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Administering That Ounce of Prevention: New Drugs and Nuclear Reactors--I

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Everyone in this audience 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. Yet, among these situations, the problem frequently recurs whether to depend for the making of decisions upon the processes that the legal profession has developed or upon

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1 I have canvassed some categories of these in *Introduction, Science and the Law Symposium*, 63 Mich. L. Rev. 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.
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—the FDA—and the Atomic Energy Commission—the 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, 

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 SEC fails to elicit a full disclosure from a corner-cutting issuer.
the informed scrutiny of the regulatory agency's experts will focus on the adequacy 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 marshall 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

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.
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 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, 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, 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 process 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

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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).
existence 15 years ago. 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 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.

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.

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

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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. Ibid.

7 See Harriss, 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 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); Harriss, supra note 7, at 182.
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. 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.

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.

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 neg-

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9 N.Y. Times, June 20, 1965, p. 61.
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.)
ligent 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, some one—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 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.

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, supra note 10, at 246. Plaintiffs' counsel have formed a foundation to facilitate the prosecution of their claims.
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 investigation use." New Drugs Regs., 21 C.F.R. § 130.3(d) (3) (1965). There are ten other grounds for termination.
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 it effectiveness unless reassuring information were 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 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 when the 1938 law had given a legal basis for such action. The new regulation17 prescribes conditions with which the manufacturer of a new drug—called the "sponsor"—has to comply in order to obtain

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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 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, supra note 10, ch. 7.

14 The case of United States v. Dr. B. A. Robin (D.D.C. 1964) is reported in Rosner, Criminal Liability for Deceiving the Food and Drug Administration, 20 Food Drug Cosm. L.J. 446, 458 (1965). (The physician lived in Silver Springs, Maryland, a suburb of Washington.)

15 See Harris, supra note 7, at 209, referring to an FDA press release reporting, inter alia, that 2,528,412 thalidomide tablets had been distributed to 1,267 physicians.


17 21 C.F.R. § 130.3 (1965).
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 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 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. 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 a voluminous literature, 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 Washin-

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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.
19 Harris, supra note 7, at 208.
20 For the most compendious collection, see Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects (Ladimer & Newman eds. 1964).
ton at the rate of seventy per month, plus amendments and supplements in the hundreds,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{24} and, since animal tests must serve as the chief basis for judgment at the 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.\textsuperscript{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.\textsuperscript{26} The burden of records and reports—"red tape" to the scientist—is a real one. The AMA warned it would divert

\textsuperscript{21} In FY 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 (Nov. 1, 1965).

\textsuperscript{22} See Kelsey, Comments in New and Investigational Drugs, 20 Food Drug Cosm. L.J. 86, 87 (1965). INDs also are reviewed by the Division of Toxicological Evaluation and the Controls Evaluation Branch.

\textsuperscript{23} See note 12, supra; see Kelsey, The Investigational Drug Branch: A Review of Objectives and Function, reprinted as Exhibit 208 in Humphrey Hearings, supra note 10, pt. 4, at 1662.

\textsuperscript{24} Examples of four instances in which the FDA permitted the use of investigational drugs to continue despite 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 Martz, supra note 10, at 571.

\textsuperscript{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, supra note 10, pt. 6, at 2921 (1963).

\textsuperscript{26} See AMA Outlines Position on Drug Regulations, AMA News 7 (Aug. 17, 1964), reprinted in Humphrey Hearings, supra note 10, pt. 6, at 3069.
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. 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 under an avalanche of these new products. 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.

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27 Dr. Sadusk has stated that the average of NDAs received in FYs 1958-60 was 360 but that this fell to 262 in 1961. The number received in FY 1962 was 282; in 1963, 179; in 1964, 160. He suggested in an address to the Pharmaceutical Manufacturers Association 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).

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 Humphry Hearings, supra note 10, pt. 2, at 640. See also Supplementary Statement by Senator Humphrey, supra note 10, pt. 5, at 2816.

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.\textsuperscript{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.\textsuperscript{31} If the rewards 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.

\textbf{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 New Drug Application or NDA.

\footnote{\textsuperscript{30} These proposals are summarized in Mintz, supra note 10, at 406-16.}

\footnote{\textsuperscript{31} The Food, Drug & Cosmetic Act § 505(i) (3) (1962), 21 U.S.C. § 355 (i) (3) (Supp. 1984) (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 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, supra note 10, pt. 4, at 1943. 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 Atm. Energy L. Rep. ¶ 11, 249.}
An NDA that complies with the FDA regulations 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. 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 contraindications. 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 disclosure of the good and bad effects of the drug in the labeling and the summarization of side effects and contraindications in its advertising.

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. 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. 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.

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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.”
36 For the regulation affording this option, see 21 C.F.R. § 130.5(d) (1965).
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 application, 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 reevaluation of the original evidence in the light of new developments, either clinical experience or scientific findings. 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. 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 delegate, none other than the Commissioner of Food and Drugs. 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. 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

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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).
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 through the administrative hearing stage. 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. So is the FDA. Another viewpoint, however, exists within the industry and on the part of some spokesmen for the medical profession. 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

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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, on evidence not of record, and, I believe, exposed to every type of direct and indirect lobbying." Austern, Sanctions in Silhouette: An Inquiry into the Enforcement of the Federal Food, Drug and Cosmetic Act, 18 Food Drug Cosm. L.J. 617, 626 (1963). For the FDA position, see Letter by Commissioner Larrick, Sept. 9, 1963, Humphrey Hearings, supra note 10, pt. 4, 1860.44 It is advocated by Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, Hearings on Drug Safety, supra note 6, pt. 1, at 289, 357, and Humphrey Hearings, supra note 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 (1984). 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, supra note 6, pt. 1, at 357.
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. (These letters refer to mono-amine oxidase and have no connection with the uninhibited Mr. Mao of Peking.) Parnate’s application became 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

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, supra note 5, which investigated the handling of the drug last June, and by Dr. J. F. Sadusky, Jr., FDA Medical Director, for presentation in the hearings. (These probably will soon be published.) The case also is discussed in Mintz, supra note 10, at 199-213.
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 pre-hearing 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. 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.” Though his staff was divided, Dr. Sadusk recommended, after informal consultations with an unprecedented number of experts, that the

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46 For a resumé of Dr. Sadusk’s career, see Hearings on Drug Safety, supra note 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 Sadusk, The Physician and the FDA, 19 Food Drug Cosm. L.J. 451, 453 (1964).
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.\(^4\)

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 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 Par-

nate's effectiveness, and they were far from conclusive. 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?

This suggestion presents new problems. Who would choose the experts? How would they meet, in private 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 would doubtless have had the panels chosen by a committee of "the best men" in the profession. This committee would choose a panel of

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49 The number of "controlled studies" is uncertain, a condition that doubtless reflects some uncertainty in the concept itself. In Mntz, supra note 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." Id. at 200. 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, supra at p. 128, 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.
"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? 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

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51 See note 43, supra; see also Humphrey Hearings, supra note 10, pt. 4, at 1857.
the use of advisory committees, one for determining tolerances for
the residues of pesticide chemicals on raw agricultural commod-
ities, the other for determining whether a color additive in a food,
drug or cosmetic is carcinoenic, that is, can cause cancer. The Act
contemplated that individuals for these committees would be nom-
inated 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 capa-
city, but it has indicated that it does not wish to provide panel
nominations for ad hoc committees for new drugs. Accordingly,
the FDA would have to make its own selections.

It is noteworthy that, though the problems of pesticide residue
tolerances and the carcinoenicity 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
whenver FDA encountered a serious problem in passing upon an
NDA. 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

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1984).
54 See Statement by Dr. R. K. Cannan, Chairman, Division of Medical
Sciences, National Academy of Sciences, National Research Council, June
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.
listing in that authoritative compendium. However, I doubt that it would resolve every case. Surely sometimes the experts would disagree. 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. The FDA

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56 The United States Pharmacopoeia is recognized 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, supra note 10, pt. 4, exhibit 182, at 1333.

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, supra note 10, at 418.
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 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—the Pharmaceutical Manufacturers Association—as co-defendants. The volume draws heavily on hearings before committees presided over by Senators Kefauver and Humphrey. 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.

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 Parlane decision last June. It directed other hearings to other close

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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 & Contemp. Probs. 61 (1933). Subsequently, Mr. Kallet left the organization and became a founder of Consumers’ Union.

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, supra note 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 3228 pages are devoted to exhibits.

61 See Hearings on Drug Safety, supra note 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.
decisions 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. He saw it as a vindication of his policy of trusting the medical profession. 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, 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

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42 E.g. 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 (Nov. 1, 1965).

43 See note 45, supra.

44 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 antidepressant drugs were ineffective.
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 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.

65 For the text of resolutions passed at a meeting of the FDA’s Medical Advisory Board, see 27 F.D.C. Rep. No. 29, at 24 (July 19, 1965).
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 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. To 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.

66 See note 34, supra. 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, 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.