have a role to play here, a very vital one. I know that we are often so overwhelmed with the attempts we make to accomplish our other objectives that we often fail to understand the relevance of this priority to what we are doing.

We would be well served if the public sector adopted a more vigorous approach to fostering more healthful food consumption practices. This should be done not only by regulation and enforcement, which admittedly has done a great deal, but also by more vigorous efforts in terms of consumer health education related to nutrition. More about this later.

Why People Want to Know About Food

Consumers are interested in a lot of different things about food and at least three different reasons may be cited for this interest.

First of all, they believe that their health may be affected by whatever substance it is that they are inquiring about. I call these the "health" reasons. They believe that if they knew and acted upon these facts, there is a high probability, on the basis of existing scientific evidence, that they would be better off or at lower risk from the standpoint of poor nutritional status. Unfortunately, many health concerns are not based on scientific fact. These misconceptions are also stated as health reasons, at least by consumers.

Demystification and Curiosity

A second reason consumers often want to know certain things is because they are curious. They feel that they have the right to know this or that bit of information, either to demystify the food supply or that they have a right to be informed before they consent to eat a particular food. These types of reasons I call the "demystification" reasons.

Wise Buying

Thirdly, there are consumer reasons. Consumers feel that they have the right to know and want to know, not only about the nutrients in foods and about other substances in foods such as lactose, cholesterol and additives, but also about the amount of energy which went into making the food and so forth. Some of these factors may have little or no

effect upon health, although this does not mean that they are not important for some other reason. For example, people want to know how much of the protein in the chicken dinner is chicken, how much soy, and so forth—for price, if no other reason.

Finding Out

It is fairly easy to find out what consumers want to know. One way is to collate their actual questions. Another is to interview a stratified random sample of persons in the population.[2]

Consumers' Need to Know Is Not Solely for Health Reasons

All too often the food industry and health professionals assume that consumers have no business in expecting responses to queries about what they do not *need to know* for health. In my view, consumers have a right to know whatever they want to. The food producer can either reveal or not reveal whatever it wishes outside of mandatory disclosures. It may be expensive to come up with answers for some of the odder requests, but in my view, the industry as a whole has more to gain and less to lose from an open sort of posture. I am not entirely sure that the frequent argument against disclosure of "giving away trade secrets" is sound enough for the great majority of these requests. More frequently, lack of information or the expense involved in finding out may be behind such statements.

Difficulty in Finding Out Best Ways to Give Consumers What They Need to Know to Foster Healthful Food Consumption Practices

Whenever we approach the issue of what consumers *need* to know in order to select a diet which better incorporates demonstrated preventive measures, we come to more uncertain ground. We are still not completely sure about which types of changes will make a difference. And, we do not always know how to motivate consumers to do the things which certainly *do* make a difference.

Consumers, for many reasons, are confused about the measures they need to take in order to best achieve healthful food consumption

[2] Dwyer, J. T. and Alston, E. "Nutrition in Family Life" Food Product Development 10:44 1976.

practices. Some of the reasons reside in the consumers themselves; others arise because the best food classifications for regulatory purposes are not the best food classifications for consumer information and educational purposes.

From my perspective, which is a clinical one, consumers are not clear on the different ways nutrients are available on the market. Even nutrition scientists, who are thought to be "expert" about nutrition, rarely know very much about how foods are classified for regulatory purposes. Thus, a whole parallel structure of homeopathic remedies or "home made" analogues exists for supplying different "doses" of nutrients in foods.

Dosage Levels of Nutrients Encountered by Consumers in the Marketplace

Consumers, for example, encounter nutrients in foods in a whole variety of ways. These include, from highest to lowest, dose-wise:

(1) As medicines, by prescription.

(2) As curative or preventive medicine, or "insurance", over-the-counter (OTC).

(3) Foods for special dietary uses.

(4) Downwardly modified foods.

(5) Foods which have been restored, enriched or fortified.

(6) Ordinary unmodified fresh or processed foods.

Dietary Analogues of These

At least in the consumer's mind, we could draw up a list of consumer's efforts from highest to lowest dose-wise in terms of foods and diets:

(1) Megadoses of vitamins to "cure" various diseases.

(2) Use of vitamin pills and minerals at more moderate levels.

(3) Use of "natural", "organic", "non-processed" or "health foods." Homeopathic remedies such as herbal teas, self-prescribed elimination diets for allergies, etc.

(4) Special self-prescribed diets, such as natural or organic diets, vegetarian diets, reducing diets, elimination of "killer" or "bad" foods.

(5) Use of foods which are believed to be especially healthy, and therefore better or more wholesome than usual foods.

(6) Use of some guide to good eating, food guides, etc.

It is obvious that some of these diets and homegrown efforts—to get plenty of nutrients for these various purposes—make eminent good sense, while others do not. Why is it that this strange potpourri exists? Obviously, it exists for many reasons. Man has eaten for millenia and he has not had nutrition as a science around to impose its peculiar, and admittedly somewhat narrow view about what food is (in terms of nutrients, etc.) for a century yet.

But, I would submit that part of the present confusion lies in the fact that legal definitions of foods and regulatory definitions on governing how foods are to be labeled and advertised may be contributory to the problem. Let me briefly try to explain what I mean.

Consumer Confusions Arising from Regulatory Classifications

From the chemical viewpoint, foods are simply nutrient carriers. The law, however, treats foods as something quite distinct from more concentrated sources of nutrients (where there is less carrier and more nutrient). These more concentrated sources of nutrients are classified as drugs or medicines.

The regulatory definition of foods *excludes* several of the categories we have been talking about—vitamins, minerals and hematinics sold as such, the special dietary foods used only under medical supervision, infant formulas, and alcohol. The regulations govern how such products are sold as well as how they are likely to be advertised. Therefore, the foods left, which are usually advertised over the mass media, are the downward modifications, the enriched, restored, and fortified foods, and ordinary unmodified fresh or processed foods. That means, in terms of "dosage" of nutrients, the lower doses.

Now this may be well and good from the standpoint of regulatory law. But, this means that very few consumers probably know very much about the higher "dosage" nutrient sources which are not as likely to be advertised. It is not that these products are not advertised at all, but it is that they are not advertised in the mass media but rather in professional journals. Even for the scientist (other than the nutrition scientist, who knows where to go to get the facts) it is not easy to find out the facts about these foods and nutrients.

The fact that objective information is not easy to come by on special dietary foods may be another reason why consumers have adopted some of the unusual diets they have. They either do not choose to take their problems to a physician or health professional or they believe that their own remedy is better.

Ways of Providing Consumers with What They Want and Need to Know

I believe that education for more healthful food consumption practices holds great promise. Let me quickly run through the list I have of challenges in 1977 which involve delivering nutrition education and consumer information in non-formal settings; that is, settings outside of the educational system. Non-formal means of education include the mass media, food packages, health care encounters, and many other vehicles of less concern to most of us today.

The implementation of these would at the same time demystify the food supply *and* help consumers to select, if they wish to, a diet which fosters healthful food consumption practices. In order, these measures include:

(1) Conducting appropriate clinical trials to determine the efficacy of nutrients or nutrient combinations available only by prescription, followed up by communication of results to both health professionals and the lay public.

(2) Reviewing the efficacy of various OTC preparations. Again, informing both the scientific and lay community about findings. Development of mass media educational campaigns by the public sector may be effective.

(3) Adoption of universal nutrient labeling and percentage ingredient labeling. Not just on processed foods, but on *all* foods.

(4) Unit pricing.

(5) Labeling for calories, P/S ratios, cholesterol, sodium and potassium.

(6) Listing of food colors by number and food flavors by artificial or natural, by number as well.

(7) Development of a data base for professional access on foods' content (for example, present or absent) with respect to various substances, such as lactose, which cause adverse reactions to food among persons with special dietary needs.

(8) Development of a method of expressing the cariogenicity of various foods rather than simply a statement of concentrated carbohydrate or sucrose content (since dental caries and not sugar is the real problem).

(9) And, above all, development of more vigorous and specific consumer education efforts, by the public sector in particular. These should include development of better guidelines for nutritional claims in the mass media and indeed for all advertising which involves nutritional claims. Better guides to good eating which are intelligible to laymen and really meet the recommended daily allowance (RDA) for *all* nutrients also need to be considered. As you know, since the RDA's of 1973 the Basic 4 do not do this. Finally, the public sector must encourage the development of bias free consumer information and educational materials.

I hope that all of us who are concerned about increasing the level of practical nutrition education of the consumer and providing for more healthful food consumption practices will vigorously debate the pros and cons of these various measures, and act on some of them.

Positive effects can be achieved, at least in my view, by relying on existing government sanctions—that is, by not endlessly extending legislation and the expansion of regulatory and enforcement activities—and by coupling this with a VERY MUCH EXPANDED GOVERNMENT SPONSORED CONSUMER EDUCATION EMPHASIS IN NUTRITION. This sort of education from the public sector would really have some teeth to it, since its purpose would be to influence consumer behavior related to healthy and thrifty food consumption practices, and might even include comparisons between brands. People need to know more clearly than they seem to at present the costs of convenience, what, nutrition wise, they are getting for their money and what the nutrients and other substances in food can and cannot do for their health, whether they be sick or well. Consumers may soon find that instead of suffering from the effects of informational anemia (as some believe they have over the past few decades) they may soon be struggling with the problems of informational overload. But, in the meantime, the food supply will have been demystified and faith in its essential healthfulness restored; thus, greater consumer sophistication will be apparent. Or at least, this is my optimistic view.

[The End]

A Compliance Program and Enforcement Activities for Marketed Drugs

By T. E. BYERS

Mr. Byers Is Associate Director for Compliance, Bureau of Drugs, Food and Drug Administration.

THE DESI PROGRAM has been the key program of the Agency for enforcing the new drug provisions of the Food and Drug Act. During the operation of this program there have evolved certain policies which have finally culminated in the current compliance policy for all marketed new drugs. (The availability of a compliance policy guide covering this activity was announced in the *Federal Register* of September 29, 1976.)

The present policy and program is a result of our experience with the DESI program and is largely influenced by the case of *Hoffman-La Roche v. Weinberger* (U. S. District Court for D. C.). The Court held that if the Food and Drug Administration (FDA) had declared prescription drugs to be a new drug, the Agency could not permit any identical, similar or related product to be marketed without prior approval of a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA). As a result of this decision, we have reaffirmed a position that all products marketed as drugs under the DESI program are new drugs and, therefore, require an approved NDA or ANDA as a condition for marketing. In view of this, we developed the compliance policy guide referred to above and are currently moving to implement it within the priorities established in that guide. The aim of the policy is to develop a strategy to deal on a

priority basis with those drugs which most affect public health and safety, provide equitable treatment for those firms involved and to have a maximum impact on involved products. To accomplish this, we have established various categories and are implementing the program with each category so that all products falling in the category will be treated in the same fashion in order not to discriminate between firms involved. The general tack to assure compliance with the Act within these priorities is to attempt to assure voluntary compliance through the issuance of a regulatory letter to each affected firm and a commitment on the part of the Agency to take appropriate regulatory action, either by seizure of product or by injunction, where voluntary compliance is not forthcoming. Let me assure you that the issuance of a regulatory letter is not an empty threat and we are committed to take appropriate action and, in fact, have been doing so since the DESI program began.

Ineffective Drugs

Let me now turn to our priorities in the current compliance policy regarding this matter. The first priority under the DESI program now established as Category 1 under the compliance policy guide is that covering ineffective drugs. This has been a highly efficient program carried out over the past several years. Under this program as of September 30, 1976, there were 899 drug products named in DESI announcements as being ineffective. 856 products are now in compliance with activities in connection with them resulting in 215 recalls and 2 seizures. There are currently 43 drug products still open, either being followed up, postponed or in litigation. In the case of drug related to those specifically named in DESI announcements we have issued 2,009 regulatory letters affecting 6,078 products. Currently, 5,856 products are in compliance in which 779 recalls and 28 seizures were involved. There are presently 221 products in this related group still open of which 218 were in some form of litigation.

In this activity, the importance of the applicability of DESI notices to identical, related and similar products as announced under Reg. 21 CFR 310.6 is evident. As you recall, our position regarding this applicability was spoken to by the Supreme Court regarding the *Bentex* case. For maximum impact and for sound enforcement of the Act, we shall continue to utilize the related and similar concept.

Bio-Products

The second category in priority implementation of our compliance policy program was the bio-products. That is, those DESI-effective prescription drugs with known or potential bioavailability or bio-equivalency problems. This program was initiated early this year and is scheduled for completion by December 31, 1976. These are the drugs identified in DHEW Publication, No. FDA 76-3009. This category involves approximately 170 drug entities and at the present time 410 drug products have been identified. The field districts have submitted 59 seizure recommendations of which 41 have been approved, 12 disapproved and there are currently 6 pending. Firms involved have made recalls of 30 products. Under compliance Program No. 7332.26 the various field districts were delegated the responsibility for issuing regulatory letters to firms covering this product and carrying out appropriate regulatory actions. In the regulatory letter, affected firms were asked the following pertinent questions:

(1) An estimate of the quantity of the drugs manufactured within the previous 12 months.

(2) An estimate of the size and frequency of shipments within the previous 12 months.

(3) An estimate of the quantity of the product in inventory under the firm's control.

(4) The firm's intention with respect to removal of outstanding stock from its direct consignees.

The time for response, as in the case of other regulatory letters, was 10 days after receipt of the letter. Where there were significant stocks of the drug manufactured remaining in trade channels, we advised that we would require recall to the consignee level. In cases where such corrective action was not promptly undertaken we advised that we were prepared to initiate prompt regulatory action which we have done as indicated by seizure actions filed.

DESI-Related Drug Products

We are currently prepared to move into Category 3 of our enforcement priorities; namely, those drug products which were DESI-related as effective, included in the Top 200 most widely prescribed drugs, but not including antibiotic topical preparations or those drugs covered in Category 1 or 2. We estimate that there are approximately 25 drug entities covered by this Category. This program will be handled similarly to the Category 2 program.

Without going into detail I will list the other categories:

(1) Category 4—Biorelated drugs

(2) Category 5—Other identical DESI-effective prescription drugs

(3) Category 6—Other related DESI-effective prescription drugs

(4) Category 7—DESI-effective prescription topical preparations, both identical and related.

In all of the above categories of priority a "final determination" has been made. In addition to these, however, are the DESI paragraph 14 drugs which are currently exempted from regulatory action to a large extent under Judge's Bryant's order. Under this program, when requirements for protocol have been established by publication in the *Federal Register,* drugs which are subject to the *Federal Register* announcement will be subject to compliance actions under Category 1 priority.

In the case of DESI, less than effective drugs such as possibly and probably effective drugs and those with current notices of opportunity for hearing, compliance activity priorities will be determined by the final determination made for these products. If the drug is deemed ineffective, it will be handled under Category 1. If it is upgraded to effective, it will be handled under the appropriate category depending on the type of the product.

Drugs Subject to Pre-1962 NDAs

Another area of concern is a certain number of drugs subject to pre-1962 NDAs which have not gone under DESI review. We are implementing procedures so that drugs or class of drugs of this type will have an effectiveness determination. When the final determination is made these drug products will be subject to compliance actions as determined priorities established above.

While the intention of this entire program is to establish a single standard for safety and effectiveness of drugs and for marketing conditions for these drugs, the Agency will not approve contracts for purchase by other federal government agencies (DOD, VA, PHS) of any drug subject to this policy which does not have an approved NDA or ANDA that is directly covered by Categories 1 through 7 previously mentioned. If offered for government purchase, such purchase will not be approved in the absence of an approved NDA or ANDA not-

withstanding the fact, that we have not implemented the program in the private sector for all compliance categories.

We intend to vigorously pursue the compliance policy setup in the compliance policy guide to the end that we will remove from the marketplace all products requiring NDAs or ANDAs which do not have such approvals. We trust that this endeavor will be completed within the next 2 years and that it will result in a single standard for the safety and efficacy of drug products which is not dependent on the calendar or availability of resources to the Agency and/or the whims of the regulated industry. Another result will be that we will not find ourselves in the embarrassing position of being ordered by the court to enforce the law or our being manipulated by firms looking for competitive advantage. Most importantly, we trust these activities will result in a reasonable assurance of safety and efficacy of prescription drug supplies for the American consumer. **[The End]**

FDA CONTINUES REGULATORY PROGRESS TOWARD OPEN AGENCY

The progress of proposed regulations to accompany the recently-issued rules on public hearings was discussed in a recent Food and Drug Administration *Talk Paper*. The Agency announced that it will soon issue regulations on consumer petitions, on the issuance of new regulations, and on other Agency responsibilities. The FDA will also continue its issuance of regulations governing enforcement procedures. The new rules will require the Agency to maintain a public calendar of meetings between top Agency officials and non-government persons and of upcoming open meetings. The rules will require that minutes of meetings be maintained for public inspection.

Rules covering recall policy and procedures for pre-prosecution or show-cause hearings have already been proposed, and others setting out criteria for the prosecution of firms or individuals and governing the FDA's policies on publicity and regulatory letters are scheduled for proposal early this year.

Unless specifically closed by the Commissioner, all FDA advisory panel meetings will be open, including deliberative sessions. Meetings may be closed only to protect trade secrets, personal privacy, or legally exempt matters. The Agency also noted that minor changes will be effected in the Freedom of Information regulations.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,812

Individual Product Licensure

By M. J. SCHIFFRIN, Ph.D.

Dr. Schiffrin Is Assistant Vice President of Hoffman-LaRoche, Inc.

ON THE SURFACE, it would appear that we in industry face a relatively easy task today. We have been asked to discuss a new policy set forth by the Food and Drug Administration (FDA). We all know how much easier it is to criticize than it is to create. It is something like building a new type of house. The architect and the builder may have done good professional jobs, yet passersby and those who examine the interior of the house, find it very easy to criticize both the architect and the builder.

Questions Regarding Policy

With this in mind, I will try to restrict myself to facts (as I know them) and questions regarding the policy. In preparing for this meeting, I examined the *Federal Register* notice of September 23, 1976 announcing the availability of an administrative guideline, "Marketed New Drugs Without Approved NDAs or ANDAs". The document was announced as being available for public view or a copy could be obtained on written request. One might ask why the policy was not published in its entirety in *Federal Register* (as was done for earlier policy on June 20, 1975). On the other hand, publication of the availability of the new policy, and the FDA's participation in this meeting must be accepted as evidence of the Agency's desire to make this policy known to all.

On October 5, 1976, I received a typescript of the policy from the Food and Drug Law Institute (FDLI). Two days later, through regular channels, I received the printed version of the document in the form of an FDA Compliance Policy Guide #7732c.08 dated October 6, 1976. It is reasonable therefore to assume that all Agency personnel and the district offices have been made aware of this policy.

Implementation of Policy

This policy guide makes reference to three other documents related to the implementation of the policy. One is D. H. E. W. Publication No. (FDA) 76-3009 (revised 6/76). A copy was in my working file. It is the well-known blue document listing the holders of approved NDAs for drugs presenting actual or potential bioequivalence problems.

The other references were to the programs identified as "C. P. 7332.02 and 7332.26". I did not have these although my file is usually up to date on compliance policy guides. As an experiment, I wrote to the Public Records and Document Center requesting copies in accord with the Freedom of Information Act. A similar request went to the FDA District Office. Through some administrative misadventure or due to the established vagaries of the postal service, (the latter is more likely), I did not get the requested documents within a reasonable time. Being a highly nervous type, I gave up this little experiment and called Mr. Lavender directly. As always, he was helpful and informative, and promised to send me the documents. On November 18, 1976, I received copies of Compliance Program Guidance Manuals #'s 7332.02 and 7332.26.

The first of these, 7332.26, is dated June 1, 1976 and is entitled, "New Drugs (Prescription) Not Covered by Approved NDA's." It bears an immediate implementation date, and is scheduled for completion in the field by September 30, 1976 and in the Bureau by December 31, 1976.

Bio-Problem List

The objective of this program is to remove from the market all products *identical* to those in the bio-problem list which do not have an approved new drug application (NDA). Since this program was completed in the field two months ago, it would be interesting to know how many products have been removed from the market as a result of this program.

The second Compliance Program Guidance Manual (#7332.02) is dated June 28, 1976, and is entitled, "Drug Efficacy Study Implementation". It has an implementation date of July 1, 1976, and is scheduled for completion in the field by September 30, 1977 and in the Bureau by March 31, 1978.

The primary objective of this program is to identify those drug products which are *related* to drugs listed in the Drug Efficacy Study Implementation (DESI) notices. First priority is given to removal

of such products from the market if they are related to drugs which have been found to be ineffective. Second priority is given to compliance for those products related to drugs which have been judged to be other than ineffective.

Category I

This program is listed under Category I of the policy being discussed today. While this category bears the heading "Ineffective Drugs", I suggest that a title such as "Ineffective Related Drugs" might, perhaps, be more descriptive.

From a review of these documents, it appears that:

(1) the policy we are discussing, has to some extent, already been implemented and,

(2) emphasis on related drugs has been underway since July of this year.

While I will speak further on related drugs, it appears that Sec. 310.6 of the regulations requires careful study by all prudent manufacturers. This is a very complex issue, and to the best of my knowledge, related drugs, as described in Secs. 310.3 and 310.6 have not been subject to judicial review.

The policy also made reference to the "Top 200" most widely prescribed drugs which have been DESI-rated as effective. The policy guide states that a list "will be prepared by the Bureau of Drugs when this portion of the policy is implemented". What are the "Top 200", is there such a list, has it been made available by the FDA? All that I could find was an article entitled, "The Top 200 Drugs" in the April 1976 issue of *Pharmacy Times*. This published list was apparently derived from the National Prescription Audit. What relationship it has to the FDA list, I do not know.

The policy under Category III contains the following first sentence, "This priority involves selecting from the "Top 200" most widely prescribed drugs those drugs which have been DESI-rated as effective." Category I (ineffective) and Category II (bio-problems) and antibiotics are not included in the FDA's Top 200.

DESI-Rated Products

In reviewing the top 25 drugs on the published list, I was able to identify 7 DESI-rated products. Eight products appear to have NDAs approved after 1962 and I assume that they are safe and effective.

According to the policy, 4 of the top 25 products will not be considered as they are antibiotics. I assume that antibiotics are excluded because they are subject to certification by the FDA and the Agency is confident that there is no marketing of non-certified antibiotics. Three of the top 25 products have bio-problems. These are in Category II and have a higher priority than the products on the Top-200 list. The remaining three products do not appear to have NDAs.

If my analysis of the top 25 is representative of the entire list of Top-200, there will be about 56 products with DESI notices. After excluding those with less than effective ratings, it would appear that the number of products in Category III is relatively small. Therefore, can one conclude that implementation of this part of the policy will proceed rapidly?

It would be very helpful to know what principles guide the Agency in its policy and what guidelines the Agency will use in the implementation of the policy. Some of the questions which might be asked are:

Determination of Category III

It appears that the determination of Category III will be based first on the number of prescriptions for each product. What will be the second criterion? Will it be the potential for serious harm to patients? For example, is the potential for harm greater for a non-NDA drug used in cancer chemotherapy than it is or an non-NDA cough suppressant?

This is the first time I have made reference to patients. To what extent has the Agency considered patient-benefit in this policy? In the four and a half printed pages of the policy, only a single reference is made which applies to patients—or physicians. On page 2 (Compliance Policy Guide 7132c.08), the statements appear: ". . . the Agency has developed a strategy to deal on a priority basis with those drugs which most affect public health and safety to provide equitable treatment among competing firms, and to have a maximum impact on violative products." Categories I and II are obviously addressed to patient-benefit since they relate to ineffective products and products with bio-problems. What is not clear, however, is how patient/physician interests will be considered in the implementation of Category III.

Patients and Physicians

I am sure that it is part of the underlying philosophy of the Agency to consider the effects of its policies and regulations on patients and

physicians. It would appear to be in the Agency's own interest to emphasize this consideration in all of its publications. In this regard, we ourselves may be faulted. This panel consists of two physicians working full-time at administrative tasks, two attorneys, an expert in regulatory compliance, and a misplaced physiologist. Who here represents the patient and the full-time medical practitioner?

Another element is the number of duplicates for each drug product. Is it the intention of the Agency to use the information it has via drug listing, to determine the extent of duplication of each drug entity? How does the Agency intend to weigh this factor in the implementation of Category III?

How will the Agency treat those drugs which were marketed before 1938? It might be argued that it would be as much in the patient's interests to assure proper manufacture and labeling of this class as it is to review those products marketed between 1938 and 1962. Or put another way, is Grandpa still alive and well? While at first he had to be 24 years of age, he now has to be at least 38 years old to qualify for his exemptions. Should this age limit be raised, lowered, or abolished?

Will any special attention be given to specific instances brought to the attention of the Agency? For example, under the Freedom of Information Act, I received a copy of a letter from a law firm to the Agency, dated November 14, 1975. The firm's client, a major pharmaceutical company, had in 1970 and 1972 brought the Agency's attention to two products marketed without approved NDAs. One of these products is an over-the-counter (OTC) topical ophthalmic preparation. The product contains an active ingredient at a concentration greater than that recommended by the OTC Ophthalmic Review Panel. To the best of my knowledge, the issue has not yet been resolved by the Agency. It would be helpful to know what priority will be assigned in such instances.

Good Laboratory Practices

With reference to priorities and time required for implementation, the Agency policy contains the statement: "With the resources presently available for attaining industry-wide compliance, it is estimated that this goal will take at least two years to achieve." It is our understanding that the Agency has had an increase of 16 million dollars in its budget to be applied for the enforcement of Good Laboratory Practices (GLPs). Since the final GLP regulations have not yet

been issued, and in view of the fact that the policy being discussed today goes to the very heart of the Act itself, it would appear that implementation of the policy would be at least as important as is the enforcement of a regulation yet to be issued. It is my understanding that at present there are about 900 operational inspectors and an additional 600 are being hired for the implementation of GLP. How many inspectors, or what proportion of their time will be allocated to implementation of the policy we are discussing? Also, it would be of interest to learn what portion of the total budgetary increase is intended for implementation of this policy.

The last major element to which I invite your attention is "related drugs." I have examined Sec. 310.3(5)(k) of the regulations which defines "related drugs". From a comparison of the language in this regulation and that in the policy, it appears that at least two new terms have been introduced without definition.

Bio-Related Drugs

The first under Category IV ("Bio-Related Drugs") is "related chemical *and* dosage forms". (Emphasis provided). The second is found in Category VI ("Other Related DESI-Effective Prescription Drugs") which refers to "related chemical dosage forms".

A related dosage form, in my view, might indicate a relationship between all tablets, all capsules, etc. Or will the Agency take the broader position that all solid oral dosage forms are "related". As for "related chemical dosage forms", does this mean dosage forms of related chemicals, or chemical dosage forms which are related and what is a "chemical dosage form"?

I can hear my friends at Law telling me to read the regulation (310.3) more carefully, for it states: "The phrase 'related drug(s)' *includes* other brands, potencies, etc. . . . ." (Emphasis provided). Thus, the original regulation might be considered by some as open-ended and permitting the Agency to add what it wishes to the definition of the related drugs.

In my view, the area of related drugs and how it will affect the implementation of this Agency policy will prove to be one of the most contentious and difficult of problems. The addition of new terms to the definition of related drugs does not appear to aid in the resolution of the problem. Surely, there must be a better way. **[The End]**

Antibiotics in Animal Feeds: Current Status

By GERALD B. GUEST, D.V.M.

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

IN ORDER TO DISCUSS the status of the antibiotics in the animal feeds program, one must first decide just how much background and knowledge the audience has on the subject. I believe that I have two advantages in this regard. First, I am reasonably certain that the individuals here have followed the program closely and most of you know a great deal about it. Secondly, you have had the privilege of hearing Dr. Solomons and Dr. Mosier speak. Since these two factors are operating, I am not planning to retrace the history of the issue. What I do want to do is talk to you about where we are today in the antibiotics of the animal feeds program, to discuss some of the things we are doing at the Food and Drug Administration (FDA) and to offer some thoughts about the future.

First, where are we today? You have heard Dr. Mosier say that his subcommittee will be filing their report with the National Advisory Food and Drug Committee (NAFDC) for the committee's consideration on January 24, 1977. For those of you who may not have attended any of the subcommittee's meetings, let me backup and tell you a few things that Dr. Mosier did not mention. First, he did not tell you how very hard the chairman, the members and the consultants have worked and how much scientific data were presented to them in a short time. You will not find a more dedicated and concerned group. I think that all of us at the FDA, who have worked with the subcommittee, have found it to be a pleasure. One appreciates the kind of good and solid effort that came from the group. The manner in which the individual meetings of the subcommittee have been conducted could serve as a model for this type of endeavor. Credit

for this situation is due largely to Chairman Dr. Mosier. No portion of any meeting was closed. Subcommittee deliberations were conducted with interested persons looking on. I believe that it is safe to say that every person who wanted to be heard was given that opportunity either during the formal open hearing portion of the meetings or during the give and take discussions which were held throughout. In short, I do not think that we or the public could have asked for more from this activity.

Data on Penicillins and Tetracyclines

The subcommittee has reviewed data on the penicillins and tetracyclines and their combination products, as well as information on sulfaquinoxaline. Again, we expect to have the advice of the NAFDC in late January, 1977. You may wonder about the other drugs which the FDA examined. The review on one drug, bacitracin, has been completed. Results indicate that its use at low levels satisfies the animal and human health criteria specified by the Antibiotics in Feeds Task Force. In other cases, our review has not yet been completed. We are still awaiting information from the drug firms about certain products for which studies have had to be repeated. For this reason we have not yet reached a decision on the status of a group of macrolide drugs under review, tylosin, oleandomycin and erythromycin.

We must be aware of a factor which has arisen since the Task Force issued its report. It must be considered in discussing this group of closely related compounds. This is the occurrence of cross-resistance to the macrolides in Gram-positive organisms. The incidence of streptococcal strains simultaneously resistant to macrolides, lincomycin and virginiamycin-like antibiotics has been markedly increasing in recent years. R-plasmids have been demonstrated in *Streptococcus agalactiae* (Group B) as well as in *Streptococcus pyogenes* (Group A) and *Streptococcus faecalis* (Group D). Tetracycline resistance is often present on another plasmid in these organisms. Some of these plasmids appear to be self-transmissible and promote transfer in a manner similar to that found in *E. coli*. In contrast, other *Streptococcus pyogenes* strains appear to transfer their R-plasmids by means of bacterial viruses, as is the case of *Staphylococcus aureus*.

Phage-Mediated Transfer

Phage-mediated transfer of plasmids containing determinants for erythromycin resistance or for penicillin or tetracycline resistance has

been demonstrated in staphylococci. As with streptococci, erythromycin resistance results in cross-resistance to other macrolides such as tylosin and oleandomycin. Furthermore, erythromycin resistance is often accompanied by resistance to lincomycin and virginiamycin-like compounds.

The appearance of streptococcal strains resistant to erythromycin and tetracycline makes it difficult to provide alternate therapy for humans allergic to penicillin. Furthermore, wide usage of macrolide antibiotics may introduce selective pressure for resistance to tylosin, a valuable therapeutic drug in veterinary medicine. For these reasons, in the future, we must carefully follow the occurrence of Gram-positive resistance to these drugs, as well as their effect on the number of Gram-negative organisms present in the gut.

Reviewing and Redefining Data

As you can see, scientific advancement never stops. The process of reviewing and refining data, no matter what the issue, should always be a continuing one. It concerns me when I hear someone refer to work on a marketed product as "defensive research." We should not think of it in a "defensive" way. It should be looked upon as an obligation to the consumer to continually search for better ways of using drug products. It is a part of the trust that we must have from the consumer. We should all continue to strive for the use of beneficial drugs and methods which will pose no threat to the public health.

What are some of the things that we are doing today? Although the committee recommendations are far from being implemented as FDA policy, based on Dr. Mosier's preliminary discussion with the NAFDC in September, 1976, we have begun to take some steps in anticipation of the future. I will describe a few of these projects.

(1) We are in the process of considering a plan to establish a statistically valid data base on the incidence and spectrum of bacterial drug resistance in domestic animals. The data would be useful in the future in measuring any change in resistance to antibacterial agents which might occur as a result of changes in use patterns of antibacterial drugs.

(2) A collection of information has begun for an analysis of the environmental impact of the policy which is being recommended. This would include both the effect of decreased use of certain drugs and the increased use of alternative drugs.

(3) An inhouse committee of scientists is extensively exploring the use of alternate drugs and methods in an attempt to identify alternatives to long-term use of penicillin and tetracyclines. This committee will be concerned particularly with those products used for the prevention and control of animal diseases.

Current Labeling

The major criteria for a substitute (or alternate) drug are current approval and appropriate current labeling. Data shall have indicated that effectiveness and safety are assured. If cross-resistances have been shown for the substitute, whether plasmid-mediated or nonplasmid mediated, this must be considered. If, for a specific disease or diseases, no alternate can be identified, endorsement may be made for continued use of penicillin or the tetracyclines, but where possible, specific periods of time in an animal's life will be specified. The primary thrust is to be the use of the drugs only for the shortest time necessary.

I believe that, in the future, it will continue to be the responsibility of the drug industry, the animal production industry, the veterinary medical profession, and the FDA to see that growth promotion and disease prevention drugs are used judiciously. Inasmuch as possible, growth promoting drugs should be those not used for therapy in man or animals. In the case of disease-preventing products, decisions become more difficult, but I believe we should continue to search for alternative methods of preventing and controlling livestock and poultry diseases. In those cases where prophylaxis with a therapeutic drug is our only alternative, the drug should be used sparingly.

Procedural and Legal Checks and Balances

As you can see, we have some distance to go yet before we complete our original task as it was stated in the April 20, 1973, policy statement. Certainly, both the animal drug industry and the FDA have made a tremendous amount of progress toward these ends. Although it is difficult under our system of procedural and legal checks and balances to predict a time for an endpoint in the present program, I am hopeful that the present review process can be closed out during calendar year 1977. However, as long as we administer drugs to animals and man consumes edible products from these animals, it is doubtful that this and similar programs will ever be completely finished, and this is precisely the way that it should be. [The End]

Section 514.111 of Title 21

By ANN B. HOLT, D.V.M.

Dr. Holt Is Acting Director for the Division of Drugs for Ruminant Species, Bureau of Veterinary Medicine, Food and Drug Administration.

THE CURRENT FORM 356V, taken from the General Provisions of Section 514, subpart A of the Regulations does not refer to Section 514.111 which is in subpart B of this section and is entitled "Administrative Actions on Applications."

Those of us who have worked for the Bureau of Veterinary Medicine for several years, and I think the administrative people for the drug industry itself, have in the past concentrated on explaining and fulfilling the provisions outlined on the Form 356V and have failed to put a great deal of emphasis on the administrative sections of the Regulations and on Section 514.111 in particular. This section captioned, "Refusal to Approve an Application," delineates the reasons the Commissioner, within 180 days after the filing of an application, may inform a drug sponsor of his intention to issue a notice of opportunity for a hearing as to why he proposes to refuse approval. Most of us that review applications, have reviewed them on their merit and have written letters to sponsors which outline and explain the deficiencies found during our review. These letters have been written as described in Section 514.100 of the Regulations and have rarely been seriously challenged. As a consequence, I think both we and the industry, have neglected to fully familiarize ourselves with Section 514.111. And we have not in our correspondence specifically delineated where an incompleteness falls as it relates to the nine paragraphs under part (a) of this regulation.

Incomplete Letter

In my experience it has really been rare, for a sponsor to seriously challenge us on an incomplete letter. In most cases where there has

been disagreement, the disagreement has been resolved with our Agency's and the Sponsor's scientists sitting around a table. However, in the past two years, with the implementation of the Freedom of Information Act and our receipt of more and more requests for descriptions of the data in applications which led us to conclude a drug is approvable, we reference this section more and more in conferences and letters.

We have thus learned that Section 514.111 is one which all of us must be acutely aware of early in the development of a product. One which people designing the protocols, in assembling the data derived from studies and in assembling the new animal drug applications prior to submission, must refer.

The first four paragraphs in this section have not been controversial, three of them relate to safety and one to manufacturing facilities and controls. It is the fifth paragraph, which has been much discussed in the last two years, because this paragraph defines what the Commissioner, and, therefore, the Food and Drug Administration (FDA) considers substantial evidence to support the efficacy of a new animal drug. The term of course, is taken directly from the Act which requires substantial evidence of well-controlled investigations, including field investigation, to support the efficacy of drugs.

New Animal Drug Amendments

Historically, when the new animal drug amendments were passed by Congress and, subsequently, Congress's wishes were spelled out in regulations for new animal drugs, many of the regulations were lifted "in toto" from the human drug sections and placed into what are now the animal drug sections. This was not only an efficient manner to do things, or to accomplish implementation of the animal drug amendments, but in addition, there are only rare instances in which the standards for an animal drug may be different than those used to demonstrate effectiveness of a human drug. Consequently, Sections 313.111 and 514.111 of the Regulations are very closely related.

At the present time, the Bureau has proposed, and I believe the proposal is in the current bureaucratic gristmill, to revise our current regulation to make it even more comparable to the human regulation.

If our proposal is adopted, we believe it will be more applicable to the development of data for therapeutic drugs used in individual

animals. The current regulation, if taken literally, is better suited for studies conducted with populations of animals, such as cattle in feed lots, than it is for the development of efficacy data for drugs used to treat diseases which occur in dogs, cats and horses and diseases such as metritis and ketosis in cattle.

Specifically, how do many investigations, including field investigations, not live up to the requirements of paragraph five?

(1) We have found that many studies reported in applications do not begin with a clear statement of the objective of the study; what the study is designed to show.

(2) In the treatment of individual animals, frequently studies are reported without any mention of how an animal was selected for the study. It is frequently left up to the reviewing officer to make the diagnosis from the raw data submitted.

(3) The studies frequently do not explain how they were designed to exclude or minimize bias on the part of the investigator. There often is no explanation of how the parameters studied are quantitated.

(4) Particularly clinical studies may lack a description of how the study was designed to compare variables such as breed, age or the environment. The latter may be particularly important if animals are treated at home by their owners and are brought in for rechecks to a small animal hospital, for example.

(5) In the past, less so frequently, the methods of recording and analyzing test results have been left up to the individual clinician and they have not been reported uniformally. As a result even more variables are entered into many of the studies.

(6) Too often the kind of control group used has not been described. The Regulation describes three types of control comparisons, the placebo or no treatment control, an active drug control and the historical control as acceptable.

(7) And finally, even though for years we have tried to emphasize the formulation of the product a firm intends to market should be used in field investigations, we still see too many instances in which a formulation other than the one proposed in the new animal drug application has been used with no explanation of how the investigational formulation compares to the formulation in the application.

Human Safety

Two of the remaining paragraphs deal with human safety, one with labeling and the last with need for environmental impact analysis report. Most people are aware of the requirements of the first three paragraphs, but it is amazing how frequently we still receive applications without an EIAR.

To return to paragraph five. The regulation also provides that a waiver from some or all of requirements of a well-controlled study may be granted by the Director of the Bureau of Veterinary Medicine following the submission of a petition. However, the petition must explain and describe why all of the eight conditions in this definition of an adequate and well-controlled investigation are not applicable to the drug or conditions of use of the product and why the manner in which the study or studies were conducted are equal to or superior to the type of well-controlled study described by the regulation. In other words, a petition for a waiver must explain why the results of a study conducted should be accepted as substantial evidence of the effectiveness of the proposed product. The regulation definitely acknowledges that there are generally more than two ways to skin a cat. It only requires that ways other than those described by it be fully explained and justified.

Substantial Evidence of Effectiveness

I have briefly outlined the deficiencies we see in reviewing studies conducted to support the substantial evidence of effectiveness requirement of the Act. I cannot emphasize too much the necessity for people sponsoring applications, both now and in the future, to ensure that each efficacy study contain a clear description of why the study was conducted, how it was designed and what parameters were used for interpreting the study, selecting the animals and minimizing investigator bias. If this cannot be done, a full explanation of why it could not be done must be made. Therefore, please have your scientists or your consultants review this regulation carefully before designing protocols or initiating studies to support the efficacy of a new animal drug when developing a new product. If this is done, I can assure you, our job will be easier and the time spent in reviewing your applications shorter. **[The End]**

The Role of the Advisory Committee

By JACOB E. MOSIER, D.V.M.

Dr. Mosier Is Head of the Department of Surgery and Medicine, College of Veterinary Medicine, Kansas State University.

MY FIRST CONTACT with a National Advisory Committee occurred in 1972 when I became a member of the National Veterinary Medicine Advisory Committee. The committee consisted of 12 persons representing veterinary medicine, animal sciences, related biomedical services, consumer interests, and the general public. This committee, phased out in 1974, and those members whose terms were not yet completed joined with similar representatives of the National Food Advisory Committee and the National Drug Advisory Committee to form a single committee, the National Advisory Food and Drug Committee. The melding of the three groups was arranged by Commissioner Schmidt, partially because of the lack of similar advisory groups for the other three bureaus of the Food and Drug Administration (FDA) and partially because of a lack of adequate formal public advisory mechanisms for matters of general agency policy. It is the National Advisory Food and Drug Committee on which I will base my remarks concerning the role of the national advisory committee in animal drugs.

The committee is structured for 18 members appointed by the secretary for overlapping terms of 4 years. Members are representatives of biomedical sciences, industrial technology, education, economics, and public affairs. The chairman of the committee is the Commissioner of Food and Drugs.

Stated Function of Committee

The stated function of the committee is that it reviews and evaluates agency programs and provides advice and guidance to the

secretary, assistant secretary for health and the commissioner of food and drugs on policy matters of national significance as they relate to the FDA's statutory mission in the areas of foods, drugs, cosmetics, medical devices, biological products and electronic products. The committee reviews and makes recommendations on applications for grants in aid for research projects relevant to the mission of the FDA as required by law.

In the foreword of the booklet entitled Food & Drug Administration Public Advisory Committees—authority, structure, functions, members—Dr. Alexander Schmidt writes, "Our public advisory committees are composed of highly qualified individuals from specialized fields with wide geographic distribution. The individuals represent the diversity of judgment, outlook, and background essential to balanced and effective programs related to human health and well being, and the protection of the consumer against ineffective and unsafe foods, drugs and products which one consumes and uses."

The National Advisory Food & Drug Committee is concerned, among others, with such issues as the adverse drug monitoring systems, revision of new drug application, review procedures, blending, truthful labeling, wholesomeness of animal foods, etc. The immediate concern is the use of antibiotics in animal feeds.

Role of the Advisory Committee

Perhaps by using this issue as an example we can explore the role of the advisory committee.

The National Veterinary Medicine Advisory Committee, then the National Food & Drug Advisory Committee received periodic reports on the use of antibiotics in feeds. Information resulting from studies mandated by the agency in 1973, discussions of risk/benefit evaluations, knowledge of the evolution of agency policy and a review of task force recommendations were brought to the committee at various times during their meetings from 1973 to 1975. It is apparent to me, that the first concern of the FDA was the education of the committee, giving the members a basic understanding of the functions involved and to delineate the known problems. In 1975, the committee expressed its interest and concern relative to antibacterials in animal feeds and elected to pursue the matter via the subcommittee route. As a consequence, a three member subcommittee was named in 1975 to study the problems and to report back to the full committee.

The subcommittee on use of antibiotics in feeds consisted of myself; Dr. Nelson Fernandez, a physician and nutritionist at the University of Puerto Rico; and Ms. Camille Haney, a consumer affairs expert from Wisconsin. The expertise of these individuals was supplemented by that of outside consultants; Dr. William Flatt, from the Agricultural Experiment Station, University of Georgia; Dr. Edward Hook, an expert on *Salmonella* from the University of Virginia Medical School; Dr. Stanley Falkow, an outstanding authority on infectious drug resistance from the University of Washington Medical School; and Dr. George Poppensiek, a microbiology professor at the Cornell Veterinary College.

Risks and Benefits

The charge to the subcommittee was to consider the risks and benefits involved with the use of a number of antibiotics and sulfonamides and to reach judgments as to whether or not the use of these drugs is worthwhile. The subcommittee was told that there are a number of factors that should enter into the judgment:

(1) Is there a risk? What is the extent and nature of that risk, and should it be accepted by consumers?

(2) What are the alternatives to the use of these drugs, either in the use of other drugs or in the use of non-drug methods?

(3) If we should accept the use of these drugs and the risks involved, are there restrictions that should be imposed, and what are those restrictions?

The subcommittee conducted a series of four (4) meetings held in January, April, July and August of this year. During these meetings the subcommittee heard data presented by the FDA staff and consultants, from studies by industry, university and the FDA laboratories, as well as literature reviews on the tetracyclines, penicillin and sulfaquinoxaline. At the open public hearing portions of the meetings the subcommittee was presented statements from representatives of industrial organizations, scientists, animal producers and veterinarians.

Antibacterial Drugs

The subcommittee recognized very early that the issues involved in the feeding of subtherapeutic levels of antibacterial drugs are extremely complex and controversial. There are apparent voids between established fact and the theoretical projections of current information. The extensive reviews presented to the subcommittee revealed dis-

parity of opinion by competent scientists as to the significance of published research and previous use history.

The subcommittee approached the task with the understanding that the stated policy of the FDA is to reduce and/or eliminate risk to the extent possible, while at the same time weighing the risks or potential risks against the benefits derived from the use of these products. In effect, therefore, our goal was to formulate a policy which might maximize the benefits and minimize the risks associated with the practice of incorporating antibacterial drugs into feeds.

It became apparent to the subcommittee that benefits derived from the use of antibacterial drugs for increasing rates of weight gain, improving feed efficiency and preventing and controlling animal disease were present and could generally be quantified. However, the amount of risk to animal or human health due to use of antibacterial agents in animal feed could not be defined.

After hearing the various papers presented at the four meetings, the subcommittee concluded that although the risks are of unknown magnitude, it would be prudent, where possible, to curtail feed use of drug products such as penicillin and tetracyclines, which are also used for therapy in man or which induce cross-resistance to drugs used for therapy in man. At the same time, we recognized that there would be a loss of benefits from a total ban of the use of antibiotics in feeds. A total ban would result in: a) increased cost and/or diminished supply of foods of animal origin; and b) reduced health status of animals with subsequent effect on food products of animal origin entering the nation's food supply.

Alternate Drugs

In most cases, alternate drugs do exist for promotion of feed efficiency and growth rate in food animals. These alternatives are considered to be effective, economically acceptable, and unlikely to encourage transfer of multiple resistance to enteric organisms. However, satisfactory alternates do not exist in all cases for prevention of disease. The challenge, then, is to identify which drugs and uses can be reduced or eliminated, in order to reduce the pool of drug resistant organisms while retaining demonstrated benefits, such as the prevention of disease to protect the wholesomeness of the food supply.

In retrospect, the role of the subcommittee has been to listen to the presentations, to listen to the discussions generated as a result

of the presentations, to engage in discussions or questions with those making presentations, with the consultants and with interested participants and to render a judgment as to the issues involved in the use of antibacterials in animal foods.

As a member of the subcommittee, I am impressed with the sincerity, the understanding, and the willingness to listen of all who attended the meetings. The subcommittee is especially indebted to the consultants who so patiently explained that which the subcommittee did not grasp and who were so important as a major resource for the subcommittee.

The subcommittee has prepared its report with recommendations concerning the use of antibacterials in animal feeds. It is the role of the National Advisory Committee to review the report of the subcommittee, to query the members of the subcommittee on points of concern and to make final recommendation to the commissioner.

It is my belief that the committee will accept the subcommittee's report and will use the report as a basis for the full committee recommendation to the commissioner.

I believe the report is a balanced, logical conclusion based on current knowledge. I believe that the process involving individuals with diverse backgrounds and outlooks and from widely separated geographic areas is highly exemplary and I congratulate the FDA on their foresight. **[The End]**

PUBLIC HEARING TO BE HELD ON GOOD LABORATORY PRACTICES

A public hearing on the proposed regulations for good laboratory practices for non-clinical laboratory studies will be held in the first floor auditorium of the HEW North Building, 330 Independence Avenue S.W., Washington, D.C. 20205 on February 15, 1977. Participants must file written notices with the Hearing Clerk. Specific areas in which the Food and Drug Administration seeks counsel include the need for and appropriateness of the proposed regulations as a means of assuring the quality and integrity of safety data, the necessity for written procedures for all laboratory activities concerned with testing protocols, and the proposed laboratory disqualification procedures.

CCH FOOD DRUG COSMETIC LAW REPORTER, ¶ 41,795

The Cosmetic Ingredient Review Program

By ROBERT P. GIOVACCHINI, Ph.D.

Dr. Giovacchini Is Vice President of Corporate Product Integrity in the Gillette Company.

THE QUESTION OF WHETHER the individual ingredients used in cosmetic/toiletry products are safe, and whether a mixture of these various ingredients, when used in a product, is safe, has occupied the time and effort of several Cosmetic, Toiletry and Fragrance Association (CTFA) scientific committees. One of the central issues in all of the CTFA technical committee discussions has been an attempt first to define the term "safe," and second to determine how adequately to substantiate safety. As we all well know, there is at present no federal regulatory definition for the term "safe." However, there certainly is sufficient information, both technical and regulatory, on what constitutes a lack of safety.

Concept of Safety

In the past it has been stated that the concept of safety exists only with respect to the dose, site of application, and concentration of the chemical or product under conditions of use or foreseeable misuse. Thus, safety is freedom from unreasonable risk of significant injury under reasonable foreseeable conditions of use. There are no harmless substances; but there are ways and means of using substances in a relatively harmless way.[1] The Commissioner of Food and Drugs has advised that cosmetic safety can be adequately substantiated through:

"(1) reliance on already available toxicological test data on individual ingredients and on product formulations that are similar in composition to the particular cosmetic

[1] Giovacchini, R. P., "Adequately Substantiating the Safety of Cosmetic Products," CTFA Cosmetic Journal, 8:3, p. 7-11 (July-September, 1976).

and (2) performance of any additional toxicological and other tests that are appropriate in light of such existing data and information."[2]

The Cosmetic Ingredient Review (CIR) program has defined "safety" as "no evidence in the available information that demonstrates or suggests reasonable grounds to suspect a hazard to the public under the conditions of use that are now current or that might reasonably be expected in the future, that is, a low incidence of minor adverse reactions (as shown in animal or human testing or product experience). Such information includes, but is not limited to, the chemical structure of the ingredient, published or unpublished tests on the ingredient and products containing the ingredient, significant human experience on products containing the ingredient during marketing and information on similar or related substances. A lack of information about an ingredient shall not be sufficient to justify a determination of "safety."[3] In turn, the CIR program has defined "conditions of use" as including:

"(1) the amount of an ingredient used in a product, (2) the intended use and reasonably foreseeable areas of use (e.g., use that is subject to ingestion or inhalation or contact with mucous membranes or is in the area of the eye), and (3) directions for use and against misuse in labeling."

Thus, the Industry has, for the first time, officially defined what is meant by the illusive concept of "safety."

Toxicological Evaluation

Toxicologists know that the sophistication of toxicological evaluation, at this time, is such that one cannot devise a complete set of animal and/or human toxicological, pharmacological, bio-chemical, or physiological tests which, under any and all conditions of possible use, demonstrate all the potential effects of an ingredient and/or product. Thus, toxicologists, faced with the practical considerations of evaluating and substantiating safety, have tried to develop relevant prognostic examinations to delineate the parameters of toxicity. This approach, while practical and technically acceptable, has led to safety judgments being made on the basis of subjective rather than objective standards. This, in turn, has led to arguments over not only the adequacy of the data but also the meaning of the findings. Thus, on any given issue one can find scientists supporting either a position that the ingredient and/or product is safe or unsafe, and both groups may be using the same data. Of course, these issues are of intense interest

[2] Schmidt, A. M., "Food, Drug and Cosmetic Products, Warning Statements," 40 *F. R.*, 8912-8929, (#42, 1975).

[3] CIR Procedures, Cosmetic Ingredient Review Program, 1133 15th Street, N. W., Washington, D. C. (Sept., 1976).

to the public. In today's world, these issues are therefore hotly debated by, among others, the politicians, consumer activists, news reporters, and university scientists. Because of this fact we now have developed the new disciplines of political toxicology, newspaper toxicology, legal toxicology and social-economic toxicology, each with its own viewpoint and jargon. Unfortunately, these newly developed disciplines do nothing more than either confuse the public or utilize appropriate portions of the scientific facts to expedite and support a particular advocate's needs and positions on any given issue. Indeed, at times the discipline of scientific toxicology seems obscured to the point of almost vanishing.

Safety of Ingredients

How, then, in this period of new so-called disciplines and the present state of the science of toxicological knowledge can one best evaluate the safety of ingredients that are used in cosmetics? This can be done by developing a review program that follows two fundamental principles. The principles are: (1) scientific integrity and (2) open reporting of the scientific data and rationale that led to a particular determination. We believe that the CIR program indeed encompasses these fundamental principles.

The CIR program proceeds on the premise that one must begin by studying each individual cosmetic ingredient. However, even this type of examination must take into account the conditions of use to which the ingredient shall be put. While it is important to know the toxic potential of an ingredient from structured laboratory studies, the results must be examined in the light of the proposed use of the ingredient.

Second, an Expert Panel composed of leading independent scientists, who will represent a balance of appropriate disciplines, will be utilized for the review. This Expert Panel will make all final scientific determinations. Responsibility for shaping and conducting review activity will rest with this expert group. In addition, three nonvoting liaison representatives, representing key interests in the program (regulatory, consumer, and industry) will work with the Expert Panel.

Third, the Expert Panel will set final program priorities and assure the broadest possible search of the scientific literature and other sources for scientific data. Information will be sought from government agencies, university researchers, independent laboratories, research and development departments of cosmetic manufacturing

companies and chemical suppliers and any other sources that might have conducted research on or had experience with the ingredient. The ingredient reviews will reflect domestic and foreign literature covering various aspects of biology and medicine relevant to cosmetic safety. They will stand as the critical review of the kind and type of research that has been conducted on the ingredient and the relevance of this research for evaluating and substantiating the ingredient as a component of cosmetics.

Fourth, when the ingredient reviews are completed the Expert Panel will issue comprehensive reports evaluating the safety of the ingredient reviewed. In each report the Expert Panel will designate the ingredient safe or not safe for use in cosmetic products. The Expert Panel's reports and supporting documentation will be available for review and comment and the final reports will be published in an appropriate scientific journal.

Consensus of Scientific Opinion

The Cosmetic Ingredient Review program will offer to us all a consensus of respected scientific opinion on which the public can rely as the basis for judgments about the safety of cosmetic ingredients. The program will save duplication of effort, offer a central repository of accurate information, and will be the first available collection of data documenting the biological activity of ingredients used in cosmetics, with objective evaluations of their implications for human health and safety. This program will employ responsible and respected scientists to evaluate a mass of technical data. The process has been clearly defined and is open for examination. There is opportunity for participation in the process by all those who are interested. The findings, of course, must stand the objective review of other scientists worldwide. **[The End]**

Cosmetic Establishment Inspections—New Approaches

By MARTIN GREIF

Mr. Greif Is Assistant to the Director of Division of Cosmetics Technology, Bureau of Foods, Food and Drug Administration.

IN THIS DISCUSSION, I will review briefly some new approaches that have been undertaken by the Food and Drug Administration (FDA) to improve the effectiveness of the Agency's cosmetic establishment inspection program.

Compliance Program

A principal feature of the FDA's compliance program for cosmetics is the inspection of establishments engaged in the manufacture and packaging of cosmetic products. The major objective of the establishment inspection is to determine whether products are produced under insanitary conditions, and to take regulatory action where necessary to achieve compliance. The goal is to reduce consumer exposure to cosmetic products which are adulterated within the meaning of Sec. 601 of the Federal Food, Drug and Cosmetic Act. In addition, the establishment inspection program affords the FDA investigator an opportunity to identify, for possible regulatory action, products which may be misbranded under the Federal Food, Drug and Cosmetic Act or the Fair Packaging and Labeling Act (FPLA).

For purposes of enforcing the Federal Food, Drug and Cosmetic Act, Sec. 704(a) authorizes duly designated employees to enter and to inspect at reasonable times and within reasonable limits any factory, warehouse, or establishment in which cosmetics are manu-

factured, processed, packed or held for introduction into interstate commerce.

Adulterated Cosmetics

The definitions of adulterated and misbranded cosmetics are well known to most persons in this audience; however, one word in the definition of "adulterated cosmetics" is very significant in the cosmetic establishment inspection program. That word is "may." Thus, Sec. 601(a) states that a cosmetic shall be deemed to be adulterated "if it bears or contains any poisonous or deleterious substance which *may* render it injurious to users under the conditions of use." (Emphasis supplied.) Sec. 601(c) of the Act states that a cosmetic shall be deemed to be adulterated "if it has been prepared, packed or held under insanitary conditions whereby it *may* have become contaminated with filth, or whereby it *may* have been rendered injurious to health." (Emphasis supplied.)

Thus the Act confers upon the investigator the authority and the responsibility to make an initial determination regarding possible adulteration based upon conditions he or she observes during an inspection.

Cosmetic Program

Several new approaches have recently been incorporated into the cosmetic program to improve the effectiveness of establishment inspection and the evaluation of industry compliance with regulatory requirements. The FDA's inspection manual outlines in detail how the field should implement the program. The manual has been greatly enlarged this year to provide investigators more information than ever before about cosmetic regulatory issues and inspection criteria. New regulations are summarized and interpreted so that investigators can thoroughly familiarize themselves with the new requirements. One section of the manual provides the investigator with in-depth background information regarding issues presently of concern to the Agency. These include safety of bubble-bath preparations, preservation of eye area cosmetics, use of methyl methacrylate monomer in nail extenders, color additives, asbestos in talc, halogenated salicylanilides, new cosmetic labeling regulations and others.

With the advent of the new cosmetic labeling regulations investigators have been instructed to report, for possible regulatory action,

products that are not in compliance with the new regulations. In order to achieve this goal, investigators will be collecting large numbers of representative labels for review in the districts. Where questions arise regarding compliance, confirmatory reviews will be conducted at headquarters. Efforts in this area will accelerate substantially next year.

Checklist on Manufacturing and Quality Control

The fiscal 1977 establishment inspection program has incorporated a checklist on manufacturing and quality control with 2 special purposes in mind, namely: (1) to guide investigators in areas needing special attention during the course of an inspection, and (2) to collect data on current practices in cosmetic manufacturing and packaging establishments. Information acquired from the establishment inspection checklist is expected to provide significant input to current good manufacturing practice (GMP) regulations for cosmetics which are presently under development. The checklist contains specific questions about the manner in which firms handle raw materials, labeling, manufacturing and processing, quality control, personnel, buildings and equipment, sanitation and housekeeping. Future surveillance activity and enforcement would be improved if good manufacturing practices could be evaluated at cosmetic establishments. For this to be accomplished, the GMP regulation must precisely identify the GMP requirements.

Cosmetic Manufacturers

Because there is no statutory requirement that cosmetic manufacturers register their establishments with the FDA, some firms may, in the past, have operated unknown to the Agency. The Division of Cosmetics Technology has undertaken a project to identify these establishments and add them to the Agency's cosmetic manufacturing establishment inventory. During the past year, more than 300 such establishments have been identified. The Agency is also presently setting up a contract with a consulting firm for the purpose of further updating this list. As a result of this project, many establishments which have never been inspected will be visited by FDA investigators this year and next. Because of limited resources, it is necessary to optimize the resources available for the cosmetic program inspectional activities. In previous years, the selection of establishments to be inspected was made by the office of the Executive Director for Regional Operations (EDRO) and by the individual districts. Beginning

with fiscal year 1977, 50% of the establishments to be inspected have been designated by the Division of Cosmetics Technology. This proportion is expected to increase to about 75% in fiscal year 1978. These selections are based upon the needs of the compliance program and take into account the past history of individual establishments.

Priority coverage is being given in the current program to firms not previously or recently inspected. Additionally, inspectional coverage will include firms with a history of poor manufacturing practices as well as those with more favorable records. Using this approach the Agency believes it will develop a good sampling of industry practices in an effort to fulfill its statutory obligation to enforce the cosmetic provisions of the Act. It is expected that this new approach will provide the Agency with inspectional observations that are more responsive to the compliance program objectives.

Establishment Inspection Reports

Prior to 1976, the districts sent, for headquarters review, copies of only those establishment inspection reports which contained recommendations for regulatory action. All other inspection reports were abstracted in accordance with a predetermined formula. Only certain key information from those reports was transmitted into existing Agency computer files. That data base provides extensive quantitative statistical information on the number of establishments inspected, number of violations reported and number of establishments found to be in compliance. However, it contains very little qualitative information dealing with the nature of violations and the kinds of practices observed.

Since early 1976, copies of all establishment inspection reports, whether violative or in compliance, are being forwarded to headquarters for detailed review and analysis. The Division of Cosmetics Technology presently supplements the Agency's data base by abstracting all pertinent qualitative data from the establishment inspection reports. Information which bears a direct relationship to the program objectives is managed in a new computer file within the Division. This file is linked by the computer to the Division's establishment registry. The system is designed to permit retrieval of statistical data on industry-wide problems, provide compliance profiles on individual establishments and allow the Division to monitor the program on a continuing basis.

Industry Compliance

Summary reports produced by the computer will provide the Agency with meaningful information concerning areas where industry compliance is generally poor as well as where it is good. The computer reports will also identify individual firms which repeatedly violate regulatory requirements and are thus candidates for more persuasive regulatory action.

Another recent innovation in the cosmetic establishment inspection program is the requirement that the program be evaluated in depth on an annual basis by the project officer and program manager. These reports are reviewed by the Commissioner to ensure that Agency-wide field program activities are effectively contributing to the attainment of FDA objectives.

The information in evaluation reports is used also by the Bureau of Foods to measure the compliance status of the industry and to identify significant industry problems. The information is relied upon: to modify existing field programs; to help concentrate resources on substantial regulatory problems; to improve field-to-headquarters and reverse communications and to provide desired and understandable communications to the industry and to the public. In this connection, the compliance program evaluation report is also made available to the public.

Establishment Inspections

On occasion representatives from the Division of Cosmetics Technology accompany investigators on establishment inspections. There are two principal reasons for this activity: first, to enable headquarters personnel to see first hand how the program, which was developed at headquarters, is being implemented in the field and second, to determine how the inspection program may be improved in the future.

In this brief review we have identified some new approaches that are being implemented in the cosmetic establishment inspection program. We have shown that headquarters staff are now more directly involved in the planning of field programs and the analysis of data received from the field. The Agency is using information derived from the inspection program to shape its future regulatory and research activities. The data and information are also being used as background for the development of improved compliance programs and future regulatory proposals. **[The End]**

FOOD DRUG COSMETIC
LAW JOURNAL

PUBLISHED BY
COMMERCE CLEARING HOUSE, INC.
PUBLISHERS of TOPICAL LAW REPORTS
4025 W. PETERSON AVE., CHICAGO, ILL. 60646
RETURN POSTAGE GUARANTEED

SECOND CLASS POSTAGE PAID
AT CHICAGO, ILLINOIS AND
AT ADDITIONAL MAILING OFFICES

A COMMERCE CLEARING HOUSE PUBLICATION

BUSINESS REPLY MAIL

No Postage Stamp Necessary if Mailed in the United States

POSTAGE WILL BE PAID BY—

COMMERCE CLEARING HOUSE, INC.

PUBLISHERS of TOPICAL LAW REPORTS

4025 W. PETERSON AVE.

CHICAGO, ILL. 60646

MAIL TODAY!

CARD

ORDER

FIRST CLASS
PERMIT NO. 57
CHICAGO, ILL.

FOOD DRUG COSMETIC
LAW JOURNAL

ORDER
CARD

MAIL TODAY!

CCH:

Please send me ..... copies of Antitrust Improvements—Law and Explanation (5435) at the following prices: 1-4 copies, $2.00 ea.; 5-9, $1.80 ea.; 10-24, $1.70 ea.; 25-49, $1.50 ea.

(To save postage, handling and billing charges, you may elect to send remittance with order. Please include sales tax where required.)

☐ Remittance herewith ☐ Bill me

Signature .....

Firm .....

Attention .....

Street & Number .....

City & State ..... **Zip** .....

(Subscribers for CCH's Trade Regulation Reports receive this item and should order only for extra copies.)

Please Indicate Your CCH Account No.

5435—2043