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Food Drug Cosmetic Law JOURNAL

A Look at FDA's New Rules of Practice—
and Problems Still Unsolved
. . . . . EARL G. SPIKER and P. GORDON STAFFORD

Administering that Ounce of Prevention:
New Drugs and Nuclear Reactors—I
. . . . . DAVID F. CAVERS

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

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FOOD DRUG COSMETIC LAW JOURNAL

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REPORTS

TO THE READER

The Common Market and Harmonization of the Food Laws.—This article, beginning on page 440, was presented by *Dr. Sergio Ventura* at the 11th Conference of the International Bar Association at Lausanne, Switzerland. The author, a member of the European Economic Community, Brussels, Belgium, discusses the economic necessity of harmonizing the various national laws that deal with foodstuffs. Dr. Ventura outlines the difficulties facing those in charge of harmonizing the laws and establishing common regulation, while respecting, as far as possible, the individual character of the different markets. He explains the operations of his organization in this area, and notes actual work in progress, especially in the area of additives. Ultimate emphasis is placed upon the need for comparative legal research.

A Look at FDA's New Rules of Practice—and Problems Still Unsolved.—*Earl G. Spiker* and *P. Gordon Stafford,* members of the Maryland and District of Columbia Bars, consider the successes and failures of the new FDA Rules of Practice and Procedure in this article, beginning on page 448. The new procedure, which governs hearings to determine the proper standard of identity for food or to determine whether a substance is hazardous, is described, as is the new expanded role of the Hearing Examiner. Criticism of the treatment of unofficial communications and the "institutional decision" is made. The authors conclude that although the new rules are an improvement over the old, they still do not provide a sufficient solution to the real problem—how the decision is made and by whom.

Administering that Ounce of Prevention: New Drugs and Nuclear Reactors—I.—This article by *David F. Cavers,* Fessenden Professor of Law at Harvard Law School, concerns the preventive legal action involving the areas of new drugs and nuclear reactors. Professor Cavers points out that the law's effort in these areas illustrates significant points of confrontation between law and science.

Part I of Professor Cavers' two-part article appears in this issue of the JOURNAL beginning on page 458. The Food and Drug Administration's problems in administering its preventive legal action over new drugs is discussed in this first part. Part II, which will be published in the October issue of the JOURNAL, examines the Atomic Energy Commission's problems and contrasts them with those of the FDA.

The article is based on the Edward G. Donley Memorial Lectures, delivered by the author at the College of Law, West Virginia University.

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The Common Market and Harmonization of the Food Laws

By DR. SERGIO VENTURA

The Following Article Was Presented on July 14, 1966 Before the International Bar Association at Its Eleventh Conference, July 11-14, Lausanne, Switzerland. Dr. Ventura Is a Member of the European Economic Community, Brussels, Belgium.

WHILE THE COMMON ORGANIZATION FOR AGRICULTURAL MARKETS has been one of the main concerns of the European political press for many years, this press has begun to deal with the harmonization of food laws only a few months ago. The discussions about the manufacture of cocoa butter and chocolate, sometimes highly animated, others still going on about the use of Erythrosin for the coloring of certain canned foods and confections, and, finally, those concerning the use of Diphenyl for the preservation of citrus fruit, lead one to believe that the public is becoming aware of the benefits and problems the food laws present to the economy of the European Economic Community (EEC) member states. Consequently, the public is realizing the importance of harmonization of these food laws for the future of the Community.

Approximation or Unification

It seems, however, that a political debate cannot bring any positive results, if only because the very term, "harmonization," is liable to contradictory interpretations. Further, the obstacles to harmonization and the efforts taken to overcome them are not always known.

We will assume that the only acceptable interpretation of the term, "harmonization," for those who have a practical vision of the problem, is one that contains the idea of either the "approximation" or the "unification" of national laws. It must be recognized that the governmental experts and the EEC Commission in charge of the harmonization of national laws are confronted with a very difficult task:

their job is to achieve a detailed common regulation which will respect, as far as possible, the individual character of national markets. (Naturally, such respect is granted only where these characteristics are not in conflict with the establishment and functioning of the Common Market.) In order to attain this aim, differences existing between national provisions regulating not only presentation and labeling, but also composition of products and characteristics of manufacture, have to be partially or totally eliminated. But any harmonization would remain without practical effect if norms for control procedures and analytical methods for detection of fraud should be neglected. Furthermore, an obstacle no less important which opposes itself to the success of harmonization work and which cannot be eliminated quickly, but only after many years of application of the new rules (approximated or unified), is the fact that any new norm inserted into the national legal systems can assume in each of them—in the context of pre-existing norms—a different significance.

The task would become still more difficult if the experts adopted an overly doctrinaire or exclusively deductive working method, fixing the meanings of terms of general character such as "food" or "additive," then passing on to the study of rules concerning each product or group of products. Such a method would involve a great deal of effort—researching, probably in vain, for a frame-regulation—effort which would be destined to encounter methodological difficulties. It would fail to arrive at concrete results in a relatively short period of time.

For this reason, the working method chosen by the EEC Commission in accordance with the experts of the member states seems justified. The method consists of the simultaneous elaboration of draft-directives of general application (such as those on additives, canned food, labeling and packaging) and of directives or regulations concerning determined products (such as jams, marmalades and fruit jellies; cocoa and chocolate; and fruit juices). This method enables one to extend the experience acquired in one of the above-mentioned sectors to other sectors.

How a Harmonization Directive Is Born

After the preparation of one or more basic documents, the working group, "Legislation on Foodstuffs," and the competent subgroup for the sector in question, composed of governmental experts and presided over by officers of the Commission, elaborates the text of a directive. When scientific questions arise, reference is made to a committee composed of experts, personally invited, who are especially

competent in medical, chemical and toxicological fields. The draft-directive is then transmitted to the organizations representing, on an EEC level, the professional circles concerned. The remarks of these organizations are discussed with the governmental experts and can operate to induce the Commission to modify the draft.

Finally, the draft is submitted to the Commission, which can adopt and transmit it as a proposal to the Council, or can ask for further data. The Council first decides whether it is necessary to consult the Parliament and the Economic and Social Committee. From a juridical point of view, the situation differs according to whether the text is based on article 43 or on article 100 of the Treaty, and according to whether or not its adoption requires modification of a formal law in at least one member state. After this, the text of the proposal is subject to thorough examination by an expert group convened *ad hoc* by the Council, and it is eventually discussed by the Committee of Permanent Representatives, and in some cases by the Special Agriculture Committee. The final stages of this long procedure are formal adoption by the Council, notification of the member states and publication in the Official Journal of the Communities.

In respect to "directives," it must be noted that the new norms are not directly applicable in the member states, and it is up to them to take appropriate measures to apply the new rules within the time fixed by the directive in question. These measures may require the modification of national provisions existing at the date of notification of the directive. However, in the case of "regulations," the new norms are directly applicable in the member states.

Work in Progress

The field in which progress is most advanced is the additives sector. Four directives on coloring matters and antimicrobial preservatives have already been adopted. Two proposals, one on anti-oxydants, a second destined to complete the preservatives directive, will be adopted by the Council shortly. A proposal on emulsifiers, stabilizers and similar agents will probably be presented to the Council by the Commission in autumn. Preparatory work has been initiated in the fields of artificial sweeteners and flavorings. On the general level, a study has been initiated relating to problems of labeling and packaging of foodstuffs. On the basis of a report furnished by two outstanding specialists, governmental experts have met several times to elaborate a draft directive on canned food, working under the guidance of Commission services.

Work is also going on in the following fields:

(a) *Processed fruit and vegetables:* The proposal of a directive on jams, marmalades and fruit jellies was presented to the Council, and a draft-regulation on fruit juices is in the last stage of elaboration.

(b) *Wines and alcoholic drinks:* The competent subgroup is now working on definitions for wines and wine-making operations, and on methods of analysis.

(c) *Processed cereals:* A draft-directive on noodles is in progress; next year flours will be the subject of harmonization measures.

(d) *Milk and milk products:* Milk powder, canned milk and butter are on the program of the competent subgroup; national dispositions in force for butter are to be harmonized shortly.

(e) *Oils and fats:* A proposal on esterification of olive oils was presented to the Council by the Commission; work on harmonization of national norms for margarine, oils and fats, excluding olive oils and butter, has been started.

(f) *Food extracts and similar products:* A draft-directive on broths, soups and sauces is being examined.

(g) *Pesticide residues:* For a certain number of pesticides, the Residues Committee and the Committee for analytical methods have reached an agreement on tolerance levels, as well as on some methods of analysis for the control of pesticidal residues on and in foodstuffs.

Finally, the Commission recently presented a proposal with a view to creating a "Foodstuff Committee." This committee, which would operate in a manner similar to that of the "Management Committees" (comités de gestion) of common organization for agricultural markets, would assist the Commission when called upon to elaborate, in the field of food legislation, measures of execution and application of norms adopted by the Council.

Harmonization work in the fields of animal nutrition and veterinary legislation takes place in close connection with the different sectors of food legislation. The working group, "Animal Feed," is at present concerned with additives employed in feed. As far as the veterinary sector is concerned, exchanges of fresh meat, livestock (cattle and pigs) and slaughtered poultry are already the subject of community norms, while a proposal of directive on canned meat and meat preparations has been on the agenda of an *ad hoc* group of the Council for quite some time.

Protection of Public Health

Although the starting point for the harmonization of food laws is the consideration of differences existing between them, hindering the exchange of foodstuffs and preventing free competition between enterprises, the EEC Commission does not lose sight of the necessity to insure the protection of public health and encourage the production of high quality food.

In regard to the protection of public health, a special place is given to some general principles arrived at during the elaboration of a regulation on chemical additives. There are, above all, the following principles inspired largely by the recommendations of the Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives:

(a) Use of additives must not be tolerated if the manufacture of food under normal conditions and according to the rules of good technological practice does not render it necessary.

(b) When use of additives corresponds to a real technological necessity, the amounts sufficient to obtain the desired effect must never be exceeded, even if they are less than the admissible amount from a toxicological point of view.

(c) Whenever it is possible to choose between different products the efficacy of which, from a technological viewpoint, is identical or equivalent, those having nutritional value should be authorized.

The general principles mentioned above induced the experts to adopt a system of "positive lists" for the drawing up of additives directives (all additives are forbidden except those explicitly authorized). Furthermore, additive lists are completed by purity tests with which authorized products must comply before use in foodstuffs.

It has not been possible to harmonize norms for conditions of use simultaneously (particularly for foodstuffs in which every additive can be incorporated). This task will be completed by the frame of work, already begun, which concerns the harmonization of provisions for each single food or group of foodstuffs. Another essential task, also involving the protection of public health, is the unification and perfection of methods of analysis and control. The EEC Commission is approaching this task with its usual fervor, notwithstanding the restricted means at its disposal. In this instance, it hopes to avail itself of the cooperation of the International Union of Pure and Applied Chemistry (IUPAC).

Besides the provisions discussed above, which have the aim of protecting the consumer against dangerous products or products of doubtful safety, norms of equal importance are destined to protect the consumer from frauds. These norms, to the extent that they insure loyalty in commercial transactions, are also intended to prevent disloyal competition. We mention in this context provisions reserving certain denominations for products the composition of which is legally defined, and rules concerning packaging, labeling and presentation of foodstuffs. Within these rules, emphasis is placed on the regulation of the net weights of foodstuffs; that is, on the capacity and real content of the containers in which foods are put on sale. In this regard, the solutions adopted by the Commission in the proposal of directives regarding, on the one hand, cocoa and chocolate, and, on the other hand, jams, marmalades and fruit jellies, are significant. Analogous solutions should be adopted for other important foodstuffs, and especially for drinks which are widely consumed.

Encouraging the Production of Quality Foods

It is well known that the notion of "quality" in foodstuffs is a relative and complex notion. It is a complex notion because the quality of a product is not determined by a single criterion or isolated factor, but by a combination of all the characteristics (chemical, physical, hygienic and organoleptic) of the product in question. It is a relative notion because those factors whose combination determines quality must be also of the sort that, by their presence, influence the consumer's acceptance of the product.

It is still too early to assess the influence that the work on harmonization of national laws will have on the quality of foodstuffs. However, it is already possible to discern that a severe but modern discipline in the field of additives, such as the one foreseen in the directives already adopted or in the course of adoption, also will have beneficial effects in the field of quality. Furthermore, where a community regulation concerning a determined group of foodstuffs has been or is being elaborated, it has turned out that the approximation of national rules has not been effected on the lowest level, in spite of the apprehensions expressed by many; on the contrary, certain developments arising from the work in Brussels may be expected to cause a gradual elevation of the quality of some products.

Of course, the problems with which experts are confronted in Brussels are not only problems of the protection of public health and the quality of products, but are also economic problems. The latter can present themselves as a consequence of a satisfactory solution to

a quality problem, such as cases in which the improvement of quality requires one or more of the member states to effect a total or partial transformation of the equipment used in production.

Even if the difficulties indicated will delay harmonization of national laws, they cannot prevent it. However, we must not have any illusions about the significance and efficacy of the new rules, even when unified and applicable in all member states. Indeed, it must not be forgotten that these juridical rules are not sufficient to regulate production and sale of foodstuffs; these can only complete and correct technical, professional and customary rules. On the other hand, juridical norms will only be efficiently applicable if a methodical education of the interested parties in the various sectors of production, distribution and consumption is realized simultaneously.

A Task for the Legal Profession

The problem of harmonization of national laws, particularly food laws, has been and is often formulated in an inexact way. Too often jurists or technologists charged with the harmonization of highly divergent norms ignore or forget the underlying reasons for this diversity (reasons which may depend in certain cases on natural, socio-economic or technical factors) and let themselves be carried away by the undoubtedly praiseworthy and legitimate desire to "harmonize," adopting solutions which are either too simplistic or too complicated. Doubtless, the task imposed upon them is very difficult. To solve the problem and solve it well, it is first necessary to realize the exact extent of the differences which divide or seem to divide the juridical rules under study. Only on the basis of the results of this research can we undertake the harmonization of legislation, if necessary. I say, "if necessary," because, in spite of the diversity of techniques adopted by the national legislators, final results are frequently less divergent than one might suspect, thanks to the administrative and judicial practice.

Comparative study of food laws actually in force in EEC member states and other important countries (United Kingdom, United States) has the undoubted merit of attracting the attention of responsible organizations. Such study also focuses public attention not only on the existing differences between the national legislations of various countries, but also on two typical aspects of all national legislations in force in this field, two typical aspects which—without taking into account the difficulties indicated—justify and urge harmonization of the food laws. I refer, on one hand, to the dissimilarity of organi-

zation and the infinite number of legislative and administrative provisions concerning foodstuffs. This diversity among provisions renders their application chaotic and precarious and, at the same time, disturbs normal production, fostering a lack of confidence in the consumer. On the other hand, I refer to the confusion which unfortunately characterizes many food laws, confusion between the aspects of health protection and market regulation, between protection of the consumer and protection of national industry or agriculture.

Thus, it seems evident that comparative legal research is the indispensable premise of any harmonization. It is the task of the legal profession to intensify this study and isolate from the complicated context of laws in force the guidelines for a new uniform legal discipline which, above all, will be clearer and more readily applicable.

[The End]

REORGANIZATION OF THE BUREAU OF MEDICINE COMPLETED

The Food and Drug Administration has announced the completion of the reorganization of the Bureau of Medicine. The Office of New Drugs will include the following units: Cardiopulmonary and Renal Drugs, Dental and Surgical Adjuncts, Metabolism and Endocrine Drugs, Anti-Infective Drugs, Oncology and Radiopharmaceuticals, and Neuropharmacological Drugs. All applications for marketing new and investigational drugs will be processed by the appropriate units.

Drug surveillance activities will be carried on by one office and all regulatory functions by another office. The Office of Drug Surveillance, consisting of a Division of Drug Monitoring, a Division of Epidemiology and a Division of Supplement Review, will monitor the use of drugs, operate an adverse reactions detection and analysis system, and review drug supplements. The Office of Medical Review, consisting of a Division of Case Review, a Division of Medical Advertising and a Division of Medical Devices, will provide medical opinion and carry out the Bureau's responsibilities under the Drug Abuse Control Amendments.

Dr. B. Harvey Minchew has been appointed as acting deputy director of the Bureau of Medicine. Dr. Robert J. Robinson continues as acting director of the Bureau. Food Drug Cosmetic Law Reports ¶ 2425.

A Look at FDA's New Rules of Practice— and Problems Still Unsolved

By EARL G. SPIKER and P. GORDON STAFFORD

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EARLY IN 1966 the Food and Drug Administration (FDA), Department of Health, Education and Welfare (HEW), established new rules of practice for hearings conducted under the Federal Food, Drug and Cosmetic Act[1] and the Federal Hazardous Substances Act.[2] The Food, Drug and Cosmetic Act is basically intended to insure that the foods, drugs and cosmetics sold to the American consumer will be safe, sanitary and informatively labeled. The Hazardous Substances Labeling Act requires that substances or products which present hazards to the public carry appropriate cautionary statements on the label. Hazards contemplated under the Act include poisoning, burning (caustic) and irritation (to skin or eyes). Under the Food, Drug and Cosmetic Act public hearings may be required for the issuance of regulations under a number of sections of the Act involving foods, drugs or cosmetics. As an example, in some circumstances a hearing is required for the establishment of a definition and standard for a particular food.[3] Though the average consumer may not be aware of it, a number of our basic foods are presently defined by federal regulations. Foods covered by such a standard must meet the requirements of the standard in order to be sold in interstate commerce as the standardized food. Bread, salad dressings, ice cream, canned vegetables and fruits and margarine are some of the foods

[1] 21 USCA 301 and following, CCH Food Drug Cosmetic Reporter, (hereafter cited as CCH) ¶ 25 and following.

[2] 15 USCA 1261 and following, ¶ 1000 and following.

[3] 21 USCA 371(e)(3), CCH, ¶ 355.

defined by these standards. Under the Federal Hazardous Substances Labeling Act, one of the FDA's responsibilities is to determine whether a particular product is a "hazardous substance" and hence subject to the requirements of the Act. A hearing may be required for such determination.

The new FDA Rules of Practice and Procedure[4] govern hearings to determine the proper standard of identity for a food or to determine whether a substance is hazardous, as well as governing many other proceedings under the Food, Drug and Cosmetic Act. Hearings under these rules may be of considerable magnitude. The recently completed hearing in connection with a proposal to establish a standard of identity for peanut butter lasted almost four and one-half months, and the hearing transcript consisted of over 7,700 pages.[5] Earlier hearings involving standards for bread and ice cream were of similar size. Each manufacturer or processor of the food involved and each supplier of ingredients or materials to such processors, in addition to the general public, has a stake in the outcome of such hearings. Every interested party vies to have his product or his ingredient included in the approved standard. Voluminous evidence is offered as to the relative merits, aesthetic, nutritional and otherwise of the various products and ingredients. Few trials are more hotly contested than hearings involving food standards.

While hearing procedures before the FDA are in many respects similar to those conducted by a number of other federal agencies, there are significant differences. Accordingly, before discussing and commenting on the new rules of practice, we will summarize the steps in such proceedings which are prescribed in the new regulations and the applicable statutes. The procedure briefly is as follows:

(a) Publication of a proposed regulation by FDA on its own initiative or after petition by an interested party.

(b) Opportunity for interested parties to comment on the proposal, after which FDA publishes an order, usually providing that the proposal shall become effective.

(c) Parties adversely affected by the order have 30 days thereafter to file objections to the order. The petitioner is given time to reply to such objections.

(d) If substantial objections are filed, a hearing is ordered and a notice of hearing and issues to be covered is published.

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[4] FDA Rules of Practice and Procedure (hereafter cited as FDA Rules), 21 CFR Part 2, Subpart F; CCH, ¶ 3800 and following.

[5] In the matter of Establishing Definitions and Standards of Identity for Peanut Butter, Docket No. FDC-76.

(e) A hearing is conducted before the Hearing Examiner of FDA.

(f) The Hearing Examiner prepares his report and transmits it and the record to the Commissioner of FDA.

(g) A tentative order including detailed findings of fact and conclusions upon which it is based is issued, and opportunity given for the filing of exceptions thereto.

(h) A final order is issued and published.

(i) Review of the Commissioner's final order lies in the United States Courts of Appeal.

Under the FDA Rules of Practice, hearings are conducted before the FDA Hearing Examiner. Until several years ago, unfortunately, the practice in the FDA was to appoint on an *ad hoc* basis a member of the Agency's Office of General Counsel as the Examiner whenever a hearing was held. When the hearing was conducted, the Examiner returned to his normal duties under the General Counsel. However, in 1964, in a large step forward, the FDA established the position of Hearing Examiner, as a permanent position, separate from the General Counsel, in the Office of FDA Commissioner. The new rules are another advance along this route.

The Examiner's New Role

The single most significant change in the new rules is the further upgrading of the Examiner's stature and function. Under the prior rules of practice the FDA Hearing Examiner conducted the hearing, admitting evidence and ruling on evidence, and at the close of the hearing certified the record in the hearing to the Commissioner of FDA, without preparing any report or recommended decision. A decision was then issued in accordance with the Act—under the signature of the Secretary of Health, Education and Welfare, of which FDA is a part. Under the new rules the Examiner is given a number of enumerated powers concerning the conduct of the hearing. For example: to establish the date and time of the hearing; to receive, rule on, exclude or limit evidence; to regulate the course of the hearing; to fix the time for filing motions and briefs; to require the parties to state their positions on the issues; and to examine witnesses.[6] His enumerated powers are substantially broader than those set forth in the prior rules of practice. In actual practice, however, the Examiner has previously exercised most of the new powers specifically mentioned in the new rules, so that the new rules should not result in

[6] FDA Rules, § 2.73; CCH, ¶ 3873.

any radical changes from those previously followed in the conduct of the hearing. Pre-hearing and post-hearing procedures, however, should be changed considerably by the new rules.

Previous rules contained no specific mention of pre-hearing conferences or other pre-hearing procedures, though pre-hearing conferences have been held. The new rules authorize the Examiner to call pre-hearing conferences for the purpose of simplification of issues; for discussions, stipulations and admissions regarding facts and documents; for discussion as to expert witnesses; for scheduling of witnesses and identification of witnesses; and for advance submission of documentary evidence.[7] These matters are of particular interest, as the rules provide that the failure of a party to produce written testimony and identify witnesses at the pre-hearing conference, without good cause shown, may result in the testimony or documents not being received in evidence. Another important pre-hearing power given the Examiner is authority to direct that summaries of the direct testimony of witnesses be prepared in writing and served on other parties in advance of the hearing. We believe this rule is an improvement over past procedures. The quality of cross-examination should be improved and the time necessary for examining witnesses may be reduced. However, one severe problem we foresee under the rule is that the attempt to "freeze" the scope of the examination of a witness prior to his testimony is not feasible. Between the time a summary of the proposed direct testimony is prepared and the date of his testimony many factors may dictate a change in the scope of questioning. For example, additional testimony may become necessary to counter or respond to matters raised by other witnesses in the interim. Traditional discovery procedures in the courts permit the examination of adverse parties in advance of trial. Discovery procedures are generally unavailable to the parties in federal administrative proceedings. We have long believed they should be. We do not regard the rule adopted by FDA as an adequate substitute.

The Examiner's post-hearing role is also greatly expanded under the new rules. Where he formerly acted merely to compile the record and send it to the Commissioner for a decision, he will, under the rules, prepare a "report" which will be transmitted to the Commissioner, along with the record.[8] Unfortunately it does not appear that the Examiner's report will be public information, and it will not have the significance of Examiners' reports or recommended decisions in

[7] FDA Rules, § 2.74 and following; CCH ¶ 3874 and following.

[8] FDA Rules, § 2.96; CCH, ¶ 3896.

many other agencies. In a number of agencies the Hearing Examiner's opinion or decision becomes final if not excepted to by the parties.[9] Under such procedures the authority and prestige of the Hearing Examiner is increased, and the amount of time between the initial proposal and the effective date of the final regulations can be significantly shortened—a prospect even lawyers should applaud. We see no necessity in FDA proceedings for the Examiner's decision to be reviewed automatically, if his decision is acceptable to the parties involved, including the agency (bearing in mind that the FDA's Office of General Counsel is a "party" to the proceedings).

Other Changes

In addition to the most important changes in the rules which are outlined above, there are several other changes we should like to mention. The first of these is the provision in the new rules regarding ex parte communications. Section 2.104 of the rules provides:

> If any official of the Food and Drug Administration is contacted by any individual in private or public life concerning any matter which is a subject of a public hearing, the official who is contacted shall prepare a memorandum setting forth the substance of the conversation and shall file this memorandum in the appropriate public docket file.

This rule, if literally interpreted, requires that any conversation between two officials of the FDA concerning the matter which is the subject of a pending hearing is required to be reported in a memorandum to be made public. We do not suppose for a moment, however, that this is an intended result. In any event it is submitted that the rule does not cover the real problem. The governing statute provides that the final order in the proceeding "shall be based *only* on substantial evidence of record at such hearing."[10] (Emphasis supplied.) Therefore, the thrust of the regulation prohibiting ex parte communications should be to prohibit the Hearing Examiner or the Commissioner, or any of his delegates participating in making the decision, from discussing the proceedings outside the hearing room with anyone, other than his own staff, or relying on any evidence except that set forth in the hearing record. The prohibition should specifically encompass representatives of any party to the proceeding, including other agency employees. Accordingly, we think the above rule can be greatly improved.[11]

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[9] See, for example, procedure in NLRB unfair labor practice proceedings, 29 CFR § 102.48; FTC Rules of Practice in Adjudicative Proceedings, § 3.21 CCH TRADE REGULATION REPORTER, ¶ 9,821.21.

[10] 21 USCA 371 (e)(3).

[11] See, for example, § 4.5, Federal Trade Commission Rules of Practice in Adjudicative Proceedings; CCH TRADE REGULATION REPORTER, ¶ 9882.05.

Another portion of the new Rules we should mention briefly is Section 2.90(b) which directs the Examiner to "require counsel for the parties to prepare a daily topical index which will be available to the presiding officer and all parties" whenever he determines that the hearing record will be of such length that such an index will permit a more orderly presentation of the evidence in the proceeding and reduce delay. Preparation of such an index under the rule would be apportioned among counsel as appears just and proper to the Examiner. We are unaware of any similar provisions in the rules of practice in any agency. No doubt in any lengthy hearing such an index would be extremely helpful, but we believe it is asking too much to require counsel engaged in 10 A.M. to 5 P.M. hearings which may last for months (and have) to prepare an index of the day's proceedings in the evening instead of working on his own client's case (or perhaps resting). In addition, since the Rules do not define who are "parties" to a hearing, it is not clear who would be subject to the obligation to index the record. We feel that those who wish should prepare their own index or purchase a transcript (the hearings are required to be reported verbatim). To conclude, this requirement is burdensome, unreasonable, and objectionable.

As mentioned previously, in accordance with usual federal administrative practice, interested parties are given an opportunity under these rules to comment on the proposed regulation. Thirty days are allowed for this purpose. Similar opportunity for comment was given under prior FDA procedures. As lawyers are inclined to do, comments were normally filed on the last day permitted or as near thereto as possible. Thus, the petitioner of the proposed regulation normally had no opportunity to file any comments in answer to objections raised. Under the new Rules the petitioner, if it is someone other than FDA, will be served by the agency with copies of each objection filed, and given two weeks (30 days would probably be more appropriate) from the date of receipt of such objections to make written reply.[12] We regard this rule as an improvement. Giving the petitioner an opportunity to answer and explain objections filed by other parties should be helpful to the agency in determining the merits of the objections, and, at least might in some cases, obviate the necessity of a hearing on the proposal.

The Food, Drug and Cosmetic Act contains no specific provision concerning the burden of proof at hearings under the Act. Accord-

[12] FDA Rules, § 2.67(d); CCH, ¶ 3867.

ingly, hearings under the Act are subject to Section 7(c) of the Administrative Procedure Act (APA), which provides that "the proponent of a rule or order shall have the burden of proof."[13] The previous rules contained nothing regarding burden of proof. The new Rules interpret the APA's requirements to provide that:

> . . . the originator of the proposal or petition for the issuance, amendment, or repeal of any regulation . . . shall be, within the meaning of section 7(c) of the Administrative Procedure Act . . . the proponent of the rule or order, and accordingly shall have the burden of proof.[14] . . . any adversely affected person filing an objection . . . which objection proposes the substitution of a new provision for that provision objected to, shall have the burden of proof in relation to the new provision so proposed.[15]

While the latter provision of this rule could provide the basis for considerable analysis and discussion, we have some question as to whether the change will result practically in any significant change from past procedures.

The Problem of the "Institutional Decision" Still Unanswered

While some criticisms can be made, no serious quarrel is raised here with the manner in which hearings are conducted now and evidence received. The question is: What happens after the hearing is over? Under the new rules the record of the hearing with the Examiner's report is transmitted to the FDA Commissioner, who issues a tentative order and later a final order. We can be certain, however, that because of his many other duties, the Commissioner himself cannot review a lengthy record and render the decision. This job is, therefore, delegated to others, whose identity is not announced. The result is a so-called "institutional decision," which has been the subject of much criticism.[16] President Kennedy took the following position concerning such decisions:

> The practice of rendering anonymous decisions, which has hitherto generally prevailed, has served as a means of escaping precision and responsibility. When the actual source of the opinion is unknown save only that it is issued in the name of the agency, it not only impairs its value as a precedent, but also makes for that very dissipation of responsibility that we are trying to reduce in our administrative action.
>
> Fortunately, from the beginning of American law, our judges assumed an individual responsibility for uttering the bases which underlay their decisions. This practice has made not only for conscientiousness in undergoing the travail of decision, but has invited examination of each proffered brick that would seek a place in the structure of our law. The adoption of this practice by the regulatory agencies would, in my opinion, tend to develop the law that they administer, as

[13] 5 USCA 1006(c).
[14] FDA Rules, § 2.63(a); CCH, ¶ 3863.
[15] FDA Rules, § 2.63(b); CCH, ¶ 3863.
[16] Davis, *Administrative Law Treatise,* Ch. 11 generally.

well as be a continual challenge to each agency member to make his contribution to the advancement of administrative justice. I am requesting a wider adoption of this practice.[17]

Where the agency's decision is anonymous, the inevitable assumption is that it probably was prepared by those in the agency most familiar with the subject matter. At first blush this might seem to produce the fairest and most informed result, but upon reflection it is clear that this is not necessarily the case. In hearings concerned with the proposed standards of identity for foods (the type of FDA hearing with which the authors are most familiar), the agency, and particularly those in the agency responsible for the issuance of food standards, usually appear as witnesses in support of a standard. Moreover, they are proponents of that particular standard issued as a proposed regulation by the agency. It is simply asking too much to expect that these same officials can, after the hearing, cast aside the opinions and convictions about which they testified and examine the record with a completely objective viewpoint. To phrase it another way, we do not, and should not, expect that any agency party intimately associated with a case can objectively judge the merits thereof. Accordingly, such FDA officials should not be permitted to decide after the hearing what the final regulation should be.

The problem of the "institutional decision" results from the lack of a proper separation of functions of the prosecutor and the decision-maker. The APA specifically requires that in so-called "adjudicative proceedings" no officer or employee who engaged in the investigative or prosecuting functions in any case shall participate in making the decision, except as counsel or witness in proceedings on the record.[18] This requirement does not apply to so-called "rule-making" proceedings. Proceedings under the Food, Drug and Cosmetic Act have been considered rule-making proceedings. We see no reason however, to limit what seems to be a basic rule of fairness to "adjudicative proceedings."

The types of proceedings we have referred to in this paper are truly adversary in nature. In proceedings to establish a food standard, the FDA issues a proposal to establish a standard of a particular type. Opponents of the standard may argue that no standard of any sort should be adopted or if one should be, that it should be different from that proposed by the agency. In proceedings to determine whether a particular product is subject to the requirements of

[17] Special Message to Congress on Regulatory Agencies of Our Government (April 13, 1961), H. Doc. 135, 107 Cong. Rec. 5814.

[18] 5 USCA 1006(c).

the Federal Hazardous Substances Labeling Act, we would assume that the government asserts that the product is subject to the Act, and that the manufacturer argues, with equal vigor, that the product is exempt from the Act (if the manufacturer agreed that his product was subject to the requirements of the Act we presume there would be no need for a hearing).

To permit the decision-maker to consult with other members of the agency's staff—such as technical experts in the subject matter at issue, or members of the prosecuting team (counsel or witnesses)—is, in practical effect, to permit the agency to argue the case off the record. We submit that the APA's distinction between adjudicative and rule-making proceedings should not be the test in resolving this question. Separation of function should be required, and ex parte communications forbidden in any proceeding by the agency, where the decision is required to be made upon the record compiled at a hearing. Certainly in any instance where the agency is realistically a party to adversary proceedings, simple justice requires such a rule.

To what extent intra-agency consultation by the decision-maker should be permitted has been a matter of some controversy for a number of years. We must confess that some eminent authorities in administrative law would consider our views "extreme".[19] If we understand Professor Davis correctly, he would—in the interests of "efficiency and economy"—permit the decision-maker to consult with other agency staff members, including those who testified as witnesses at the hearing.[20] We cannot agree, but believe that at every stage of such proceedings, each of the parties should have an equal right to hear, and to cross-examine and question the evidence and opinions offered by other parties. A system which does not protect this right is inherently defective.

Conclusion

We would propose to do away with the institutional decision in these proceedings and recommend: (1) that the Hearing Examiner be authorized to prepare an initial decision, including proposed findings and conclusions, and a proposed regulation which should become final if not objected to by the parties or other persons adversely affected, and (2) if objection is raised to the Hearing Examiner's decision, the final decision should be made by someone who had no part in the hearing or in the formulation of the proposed order. This per-

[19] Davis, *Administrative Law Treatise*, § 13.10.

[20] See footnote 19, § 11.21, 13.11.

son (or board) should be appointed to a permanent position established to act for the Secretary of HEW under powers delegated by him.[21] An even better solution would be the establishment of a totally independent Federal Office of Examiners to render decisions in such cases. Such handling is not possible under the terms of the present Act. The changes we have proposed above, however, could be easily effected by regulation and delegation of authority within the framework of the existing Act.

In summary, it is safe to conclude that the new rules are an improvement over the old, as far as they go. We are of the strong opinion that the rules fall far short of providing a satisfactory solution to the real problem—how the decision is made and by whom.

[The End]

"CLINICAL EXPERIENCE" DEFINED BY COURT OF APPEALS

The U. S. Court of Appeals for the seventh circuit has interpreted the term "clinical experience" to include any experience learned before and after the effective date of approval. The Food and Drug Administration's Commissioner may re-evaluate the approved new-drug application on the basis of clinical experience without using new tests learned after the effective date of approval. Therefore, the clinical experience showing that the use of diethylstilbesterol pellets in poultry presented a potential cancer hazard in man was sufficient for suspending the new-drug application. *Bell v. Goddard,* U. S. Court of Appeals (CA-7), August 11, 1966, FOOD DRUG COSMETIC LAW REPORTS ¶ 80,144.

[21] The Judicial Officer of the U. S. Department of Agriculture (who acts for the Secretary of Agriculture) is the type of official we have in mind.

Administering That Ounce of Prevention: New Drugs and Nuclear Reactors

By DAVID F. CAVERS

This Article, Reprinted from the *West Virginia Law Review* (Vol. 68, No. 2, February 1966) with the Permission of the West Virginia University College of Law and of the Author, Is a Slightly Revised Version of the Edward G. Donley Memorial Lectures, Delivered December 2 and 3, 1965, at the College of Law, West Virginia University. David F. Cavers Is Fessenden Professor of Law, Harvard Law School.

EVERYONE WILL UNDOUBTEDLY AGREE that an ounce of prevention is better than a pound of cure, though some conservatives may consider the 16-to-1 ratio is on the high side and prefer the 9-to-1 ratio embodied in the proposition that a stitch in time saves nine. Yet, for the two subjects of preventive action to which I shall direct these lectures—new drugs and nuclear reactors—I think it will appear that even the 16-to-1 ratio is far too modest.

I am concerned with the law's preference for prevention over cure in these matters not only because I wish to examine with you some problems of preventive legal action but much more because the law's efforts in these two areas illustrate significant points of confrontation between law and science.

In these days, in remarking the importance of science and technology in the problems that concern modern law, one is struck by the great diversity of points of confrontation between the two disciplines. They range from such matters as the proper test for criminal responsibility to the proper rules to govern the behavior of man in outer space.[1] Yet, among these situations, the problem frequently

[1] I have canvassed some categories of these in "Introduction, Science and the Law Symposium," 63 *Michigan Law Review* 1325 (1965), and, somewhat more extensively, in an introductory paper, "Law and Science: Some Points of Confrontation" for a conference on "Law and the Social Role of Science" at the Rockefeller Institute, New York City, April 8-9, 1965, the proceedings of which are to be published.

recurs whether to depend for the making of decisions upon the processes that the legal profession has developed or upon those to which the science-based professions are accustomed. We shall see that issue emerge as we observe in these lectures the difficulties encountered in resolving what at first glance may appear to be essentially medical and engineering questions.

There is, of course, nothing extraordinary today in a legal requirement obliging a duly authorized body to pass upon a proposed action on the basis of scientific or technological evidence. To give a homely illustration, I need only instance the building permit. I have chosen from among the many examples of such requirements the two very different determinations provided for new drugs and the nuclear reactors for several reasons:

(1) Because of the intrinsic difficulty of the scientific and technological judgments that have to be reached by the decision-maker.

(2) Because of the importance to the applicant of the approval it seeks and, still more, the seriousness of the consequences of a mistake or error of judgment if the procedure fails to prevent one, and also because of the inadequacies of remedial measures available after a mistake has been made.[2]

(3) Because, especially, of the perplexing difficulty of devising a satisfactory procedure for granting approvals and for withdrawing them when necessary, a difficulty in which the different roles played by the lawyer and the scientific expert are implicated. (I should explain, incidentally, that I shall use the term "expert" to cover the various categories of persons learned in the basic and applied sciences whose scientific or professional knowledge is drawn upon in decision-making in the two areas with which I shall be concerned.)

The approval procedures of both the Food and Drug Administration (FDA) and the Atomic Energy Commission (AEC) follow the same general pattern: first comes an administrative evaluation of a proposal submitted usually by an industrial concern, buttressed by scientific and technological data. In this evaluation, the informed scrutiny of the regulatory agency's experts will focus on the ade-

[2] Related to these considerations is the dependence of the exposed publics on the correctness of the approval, the inability of drug users (sometimes even physicians) and of the reactor's down-wind neighbors to make their own evaluations. In contrast, the purchaser of securities, aided by professional analysts, is likely to fare relatively better if the Securities and Exchange Commission (SEC) fails to elicit a full disclosure from a corner-cutting issuer.

quacy of the investigations and tests that have been performed and the experimental data these have yielded, and will sometimes lead to improving proposed safeguards against whatever hazards the new drug or nuclear reactor may create. Ordinarily this administrative process is expected to terminate in definitive action: the approval of a meritorious proposal or the disapproval of a deficient one. However, should the views of the applicant's experts conflict with those of the agency's, then the applicant has the choice either to attempt to develop the bases of his application further or to invoke the adversary process.

Up to this point, the lawyer has played a subsidiary role devoted chiefly to organizing presentations and findings and assuring conformity to regulatory specifications. If the applicant chooses the adversary process, the lawyer is now expected to take the center of the stage, to marshal the data and expert opinions of the side he represents while probing, with the aid of his experts, for weaknesses in the adversary's case. Above this battle sits the commissioner or the commission charged with deciding between the conflicting masses of testimony, striving where possible to cast findings in terms of a choice between ascertained truth and disclosed error (which may, of course, take the form of a deficiency of needed data). Where, however, the problem is one of degree, the issue must be resolved in terms of a judgment which may be confined to the particulars of the specific case but which is likely to reflect broader considerations of policy. At this stage, within limits that the courts themselves have sought to keep narrow, the defeated party can have recourse to judicial review. Should the court afford no relief, there remains only the last resort, political action, figuratively described as "going to the polls," more aptly, as calling in the lobbyists.[3]

This pattern is the product of over half a century's experience in the United States in fashioning the procedures of federal regulatory agencies. Experience, however, has been teaching that that pattern does not fit the tasks which the FDA and the AEC are trying to perform in administering their respective ounces of prevention. That experience has shown that so much of the pattern as looks to putting the adversary system into play just has not worked. The disappointed applicant will not stand up and fight, however strongly it may believe in the merits of its cause. As a result, the lawyer has no chance to perform his distinctive function; contested hearings are few, and the

[3] Of course, political assistance need not be a "last resort"; it is a remedy that can be, and sometimes is, administered concurrently. The exhaustion-of-remedies doctrine does not pose a condition to its use.

courts have rarely been called on to review the administrator's judgments.

This may seem a consummation devoutly to be wished, even to an audience of lawyers, at least to such an audience outside the District of Columbia. Yet, though the problems presented by new drug and reactor applications may come closer to the truth end of that spectrum between truth and power which Dean Price identifies in his recent volume on *The Scientific Estate*,[4] the policy ingredient cannot be eliminated from the issues to be resolved. Wherever a policy issue is present, some members of the public are likely to challenge any exercise of the power to decide that issue which does not afford an opportunity for the public to observe, if not to participate in, the decisional process.

As will be noted as I describe the predicaments in which the two agencies have found themselves, it has been the FDA in which decision-making has been left largely within the recesses of its bureaucracy,[5] whereas the AEC has sought, with uneven success, to provide a reasonable facsimile of the traditional regulatory agency's procedure. It is the FDA's procedure that I shall consider in this first lecture, but, before I do so, I shall pause to demonstrate the importance of prevention as distinguished from cure in the FDA's control of new drugs.

The Importance of Prevention: New Drugs

Today great progress is being made in developing effective forms of medication. New remedies have been proliferating until perhaps 90 percent of the prescriptions now being filled call for drugs not in existence 15 years ago.[6] As was true of the drugs that preceded them, for these new drugs "safety" is a relative concept. Even when made and used carefully, drugs may cause harm. Individual reactions to

[4] At 135. To this penetrating study of the relations of science and government, published in 1965, which cuts across a wide range of problems, these lectures can add no more than a specialized appendix.

[5] Although its proceedings remain secret, the FDA has been endeavoring to communicate the bases of its decisions with respect to limitations on the use of drugs and warnings concerning side effects and contra-indications by resort to the brochures which must accompany drug samples sent to physicians and drug shipments to pharmacists. The drug's manufacturer is required to disclose in the brochure clinical and other evidence giving rise to the limitations or warnings. See 21 C.F.R. § 1.106(b) (3) & (4) (1965).

[6] Statement of George P. Larrick, Commissioner of Food and Drugs, *Hearings on Drug Safety before Subcommittee on Intergovernmental Relations, House Committee on Governmental Operations,* 88th Cong., 2d Sess., 14 (1964). The amount spent on prescription drugs by consumers has grown from about $150 million in 1940 to $2.2 billion in 1964.

them vary widely. Dosage that is safe and effective for one person may be ineffective or harmful for another. Moreover, an intrinsically harmless drug may be exceedingly dangerous if it is ineffective, since the ill—and their physicians—may rely upon that drug until too late to resort to another, effective remedy. Yet, if a drug is effective, its value in the absence of satisfactory alternatives may amply justify running whatever risks its use may create.

We have had a near-miss from a grim demonstration of the tragedy that failure to detect and prohibit an unsafe drug can cause. The drug that would have provided that demonstration—thalidomide —also provided the political impetus for the Drug Amendments Act of 1962 on which my lecture is focused.[7]

Thalidomide is a tranquilizer developed in Germany and sold abroad in large volume under various trade names. An American pharmaceutical firm undertook to produce it here, filing an application with the FDA under the "New Drug" provisions of the 1938 Food, Drug and Cosmetic Act, provisions themselves the product of a drug tragedy—the sale of the poisonous Elixir Sulfanilamide which killed over 100 people before it could be withdrawn.[8]

Probably all of you know the story of the stubborn refusal of FDA's Dr. Frances Kelsey to clear thalidomide for use in this country before doubts as to its safety had been put to rest. While these doubts persisted, news came from Europe of countless cases of phocomelia—they totaled 5,900 in West Germany alone. Babies whose mothers had taken thalidomide in early pregnancy were born without arms or legs, their hands attached to their shoulders, producing seal-like flippers. To this story I shall add only a word as to some of its consequences abroad. Last spring the *Times* reported that an association has been formed in Germany by parents with thalidomide-deformed offspring. They are pressing the state for help both in money and in special educational aids for their children. The German Government had already appropriated nearly $2,000,000 to care for these children, and this is recognized as only the beginning.[9] Yet, obviously money is no measure of the price in heartbreak and despair that the children and their families must pay for decades to come.

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[7] See Harris, *The Real Voice* 181-93, 209 (1964). The book provides a colorful account of the legislative history of the 1962 amendments, including the crucial role played by the thalidomide tragedy.

[8] The victims totaled 107, many of whom were children. See Young, "Social History of American Drug Legislation" in *Drugs in Our Society* 217, 227 (Talalay ed. 1964); Harris, cited at footnote 7, at 182.

[9] *N. Y. Times,* June 20, 1965, p. 61.

Even when a drug is approved after an investigation of its properties, a mistake by the sponsor which escaped detection or an error in judgment by the evaluator can lead to a heavy cost in human suffering to its users and to the erring manufacturer. A vivid example of this danger appears in the case of Mer/29, a drug developed to reduce cholesterol deposits in the arteries, a suspected cause of coronary and arterial disease. The drug was approved on the basis of reports by the manufacturer that had suppressed certain unfavorable data, a suppression that later led to the criminal conviction of the corporation and three of its staff. However, long before this was known, Mer/29 was widely marketed with much fanfare. Many physicians prescribed it. After a year or so, however, a slow dribble of cases began in which patients using the drug had developed cataracts or had experienced other, less serious, side effects.[10]

These revelations accompanied a growing doubt as to the drug's effectiveness. The FDA ordered its withdrawal, and its decision was not contested. Since then the manufacturer has been the target of over 700 law suits by users alleging injury. It has settled over 200 of these. In one of the few that have gone to trial, a verdict of $175,000 in compensatory damages and $500,000 in punitive damages was reduced on appeal to $425.000, the punitive damages having been sliced in half. However, recently in Florida a jury was instructed that the drug's maker would be liable only if negligent in failing to foresee the kind of harm experienced by the plaintiff, and it returned a verdict for the defendant. I suspect such victories for the defendant will be few; before the troubles of Mer/29 have come to an end, someone—the maker or its insurers—will have had to pay millions of dollars in settlements and judgments. Again, money damages are poor recompense for damaged eyesight.[11]

Once we are agreed that prevention is the end to be achieved, we have to confront some basic questions. How much prevention is enough? Pushing prevention as a goal to the extreme would deprive humanity of many useful drugs. Rather than sacrifice the therapy

[10] The Mer/29 case is reported in Mintz, *The Therapeutic Nightmare* ch. 11 (1965). It is also the subject of testimony and numerous exhibits in *Hearings on Interagency Coordination in Drug Research and Regulation Before the Subcommittee on Reorganization and International Organizations, Senate Committee on Governmental Operations*, 88th Cong., 1st Sess., pt. 3 (1963). (These hearings, chaired by Senator Humphrey, will hereinafter be cited as *Humphrey Hearings.*)

[11] For a report on the State of Mer/29 litigation, see 27 FDC Rep., Drugs and Cosmetics ("The Pink Sheet") No. 32, 8 (Aug. 9, 1965) (hereinafter cited FDC Rep.). See also Mintz, cited at footnote 10, at 246. Plaintiffs' counsel have formed a foundation to facilitate the prosecution of their claims.

that would thereby be lost, our law permits some balancing of risks against benefits. The question then becomes: how much risk is too much risk? And where effectiveness is at issue, the question may be: how much risk should be run for how little efficacy? These questions are often posed for the FDA by the filing of a new drug application and sometimes by the filing of a notice that exemption is claimed for a drug for investigational use.[12]

Investigating Drug Safety and Effectiveness: Herein of the IND

Whenever an application is relied on to present to an administrator both the facts and the question he must decide, there is no adversary party to challenge the adequacy or the accuracy of the case made by the applicant as he puts his best foot forward. Moreover, since action on a really new drug application must precede experience with the drug in general use, the hazards of the applicant's product can be determined in advance only as these may be revealed by the tests and clinical trials conducted by the applicant or reported in the literature relating to similar products. Clinical experience based on trials with 1,000 patients can provide no assurance that the hazard that manifests itself in one case in 10,000 has been detected.

This situation confronted the FDA as it operated under the 1938 Act's "New Drug" provisions. The FDA expert had to evaluate such evidence as the applicant laid before him, guided perhaps more by his confidence or lack of confidence in the applicant than by the conclusiveness of the data presented.[13] Where doubts arose, the standard tactic was to find the application incomplete, denying its effectiveness unless reassuring information was provided on this or that point. Since compliance was often time-consuming and costly, representatives of the applicant would seek by pressure, by persuasion, or by shrinking its labeling claims and adding to its warnings to get clearance from the understaffed administrators.

More serious practices developed. The conviction in 1963 of a Washington physician for submitting reports of non-existent clinical

[12] The FDA may terminate an exemption permitting interstate shipment of an investigational drug if, "there is substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use." New Drugs Regs., 21 C.F.R. § 130.3(d) (3) (1965). There are ten other grounds for termination.

[13] The sponsor of a new drug was not required to give the FDA advance notice of his investigatory plan or the qualifications of his investigators, and the New Drug Application (NDA) requirements were less demanding than those now in force. See 21 C.F.R. pt. 2 (Cum. Supp. 1947). Charges of loose practice were not uncommon. See Mintz, cited at footnote 10, ch. 7.

trials leads one to wonder how often creative imagination was substituted for clinical observations.[14] Even reputable pharmaceutical firms distributed investigational drugs so widely that when, for example, the FDA sought to mop up the supply of thalidomide, it had trouble in locating all the distributees, and many of the latter had taken their duties so lightly that they could not identify all the recipients among their patients.[15] Some marginal firms even found it possible to operate commercially by marketing an investigational drug for years—for eleven years in one case.[16]

Just before the 1962 amendments the FDA took a step by regulation which it had hesitated to take during the 24 preceding years during which the 1938 law had given a legal basis for such action. The new regulation[17] prescribes conditions with which the manufacturer of a new drug—called the "sponsor"—has to comply in order to obtain an exemption enabling it to ship the drug in interstate commerce for investigational use prior to its approval by the FDA. The regulation also requires the sponsor to notify the FDA that it is claiming exemption, and with that notice it must file its plan of investigation. The regulation specifies[18] that the plan include one or more of three phases, to be preceded by animal testing and other studies to show that the investigational plan can be undertaken safely. The first phase calls for testing physiological reactions to the drug, and the second for testing its effects on a limited number of patients. The third phase requires clinical trials, often involving large numbers of patients, to test the drug's capacity to achieve the therapeutic objectives the sponsor claims for it.

Together with its plan, the sponsor must send to Washington all available information concerning the drug. Moreover, it must furnish the names of the individual investigators who are to conduct the plan, stating their qualifications for the type of work to be done. The

[14] The case of *United States v. Dr. B. A. Robin* (D.D.C. 1964) is reported in George Rosner, "Criminal Liability for Deceiving the Food and Drug Administration," 20 Food Drug Cosmetic Law Journal 446 (August 1965). (The physician lived in Silver Springs, Maryland, a suburb of Washington.)

[15] See Harris, cited at footnote 7, at 209, referring to an FDA press release reporting, among other things, that 2,528,412 thalidomide tablets had been distributed to 1,267 physicians.

[16] *Turkel v. Food & Drug Administration,* 334 F. 2d 844 (6th Cir. 1964). Krebiozen was marketed as an investigational drug for over ten years. See H. Thomas Austern, "Drug Regulation and the Public Health," 19 Food Drug Cosmetic Law Journal 259 (May 1964).

[17] 21 C.F.R. § 130.3 (1965).

[18] Form FD 1571, 21 C.F.R. § 130.3 (a) (2) (1965), requires that, in attachment 10, the sponsor outline the phases of the planned investigation to cover (a) clinical pharmacology (in two phases) and (b) clinical trial.

sponsor and each investigator are required to keep records and file periodic progress reports (though only the sponsor is required to report to the FDA). If any alarming reaction occurs, the FDA must be notified "immediately." Other adverse reactions also must be reported "promptly." Moreover, since human beings are to be used, not guinea pigs, all investigators are required to obtain the consent of the subjects, "except where they deem it not feasible or, in their professional judgment, contrary to the best interests," of the subjects. Some senators had tried to include in the 1962 amendments a rigid requirement of consent.[19] This had to be modified; sometimes the patient would lack capacity to consent, and sometimes knowledge of the trial would be harmful to him. The legal and ethical problems posed by human investigation are interesting and complex enough to sustain another lecture, but, since they are already the subject of voluminous literature,[20] I shall not pursue them further.

All the information that the FDA requires goes into the notice claiming exemption, a document known as the IND, letters symbolizing investigational drugs. These INDs, now arriving in Washington at the rate of seventy per month, plus amendments and supplements in the hundreds,[21] are screened by none other than Dr. Kelsey, now head of FDA's Investigational Drug Branch. Not long ago her staff numbered 13 physicians and three other scientists working under her direction; it now may be much bigger.[22] If, in this screening, an IND reveals a dangerous or inadequate investigation plan, she gives that IND priority in the staff's work. In case of danger, the exemption may be terminated by order.[23] More often the FDA simply calls attention to the IND's shortcomings, and the sponsor withdraws it pending the correction of its investigatory plan.

Needless to say, a screening process cannot be infallible,[24] and, since animal tests must serve as the chief basis for judgment at the

[19] Harris, cited at footnote 7, at 208.

[20] For the most compendious collection, see *Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects* (Ladimer & Newman eds. 1964).

[21] In fiscal year 1965, the FDA received 762 INDs, bringing the total number received by the end of the year to 2,727. Twenty-six were withdrawn at the FDA's request; 346, by their sponsors. Statement by Assistant Commissioner Rankin, reported in FDC REP. No. 44 (November 1, 1965).

[22] See Frances O. Kelsey, "Comments in New and Investigational Drugs," 20 FOOD DRUG COSMETIC LAW JOURNAL 86 (February 1965). INDs also are reviewed by the Division of Toxicological Evaluation and the Controls Evaluation Branch.

[23] See footnote 12; see Frances O. Kelsey, "The Investigational Drug Branch: A Review of Objectives and Function," reprinted as Exhibit 208 in *Humphrey Hearings*, cited at footnote 10, pt. 4, at 1662.

[24] Examples of 4 instances in which the FDA permitted the use of investigational drugs to continue despite

(Continued on following page.)

IND stage, uncertainties as to the inferences to be drawn from these tests can lead to debatable conclusions. However, plainly the new procedure has provided a more solid basis of fact for new drug approvals and for reducing the hazards of drug investigation. One might have supposed that its adoption would have been hailed by the medical profession. However, the first IND regulations the FDA proposed were blasted by the American Medical Association (AMA).[25] The AMA critics thought the FDA was putting the clinical investigation of drugs into a straight-jacket and was usurping the medical profession's responsibilities. Some criticisms were based on misunderstandings, and clarifying amendments were helpful, but the AMA still is not reconciled.[26] The burden of records and reports—"red tape" to the scientist—is a real one. The AMA warned it would divert scientific talent from drug investigation just as need for it was expanding. The pharmaceutical industry echoed this warning.

Perhaps there has been some withdrawal of professional personnel from the field. Certainly the expense of the investigational process is greater, not only because of record-keeping and reporting requirements, but, much more importantly, because of the obligation to establish the safety and effectiveness of drugs by thorough investigation. Pharmaceutical firms have been producing fewer new drugs, though how much of the shrinkage is due to the restrictive effects of the new regime and how much to the higher standards imposed is not easily determined.[27] Moreover, some students of drug therapy view the smaller numbers as a blessing in disguise; the industry is said to have been far too prolific in drugs that merely modified drugs already available in very minor respects while submerging physicians

(Footnote [24] continued)
warnings from staff pharmacologists, drawn from (as yet unpublished) hearings before the Subcommittee on Intergovernmental Relations of the House Committee on Governmental Operations, March 23, 24 & May 4, 1965, are reported in Mintz, cited at footnote 10, at 571.

[25] See Comments of American Medical Association, Proposal to Amend Regulations Pertaining to New Drugs for Investigational Use, October 9, 1962, reproduced as Exhibit N in *Humphrey Hearings*, cited at footnote 10, pt. 6, at 2921 (1963).

[26] See "AMA Outlines Position on Drug Regulations," *AMA News* 7 (Aug. 17, 1964), reprinted in *Humphrey Hearings*, cited at footnote 10, pt. 6, at 3069.

[27] Dr. Sadusk has stated that the average of NDAs received in fiscal years 1958-60 was 360 but that this fell to 262 in 1961. The number received in fiscal year 1962 was 282; in 1963, 179; in 1964, 160. He suggested in an address to the Pharmaceutical Manufacturers Association (PMA) that the high level attained in the late 1950's was due to important drug discoveries in the preceding years and that the "industry needs some more breakthroughs in new drug entities to keep up with the pace of the early 1950's." FDC Rep. No. 15, 18 (April 5, 1965).

under an avalanche of these new products.[28] Moreover, the new rigor has given great impetus to the science of clinical pharmacology, long a step-child among medical specialties. The new requirements necessitate new techniques of investigation, especially to check effectiveness and to identify side effects. Inevitably, we shall learn much more about the effects of drug action in the human body.

More serious are charges that challenge the objectivity of the investigatory system. Clinical trials are conducted by physicians under contract with sponsoring firms. The fees paid for this service may be substantial, and out of this fact may arise the temptation to provide the answers the sponsors would like to receive, a temptation that is enhanced wherever subjective elements bulk large in the investigator's appraisal.[29]

Moved by these considerations, critics have proposed drastic institutional innovations, among them, the creation of non-profit centers for all testing or for testing in specific fields, the pooling of industry funds to be paid to investigators by a disinterested body, the certification of clinical investigators so that a "CCI" would have a standing comparable to that of a CPA.[30] None of these measures seems likely to be resorted to unless abuses under the existing system grow widespread. Most of the past criticisms have reflected the loose practices prevailing before the new regulations not only required investigators' qualifications to be reported but also imposed record-keeping and reporting requirements upon them. However, a further safeguard could be added and that, I believe without statutory change. The sponsor could be required to include in its new drug application the terms of its contractual arrangements with its investigators.[31] If the re-

[28] Exemplifying professional concern are two articles: Friend, "Current Drug Therapy," 3 *Clin. Pharmacol. & Therapeutics* 557 (1962), and Sheps & Shapiro, "The Physician's Responsibility in the Age of Therapeutic Plenty," 25 *Circulation* 399 (1962), both reprinted as Exhibits 99 and 100 in *Humphrey Hearings,* cited at footnote 10, pt. 2, at 640. See also Supplementary Statement by Senator Humphrey, cited at footnote 10, pt. 5, at 2816.

[29] See Payment for Drug Testing; "The Uneasy Muddle," Mintz, cited at footnote 10, ch. 14. For material bearing on this problem, see *Humphrey Hearings,* cited at footnote 10, pt. 4, Exhibits 206-7, at 1641.

[30] These proposals are summarized in Mintz, cited at footnote 10, at 406-16.

[31] The Food, Drug & Cosmetic Act § 505(i) (3) (1962), 21 U.S.C. § 355(i) (3) (Supp. 1964) (hereafter cited as "Act"), permits conditioning an exemption of a drug for investigational use on "the making of such reports . . . by . . . the sponsor of the investigation (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an

(Continued on following page.)

wards seemed disproportionate to the difficulty of the investigation and the standing of the investigator, the FDA could proceed with duly enhanced vigilance. Moreover, if these reports evidenced a disturbing trend, they would lay a basis for further-reaching measures.

Evaluating Drug Safety and Effectiveness: Herein of the NDA

So much for the IND. When after months, perhaps years, a new drug's sponsor has brought investigations under its IND to what it considers a successful conclusion, its next major step is to file with the FDA its NDA.

An NDA that complies with the FDA regulations[32] is likely to be a formidable volume—or volumes. It reports the results of the investigations, the bad along with the good. It cannot draw on investigations reported in NDAs filed for similar drugs by the applicant's competitors since NDAs are held confidential.[33] The NDA must also summarize the relevant literature and submit the labeling the sponsor proposes to use in marketing his product. The importance of the labeling may later be crucial since the ultimate issue will be whether the drug is safe and effective under the conditions of use specified in the labeling. Moreover, the labeling must not only claim what the drug can do but must also specify its dosage and other conditions of use and identify side effects and contra-indications. If the drug is too hazardous for self-medication, it is classed as a prescription drug and subjected to special requirements, among them a full dis-

(Footnote [31] continued)
application. . . ." Information as to fees paid for such investigational use would not seem irrelevant to the drug's evaluation. If this provision seems too restrictive, resort could be had to the, "authority to promulgate regulations for the efficient enforcement of this Act," conferred by § 701(a), 21 U.S.C. § 371(a) (Supp. 1964). However, the FDA believes that it cannot compel fee disclosure. See *Humphrey Hearings,* cited at footnote 10, pt. 4, at 1643. An AEC licensing board has required the applicant to submit for *in camera* review portions of the contract between it and its turnkey-contractor bearing on their respective safety responsibilities, a requirement that does not appear to have been challenged in an unsuccessful attack on other conditions imposed by the board. See In the Matter of Jersey Central Power & Light Co., Docket No. 50-219, Initial Decision, Dec. 4, 1964, *aff'd* in AEC Opinions & Orders, Feb. 18, March 21 & May 6, 1965, 2 CCH ATOMIC ENERGY LAW REPORTER ¶ 11,249.

[32] 21 C.F.R. § 130.4 (1965).

[33] 21 C.F.R. § 130.32 (1965), citing the Act § 301(j), 21 U.S.C. § 331(j) (Supp. 1964), which, the regulation states, "makes it an offense to divulge to unauthorized persons any information acquired from a new-drug application concerning any process or method that is a trade secret."

closure of the good and bad effects of the drug in the labeling and the summarization of side effects and contra-indications in its advertising.[34]

The NDA, one of which has been known to absorb nine feet of shelf space, goes to the Division of New Drugs in the FDA's Bureau of Medicine. The 1962 Act gives the FDA 180 days to decide whether to approve or disapprove.[35] Suppose after, say, 150 days, the Division were to tell the sponsor that more data were needed on this point or more tests on that. If the sponsor refused to comply, the FDA would rule the application incomplete and the applicant would have the option to request the filing of the application over protest, thereby assuring a re-evaluation of the application within 30 days and, if it were not approved, the opportunity for a hearing to decide whether it is approvable.[36] A hearing then would absorb much more time than that needed to furnish the data. Therefore, the information, if obtainable, will be added in an amended application. The clock then starts running all over again. Clearly the 180-day time limit means little; indeed, 540 days is said not to be unprecedented as a period between initial filing and final approval. The FDA hopes, however, that a larger staff, more advance guidance to applicants, and, I need scarcely add, some computerization will speed up its NDA operations.

The approval process is not one in which the FDA staff proceeds between the dates of filing an application and final action on it in isolation from the applicant. On the contrary, the FDA's requests for additional studies and proposals for labeling changes may give rise to, "many months or years of negotiation," to quote a phrase used by a scientist with a major pharmaceutical firm, referring, no doubt, to informal discussions and correspondence with FDA staff members. "Nonetheless," he continues, "with patience, perseverance, time, and sometimes extraordinary effort, the NDA may be approved."[37]

Sometimes, of course, FDA demands for more information or tests cannot be met; the drug is one that simply cannot be shown to be safe or effective. Facing that fact, the sponsor will drop its applica-

[34] Act § 503(b), 21 U.S.C. § 353(b) (Supp. 1964), defining "prescription drugs," and § 502(n) (3), 21 U.S.C. § 352(n) (3) (Supp. 1964), requiring the summaries and giving to the FDA regulatory power over them to the exclusion of the Federal Trade Commission (FTC). For the requirement of fuller disclosure in labeling, see § 505(f), 21 U.S.C. § 352(f) (Supp. 1964), and 21 C.F.R. § 1.106 (1965).

[35] Act § 505(c), 21 U.S.C. § 355(c) (Supp. 1964).

[36] For the regulation affording this option, see 21 C.F.R. § 130.5(d) (1965).

[37] See Karl M. Beyer, Jr., "New and Investigational Drugs," 20 Food Drug Cosmetic Law Journal 75, (February 1965).

tion, a less painful way of terminating its undertaking than to have it denied. It is when the sponsor's executives firmly believe in a drug and the FDA is not convinced that the really acute questions in administering the ounce of prevention for new drugs actually arise. The problem is essentially that of evaluating the evidence. Where the tests show that the drug does some good and some harm as well, does the benefit outweigh the risk?

If the application is denied, some people whom the drug might have helped will be denied relief. The responsibility for decision is a grave one. The final decision is made by the Commissioner of Food and Drugs who, from 1906 until January, 1966, had never been a physician, although some incumbents, including the first one, the famous Dr. Harvey W. Wiley, had been scientists.

The Review of Denials of Approval and Withdrawals

What is a sponsor to do when its drug is denied approval? It may have invested much money and many hopes in the product. Its scientists may be convinced that the FDA is wrong. Doubtless its lawyers will want the decision reviewed.

If there is pressure for review where approval has been denied, plainly there is even more when an approval, once given, is withdrawn. The FDA may do this on the basis of new evidence or a revaluation of the original evidence in the light of new developments, either clinical experience or scientific findings.[38] The withdrawal not only destroys the market for a possibly profitable product, but it lowers the standing of the applicant, and this may hurt the sale of its other products as well. It also may affect adversely the outcome of pending liability suits.

To meet an applicant's desire for review, the law has provided an elaborate mechanism. As I reported early in this lecture, that mechanism has not worked, or, to be more accurate, has not been tried.

The 1962 amendments provide a procedure to review an order denying approval or withdrawing a prior approval that is basically similar to that provided in the new drug provisions of the 1938 act. The aggrieved applicant is entitled to full public hearing before the Secretary of Health, Education and Welfare (HEW).[39] In actual fact the hearing would be held before a hearing examiner. His report would be reviewed and a decision reached by the Secretary's dele-

[38] Act § 505(e), 21 U.S.C. § 355(e) (Supp. 1964).

[39] Act § 505(c), 21 U.S.C. § 355(c) (Supp. 1964).

gate, none other than the Commissioner of Food and Drugs.[40] One may predict with some confidence that, unless the applicant can bring significant new testimony to the fore or can dissipate misunderstandings concerning its product, the Commissioner will reach the same decision after the hearing that he had reached before it, since the latter decision would have been rendered only after a careful appraisal of the applicant's case informally presented.

Once the Commissioner has decided to stand his ground, the applicant may take the case to a federal court of appeals for judicial review.[41] The review is on the record, and no new ground of objection may be presented unless there were reasonable grounds for failing to urge it below. Moreover, the Act prescribes that, "the finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive." More evidence may be taken if the court finds there were reasonable grounds for its non-production, but it is the Commissioner who must evaluate the new evidence. If the court upholds his order, the court's decision is subject only to review in the Supreme Court on petition of certiorari, a petition one may predict that body will be reluctant to grant.

In 27 years, under the 1938 and 1962 acts, about 13,000 applications have been processed and many denied or withdrawn. Yet only a single applicant has carried its case though the administrative hearing stage.[42] Having lost there, it went no further. Accordingly, we see that the new drug decisions are made wholly within the FDA without public scrutiny—you will recall that NDAs are confidential—without public hearing, and without any formal review.

Maybe this is as it should be. Maybe the only way to get the best possible decisions is by getting the best possible people on the FDA staff, providing decent quarters and adequate equipment, giving them some chance for research of their own and access to first-rate expert advice when they believe they need it. Some important segments of the industry are of this view.[43] So is the FDA. Another viewpoint,

[40] Full provisions governing the procedure for new drug hearings, including their conduct by a hearing examiner, appear in 21 C.F.R. §§ 130.14-130.26 (1965).

[41] Act § 505(h), 21 U.S.C. § 355(h) (Supp. 1964).

[42] This was a withdrawal hearing. In the matter of "Altafur Tablets," Docket No. FDC-D-62, summarized in 24 FDC Rep. No. 34, at T & G 4 (Aug. 20, 1962). See also *Humphrey Hearings*, cited at footnote 10, pt. 3, exhibits 130, 131, at 945.

[43] In objecting to, "an extracurricular advisory committee," H. Thomas Austern of the Washington bar, who is active in food and drug law practice and an Adjunct Professor of Law at New York University, has declared, "These groups will be active privately,

(Continued on following page.)

however, exists within the industry and on the part of some spokesmen for the medical profession.[44] Those who hold it contend that an applicant ought not to be at the mercy of a bureaucratic judgment even if able people have become bureaucrats. The best obtainable regulatory officials are not likely to have a professional and scientific standing equal to that of the leaders in the particular fields of medicine and science that may be involved. Before a final decision is reached at the administrative level, these critics contend, an applicant ought to be able to present his case to a panel of expert advisers. They may not often decide in his favor, but if and when they do, their decision is likely to be respected by the Commissioner. Moreover, the critics argue that the mere power to demand review will assure the applicant a more careful evaluation of its NDA.

This difference of opinion as to the decision-making process marked a case which came closer to the hearing stage than any since the Drug Amendments of 1962 were enacted. At the risk of oversimplifying its medical aspects, I shall describe the problem of decision-making that it posed.

The Parnate Case

The drug in question is Parnate, trade name for tranylcypromine, one of a class of anti-depressant drugs known as MAO inhibitors.[45] (These letters refer to mono-amine oxidase and have no connection with the uninhibited Mr. Mao of Peking.) Parnate's application be-

(Footnote [43] continued)
on evidence not of record, and, I believe, exposed to every type of direct and indirect lobbying." H. Thomas Austern, "Sanctions in Silhouette: An Inquiry into the Enforcement of the Federal Food, Drug and Cosmetic Act," 18 FOOD DRUG COSMETIC LAW JOURNAL 617 (1963). For the FDA position, see Letter by Commissioner Larrick, September 9, 1963, *Humphrey Hearings* cited at footnote 10, pt. 4, 1860.

[44] It is advocated by Dr. Austin Smith, president of the PMA, *Hearings on Drug Safety,* cited at footnote 6, pt. 1, at 289, 357, and *Humphrey Hearings,* cited at footnote 10, pt. 5, at 2221, and by Lloyd N. Cutler, who has served as counsel to the same body, in "Practical Aspects of Drug Legislation" in *Drugs in Our Society* 149, 154 (1964). Dr. I. S. Ravdin, vice president for medical affairs, University of Pennsylvania, urged an, "independent, impartial reviewing council made up of highly qualified practitioners and scientists," in a letter in the *AMA News* (April 27, 1964). His view was endorsed by the Greater Philadelphia Commission for Medical-Pharmaceutical Sciences. *Hearings on Drug Safety,* cited at footnote 6, pt. 1, at 357.

[45] My brief report of the Parnate case is based on summaries of the case prepared by the staff of the Subcommittee on Intergovernmental Relations, cited at footnote 5, which investigated the handling of the drug last June, and by Dr. J. F. Sadusk, Jr., FDA Medical Director, for presentation in the hearings. (These probably will soon be published.) The case also is discussed in Mintz, cited at footnote 10, at 199-213.

came effective in February 1961. Its sales and sales abroad of tranylcypromine under other trade names were large. In six months, however, came reports of three cases in England and four in the United States in which tranylcypromine users suffered hypertension manifested by severe headaches and rapidly rising blood pressure. These led the FDA to require a warning of this reaction to be inserted in Parnate's labeling.

As time went on, reports of adverse reactions stepped up. Moreover, these went beyond headaches and high blood pressure. Strokes —cerebro-vascular accidents, as the profession calls them—began to be reported, with 14 deaths. An odd phenomenon appeared, first reported in England, most dramatically in the case of a 19 year-old boy who, though depressed, was in good physical health and at work. After a hearty lunch of bread and cheese one day, the boy took the prescribed dose of the drug and in two hours was dead. His case and certain others revealed that the drug suppressed an enzyme which would otherwise have coped with the tendency of amines in the cheese to increase blood pressure. Certain other foods have since been detected in this sinister interaction, pickled herring among them.

In September 1963, at the FDA's behest, the company sent out a strong warning letter—commonly called a "Dear doctor" letter. This was mailed to nearly 270,000 medical men. It led to an influx of new reports of adverse reactions. The FDA then solicited the opinions of eleven experts whose consensus was distinctly adverse to the drug. They thought it not effective enough to justify the risks its users were running. In February 1964, after conferring with the company, Commissioner George Larrick proposed to hold a hearing with a view to an order of withdrawal. The company then announced a decision to withdraw Parnate from the market but refused to withdraw the approval of its application. It asked that the hearing not be public, but the Commissioner refused. It also asked that the views of AMA and American Psychiatric Association committees first be received. This too was declined on the ground that experts had already been consulted. Battle-lines had been drawn when, at a prehearing conference, the company proposed an extensive revision of Parnate labeling.

Just before this action, the long vacant directorship of FDA's Bureau of Medicine had been filled. The new director was Dr. Joseph F. Sadusk, Jr., a highly respected physician, head of the Department of Preventive Medicine of George Washington University School of

Medicine.[46] Dr. Sadusk may have seen in the Parnate case a chance to put to the test his philosophy that the FDA must, "depend on the physician to apply those principles of balancing efficacy against toxicity at the individual patient level."[47] Though his staff was divided, Dr. Sadusk recommended, after informal consultations with an unprecedented number of experts, that the FDA accept a revision of Parnate's labeling, and, on the very eve of the public hearing for its withdrawal, the hearing was canceled. The new labeling required that Parnate's use be confined to cases of severe depression for patients under close observation for whom other anti-depressant drugs and electro-convulsive therapy were contra-indicated and who were not over 60 years of age and had no prior history of hypertension. The permitted dosage was reduced to half the previous dosage, and warnings were appended against use with cheese and with certain other suspected foods and drugs.

Parnate went back to the market, but opinion remained divided. Some viewed FDA's action as a capitulation to industry. Others saw it as a balanced judgment in which benefit had been wisely set off against risk, avoiding a protracted hearing, with one array of experts pitted against another.

The FDA almost certainly could have found substantial evidence to sustain its order on the ground that the drug was unsafe. For rulings as to effectiveness, a special definition of "substantial evidence" is prescribed by the 1962 amendments, and the burden of satisfying this rests with the applicant. For this purpose, "substantial evidence" means

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling of the drug.[48]

It should be noted that an applicant who satisfies this exacting definition is protected from an adverse finding based on the fact that the record includes other evidence to the contrary which could be

[46] For a resumé of Dr. Sadusk's career, see *Hearings on Drug Safety*, cited at footnote 6, pt. 1, at 168.

[47] The quotation is from an address by Dr. Sadusk at the AMA Convention on June 23, 1964, about a week after the Parnate decision. For the text of the address, which discusses the Parnate case, see Dr. Joseph Sadusk, Jr., "The Physician and the FDA," 19 Food Drug Cosmetic Law Journal 451 (August 1964).

[48] Act § 505(d), 21 U.S.C. § 355(d) (Supp. 1964).

viewed as "substantial." However, the makers of Parnate were not in a good position to take advantage of the term. Only a few carefully controlled investigations had been performed to test Parnate's effectiveness, and they were far from conclusive.[49] Though the relevant field of medicine is not one wherein reliable judgments are easy to come by, most of the testimony which Parnate's makers had amassed reported the opinions of clinicians and case reports in their files. Only under a most relaxed interpretation of the "substantial evidence" test could Parnate have been found effective. Moreover, a finding by the Commissioner that the applicant had failed to present substantial evidence in the defined sense would itself have been a finding of fact supported by substantial evidence in the usual sense. Therefore, it would be sustained by the Act's provision that the Secretary's finding as to the facts, if supported by substantial evidence, shall be conclusive. It seems plain that the FDA was under no legal compulsion to clear Parnate.

Review by a Panel of Experts?

Would a better way of resolving the problem have been to accept the proposal of Parnate to submit its claim to the judgment of a panel of experts, despite the extensive informal consultation of experts that had preceded the decision?[50]

This suggestion presents new problems. Who would choose the experts? How would they meet, privately or publicly? What evidence might they consider? Whom might they consult?

If the experts themselves had been asked, I think they would have had quick answers for these lawyers' problems. The experts

[49] The number of "controlled studies" is uncertain, a condition that doubtless reflects some uncertainty in the concept itself. In Mintz, cited at footnote 10, at 199, it is stated that the 190 articles discussing tranylcypromine published by the spring of 1964 included only four controlled clinical studies and that these had not, "yielded clear-cut evidence of efficacy." In Dr. Sadusk's statement to the Subcommittee on Governmental Operations in its June, 1965 hearings on Parnate, as yet unpublished, he refers to eleven controlled studies evaluated for the FDA by Dr. Jonathan Cole of the Psychopharmacology Service Center. The Subcommittee's summary of the testimony at its Parnate hearing reports Dr. Sadusk as having stated in a meeting with Parnate's manufacturer that, "the studies available at the time [June 5, 1964] did not meet the definition of 'substantial evidence' of effectiveness under the Drug Amendments of 1962." Criticism of the studies in the hearing lends support to this view.

[50] As reported in the text, above at p. 126, Parnate's makers proposed that the views of AMA and American Psychiatric Association committees be received before any hearing was held. I am informed that the FDA obtained informally the views of more than 100 physicians.

would doubtless have had the panels chosen by a committee of "the best men" in the profession. This committee would choose a panel of "the best men" in the branches of the profession most concerned with the problem. The panelists would, if they felt any need for help, then consult with the people whom they considered "the best men" to afford them aid. They would talk to whom they pleased and listen to whom they pleased, making such discounts as the existence of conflicts in interest among their informants suggested. When the time came to make up their minds, they would meet privately, and let the Commissioner have their conclusions, not a transcript of their discussions.

To lawyers this procedure is shocking. What is to prevent backstairs influence, lobbying with the panel, *ex parte* presentation of a one-sided story which the other side has no opportunity to rebut?[51] Is it enough that conflicts of interest be recognized in order to avoid them? The conflicts question is consequential since virtually all potential panelists would have done work on occasion for pharmaceutical firms.

The division on this issue throws light on a basic difference in approach between scientists and lawyers. Scientists—and related professionals as well—want to get the best man or men to resolve a problem and then to leave the matter up to them, giving them freedom to work privately and in confidence. Moreover, the scientists are confident that they can tell who the best men are, that they know whom they can fully trust.

The lawyer, on the other hand, wants the best procedure, one that will provide the greatest assurance of fair play and minimize the chance for manipulation, even when the people who operate it and on whom it operates are not "the best men" and, indeed, may, if not carefully watched, prove all too susceptible to bias and pressures.

Perhaps these differences reflect differences in the fields of learning and in the people with which the two groups must deal. These differences, I suspect, may affect many of the relations between what we call "law" and "science."

There are two other provisions for administrative approvals in the Food, Drug and Cosmetic Act which make specific provision for the use of advisory committees, one for determining tolerances for the residues of pesticide chemicals on raw agricultural commodities,[52]

[51] See footnote 43; see also *Humphrey Hearings,* cited at footnote 10, pt. 4, at 1857.

[52] Act § 408(1)(d) (1954), 21 U.S.C. § 346a(1)(d) (Supp. 1964).

the other for determining whether a color additive in a food, drug or cosmetic is carcinogenic, that is, can cause cancer.[53] The Act contemplated that individuals for these committees would be nominated by the National Academy of Sciences but, if it declined to do so, by the Secretary of HEW, that is, by the Commissioner of Food and Drugs. The National Academy has served in this capacity, but it has indicated that it does not wish to provide panel nominations for *ad hoc* committees for new drugs.[54] Accordingly, the FDA would have to make its own selections.

It is noteworthy that, though the problems of pesticide residue tolerances and the carcinogenicity of color additives are distinctly controversial, panels have been summoned very seldom in formal proceedings though the FDA has often consulted expert groups. Of course, the applicant's right to demand a panel may have induced the FDA to turn more often to outside experts before its decisions were reached. This suggests the possibility that their use could advantageously be institutionalized for new drug clearances and withdrawals. For each branch of medicine a panel of experts might be chosen by their peers and be prepared to serve as consultants whenever FDA encountered a serious problem in passing upon an NDA.[55] An eminent pharmacologist of my acquaintance is convinced not only that this practice would yield sound decisions but also that having the back-up of outside experts would enable the FDA staff to reach decisions more quickly and so would help in cutting down the big backlog of NDAs.

Such a procedure might work well. It has an analogue in an important unofficial body, the Committee of Revision of the United States Pharmacopoeia which determines the eligibility of drugs for listing in that authoritative compendium.[56] However, I doubt that it would resolve every case. Surely sometimes the experts would dis-

[53] Act § 706(b)(5)(B) (1960), 21 U.S.C. § 376(b)(5)(13) (Supp. 1964).

[54] See Statement by Dr. R. K. Cannan, Chairman, Division of Medical Sciences, National Academy of Sciences, National Research Council, June 21, 1963, *Humphrey Hearings* cited at footnote 10, pt. 3, at 983; see also pt. 4, at 1857. The Academy's position reflected a decision to form its own committee system for drug research.

[55] The FDA is now establishing advisory committees in various branches of medicine. The principal difference between these and the plan suggested in the text is that the suggested advisers would be consulted with greater frequency and as individuals rather than as a committee.

[56] The United States Pharmacopoeia is recognized as an "official compendium" and, as such, as a source of standards of strength, quality and purity for the drugs recognized therein. See Act § 501(b), 21 U.S.C. § 351(b) (Supp. 1964). For a description of the Pharmacopoeia's structure, together with the personnel of its committees, see *Humphrey Hearings* cited at footnote 10, pt. 4, exhibit 182, at 1333.

agree. Provision has to be made for the case where the FDA and the applicant are deadlocked, however seldom that case may arise.

In such a case a public hearing would be necessary, even though the applicant might prefer his case to be decided behind closed doors. But who should sit in judgment? Certainly the Commissioner cannot do so. His duties do not permit him to spend days and perhaps weeks in presiding as a judge in a hard-fought hearing. Probably, moreover, he will be neither a lawyer nor a physician. His instincts may be sound in gauging the wise policy to follow once the facts have emerged, but, if these are in doubt, he is not likely to be expert in evaluating the conflicting testimony. Certainly the ordinary hearing examiner is not. He is a lawyer skilled in guiding the course of the hearing as its presiding officer and in ruling on procedural points. However, if he makes findings of his own, they are the findings of a layman. The Commissioner, whether layman, scientist or physician, is not materially advanced by them in reaching his own decision.

Spokesmen For The Consumer Are Heard From

So far, I have discussed problems of decision-making as if the only question were how to assure fair treatment of the applicant against biased or ill-informed bureaucrats. However, there is another question for us to worry about: can the bureaucrat always be counted on to protect the public interest?

The phenomenon of the regulators' becoming the protectors of the regulated is not unknown to Washington. Indeed, it is commonly charged that, in the course of time, staffs of regulatory agencies either become prone to adopt the viewpoint of the regulated industry (which, unlike the drug industry, is often in economic difficulties) or, worse, become hopeful of joining its ranks.[57] The FDA has fared better than most agencies in avoiding suspicion on these counts, but it has not escaped unscathed. The drive for legislation that led to the 1938 Act was initiated by a volume entitled *One Hundred Million Guinea Pigs*[58]

[57] The charge is made as to regulatory agencies generally by Senator Paul H. Douglas in *Ethics in Government* 29-30 (1952). It is quoted and applied to the FDA in Mintz, cited at footnote 10, at 418.

[58] This volume by Arthur Kallet and F. J. Schlink was published in 1933. It soon became a best-seller. Mr. Schlink was co-author with Stuart Chase of *Your Money's Worth* published in 1927. This volume led to the formation of Consumers' Research, Inc., which, in addition to evaluating consumer products, urged better consumer legislation. See Corbett, "The Activities of Consumers' Organizations," 1 *Law & Contemporary Problems* 61 (1933). Subsequently, Mr. Kallet left the organization and became a founder of Consumers' Union.

which directed its polemics not only against the industries but also against the FDA. So does the newly published volume. *The Therapeutic Nightmare,* by Morton Mintz, which joins the FDA with the AMA and the PMA as co-defendants. The volume draws heavily on hearings before committees presided over by Senators Kefauver[59] and Humphrey.[60] Only last spring the subcommittee on Intergovernmental Relations of the House Committee on Government Operations, chaired by Representative Fountain of North Carolina, brought the FDA's administration of the new drug laws under fire.[61]

These hearings, particularly the most recent, demonstrate the difficulty of administering a regulatory law behind closed doors. The Fountain Committee wants to know just how FDA's decisions were reached, by whom, and on the basis of what deliberations. For example, the Subcommittee spent two days of hearings on the Parnate decision last June. It directed other hearings to other close decisions[62] and, if one may gauge the assumptions with which it began the tenor of its inquiries, the Subcommittee and its staff believe that the FDA had been soft on the drug industry to the detriment of the public.

Dr. Sadusk of the FDA stoutly defended his Parnate decision.[63] He saw it as a vindication of his policy of trusting the medical pro-

[59] See *Hearings on Administered Prices Before the Antitrust and Monopoly Subcommittee, Senate Committee on the Judiciary,* 86th Cong., 2d Sess., pts. 14 & 15 (Corticosteroids); pts. 15 & 17 (Tranquilizers); pt. 18 (General: Physicians and Other Professional Authorities); pt. 19 (General: Pharmaceutical Manufacturers Association); pt. 20 (Oral Antidiabetic Drugs); pt. 21 (General: Generic and Brand Names); pt. 22 (The Food and Drug Administration); pts. 24, 25 & 26 (Antibiotics) (1960-61).

[60] See *Humphrey Hearings,* cited at footnote 10, pts. 1 & 2 (Review of Cooperation on Drug Policies among Agencies) (1963); pt. 3 (The Bureau of Medicine in the Food and Drug Administration) (1963); pt. 4 (Specialized Drugs and Drug Problems) (1964); pt. 5 ((1) Commission on Drug Safety, (2) Pharmaceutical Manufacturers Association, (3) Medical Education on Drug Therapy and Other Drug Issues) (1964); pt. 6 (Drug Activities of the American Medical Association) (1964). The dates are of publication; the hearings in parts 1 and 2 were held in 1962; the others, in 1963. Many of the 3,228 pages are devoted to exhibits.

[61] See *Hearings on Drug Safety,* cited at footnote 6, pts. 1 & 2, reporting hearings held between March 24 and June 18, 1964. Hearings held in the spring of 1965 are as yet unpublished.

[62] For example, to meclizine (sold as Bonine) and cyclizine (sold as Marezine), over-the-counter drugs used in treating nausea, dizziness, and motion sickness, which have been suspected, on the basis of animal studies only, of causing birth deformities. The changes in position by Dr. Sadusk on the questions whether these drugs should be declared prescription drugs and, if not, what warning label they should bear were a subject of inquiry. Their handling is described in Ridgeway, "Feeling Dizzy?," *The New Republic* 15 (Oct. 1965). For criticism of FDA's later decision to require a strict warning, see "Cure That Kills," *Barron's* 1 (November 1, 1965).

[63] See footnote 45.

fession. He pointed out that, since August 1964, when Parnate went back on the market, it had been administered to an estimated 122,000 patients. Only four strokes involving users had been reported in the United States since the drug's marketing under its new labeling, no deaths having resulted in the four cases. (Since then a questionable new case of mortality has been reported.) Dr. Sadusk noted that the incidence of reported strokes to patients treated with Parnate is .33 per 10,000 which he compared with the mortality rates for other anti-depression treatments: 8 fatalities among 10,000 patients given electric-shock therapy; 10 fatalities among the same number treated by central nervous system stimulants; and 60 fatalities among 10,000 for insulin shock therapy. Behind these figures is another which he did not present: the grim suicide rate in cases of severe depression,[64] a factor which brings Parnate's dubious efficacy into the evaluation of its safety.

With his administration of the Medical Bureau under fire, Dr. Sadusk assembled the FDA's Medical Advisory Board for a meeting last July. The Board, after a review of the Parnate and other problem cases, agreed with his judgment and complimented him on the progress of his administration. Then it turned its guns on the Subcommittee's position on the issues of confidentiality of the Bureau's decision-making.[65]

Counsel to the Subcommittee had asked for records of adverse reactions reported to the FDA with respect to certain drugs, seeking the names of the patients, their physicians and hospitals. The Advisory Board declared this a violation of the confidential doctor-patient relationship that had to be preserved if the adverse reaction reporting system which the FDA is striving to develop is to survive. The Subcommittee also had sought transcripts of conferences between the FDA staff, its medical advisers and industry representatives. In such joint conferences, the Board declared, "the most effective method of

[64] Statistical rates as to suicides among severely depressed persons (of which psychiatry recognizes several categories) present diversities which reflect the variety of universes from which the samples are taken. Clearly, however, these suicide rates are many times higher than the mortality rates among patients being treated by any of the methods which Dr. Sadusk compared to Parnate. If Parnate were materially less effective than those other methods in preventing suicide, the fact that it did not cause deaths through its own action would not, of course, justify its use. However, the new required labeling indicated Parnate for use only where electroconvulsive therapy could not be used and other anti-depressant drugs were ineffective.

[65] For the text of resolutions passed at a meeting of the FDA's Medical Advisory Board, see 27 FDC Rep. No. 29, at 24 (July 19, 1965).

communication involves a high degree of mutual respect and courtesy." Evidently the Board anticipated congressional criticism on the score of failure to maintain the adversary spirit in these contacts with the industry.

The Board also resolved that the Subcommittee's efforts to secure the tapes and transcripts of advisory committee meetings would destroy the usefulness of such gatherings. It pointed out that, on controversial issues, there would be differences of opinion that should be aired in a frank and free discussion. This should be recorded to permit review. After review and the making of recommendations, the tapes and transcripts should be destroyed. "Under no circumstances," the Board declared, should they be, "transmitted to a third party."

Finally, the Board noted that the Subcommittee was probing the differences of opinion as to the handling of problem cases within the FDA's medical staff, differences that apparently had been sharp. The Board declared that the final decision must be that of the head of the medical staff and that, accordingly, the contrary views of his subordinates should not be set against his. This issue has long been a bone of contention between the Executive Branch and the Congress. When the Congress is challenging decisions made by department or bureau heads, it likes to look for dissent and to attack a bureau chief's views by invoking his staff's arguments which he had rejected in reaching his own conclusion.

Through all these problems that the Subcommittee's probe has brought to the fore, there runs a recurrent conflict of values. On the one hand, we have the concern of the governmental agency to enlist the full cooperation of a profession which has long been committed to confidentiality and hostile to the adversary process. On the other hand, we have the public's concern to assure the vigilance of its protectors in preventing harm from risks created by an industry that may be over-eager to exploit new and hazardous drugs. Secrecy in the decision-making process, the denial of knowledge concerning it to the public, breeds the suspicion that the public's interest is being sacrificed, a suspicion that can be scarcely be overcome by the FDA's practice of requiring extensive disclosure of adverse findings in the brochures accompanying the prescription drugs that it approves.[66] To

[66] See footnote 34. The disclosures currently required, while necessarily abbreviated and unable to provide analyses of the investigatory procedures followed, are more revealing than may be supposed. Thus the brochure (commonly called the "package insert") for Indocin (trade name for indomethacin), a new and apparently effective "anti-rheumatic" drug with a unique chemical structure, is accompanied,

(Continued on following page.)

satisfy the public's desire to know fully would play hob with the industry's interest in being able to reap the reward of successful research in discovering and developing a new drug. This it can best do by concealing its investigational procedures and experience and its manufacturing techniques from its rivals long enough to establish a firm grip on the market for the drug. Public proceedings also may bring new problems to the fore, as the AEC has found in the licensing of nuclear reactors. In my next lecture, I shall examine the AEC's problems in administering its ounce of prevention and contrast them with those of the FDA. The AEC's experience has suggested to me some measures which might on occasion afford a means of escaping the dilemma that confronts the FDA.

[To be continued in the October issue]

STUFFED TURKEY DECISION AFFIRMED BY U. S. COURT OF APPEALS

The Supremacy Clause of the United States Constitution was not violated by a New York State law which required packers of frozen stuffed turkeys to state the net weight of each turkey, stuffed or unstuffed, on a label. The federal law required an "approved" label of the net weight of each frozen turkey. Even though the Department of Agriculture had rejected a proposed label of the packers which would have complied with New York state law, a direct conflict was not shown because the packers failed to exhaust their administrative remedies by requesting a hearing from the decision. *Swift and Co.*, U. S. Court of Appeals (CA-2), July 12, 1966, FOOD DRUG COSMETIC LAW REPORTS ¶ 40,234.

(Footnote 66 continued.)
perhaps because of its uniqueness, by a statement about 750 words long reporting contra-indications, a warning, precautions and adverse reactions. For example, it notes toleration of the drug by a few patients with regional enteritis treated for from four to six months but adds, "in view of the paucity of the data," the drug should not as yet be given to patients in that category. It reports that "[s]tudies in mice demonstrated that Indocin crosses the placental barrier," and concedes that its "safety for use in pregnant patients has not been established." It recognizes that the drug may cause gastro-intestinal ulceration, and adds, "There have been reports of severe bleeding and of perforation with a few fatalities." Other adverse reactions are similarly treated.

WASHINGTON

REGULATIONS
of the Food and Drug Administration

"Consent" Required for the Use of Investigational Drugs Defined by FDA.—Regulations have been issued by the Food and Drug Administration defining the "consent" that is required from a patient to whom an investigational new drug will be administered. Except in unusual cases, physicians must obtain the written consent of patients for the use of investigational drugs. This provision is contained in Section 505(i) of the Federal Food, Drug and Cosmetic Act. The patient must have legal capacity and freedom of choice, and must be given necessary information about the investigational drug. An exception will be limited to cases where the patient cannot communicate, his representative is not available, and it is necessary to administer the drug without delay. Also, the consent requirement may be omitted if the patient's condition would suffer if consent were sought. Reg. § 130.37, FOOD DRUG COSMETIC LAW REPORTS ¶ 71,337.

Antibiotic Drug Report Spurs FDA to Action.—In response to a report on the use of antibiotics, the Food and Drug Administration has issued a statement of policy and has proposed to revoke two regulations, Reg. §§ 120.117 and 120.148. The statement of policy requires sponsors of antibiotic drugs used in food-producing animals to submit data for evaluation to determine whether or not such antibiotics are present as residues in edible tissues, milk, and eggs from the treated animals. The proposed revocation of Reg. §§ 120.117 and 120.148, which establish tolerances for residues of Chlortetracycline and Oxytetracycline in or on raw poultry, fish, and shellfish, is based on the failure of these antibiotics to meet guidelines set up by the Committee for evaluating antibiotics used in food preservation.

In an effort to determine effectiveness and safety, the FDA with the cooperation of the Department of Agriculture will seek new information on other antibiotics. Information about antibiotic contamination in foods and drugs will be sent to concerned parties, such as physicians, veterinarians and farmers. Reg. § 3.55, FOOD DRUG COSMETIC LAW REPORTS ¶ 4055 and Proposed Revocation, ¶ 60,146.

Official Drug Names have been Proposed by FDA.—A proposal to establish a new regulation to designate official names for 28 drugs has been issued by the Food and Drug Administration. The official name classification is an attempt to clarify the names by which drugs are designated in the interest of usefulness and simplicity. If adopted, the 28 official names are the names that must appear on the drug labeling for those drugs. View and comments by interested persons may be filed by October 14, 1966. FOOD DRUG COSMETIC LAW REPORTS ¶ 80,142.

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