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

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

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VOLUME 23 NUMBER 1

FOOD DRUG COSMETIC LAW JOURNAL

Editorial Advisory Board

REPORTS

TO THE READER

1967 FDLI-FDA Conference.—Additional papers presented at the Eleventh Annual Joint Educational Conference of the Food and Drug Law Institute, Inc. and the Food and Drug Administration are included in this issue of the JOURNAL. Previous papers presented at the Conference were in the December, 1967 issue.

Pointing out the benefits that Good Manufacturing Practice regulations would bring to industry, state and local officials, and the FDA is the concern of *Alfred Barnard* in his article "The Need for Formal GMP Guidelines in the Food Industry," which begins on page 4. Mr. Barnard is the Director of the Bureau of Regulatory Compliance of the FDA.

In his article, "Sampling and Testing of Drugs," beginning on page 8, *M. L. Yakovitz*, Director of the Division of Case Supervision, Bureau of Regulatory Compliance, FDA, lists five precepts followed by the forward-looking drug manufacturer.

"The Prescription Drug Advertising and Labeling Regulations" is the subject of the article by *Vincent A. Kleinfeld*, which begins on page 12. The author, a Washington, D. C. lawyer, has three recommendations to make with respect to the Food and Drug Regulations.

That the FDA and the industries subject to regulation are in broad agreement on a number of essentials involving the advertising of prescription drugs is the contention of *Julius Hauser*, Assistant for Regulations, Office of the Associate Commissioner for Compliance, FDA. His article, "Drug Advertising Regulations," begins on page 21.

Dr. R. W. Ballard, Executive Medical Director, McNeil Laboratories, Inc., feels that research on humans is absolutely essential and that most risks are either minimal or tolerable if the early clinical trials are conducted properly. His article, "Risks vs. Benefits in Drug Development," begins on page 25.

Dr. Kenneth M. Endicott, Director of the National Cancer Institute, carries the discussion of the dangers and values of experimental chemotherapy into the specifics of his own field. His article, "Risks vs. Benefits in Cancer Drug Development," begins on page 29.

Beginning on page 32, *R. Keith Cannan*, Special Assistant to the President of the National Academy of Sciences-National Research Council, discusses the "Status of the Drug Efficacy Study of the NAS-NRC."

D. G. Chapman, Assistant Director-General, Foods, in the Canadian Food and Drug Directorate, discusses food and drug legislation in Canada, and considers the possibility of international standards, in "A Neighbor Comments upon Some National and International Aspects of Food and Drug Legislation," which starts on page 36.

Current Tidings and Trends in Drug Appraisal.—The various problems experienced by both the FDA and the drug industry is the subject of the article by *Bernard L. Oser*, Ph.D., which begins on page 42. These problems, which impede the introduction of new drugs in the United States, will require cooperation and patience on both sides if they are to be solved. The author, this magazine's Scientific Editor, is with the Food and Drug Research Laboratories, Inc., Maspeth, New York. The article was presented as a speech at the fall luncheon meeting of the Drug, Chemical and Allied Trades Association in New York on November 20, 1967.

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Food·Drug·Cosmetic Law
Journal

The Need for Formal GMP Guidelines in the Food Industry

By ALFRED BARNARD

The Following Report Was Presented at the Food and Drug Law Institute, Inc.—Food and Drug Administration's Eleventh Annual Educational Conference at Washington, D. C., on November 27, 1967. Mr. Barnard Is the Director of the Bureau of Regulatory Compliance of the Food and Drug Administration of the U. S. Department of Health, Education and Welfare. The Seven Succeeding Articles in This Issue Were Presented at the Same Conference.

THE FIRST THING I should comment on is the present status of the so-called food umbrella Good Manufacturing Practice (GMP) regulation. I am pleased to advise that the proposed regulations have been forwarded to the printing process and should make the Federal Register shortly.*

There are reasons for and against so-called GMP's for the food industry. I will present the affirmative side. In self-defense and just to prove that I have some knowledge of both sides of the question, I invite your attention to the talk I made to the Association of Food and Drug Officials of the United States last summer in St. Paul, which was reproduced in the FOOD DRUG COSMETIC LAW JOURNAL for Septem-

* The proposed regulations have been issued. See 22 FOOD DRUG COSMETIC LAW JOURNAL 671 (December, 1967).

ber.[1] That talk pretty well spells out some of the problems involved in the concept and outlines why no regulations have been developed in this area in the almost thirty years which have elapsed since the passage of the 1938 Act.

One other point I would like to make before dealing specifically with the subject at hand, and that is that the proposed regulations deal with sanitation. The scope of Section 402(a)(4) itself is broad enough to encompass other considerations, and as we proceed with the development of individual appendices the areas of consideration may expand to include such things as in-plant pest control practices, raw material controls over such factors as decomposition, pathogenic microorganisms, etc.

Turning now to the subject at hand, we see in the promulgation of GMP regulations under Section 402(a)(4) basically a process of setting standards, for the first time, for what constitute insanitary conditions whereby a food may become contaminated with filth or rendered injurious to health. Such standards will be of value to:

1. The regulated industry;
2. State and local enforcement officials;
3. The Food and Drug Administration (FDA) itself.

They will therefore be of significant benefit to the consumer.

Let us briefly explore the nature of the benefits to each.

Benefits to Industry

In the case of industry, there will be on the record for the first time a clear statement of the FDA view of what constitutes compliance with Section 402(2)(4). Industry will be provided with a standard by which it can measure its own performance and against which top management can measure the performance of individual staff members responsible for plant sanitation. It will also be provided with a sound basis upon which specific sanitation programs can be developed, planned and costed out with a clearer understanding of what the current demands of the regulatory agency are with respect to its particular operations.

Benefits to State and Local Officials

State and local officials will profit in a number of ways from the existence of established GMP regulations under Section 402(a)(4). In the first place, it is difficult for state, and especially local, officials to

[1] Barnard, "Good Manufacturing Practices Regulations in the Food Industry" 22 Food Drug Cosmetic Law Journal 511 (September, 1967).

have access to the broad picture of the current state of the art on a Nationwide basis in a given industry. A Federally promulgated standard will provide these officials with sound guidance as to what can appropriately be expected and required. This fact, of course, underlines our obligation to keep these regulations in step with modern technology.

There have been instances where we have encountered difficulty in carrying out effective joint planning with state and local officials in the area of plant sanitation because of a lack of agreement between the two agencies on sanitary standards. As these regulations come into being, the states will have a clear statement of the standards to which FDA will expect industry to adhere and toward which joint planning with FDA will be expected. This becomes increasingly important in view of the growing state and local participation in FDA programs in the food sanitation area.

It might seem almost to go without saying, but the promulgation of GMP regulations will provide the states with a basis for their own training programs and planning activities, which has not been available in the past.

Benefits to FDA

For FDA, we see four major pluses. Perhaps the most important of all the benefits will be found in our enhanced capability to carry out joint planning and to execute joint programs with our state and local counterparts.

In the second place, FDA will have for the first time an objective standard against which it can judge industry performance and its own accomplishments. In the past, we have made sanitation inspections, found insanitary conditions, and initiated various sorts of action to achieve compliance. Subsequent inspections have revealed varying degrees of improvement and in some instances additional enforcement action has been necessary. We have never had, however, a basis upon which we could clearly compare the condition of a given firm or industry on an objective basis with its condition at some previous or subsequent time.

We are looking forward to including in our data retrieval system information on specific deviations from current GMP regulations. This will enable us to establish measures of industry compliance, identify key indicators of the likelihood that finished products will actually be contaminated, and establish some bases upon which FDA top management can make better informed decisions about future programs. I

might point out in passing that, as we develop such data, they will be made available in general terms to interested industry.

Thirdly, we will have a tool which we can use within FDA to compare plants in one part of the country with another, or sanitary inspections made by one inspector with those made by another. In the past, when inspections have revealed clearly violative conditions, there has been little or no difficulty in reaching agreement within FDA. We do believe, however, that there has been inconsistency in the evaluation of borderline findings by different inspectors and different administrative reviewers. This factor has made it difficult for us in FDA to come to any concrete conclusions about the progress, or lack thereof, which we have been able to achieve through our various compliance programs. It has made it difficult to identify specific areas where additional resources may be more urgently needed than others.

And lastly, for all these reasons, we believe that we can more effectively achieve overall compliance with the provisions of Section 402(a)(4) if we have clear-cut regulations which everyone understands. Also, in those instances where we ultimately become involved in legal action, we believe it will be helpful for the court to have such regulations before it. The language of the court in the so-called *Smith Canning Company* cases[2] makes this rather clear.

In conclusion, we are convinced that these pluses far outweigh the potential problems and disadvantages involved in the food GMP regulation approach. **[The End]**

ACTION AGAINST DRUG MAKER BARRED BY DELAY

A hospital patient who was treated with an antibiotic and as a result sustained a serious hearing loss could not maintain an action against the manufacturer of the drug on the theory that it was marketed with insufficient warning of the possibility of the drug's causing deafness.

Because plaintiff's injuries occurred more than four years prior to his commencement of action, and he should have known at least three years prior to the institution of action what had caused his deafness, the action was barred by the one-year statute of limitations. The federal district court in New Orleans entered summary judgment for the manufacturer.

Breaux v. Aetna Casualty & Surety Co. et al., USDC Louisiana (1967), CCH PRODUCTS LIABILITY REPORTS, ¶ 5864

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[2] *Fifteen Hundred Cases of Canned Tomato Paste (Smith Canning Co., Claimant)*; *U. S. v.*, 236 F. 2d 208, (CA-7 1956 aff'g in part and rev'g in part DC Ill.)

Sampling and Testing of Drugs

By M. L. YAKOWITZ

Mr. Yakowitz Is the Director of the Division of Case Supervision, Bureau of Regulatory Compliance, FDA.

THE CURRENT PRINCIPLES OF DRUG TESTING are best illustrated by considering a typical example of new drug development.

Testing of a new drug proceeds in three stages; (1) intensive testing of the new drug substance, (2) intensive testing of proposed dosage-forms containing the new drug substance, and (3) standardized control testing of commercial batches of the dosage form approved by the Food & Drug Administration.

The goal of stages 1 and 2 is to develop a drug product with beneficial medical effects while the goal of stage 3 is to insure that every dosage unit of every batch produces those same beneficial effects. Uniformity of output is the target at the center of this last goal.

Use of Advanced Methodology

Today's drug testing procedures utilize a highly advanced methodology based on new scientific knowledge and recently developed techniques and instruments. Because of their versatility, sensitivity, and accuracy, these new techniques and test instruments have revolutionized drug testing. The modern drug manufacturer employs a wide variety of these new tools such as thin layer chromatographs, gas-liquid chromatographs, infrared, visual, ultraviolet, and Raman spectrographs, polarographs, X-ray diffraction equipment, and nuclear magnetic resonance devices.

Using the new methodology, the drug manufacturer can ascertain the molecular composition of the new drug substance, whether there are isomers to be concerned with, whether there are polymorphic forms to be concerned with, what the trace impurities are, and how the new drug substance behaves under various environmental conditions. With this array of precise information, he can work out the

best procedure for making and purifying the new drug substance, and he can set tight specifications which each batch of the new drug substance must meet before it is incorporated in a dosage form.

In developing the dosage form, the prudent manufacturer attempts to restrict the other components, such as excipients and diluents, to those substances for which he already has reliable suppliers. To the extent that it is feasible to do, the drug manufacturer purchases such components from the primary manufacturer. In many cases, he will send his own inspector to the plant where the material is made in order to check on the manufacturing procedure and controls. Additionally, the conscientious drug manufacturer inspects and tests each shipment delivered to him to make sure the material meets specifications.

When the new product in dosage form approaches the stage of plant-scale manufacture, the proposed formulation and the details of batch manufacture are studied intensively. This study results in establishment of the master-formula for the dosage form, the detailed working directions for making each batch, and the tests and specifications used for in-process control and analysis of the finished dosage form. All of this study is designed to ensure uniformity of product, batch after batch.

Importance of Thorough Study

The importance of thorough study of each step of the manufacturing process cannot be overemphasized. Even such an apparently simple process as mixing several powders for tablet making has its pitfalls. Special precautions may be necessary to achieve and maintain a uniform mix up to the moment the granulation is compressed into tablets. This is particularly important if the active ingredient is very potent and constitutes only a small proportion of the tablet weight.

Manufacturer Relies on Manufacturing Directions

The experienced manufacturer places his major reliance on the manufacturing directions he has developed for ensuring uniformity of product. However, he will invariably assay the completed batch to help ensure uniformity. In the case of tablets containing a small proportion of a very potent ingredient he may even assay a series of individual tablets from each batch. Some firms have developed automated assay procedures for checking the strength of a series of individual tablets.

The importance of thorough study of the manufacturing process becomes even more apparent when we consider hypodermic drugs. Every unit in the batch must be sterile but this cannot be assured by simply testing samples from the finished batch. Even though every ampul or vial in the sample tests out sterile, this is only presumptive evidence that the entire batch is sterile. However, this presumption approaches certainty if exhaustive study with test batches has demonstrated that units throughout the test batches were rendered sterile by the selected process.

Obviously, the processing conditions must be carefully controlled so that all subsequent batches receive exactly the same treatment as the test batches.

The United States Pharmacopeia and the National Formulary recognize this problem and both volumes include a discussion of sterilization procedures. The lead paragraphs of the USP and NF are almost identical and contain the following key admonition (the quote is from the USP): "The sterilization process requires not only vigilant supervision of equipment and procedures by personnel well trained in devising and applying methods for attaining sterility, but also adequate proof of the effectiveness of the procedures used." Both the USP and NF mention some of the sterilization problems, such as the possibility of air pockets in steam autoclaves, and how to test the sterilization procedure to determine whether it is dependable.

FDA's experts recognize that testing of the finished product can not provide conclusive proof that the batch is sterile. Thus, the September, 1967 issue of "FDA Papers" features the following quote from an article by Dr. Carl W. Bruch, Chief of FDA's Bacteriological Branch. "Sterility cannot be inspected into the product, but must be a result of the total system employed in production, sterilization, and distribution of it."

Stability Tested

We turn finally to the matter of stability. The careful manufacturer studies the behavior of his new drug substance under a variety of conditions and this information helps him decide on the final dosage formulation and the type of container. He continues to monitor the stability of the product after it is in commercial production. This stability testing program may show the need for labeling the product with storage instructions such as "Keep in a cool place", or may show the need for labeling each batch with an expiration date.

Summary

In summation, the precepts followed by forward-looking drug manufacturers are as follows:

1. Study the new drug substance and the proposed dosage forms just as far as scientific methodology permits.

2. Study the manufacturing process very thoroughly in order to discover its critical features.

3. Based on the information obtained in 1 and 2, develop the best possible manufacturing process for the product.

4. Employ comprehensive in-process controls and final product testing to help assure a uniform and reliable output of safe and effective medication.

These principles form the basis for the credo of this country's leading drug manufacturers: "Quality must be built into the product during research, development, and production." **[The End]**

LABELING REGULATIONS ISSUED BY FDA

The Food and Drug Administration has established labeling requirements for drugs, devices and cosmetics under the authority of the Fair Packaging and Labeling Act and the Federal Food, Drug and Cosmetic Act. The regulations will become effective on July 1, 1968. However, valid objections to the regulations filed on or before February 10, 1968 could stay their effective date.

Detailed requirements are established concerning identification of the product, the name of the manufacturer, packer, or distributor, his place of business and the net quantity on the principal display panel.

Highlights of the requirements include:

Drugs and Devices: identifying a prescription drug by its established name; listing the active ingredients of over-the-counter drugs and specifying the effect of each; augmenting the quantity statement of a drug available in several dosage forms; and excluding qualifying words like "giant pint."

Over-the-counter veterinary injection preparations are exempted from fluid ounce and dual declaration requirements provided the quantity is expressed in the metric system of measure.

Cosmetics: permitting the use of a fanciful name for a product provided the identity of the product is apparent; using tear-away tags, tapes or wrappers on certain decorative and small containers; and declaring the quantity of contents of "cosmetic kits" in terms of the number of applications. Reg. §§ 1.1, 1.1(c), 1.101a—1.202b, CCH FOOD DRUG, COSMETIC LAW REPORTS ¶ 9851, 9854, 9911—9942.

The Prescription Drug Advertising and Labeling Regulations

By VINCENT A. KLEINFELD

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BECAUSE OF THALIDOMIDE, the Food and Drug Administration could probably have secured from Congress as part of the Drug Amendments of 1962 virtually any authority it wished. Nevertheless, hardly had the Amendments been passed before various sections were administratively construed to a point which no one (at least in industry) had contemplated.

Certainly the Amendments do not specifically state, for example, that the established name of a drug must accompany, in labeling and advertising, each appearance of the proprietary name. The position taken by the government may have pleased some of the congressional sponsors of the 1962 Amendments or various lay-science writers, but that is hardly a sound, let alone legal, reason for reaching a conclusion which is of no merit. How is the physician or public protected by a requirement that the generic name must follow the proprietary name of a drug each and every time the latter is employed? It would seem that a different position could and should have been taken by the government.

The proposed revision of the labeling portions of these regulations, section 1.106, continues to utilize the ingenious ploy that the labeling of prescription drugs cannot comply with the requirement of Section 502 (f) (1) of the Act relating to "adequate directions for use." Therefore, according to the Food and Drug Administration, the only way those products can escape being misbranded for failure

of its labeling to bear adequate directions for use is if they are exempted from the statutory mandate. This is the reason why regulation 1.106(b) is phrased in terms of an "Exemption for prescription drugs." In order to qualify for the exemption, the regulations create the concept of "full disclosure" and require that such "full disclosure" information, or variants thereof, appear not only with the immediate package of the drug but also as part of a myriad of other material, some of which clearly is not "labeling" as defined by the Act.

The substantive premise upon which the full disclosure regulations rest, that Congress imposed a statutory requirement that could not possibly be complied with directly, is patently invalid. While there is merit in the end sought, full disclosure, the means by which it has been accomplished amount to an unnecessary sleight of hand.

Why could not the government have requested what it would readily have obtained, direct statutory authorization for "full disclosure"? Instead, the Agency has developed the concept in a complicated and circuitous manner of doubtful legal validity.

Difficulties Compounded

The difficulties which have been occasioned by many of the administrative positions taken both before and after the passage of the 1962 Amendments are indeed compounded by the proposed prescription drug advertising regulations. I liken them to the Gleipner Chain with which, according to Norse mythology, the gods had bound the Fenris wolf. The chain was made of the noise of a cat's footfall, the beard of women, the roots of stones, the breath of fish, and the spittle of birds. The comparison with the regulations is clear, for many of them (1) go beyond the statutory authority, (2) are so vague and ambiguous as to be almost incomprehensible, and (3) serve no useful purpose.

Regulations with respect to the providing of information in advertising in brief summary relating to side effects, contraindications and effectiveness are called for by Section 502(n) of the Act, but those which have been proposed have gone far beyond this directive. I do not intend to discuss each item of the regulations. This would take hours, and I am sure that members of the drug industry have made their opinions and suggestions entirely clear. I intend merely to discuss a few examples.

I am sufficiently illiberal to believe that Congress should pass our laws, even in the unique food and drug area, and that positions should

not be taken based on the personal predilections of some particular administrative official, physician or lawyer acting as physician. This would seem to be particularly true in this field, where there is no real difficulty in obtaining congressional action when any real need is demonstrated. Like Macaulay, I cannot agree with the creed that "I am in the right, and you are in the wrong. When you are the stronger, you ought to tolerate me, for it is your duty to tolerate truth. But when I am the stronger, I shall persecute you, for it is my duty to persecute error." After these expressions of personal philosophy, let us turn to an examination of some of the proposed prescription drug advertising and labeling regulations.

First of all, what is the point in setting forth regulation after regulation which merely parrots the law? As stated by a Food and Drug Administration official this year, "there are, of course, many difficulties in trying to write regulations. . . . If they are too broad, they become essentially meaningless because they add nothing to the statutory language." What is gained, for example, in saying that an advertisement for a prescription drug covered by a new drug application approved after October 10, 1962, shall not recommend or suggest any use that is not in the approved labeling, or that the advertisement of a prescription drug covered by a new drug application which became effective prior to October 10, 1962, may recommend uses contained in the approved labeling and additional uses contained in labeling in commercial use on October 9, 1962, to the extent that such uses did not cause the drug to be an unapproved new drug?

Unnecessary Items

What useful purpose is served by setting forth 34 instances when an advertisement will not satisfy the requirement that it present a "true statement" of information in brief summary relating to side effects, contraindications and effectiveness if, in a number of those instances, the practices specified are clearly violative of the Act? What is the necessity for proscribing, for instance, in lengthy and laborious regulations, the failure to reveal material facts, or the use of information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does, or the employment of literature references that may exaggerate the effectiveness of a drug, or the use of data or conclusions from studies of a drug in animals or in vitro in a way that suggests they represent clinical studies, or in a way that suggests they have clinical significance when, in fact, no such clinical significance

has been demonstrated, or utilizes a quote or paraphrase out of context to convey a false or misleading idea, or uses literature quotations or references which purport to support a claim but in fact do not support the claim or have relevance to it, or contains claims concerning the mechanism or site of drug action that are not supported by substantial evidence?

These are not all of the unnecessary items which are set forth in the proposed regulations as not satisfying a requirement that an advertisement for a prescription drug present a "true statement" of information in brief summary relating to side effects, contraindications and effectiveness. But they are typical examples of what, in my opinion, serve no useful purpose other than to complicate further an already complex situation and set up some strawmen.

Other Regulations Confusing

Other of the regulations are confusing and go beyond the provisions of the statute. One example is the requirement in section 1.105(e)(1)(ii) that a "reminder" advertisement must not only not make any claim for safety or effectiveness but also must not make any claim with respect to any "other quality of the drug." Section 1.105(e)(2)(i), providing that "each representation and suggestion" in an advertisement shall be consistent with the requirement that it present a true statement of information in brief summary, imposes an impossible and unrealistic burden and one not authorized by the Act. The provision in section 1.105(e)(2)(iii) that an advertisement shall disclose all the side effects pertinent not only to the uses of the dosage forms set forth in the advertisement, but also all other uses for which the advertised dosage form is commonly prescribed and all other uses for which such dosage forms are recommended in any labeling or advertising disseminated by the manufacturer can only lead to an unnecessary cluttering up of advertisements. As a matter of fact, the requirement that the advertisement set forth the side effects and contraindications for the uses for which the advertised dosage form "is commonly prescribed" could raise new drug questions. The provision in section 1.105(e)(i)(a) that an advertisement for a new drug shall contain each side effect and contraindication "idea" in the labeling is a particularly vague one, and I fail to see how this conforms to the statutory criterion of "brief summary."

Section 1.105(e)(3)(iii)(a), (b), (c) and (d) is particularly complicated. Of course, a drug which is generally recognized as safe

and effective by qualified experts for the conditions for which it is offered is not a new drug. But if there is no such general recognition of safety and effectiveness the product would presumably be a new drug even if substantial evidence of safety and effectiveness does exist, and nothwithstanding that substantial clinical experience exists, adequately documented in medical literature or by other data on the basis of which it can be concluded by qualified experts that the product is safe and effective. Can it be that these regulations are designed to whittle down the statutory definition of a new drug? Is a miracle occurring? Certainly the distinction between (a) and (b) is indeed a tenuous one. Similarly, subsection (d) appears to be incomprehensible.

Decision Left to Judgment of Officials

The references to "fair balance" between claims for safety or effectiveness and information relating to the limitations of safety or effectiveness open a Pandora's box, and leave the decision in each instance to the judgment of particular officials whose opinions may differ from day to day. Honest and qualified persons may differ on so-called "fair balance," and Congress did not choose to employ a term of such ambiguity. Here, again, the statutory term "brief summary" is further perverted by administrative fiat.

Section 1.105(e)(5)(i) states that an advertisement for a prescription drug is false, "lacking in fair balance," or otherwise misleading if it contains a representation, not approved or permitted for use in the package labeling, that a drug is better, more effective, more useful, safer, has fewer side effects, etc., "than has been demonstrated by substantial evidence." Presumably this permissiveness does not apply to approved new drugs, but the section does not say so. Subsection (ii) declares that a prescription drug advertisement will violate the law if it contains a drug comparison claiming advantages for a drug without "simultaneously" disclosing any pertinent disadvantages. This is of dubious legal validity and serves no really useful purpose.

Section 1.105(e)(5)(xi) contains other particularly ambiguous phraseology in stating that an advertisement will be misleading if it contains information from a study "that lacks significance" because it was uncontrolled, "or for other reasons." What are these "other reasons," and will they change from day to day due to changes in administrative thinking or because some new official has some new thoughts or "reasons" or decides to change his mind?

Subsection (xiv) of section 1.105(e)(5) declares that an advertisement will be false, misleading or lacking in fair balance if it uses literature or references to recommend conditions of use that are not approved or permitted in the drug package labeling or for which there is insufficient evidence to establish safety and effectiveness. Does this mean that, even though certain conditions are not approved or permitted in the labeling, a drug may be offered for other conditions for which there is, in someone's opinion, sufficient evidence to establish safety and effectiveness?

Meaning of "Brief Summary"

I see nothing in the Act which justifies the provision in subsections (xxvii) and (xxviii) that limitations on the effectiveness of a drug must be placed "in immediate conjunction with and as prominently as any claim for effectiveness, whether or not such limitations are disclosed in another part of the advertisement," or which requires that specific side effects or contraindications pertinent to any claim for safety must be placed "in immediate conjunction with each claim for safety even though such limitations are disclosed in another part of the advertisement." Is this what Congress meant by "brief summary"? Nothing in the legislative history so indicates.

Subsection (xxix) (a) is particularly unclear in the vague and extra-legal use of such terms as "in as much depth and detail," "taking into account the length of the advertisement and the nature of its message," "two permissive levels of summarization," "are presented briefly," and may be presented concisely provided that "each such idea" expressed in the drug package is presented in a brief summary. Subsection (b) pulls a new and startling rabbit out of nowhere by creating a new concept, " 'Brief Discussion Summary,' comparable in depth and detail with the information required in the drug package labeling under section 1.106(b)(3)." Again, what has happened to the statutory directive that a brief summary be provided? Subsection (xxxi) is equally vague and sets forth requirements outside of the Act and which serve no useful purpose.

Things Included in "Labeling"

The regulations designate as "labeling," among other things, brochures, booklets, mailing pieces, calendars, price lists, letters, motion picture films, sound recordings, exhibits, and similar pieces "of printed, audio, or visual matter" concerning a drug and which

are disseminated by its manufacturer, including reference publications such as the Physicians' Desk Reference. There is hardly the slightest obeisance to section 201(m), since there is not even a reference to whether the material must "accompany" the drug. And how audio material may be designated as coming within the definition of that section is difficult indeed to understand. Nothing in *Kordel*[1] or *Urbeteit*[2], decided by the Supreme Court, lends any genuine support to the regulation.

The blithe assumption that motion picture films and audio and visual material are labeling is without statutory or judicial sanction. Perhaps it was thought that the law had to be stretched when the Food and Drug Administration did not have jurisdiction of prescription drug advertising. But that reason, hallowed though it may have become, no longer exists.

Ambiguity and Shifts in Administrative Thought

The ambiguity and shifts in administrative thought and construction, so hazardous to those who wish to comply with the law, are evidenced by the fact that only several years ago a Food and Drug Administration official said that "It is our present view that the fixed exhibit for a prescription drug be considered advertising, subject to the same rules that govern advertisements in medical journals." Again, there may have been some administrative reason for reaching that conclusion at that time, but the supposed benefits to be gained by designating something as labeling or advertising should not be the determinative legal factor. And another Food and Drug Administration official stated, at the "FDA Conference on the Kefauver-Harris Drug Amendments and Proposed Regulations, held February 15, 1963," that "it does not seem impossible or unreasonable to require the 'full disclosure' information to appear in conjunction with the exhibit."

The revision of section 1.106, dealing with directions for use in labeling, refers to incorporating adequate information as to full disclosure as "an integral part of such labeling." I see nothing in the Act which makes or authorizes such a provision, and there is little that is more indefinite than a reference to an "integral part." And the term "full warning disclosure," concocted by the regulations, only serves to confuse further an existing tremendously complicated situation.

[1] *Kordel v. U. S.*, ('48) 335 U.S. 345, 336 U.S. 911, 69 S. Ct. 706.

[2] *U.S. v. Urbeteit*, ('48) 335 U.S. 355.

The provision amending section 1.106 by revising paragraph (b) (4) to add (i)(c), requiring a "brief summary" for labeling under certain conditions, is virtually incomprehensible, particularly when the immediately preceding subsection is read. It should not be necessary that one be a learned expert in semantics or a talmudic or jesuit scholar or logician to be able to understand a regulation presumably having the force and effect of law. And as far as so-called "reminder labeling" is concerned, in (d), what are the compelling reasons for not permitting labeling to contain "other information or representation in words or by means of graphic matter" than the name and established name of the drug, the dosage form, quantitative ingredient information and information relating to quantity, price and name of the manufacturer?

Constitutional Issues

An important problem, involving the constitutional rights of free speech and free press, is created by the regulation dealing with motion picture films, sound recordings, "and related audio or visual promotional labeling." There appears to be a studied attempt to prevent a manufacturer of a drug from distributing material concerning a product or class of products, even though it is educational, if the government disagrees with the contents in whole or in part. I suggest that this appears to be part of a campaign to apply what amounts to censorship to any and every discussion of a drug which has not been approved in advance by the government.

This is accentuated by the Proposed Statement of Policy dealing with the "Promotional Labeling of Oral Contraceptives," published in the Federal Register of September 13, 1967. For example, section 3(b)(1) states that films which are generally promotional in the sense that they relate to oral contraceptives as a class, a member of which is marketed by the firm sponsoring the presentation, is regarded as labeling if promotionally slanted through use of information that is false or misleading or lacking in balance. I should think that educational material does not become labeling because, in the opinion of some official, a statement is false or misleading. If material is in fact educational it is not the proper concern of the government.

In addition, the requirement that the "major side effects and contraindications" be an integral part of the "audio or visual presentation" presents a recent major change of position or some whim on

the part of some particular official or officials. I see no legal authority for this, even assuming that the requirement can be met. Of course, by designating the items in question as labeling for new drugs, censorship is required. But as indicated, it would seem strange indeed, at least to those not immersed for years in the food and drug area, to hold that these items come within the definition of labeling in section 201(m). And again, how much more vague can language be than expressions such as "integral part"? And if a motion picture, by some magical metamorphosis, is labeling, why should not the presence and distribution of the package insert or full disclosure suffice?

In the 1963 Food and Drug Administration Conference which I have referred to, a prominent Food and Drug Administration official stated, in part, that "We believe that unless the movie presents the whole story about the drug, then the persons who view the movie should be presented with a full disclosure brochure containing all of the information needed for proper use of the drug." I should think that this made some sense, that industry has a right to rely on such public pronouncements, and that in any event the law is not amended when some official decides to change his mind because of his personal views.

Three Recommendations

I have three recommendations to make with respect to the regulations. First, a scalpel should be wielded mercilessly to delete the many unnecessary provisions which add nothing but verbiage. Second, it should not be a Herculean tasks to render those which are left reasonably intelligible. Third, the regulations should be in accord with what Congress provided, admitting, as we should admit, that the Act should be construed so as to effect its remedial purposes. The Commissioner stated recently, and I quote:

> I have frequently wished that the managements of food, drug and cosmetic companies and their advisors would pay closer attention to what Congress has decreed and make a real effort to conform to it.

I say "Amen" to this, but I suggest that the admonition be pursued so that it would say, also:

> I have frequently wished that the management of the Food and Drug Administration and its advisors would pay closer attention to what Congress has decreed and make a real effort to conform to it.

[The End]

Drug Advertising Regulations

By JULIUS HAUSER

Mr. Hauser Is Assistant for Regulations, Office of the Associate Commissioner for Compliance, FDA.

THE FOOD AND DRUG ADMINISTRATION and the industries subject to regulation under the drug advertising provisions of the Federal Food, Drug, and Cosmetic Act are in broad agreement on a number of essentials involving the advertising of prescription drugs. This is evidenced by the following public statements:

(1) "We believe that good medical advertising is essential to good health in America today." This is not quoted from a statement made by representatives of advertising agencies or drug manufacturers but from a statement issued by the Food and Drug Administration on April 17, 1967.

(2) "* * * we believe that prescription drug advertisements must be impeccable as to accuracy, honesty and truthfulness, and should comply with the law and with Congressional intent * * * Good medical advertising sells drugs through the factual, accurate and timely presentation of information. Its function is to promote the use of a drug within its therapeutic potential for the alleviation of illness and to do so in accord with good medical and good business practices." This statement is not a quotation from a Food and Drug Administration source, but is part of a sentence appearing in the written comment from the Pharmaceutical Advertising Club, Inc., of New York on the proposed revision of the advertising regulations published by FDA in the *Federal Register* of May 23, 1967.[1]

(3) "There can be no compromising with the basic requirement that prescription drug promotion and advertising must be honest, truthful, and accurate. We recognize that it is to the advantage of the public, the medical profession and the pharma-

[1] 32 *Federal Register* 7533.

ceutical industry that there be clear laws setting forth the restrictions in support of these objectives." This statement is quoted from the written comment of the Pharmaceutical Manufacturers Association on FDA's proposed revision of the prescription drug advertising regulations.

Promulgation of Current Regulations

In view of this apparent consensus, it is remarkable that the current regulations under section 502(n) of the FD&C Act were promulgated with finality only after initiation of a public hearing based on objections to the 1963 proposals by the PMA, member firms and others. The request for a hearing was withdrawn and it was adjourned after an informal exchange of correspondence led to agreement on the current regulations.

Since the current advertising regulations were promulgated, from the viewpoint of FDA the advertising of prescription drugs has become progressively more informative and truthful, and much of it is now in substantial compliance with the requirements of the Act and regulations as interpreted by FDA. Further, this change has occurred without any notable decline in the volume of prescription drug advertising and without sacrificing the creativity of promotional messages. This is to the credit of the pharmaceutical and advertising industries, but despite this FDA has found it necessary to initiate a handful of seizure and prosecution actions and roughly a baker's dozen "Dear Doctor" letters intended to correct the damage done by offensive advertising.

The proposed revision of the regulations published in the *Federal Register* of May 23, 1967, are based on FDA experience with the operation of the existing regulations and were in response to industry requests for their clarification. For example, a letter from a manufacturer member of the PMA includes the statements:

> From time to time the Food and Drug Administration has criticized some of the prescription drug advertisements, and members of the industry have periodically requested some clarification from the agency regarding the application of the present regulations. It is apparent that in view of the confusion which has existed concerning the implementation of the statutory authority new regulations are needed.

Study of Comments

It is also remarkable, but not surprising, that of 96 comments on the recently proposed revisions of the advertising regulations from pharmaceutical manufacturers, publishers of medical publications,

advertising agencies, trade associations and two physicians, all were opposed to virtually every aspect of the proposals. But perhaps more significant than these communications is a letter of October 13, 1967, to the Hearing Clerk which reads as follows:

Dear Sir:

We wish to express our opinion on the new proposed laws for stricter labeling laws, especially in the Drugs department.

We are definitely in favor of extremely strict laws in drug labels.

Thank you.

Mr. and Mrs. .....
Waterbury, Connecticut

All of us may well consider whether this letter may not be an accurate reflection of the attitudes of the customers of the regulated industries, and of the public served by the Food and Drug Administration.

But FDA is giving serious study to all of the comment received on these proposals. One of the comments, "As proposed, the regulations would place FDA in the position of prosecutor, judge and jury based on their subjective interpretation of loosely defined qualifying adjectives, such as 'significant,' 'authoritative,' and the like," characterizes a submission of an honesty and level of intellectual appeal frequently associated with advertising.

However, much of industry's written comment on the proposed regulations will materially assist the revision of the proposals to further clarify their intent to establish strong but reasonable controls. It is obvious that industry has expended a vast quantity of talent in the analysis of these proposals and FDA will welcome additional contributions of such talent to develop the language changes necessary to minimize uncertainties. We are confident that the actual intent of the proposals is abhorrently clear to the industries' analysts.

Maintenance of Basic Concepts

It may be anticipated that FDA will not abandon these basic concepts embodied in the published proposals:

(1) The provisions of the Act and regulations affecting the advertising of prescription drugs apply to all representations and suggestions in an advertisement with respect to the side effects, contraindications and effectiveness of a drug. Jurisdiction is not limited to a small part of an ad designated as the "Brief Summary."

(2) No part of an advertisement may be false or misleading with respect to side effects, contraindications or effectiveness of a drug. A featured representation that is misleading for lack of

adequate qualification cannot be corrected by a contradictory factual statement in the "Brief Summary."

(3) The side effects and contraindications information in an advertisement will be required to disclose all of the side effects, precautions, warnings and contraindications that are required to be disclosed in the labeling that is part of the drug package.

(4) A lack of "fair balance" will continue to be defined as misleading.

(5) A list of frequently encountered offensive advertising practices will be retained to make the rules quite clear even to those most persistent in professing their inability to understand the regulations.

(6) The regulations will establish rules as to the format of advertising to the extent necessary to avoid undue subordination of information concerning side effects and contraindications.

This is not an exhaustive list of the concepts the regulated industries should learn to accept. Industry-FDA cooperation to phrase the regulations embodying sound concepts in a mutually acceptable manner is the most desirable course and in the public interest. It is a pleasure, therefore, to note that informal discussions with responsible members of industry show this view is mutual and the elimination or minimizing of differences is a distinct possibility. **[The End]**

NEW UNITS ESTABLISHED FOR CERTIFICATION OF ANTIBIOTICS OR INSULIN

A reorganization of the Food and Drug Administration's system for the analysis and certification of antibiotics and insulin has been established. The new Office of Certification Services, under the direction of the Associate Commissioner for Compliance, will be responsible for administrative action for sample certification, reviewing requests for exemption from certification, and preparing and coordinating antibiotic regulations.

The National Center for Antibiotics and Insulin Analysis, part of the Bureau of Science, Division of Pharmaceutical Sciences, will be responsible for batch-by-batch testing of antibiotic and insulin samples submitted to the FDA for certification. The FDA's New York District Office has been assigned the responsibility for the inspection of foreign firms seeking certification of antibiotic products for import into the United States. 32 *Federal Register* 15721, CCH FOOD DRUG COSMETIC LAW REPORTS ¶ 2441.

Risks vs. Benefits in Drug Development

By R. W. BALLARD, M.D.

The Author, R. W. Ballard, M.D., Is the Executive Medical Director of McNeil Laboratories, Inc.

LOUIS PASTEUR ONCE SAID, "It is only when I can state that I can vaccinate with complete safety any number of bitten dogs that I shall dare to start vaccinating human beings. Even then my hand will tremble because what is possible in dogs may not be possible in man."[1] This was a recognition of potential risk when going from animal to man. Yet Pasteur weighed the risk of treatment against the hazard of the disease in man and we are all the better for it.

Let us recognize an inescapable truth. Research on humans is absolutely essential if there is to be progress in the knowledge of diseases and their prevention, treatment, and cure.[2] This is a general statement applicable to all types of clinical research, but here we are concerned with drug research specifically.

Since the advent of the sulfonamides in the 1930s, we have seen a great and steady increase in the introduction of new therapeutic drugs. None of these has been introduced without animal and human research prior to their general availability. This has been one of the benefits in drug development, and it should be stated here that the vast majority of the valuable new drugs has been discovered in the laboratories of the pharmaceutical industry.[3] Two notable exceptions here are penicillin and streptomycin, but even here the pharmaceutical industry's technology and production know-how made them rapidly and readily available to all.

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[1] Boissier, J. R., Lechat, P., "Can Side Effects of Drugs Be Predicted on the Basis of Pharmacological Tests?," *Proc. European Society for the Study of Drug Toxicity* Vol. II, 1963, pp. 35-42.

[2] Committee on Public Health, The N. Y. Academy of Medicine, "Medical and Biological Research on Human Beings," *Bull. N. Y. Acad. Med.* 43 (6):525-27 (June) 1967.

[3] Dunlop, D., "Use and Abuse of Drugs," *Brit. Med. J.* 2:437-441 (Aug. 21) 1965.

What Risks Are Involved?

What are the risks involved in drug development? The statement that no drug is completely safe has been made many times, but to make such a statement does not bring things into the proper perspective. Many assessments must be made when considering any drug. What is the condition to be treated? Are other effective drugs available? Is this a life-saving situation? Is it merely for symptom relief? Are other drugs being used at the same time? What is the age, weight, height, sex and condition of the patient? Already we can see the myriad of variabilities and problems that arises when a doctor starts to treat a patient. All of these arise when a known drug is to be administered to a patient, but when the same doctor is confronted with an experimental drug for the same patient, a different set of variables is immediately added to the first group.

The state of the art in drug development is at a stage when most risks are either minimal or tolerable, but nothing is 100 per cent in this field. The greatest difficulty in interpreting animal tests is that none of them gives absolute proof that a drug is safe for human beings. However, they are useful guides and if the early clinical trials in man are conducted properly, potential adverse effects can be elicited without undue harm.

As an example of this, I would like to cite the experience we had recently in our own laboratory with a new compound. This drug in animals was decidely superior to anything presently available in its particular field. No adverse reactions were noted in the animals and the toxicity tests showed a good therapeutic margin, with no disturbances in the blood clotting mechanism even in primates. But the reason we checked specifically for clotting problems was that a related congener had caused bleeding in one animal species. Our initial safety trial in humans was run on volunteers at a low, medium and high single dose, with all laboratory parameters run before and after dosing. Everything was normal; then came the continuous trial for 2 weeks at 2 dose levels that were not as high as the single doses. Again, all laboratory parameters were measured, including all known tests involving blood clotting. At the end of the first week all was normal. On the last day of the second week, one of the volunteers noticed blood in the urine and bleeding from the mouth and rectum. The drug was stopped on all volunteers. Platelet values for the one volunteer were practically nil and 4 other volunteers showed low platelets but no bleeding. The one patient was transfused with one unit of blood and all bleeding stopped. Within one week the platelet

counts were returning to normal and in 2 weeks all were normal. No sequelae have been seen at 2 months post therapy.

This illustrates proper planning for trial and even in the face of serious toxicity no severe harm resulted because of the precautions taken. Here, in the face of negative animal work, the toxicity appeared in man. This is one of the risks, but can be obviated in most instances with the proper safeguards in the early trials.

Unpredictable Areas

The animal screen is not infallible, but over-all experience at this stage of our art shows it to be sufficiently accurate to permit the transition from animal test to clinical trial with a tolerable element of risk. There are, however, 4 main areas in which the animal screen cannot predict and for which at least Phase I clinical trial is necessary; and, even here, they may not show up in the first limited numbers of patients. They are:

1. Adverse effects, particularly toxic psychoses, skin lesions and allergenic reactions;

2. Optimum therapeutic benefits in a given disease in cases where there are no exact counterparts of a human disease in one or more laboratory animals;

3. Dose response curves, maximum tolerated doses and pathways of metabolic degradation (these must be discovered in the human since they may differ from those established for certain animal species or strain);

4. Essential biological elimination of a remedial agent which must be measured in humans and compared with that determined in animals.[4]

Because of species variance and variations in strains within species, potential adverse effects may not be found in animals. The same variations can be seen in man himself. Variability in rates of metabolism can lead to toxic reactions. The same daily dose of a drug may cure, cause severe toxicity, or have no effect whatsoever.[5] So long as we are aware of these possibilities in our early trials and later in the Phase III or widespread trials, prompt action can be taken to handle the problem. Naturally, there are some side effects that will not show up until a drug is used by many thousands, and this means that it is already on the market. The government, industry, and the

[4] Koppanyi, T., Avery, M. A., "Species Differences and the Clinical Trial of New Drugs: A Review," *J. Clin. Pharmacol. Therap.* 7:250-270 (1966).

[5] Brodie, B. B., Cosmides, G. J., Roll, D. P., Toxicology and The Biomedical Sciences," *Science* 148:1547-1554, No. 3677 (June 18) 1965.

medical profession are aware of this; and the adverse reaction reporting system is now beginning to function so that the necessary warnings can be issued to prevent any tragedy.

On the other side of the coin we have no way of knowing when an agent that might have been effective for human treatment is rejected by animal screening tests. Only occasional accidents or perhaps serendipity bring to light clinically effective drugs that had been discarded in animal tests. N-allylnormorphine was found to be a powerful analgesic when given to human patients for other reasons, though it was originally eliminated by the animal tests for analgesia.[6] This was the clue that led to the development of one of the new nonnarcotic analgesics that is now available.

The Public: Information and Protection

An important risk we all face today is the journalistic zealot or the overly ambitious politician who will take isolated instances and put them in the wrong perspective, thus frightening an already uneasy public. Until such time as the public is better educated to the risks and benefits of research, we should all refrain from premature public release of information that could be misinterpreted or played up out of proportion to reality; and thereby bringing about restrictive legislation that would seriously hamper research and development and unnecessarily restrain the practicing physician.

The public already has a large measure of protection. The basic desire of the physician is to heal. If something goes amiss in research, it is not likely to be fruitful for the patient, humanity, the physician, or for the science of medicine.

There are many guidelines and restraints already available to protect the patient. Among them are the Nuremberg Code, The Declaration of Helsinki from the World Health Organization, The Code of Ethics of the American Medical Association, and the patient consent section of the government regulations governing research on humans.

Conclusion

Time does not permit the revelation of many specific details and facets pertaining to this complex problem of risks vs. benefits, but with so many diseases yet to conquer and the unravelling of the aging process, we must move ahead, accepting a certain amount of risk to gain the benefit. **[The End]**

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[6] Greiner, T. H., "The Gap Between Pharmacology and Therapeutics," *J. New Drugs* 6(2); 69-76 (Mar.-Apr.) 1967.

Risks vs. Benefits in Cancer Drug Development

By KENNETH M. ENDICOTT, M.D.

Dr. Endicott Is Director of the National Cancer Institute.

THE PRECEDING ARTICLE ON THIS SUBJECT dealt with the general problem of risk versus benefit and emphasized the role of preclinical pharmacology in reducing risk. I shall discuss the risks and benefits in cancer drug development, the field I know best.

Before considering the risk of drug therapy and the potential benefit, it is necessary to consider the disease itself and the effectiveness of conventional therapy.

Cancer is a fatal disease in most cases if left untreated. If treated by the accepted forms of surgical and radiation therapy, only 35 percent of patients survive 5 years. The outlook varies with the type of cancer and the stage of the disease. Some forms are invariably fatal in a matter of months. In other forms such as skin cancer, the chance for cure is as high as 95 percent. Conventional surgical and radiation therapy may carry substantial risk. Surgical mortality as high as 20 percent has been observed in some studies. Some degree of residual disability is seen in most of the cures, and in many the disability is severe. Even so, there is general agreement that if there is a possibilty of cure through surgery or radiation the patient should receive the benefit of such lifesaving therapy.

Experimental chemotherapy has been limited to those cases beyond any hope for cure by conventional therapy. Here the prognosis is hopeless without chemotherapy and the potential benefit is life itself. Most patients and their families are more than willing to accept great risks.

Most of the drugs in use or under study are highly toxic and to be effective must often be pushed to toxic levels. Even the hor-

mones being used may have serious side-effects at useful doses. Thus the risks of drug therapy may also be substantial, but in the ordinary course of events everyone concerned elects to accept the risks and hope for the benefits.

In actual practice both risk and benefit usually turn out to be less than a life and death matter. Drug toxicity, though often severe, is seldom fatal. Benefits, when they are seen, are generally of a palliative nature with partial or temporary remission with or without some prolongation of useful and comfortable life.

With each new drug there is always the hope that the results may be better, and sometimes they are.

Given a situation where death from the disease is virtually certain and the patient and his family are desperate, the safeguard of informed consent provides inadequate protection to the patient. The conscientious clinical investigator working to help the patient is himself in a psychological trap of desperation and tends to underestimate risk and overestimate the benefit of drug therapy in the face of the dismal prognosis. What this adds up to in my view is that those of us who have responsibility for drug development and clinical trials in this area must go out of our way to be sure that the risks taken are justified and that the patient's best interests are served.

The Best Safeguard

In studying anticancer drugs, the best safeguard is a tight protocol, every phase of which has been developed with the patient's best interests clearly in mind. Alternatives should always be built in to shift the individual patient who would be harmed by continuing the study onto another therapeutic track. If in the course of the study unanticipated difficulties arise there must be no hesitation in amending the protocol. There is no excuse for continuing the risk after the potential benefit has evaporated. Experience has shown that adherence to these principles in no way necessitates a departure from sound scientific appraisal of a new drug. As an added precaution, it is wise to have protocols reviewed by a jury of peers.

In the foregoing remarks I have been referring to cancer patients who are beyond hope of cure through surgery and radiation. This is familiar territory for the cancer chemotherapist. Now, thank God,

we are beginning to have enough success with drugs that new problems have arisen. There are drugs and regimens for acute leukemia which produce remissions lasting 5 years or longer. One can no longer test new drugs in fresh cases of acute leukemia until the established drugs have failed.

Drug treatment of choriocarcinoma is sufficiently effective that it is now used for patients with localized disease instead of surgical removal of the uterus, thus preserving the childbearing capability of young women. Here too new drugs cannot be tested until after established drugs have failed.

Another area deserving a few comments is the use of drugs in combination with surgery early in localized cancer of the colon, stomach, lung and breast. Obviously, such studies are not appropriate for untested drugs but must be limited to drugs which have already been shown to be active against that form of cancer in advanced cases. Even so, such studies may carry a special risk which must be weighed with the greatest care. Nearly all the candidate drugs depress the bone marrow and therefore may increase the risk of hemorrhage and infection which in radical surgery may tip the scale and greatly increase the surgical mortality. The chance for cure from surgery alone may be, let's say, 30 percent. If the chance could be improved by using drugs to, let's say, 75 percent, one would have to accept some increase in surgical mortality as reasonable. On the other hand, a minor improvement in cure rate could easily be cancelled out by increased surgical mortality.

The great difficulty is weighing risks and benefits, and especially in deciding when to terminate a study lies in the fact that the damage from the drugs generally occurs early while the benefits may not become apparent until months or years later.

In closing my remarks, I wish to point out that in experimental therapy I have always worked at the so-called "policy level" and never at the bedside. From such a lofty post it is easy to be critical, and I have always thought it my duty to play such a role. In all honesty, though, I must pay tribute to the generation of clinical investigators who have brought us to the present stage of cancer chemotherapy. I have found them to be unusually compassionate physicians who put the patient's welfare first and science second — which is as it should be. **[The End]**

Status of the Drug Efficacy Study of the National Academy of Sciences— National Research Council

By R. KEITH CANNAN

R. Keith Cannan D.Sc., Is Special Assistant to the President of the National Academy of Sciences-National Research Council.

THE FOOD, DRUG AND COSMETIC ACT OF 1938 required that evidence of the safety of a new drug should be submitted to and be accepted by the Food and Drug Administration (FDA) before the drug could be placed on the market. The Kefauver-Harris Amendments of October 1962, added the requirement that evidence of the effectiveness for the therapeutic claims made for the drug should also be submitted to and be accepted by FDA. The Administration interpreted this amendment to apply retroactively to all drugs for which new drug applications had been filed in the period 1938-62. This presented the staff of FDA with the overwhelming task of reviewing, within a reasonable period of time, the effectiveness of almost 90% of all drugs currently on the market.

In this situation, Commissioner Goddard sought the help of the National Academy of Sciences — National Research Council (NAS-NRC). The first informal approach was made in April 1966. A detailed proposal for the conduct of the study by the Academy was submitted to FDA early in June and a contract for the undertaking was signed on July 17.

A few days earlier, FDA published in the Federal Register a statement on the proposed study together with instructions on the procedures drug houses should follow for all drugs that they wished

to have reviewed. The original deadline for submission was September 9, 1966 and was honored by the great majority of firms. To accommodate the few laggards the deadline was extended several times and finally sealed at June 1, 1967.

By the end of July, 1966, the Academy had appointed a Policy Advisory Committee of 29 members and the chairmen of 27 evaluating panels and these had met in conference with representatives of the professions of medicine and pharmacy, of the pharmaceutical industry and FDA. From this conference emerged a public document known as the "Guidelines" which outlined procedures for the administration and conduct of the study.

Meanwhile office quarters had been secured and furnished and ten physicians of the Public Health Service had been assigned to the Academy by FDA to provide staff support for the work of the panels. Before the end of September the membership of the 27 panels (there are now 30) of six members each had been completed and the bulk of the submissions by pharmaceutical firms of claims and supporting data had been received.

All in all, 237 firms have submitted a total of 3637 drug preparations for review. Each claim for each drug is separately evaluated and a categorical judgment is made that the drug is "effective," "probably effective," "possibly effective," or "ineffective" for each stated claim, in accordance with definitions of these categories in the "Guidelines." For the majority of drugs multiple claims are made covering distinctive medical conditions that may require evaluation by different panels. In the case of one small class of drugs, 10 to 15 panels have been consulted. By the time that the study shall have been completed it is likely that it will incorporate more than 10,000 separate therapeutic evaluations. At the present time we estimate that we are two-thirds along the way and that review will be substantially completed by midsummer of 1968.

The panel members have had access not only to the material submitted by the proponents of the drugs but also to the medical literature and to pertinent data in the files of FDA. Members may request additional information from the sponsoring pharmaceutical firms and are quite free to draw upon their own individual clinical experience with the drugs under review. The four categories of decision listed above were established at the request of FDA to facilitate its handling of the reports. In most cases the panels have been constrained,

and have been encouraged, to elaborate and qualify their categorical judgments in extended explanatory comments.

The indications thus far in the Study are that few totally ineffective drugs are marketed, although there are wide areas in which modification or elimination of specific claims will be recommended. In a number of cases, the package inserts for effective drugs make additional claims that are unwarranted. Some drugs, originally marketed for one condition, have since been found to be effective for others, but the additional indications have not been included in the package insert. Finally, it has been noted that the package inserts even for drugs judged completely effective are very frequently out-of-date by many years. A number of the inserts have not, in fact, been revised since the drug was orginally marketed. In many cases the recommended dosages are no longer acceptable. Experience has shown that some of the stated precautions are not necessary, whereas new contraindications have come to light in the interim. Indeed, some panels have gone so far as to draft entirely new and uniform model package inserts for important drugs that are marketed by several producers accompanied by deviant insert materials.

Uniqueness of the Study

The Drug Efficacy Study is unique in a number of respects. It is uniquely extensive in scope and uniquely intensive in time. It is unique also in the therapeutic experience and competence of the evaluating team and in the climate of goodwill in which it is operating.

Although the study was undertaken in response to a request for advice from a regulatory agency it has not been influenced by the constraints that inevitably tend to formalize the execution of a statutory obligation. In other words, the reports that will be submitted to FDA will be, in tone and in substance, essentially the reports that would have been rendered had they been requested by a medical or an industrial group. Those who engage in a unique enterprise learn much from the experience. When the study shall have been completed there will remain the obligation to disseminate the fruits of this experience to all of those in medicine, in government and in industry who can profit from them.

First, there is need to bring to the attention of those who prescribe and distribute drugs the authoritative information on individual drugs that has been developed in a more effective way than the labelling and package inserts now achieve. Second, the reports on

individual drugs and on classes of drugs are a rich resource for the development of authoritative critiques of the precepts of current therapeutic practice—critiques in terms of categories of disease, of types of patients and of classes of drugs and critiques of the conventions of dosimetry, of therapeutic equivalency and of the uses of compound drugs.

Third, much has been learned about the good ways and the bad ways of getting down to the very practical business of evaluating the efficacy of drugs. This experience should be helpful to those who will guide the future conduct of the regulatory function of government and, indeed, to all who market, prescribe or distribute drugs.

Industry, the profession and government have a common interest in seeing that these jobs do not go by default. It will not do to leave them to George, that is, to the Drug Efficacy Study. They should be joint enterprises cooperatively undertaken. If these things are done in this spirit, there could develop in the world of drug affairs a warmer climate of understanding and goodwill than has prevailed in the past. **[The End]**

RECORD INSPECTION REQUIRED SEARCH WARRANT

Although the FDA has the right, under § 704 of the Federal Food, Drug and Cosmetic Act, to conduct reasonable inspections of certain documents, it must delimit the confines of search by designating the needed documents in a search warrant. On these grounds, the U. S. Court of Appeals in Philadelphia has reversed a criminal conviction of drug repackers for refusing to produce records requested by the FDA without a search warrant. During the course of a routine drug factory inspection, an examination of drugs on the repackers' shelves led the FDA inspector to suspect misbranding of prescription drugs, which brought about a request to inspect the records of receipt and distribution. The repackers refused to produce the records because they contained financial data. Following a determination by the inspector that labels he was permitted to take with him provided insufficient information, the inspector returned to the factory and was again refused access to the records. The court held that although the repackers had allowed a factory inspection, they were protected by the Fourth Amendment because the written notice of inspection did not authorize an inspection of their records. *U. S. v. Stanack Sales Co., Inc.*, CCH FOOD DRUG COSMETIC LAW REPORTS ¶ 40,284.

A Neighbor Comments Upon Some National and International Aspects of Food and Drug Legislation

By D. G. CHAPMAN

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Beginning of Food and Drug Legislation in Canada

In Canada, the first federal legislation dealing with the adulteration of foods and drugs was enacted 92 years ago. Its enactment resulted from the fact that many people at that time were consuming large quantities of grossly adulterated liquor. Now I understand that here in the United States your legislators were faced with a similar problem at that time. Your law makers evaluated the situation, and in their wisdom placed a prohibition on the manufacture and sale of liquor.

In Canada, similar action was considered. However, due to some considerable extent, to representations from French Canadians, our legislators took the stand that it was not liquor as such that should be banned but bad liquor. Hence, on and after January 1, 1875, any manufacturer of liquor found guilty of adulterating his product with such items as common salt, copper sulphate, opium, tobacco, Indian hemp or salts of lead and zinc, was sentenced to a fine of $100 and a month in jail with or without hard labour. The second offense carried a $400 fine and three months in jail.

In addition to the adulteration of liquor, other foods were also being adulterated at that time. We read in the first report in 1877, dealing with the adulteration of foods in Canada, that 90 per cent of the coffee contained from practically zero to 50 per cent of coffee

mixed with varying amounts of chicory, roasted wheat, peas or beans, and, in one case, toasted bread crumbs. All samples of mustard were found to be adulterated with flour colored with turmeric. Most of the pepper was found to contain from 25 per cent and upwards of roasted flour. Approximately 60 per cent of the milk was found to have had its water or fat content altered. I am sure that the situation in the United States at that time was not as serious as in Canada.

How far have we come since 1875? In our time, we have passed from the era of the bulk container of food, the cracker barrel, through the packaged food era to the present "convenience" food era. The trend is to more and more "convenience" foods containing more and more chemical additives. We as legislators must be cognizant of these facts and must insure that the legislation being developed is consistent with these advances and that such legislation does not stifle technological progress.

We must, of course, satisfy ourselves that all foods are safe. One Canadian citizen is quite apprehensive about the safety of our food supply and he has written to us as follows:

> Either you are ignorant or you are not doing your duty. Why do you think you are being paid if not for protecting the public. Do you know that if you had been working for a private company you would all be out of work. . . . Society is not supposed to serve as guinea pigs to chemists. Everybody knows that there is more cancer than ever and I personally believe that the main cause is the food we eat. I trust you will read this letter before throwing it in the waste basket.

The writer sent a copy of his letter to our Prime Minister, Mr. Pearson, to alert him to our ignorance and failure to do our duty.

Standardization of Foods

Much has been written and much has been said on the value of standards to the consumer, the food processor and the enforcement agency. Much has also been said regarding the possible adverse effect that standards may have upon technological advances in the food field. I know that the U.S. Food and Drug Administration is quite aware of all these aspects, as I hope we are in the Canadian Food and Drug Directorate, and that we govern ourselves accordingly.

Speaking first of activities at the national level, I have the impression that we in the Food and Drug Directorate in Canada are not as active in the standard-writing field as is the U.S. Food and Drug Administration. I have noted that Commissioner Goddard is reported to have asked that standards be written for frozen foods, baked goods, fish, nuts, fruit pies, pork and beans, and substitute dairy products. This is a formidable task and I understand that FDA's budget, at one point, included an item of $241,300 to cover

the work on new food standards, and that 16 new positions were requested in this area.

While, in Canada, we are continually amending our current food standards and writing some new ones, we have no crash program, at this time, for the preparation of large numbers of new standards.

At the international level, most of us are now aware of and some of us are actively involved in the work of the Codex Alimentarius Commission and its Committees. This attempt by the Food and Agriculture Organization and the World Health Organization to obtain international agreement on food standards warrants our serious support. Agreement will not come easily. It is only natural that governments will jealously guard their present food standards and food legislation and not wish to make a change. We must all enter into the discussions on international food standards with willingness to give and take in the interests of the international community. At the same time, we must, of course, insist upon requirements in the standards which will provide the consumer with a safe, wholesome food that is of reasonable quality and is correctly labelled.

I feel that one area of difficulty in obtaining international agreement on food standards will be the use of food additives. May I cite one example to illustrate this fact. Wine technologists tell us that sulphur dioxide is essential for the production of wine. As you know, sulphur dioxide is also used in preserving dried fruits and vegetables, fruit pulp, and is present in beer and other foods. The Joint Food and Agriculture Organization—World Health Organization Expert Committee on Food Additives has suggested that 90 milligrams of sulphur dioxide is the maximum amount which man can safely consume day after day. The consumption of foods in Canada containing sulphur dioxide is not large. The Canadian people as a whole have not developed that excellent European custom of drinking wine with their meals. As a result, the per capita consumption of wine per day in Canada is less than a tablespoonful. Hence, our intake of sulphur dioxide from wine is not large. This is not the case, however, in some countries. In Italy, statistics would suggest that every man, woman and child consumes on the average 300 millilitres of wine per day. In France it reaches 350 millilitres—or roughly 12 ounces. Now the International Wine Office in Paris advises us that wine cannot be made without the use of sulphur dioxide and that some wines require as much as 300 parts per million. If this is the case, then the person drinking 300 millilitres of such wine would be consuming 90 mg of sulphur dioxide. This means that all of the suggested safe level of

sulphur dioxide would be used up in wine alone. If the level of 90 mg is not to be exceeded, then sulphur dioxide could not be used in any other foods. Hence, each country when considering the use of food additives must be cognizant of the eating and drinking habits of its people and make its recommendations accordingly. To reach international agreement on such differing recommendations will require patience and understanding.

Now that the time is rapidly approaching when governments will be formally invited to accept the Codex Standards. The Food and Drug Directorate, is carefully comparing present Canadian standards with those being proposed at the international level. If Canada accepts these standards, it would seem desirable, for enforcement purposes, to incorporate such standards, at least in part, into the Food and Drug Regulations or other appropriate regulations.

References to Polyunsaturated Fatty Acids

We, in Canada, as you in the United States, have, in recent years, been wrestling with the question of the desirability of restricting the references to and claims for cholesterol and polyunsaturated fatty acids as they relate to foods. The following are examples of statements which have appeared on labels or in advertisements for foods in an attempt to influence the purchaser:

(i) Best for people concerned about saturated fats.

(ii) Now increased in polyunsaturates for health-minded families.

(iii) The kind of unsaturated liquid oil more and more doctors are recommending for good nutrition.

(iv) Highest ratio of polyunsaturated to saturated fat.

(v) It has more polyunsaturated fats and fewer saturated fats than any of the margarines made with other oils.

The Food and Drug Directorate does not wish to become involved in the controversy regarding the desirability of lowering cholesterol levels. We are aware, however, that many physicians wish to recommend diets containing high levels of polyunsaturated fatty acids. We know from surveys of the market that there is little relation between claims made for polyunsaturated fatty acids and their actual content of these substances. We, therefore, feel that we have a responsibility to ensure that meaningful labelling and advertising are available to assist the doctor in choosing or suggesting foods which, in his opinion, may be of value to his patient.

On October 30, 1967, the Directorate released what *may become* the regulations governing the claims pertaining to the fatty acid content of foods in Canada. These regulations will control both the

statements on the labels of foods as well as in advertisements. The effect of these regulations is that no reference may be made to fatty acid or cholesterol content of a food unless the food is an oil containing 40 per cent polyunsaturated fatty acids and not more than 20 per cent saturated fatty acids or it is a margarine-type product containing in its fat at least 25 per cent polyunsaturated fatty acids and not more than 20 per cent saturated fatty acids. If these conditions are met, then the percentages of polyunsaturated and saturated fatty acids may be referred to on a label or in an advertisement. No other claims would be permitted.

The practical effect of these proposals will be to restrict statements on polyunsaturates to oils such as corn, sesame, sunflower, safflower and soybean oil. Two margarines currently on the Canadian market would qualify to make statements regarding the fatty acid content. I understand that Commissioner Goddard and officers of the U.S. Food and Drug Administration are also actively examining this question of claims for fatty acids.

Hazardous Substances

May I now turn briefly to Canadian activities in the field of legislation to control hazardous substances. While we have federal legislation which controls the manner in which many potentially harmful substances, such as drugs and pesticides, may be offered for sale, there is, nevertheless, a large number of commonly used household substances over which there is no federal control and which, if misused, might represent a hazard to health.

We have, of course, been aware of and have carefully examined the U.S. Federal Hazardous Substances Labeling Act of 1960 and The Child Protection Act of 1966. In 1966, Dr. C. A. Morrell, the former Director-General of the Food and Drug Directorate, carried out a study of the need for and the manner in which legislation to control hazardous substances might be carried out.

As a result, a Hazardous Substances Act has been drafted and was given a first reading in the Canadian Senate on October 31, 1967. The Act has now been given a second reading and has been referred to a Committee for detailed study. If finalized in its present form, it will provide the Governor in Council with authority to prohibit the sale of certain designated hazardous substances, and permit the sale of certain other designated hazardous substances under prescribed conditions.

Attached to the proposed Act is a Schedule made up of Part I and Part II. Part I contains a listing of those articles which may

not be advertised or sold in Canada, such as: (a) jequirity beans; (b) furniture, toys and other articles intended for children, painted with a paint containing lead in excess of 0.1% expressed as lead oxide and; (c) paints for household use having a flashpoint of less than 40° F.

Part II, on the other hand, contains a listing of which may be sold under specified conditions. Examples of these are, (a) bleaches, cleaners and sanitizers for household use containing chlorine or its compounds; (b) cleansers, for household use, containing sodium hydroxide, potassium hydroxide, sodium bisulphate, hydrochloric acid or phosphoric acid; (c) household polishes and cleaning agents containing petroleum distillates or chlorinated aliphatic hydrocarbons and; (d) glues for household or hobbycraft use containing aliphatic or aromatic hydrocarbon solvents or ketone solvents.

This Hazardous Substances Act, if and when it becomes law, will probably be administered by the Food and Drug Directorate.

LSD

It appears to be impossible for any Food and Drug officer to make any statement today without a reference to LSD. Under the present Food and Drugs Act, LSD is listed as a Schedule H drug. Another section of the Act states that no person shall sell any drug listed in Schedule H. An Act to amend the Food and Drugs Act with respect to LSD was introduced in the Canadian Senate on October 31, 1967. This amendment has now been given second reading and has been referred to a committee for detailed study. The purpose of this proposed amendment is to classify LSD as a restricted drug and to make it an offense for any person except under the authority of the Act (1) to have LSD in his possession; (2) to traffic in LSD; or (3) to have LSD in his possession for the purpose of trafficking.

Conclusion

We in the Canadian Food and Drug Directorate have appreciated the co-operation and assistance extended to us by officials of the United States Food and Drug Administration. In our attempts to insure that foods and drugs in Canada are safe and are not deceptive in their presentation to the consumer, we have drawn from the activities and practices of the United States Food and Drug Administration. While we are a very small group, population-wise, we are rather proud of what we have done in Canada with regard to food and drug legislation. We like to think that other countries, even the United States, might, on occasion, find something of interest and of value in our legislation. **[The End]**

Current Tidings and Trends in Drug Appraisal

By BERNARD L. OSER

The Following Article Was Presented at the Fall Luncheon Meeting of the Drug, Chemical and Allied Trades Association in New York on November 20, 1967. Dr. Oser, This Magazine's Scientific Editor, Is with the Food and Drug Research Laboratories, Inc., Maspeth, New York.

THE DRUG INDUSTRY IS CURRENTLY in the throes of difficult times. It can no longer operate as it did as recently as 5 years ago. The procedures involved in the introduction of new drugs are becoming increasingly complex, and one can't even be certain that drugs that have been on the market for a number of years will be marketable a year from now. Congress has handed the Food and Drug Administration (FDA) a big stick in the form of the Drug Amendments of 1962 and since then the agency has been developing muscles to wield it. By means of detailed and broad-ranging regulations, FDA has become increasingly involved in procedures for evaluating, manufacturing, handling and marketing of drugs.

One wonders whether Congress fully appreciated the burden placed upon the shoulders not only of the drug industry but of FDA and the medical profession, when it demanded "proof" of effectiveness, as well as of safety, of new drugs. That the administrative agency was not prepared in terms of qualified scientific and medical manpower to fulfill its obligations under the New Drug Amendments became clear from the intensive search which was undertaken to fill staff positions and the numerous resignations and reorganizations which compounded the difficulties. The Pesticide, Food Additives and Color Additives amendments to the Act adopted since 1954 have contributed their share to the growing pains in the administrative agency. FDA's annual budget was relatively stable at about $5 to $7 million for the years preceding 1957, but it has steadily increased to

over $60 million in 1967. At the same time, the number of persons employed has risen from about 900 to approximately 5,000. It takes an understanding of their respective obligations and responsibilities to feel the deepest sympathy for both FDA and the industries it polices.

The decision to subject "old" new drugs to reappraisal for effectiveness resulted in FDA's entering into a contract with the National Academy of Science-National Research Council which undertook last year to review about 3600 drug formulations on the market since 1938. On the basis of guidelines established by 30 panels of medical specialists judgements as to degree of effectiveness ("effective," "probably effective," "possibly effective" and "ineffective") will be submitted to FDA. What action will be taken by FDA on those drugs rated as less than "effective" is not known at this time. The first series of recommendations emanating from this Drug Efficacy Study is expected to be rendered shortly. It will be followed by a critique of drug classes and a statement on the criteria deemed to be most meaningful for future evaluations.

Difficulties In Enforcement

The size of the load is only one aspect of the difficulties being encountered in the enforcement of the new drug provisions. Sitting between scientists and practitioners in the pharmaceutical industry and those in FDA, we hear complaints about the problems of finding and enlisting competent clinical investigators who are willing to contend with the mass of record-keeping and other restrictions involved in new drug studies, who are able or willing to obtain informed consent from their patients, or who will override ethical considerations and administer placebos or no treatment at all to "control" patients. We hear criticism from reputable biomedical scientists that FDA personnel, some of whom have been out of touch with medical research or practice, insist on extensive laboratory studies of questionable relevance or predictability even in cases where sufficient clinical experience exists to support the safe use of a drug. Experienced pharmacologists, clinical investigators and medical practitioners employed or retained by pharmaceutical companies have rebelled against the need to pit their judgement against that of FDA reviewers. It is no wonder then that many companies are exploring foreign territory as a source of new drugs, even to the extent of having permanent representation in Europe, where the legal and medical restrictions are not nearly so burdensome or costly.

Drop-Off in New Drug Applications

At a recent meeting of the Caduceus Society of Cornell University, Commissioner Goddard noted a drop-off in New Drug Applications, but said that it was not related to the 1962 Amendment, that the decline began after the peak year of 1955. He pointed out that in 1956, 260 prescription drugs were approved by FDA. The fall-off was gradual during 1957-8 but was followed by a sharp drop to 148 in 1960 which continued precipitously to only 76 approvals in 1962. However the public hearings and the threatened new legislation were not without their effect on the introduction of new drugs. The Paul deHaen New Products Survey reveals that in the 5 years preceding the Kefauver-Harris Amendments 242 single new drug entities were introduced whereas in the next 5 years a total of only 95 entered the market, representing a drop of 61 per cent. It is not possible to state unequivocally that the decline in the rate of introduction of new drug entities and combinations has been a direct consequence of the intensified regulatory controls. When we consider the tremendous progress that has been made in medical research during the past 25 years, not only by the pharmaceutical industry but in academic and other government supported research agencies, it seems difficult to believe that the wells are drying up, or that much of the research and development in drug products is too shoddy to meet present standards of the medical community.

Despite the fact that FDA is an enforcement or policing agency, it is easy to understand why many companies seek its advice as to whether or not a drug is "new" and if so, what investigational and legal procedures must be followed to gain official approval. Advice thus given tends toward the conservative, often entailing more time, money, and effort than the potential sponsor is able or willing to invest. But unless the solicited advice is taken the prospects of approval are slim. Unfortunately it has been the experience of some sponsors that even after submitting the suggested evidence, subsequent reviews by different FDA personnel may result in the request for still more data. In passing it is interesting to note the complaint of a veterinarian from Indiana University which appeared in a recent letter in Science magazine. This veterinarian and probably several hundred others across the country, had been using a Sandoz drug for the past 15 years as an anesthetic for cold-blooded vertebrates (fish, frogs, etc.). Well, Sandoz is no longer supplying the drug because FDA declared it to be a "new" drug in the veterinary category, requiring an IND (Investigational New Drug). The accompanying

expense, red tape, and record keeping necessary to comply with the new drug regulations could not be justified by this limited use for the drug. Now these vets have to find a substitute if they can.

Some of the major problems encountered by the drug industry arise from the administrative interpretations assigned to general language of the Federal Food, Drug and Cosmetic Act. The broad, but precise, definitions of what makes a "new drug" new or of what is meant by "good manufacturing practice," caught the regulated industries by surprise. The official view that "harmless" meant harmless regardless of conditions of use, or that "color additive" applied not only to the pigment but to the entire cosmetic preparation, are examples of what many believe to have been administrative afterthoughts. Similarly the term "no residue" as applied to certain pesticides in food, or "zero tolerance" as applied to salmonella contamination, have had to be reinterpreted in the light of practical analytical considerations.

Much has been written and said on the subject of "current good manufacturing practice" (GMP). When used to determine adulteration it means not only that the end product must be acceptable but that all conditions relevant to the operation of the plant, including the process from start to finish, must also be acceptable. Section 501 of the Act provides that a drug shall be deemed adulterated "if the methods used in, or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices to assure that the drug meets the requirements of the Act as to safety and has the identity and strength and meets the quality and purity characteristics which it purports or is represented to possess."

Section 133 of the Code of Federal Regulations defines "good manufacturing practice" as conceived by the Food and Drug Administration. It covers the conditions in any pharmaceutical manufacturing plant respecting buildings, equipment, personnel, components, master formulas and batch production records, production and control procedures, containers, packaging, labeling, laboratory controls, distribution records, stability of components, and maintenance of complaint files. Even if the final drug product is satisfactory, and complies with the law in every other respect, it can still be ruled to be adulterated if the manufacturer has not complied with the prescribed conditions of GMP. For example, a failure to take recommended steps to guard against cross-contamination can result in an

adulterated drug—even though no cross-contamination has occurred. A similar failure might occur if a manufacturer has an inadequate recall system — even though a recall never became necessary.

How to conform to these conditions is a matter for each company to decide within the framework of its own facilities and operations. Under its inspection authority, the FDA has the obligation at least once every two years to conduct plant inspections with the view toward revealing conditions which might lead to adulteration of drugs, including non-compliance with the regulations concerning GMP. In addition to their own internal checks, some companies have tried to avoid the risk of punitive action by engaging the services of outside agencies to make occasional inspections and to advise how to correct conditions where necessary.

Intra-Industry Problem

An intra-industry problem has arisen lately as a result of the request of certain large customers for permission to make their own inspections of the plants and facilities of chemical suppliers in order to provide assurance that the ingredients they purchase are manufactured under conditions which comply with the terms of GMP. Federal inspection is a legal right and the law gives manufacturers some protection against the misuse of trade secrets by FDA employes. But inspection by customer representatives is not covered by the same guarantee of protection, and one can hardly blame a company for denying this privilege.

Another matter for serious concern on the part of the drug industry is the frequency of recalls from the channels of distribution of drugs found to be adulterated within the strict terms of the law. During the past five months there were about 120 recalls. Forty were for failure to meet potency claims, about 20 for reasons of pyrogenicity, non-sterility, or the presence of salmonella, 2- because of physical defects such as particulate matter in parenteral preparations or a breakdown in a suspension, 20 for packaging failures, 9 for mislabeling, and 4 for the presence of a non-permitted ingredient or other contaminant. Another reason for recalling a drug, fortunately not very common, is the discovery of a new side-effect. The seriousness of a violation generally determines the depth of the recall; that is, how far it extends from the manufacturer to the retailer or professional dispenser. The extent of the recent recalls is indicated by the following figures:

44 per cent involved retailers;

24 per cent involved wholesalers;

30 per cent involved M.D.s and hospitals;

2 per cent involved manufacturers.

Companies that have undergone the painful and costly experience of a recall, even when done "voluntarily," have had cause to wonder whether the punishment fits the crime. But when FDA makes use of its most powerful weapon, the press release, the effect on a product and the reputation of its manufacturer can be devastating. Even voluntary recalls, which are often as effective as those ordered by FDA, are not without the risk of a bad press. That cautious judgement needs to be exercised in giving wide publicity to a recall was emphatically illustrated by the recent episode involving an anticoagulant whose potency was alleged to have differed from the declared level. The alarm engendered among cardiac patients necessitated a prompt warning by the Commissioner not to discontinue use of the drug except on the advice of their physicians.

To its great credit, FDA has recently initiated the policy of issuing quarterly reports prepared by computers on the status of pending New Drug Applications (NDA's). They indicate the Divisions within the Bureau of Medicine to which each application is assigned, the staff scientist (chemist, pharmacologist or medical officer) in whose hands material has been placed, and the date of each past and current action. These reports will be welcomed with open arms by sponsors of new drugs.

Notwithstanding the complaint from industry, it should be emphasized that much of the blame for delays and rejection of NDA's is due to the sponsors themselves, not to FDA. Commissioner Goddard has declared that three times as many applications were returned as "incomplete" during this fiscal year as were approved in the first quarter. He has stated that "Well over half of these were deficient in data to demonstrate clinical safety, or efficacy, or both. Other deficiencies included insufficient component and composition data on the drug, unacceptable samples, inadequate assurance of quality control standards, and unacceptable labeling. . . ." This in itself has involved a tremendous waste of manpower which could be avoided by more careful attention to the regulatory requirements and espe-

cially to the guidelines which FDA has been furnishing upon request. In this connection mention should be made of the Workshops which FDA has been conducting to advise and instruct industrial scientists and technicians in some of the more intricate procedures involved in food and drug testing.

The rigor with which FDA attacks its enforcement responsibilities is understandable in the light of the constant attention directed to its activities by a vigilant Congress, to which it must appeal annually for appropriations. Some of the recent obligations assigned to FDA will take years of patient effort to effectuate satisfactorily and merely appropriating funds will not expedite results. New laws have created a great need for scientific and technical manpower in the fields of toxicology, pharmacology, pathology, and related biomedical areas. Shortages will remain acute for the next decade since training programs have only recently been getting underway. What has been accomplished by both FDA and the regulated industries was unpredictable 10 years ago.

Conclusion

I have pointed out some of the barriers which are believed to be responsible for slowing up the introduction of new drugs in this country. Whatever the causes of the lag in bringing to the public the benefits of medical advances, it cannot be denied that they are a matter of increasing concern to both the profession and the regulatory agencies. This is reflected in the announcement last week of the appointment of a Board of Medicine by the National Academy of Sciences. Among the problems it will attack are the legal and ethical aspects of research on human subjects and how to shorten the interval between the acquisition of new knowledge and its application in practice.

In summary, I have tried to direct attention to a few of the trials and tribulations being experienced by both FDA and the drug industry in this scientific age, when public awareness of the hazards of foods, drugs, cosmetics, air, water and all other aspects of the environment has become so acute. It will take much understanding, patience, and cooperation on all sides to effect the improvement so eagerly sought in the public interest. **[The End]**