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COMMENT

OMB INVOLVEMENT IN FDA DRUG REGULATIONS: REGULATING THE REGULATORS

The Nuremberg Code sets forth the first universal principles of medical ethics governing experimentation on human beings.¹ The primary objective of the Code is to ensure that clinical researchers use the utmost care in protecting the rights and welfare of human test subjects.² A modern adaptation of the Code for contemporary clinical research counsels that the three basic principles which should govern medical experimentation on humans are respect, justice and beneficence.³

1. The ten principles now known as the Nuremberg Code were set forth in the judgment at the Nuremberg trials. *United States v. Brandt*, 2 TRIAL OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNAL UNDER CONTROL COUNCIL LAW NO. 10 at 181, *reprinted in* J. KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* 305 (1972). The ten principles outline the moral and ethical obligations that the scientist must meet before commencing research on human beings. These principles include the obligation of the researcher to obtain the voluntary and informed consent of the human test subject; to insure that the subject has the freedom to terminate the experiment at any stage if the subject is not physically or mentally capable of continuing; to insure that the experiment is necessary, is based on results of animal experimentation, and is designed to produce results which are beneficial to society; to conduct the experiment in such a way as to minimize risk to the human subject; and to insure that the experiment is conducted by highly qualified scientists who exercise good judgment in the continual monitoring of the experiment. *Id.*

2. In *Brandt* the Nuremberg military tribunal wrote:

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that [the principles set forth in the Nuremberg Code] must be observed in order to satisfy moral, ethical, and legal concepts . . .

Id.

3. Thus, researchers must treat patients with respect, fairness, and with consideration toward promoting the well-being of individuals and society. *See* PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, *SUMMING UP: FINAL REPORT ON STUDIES OF THE ETHICAL AND LEGAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH* 66-71 (1983) [hereinafter *SUMMING UP*]; R. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 11-17 (2d ed. 1986).

Treating patients with respect means giving patients information about alternative health

Historically, United States laws regulating experimental research on human beings have emulated the principles set forth in the Nuremberg Code.⁴ The dominant area of research involving the use of human test subjects in the United States is drug research. The Food and Drug Administration (FDA), which regulates the drug industry, was the first federal agency to establish rules governing private sector use of human beings as research subjects.⁵ Like the Nuremberg Code, the FDA regulations seek to protect

care choices, honoring those choices where possible, protecting the privacy rights of patients, and ensuring that researchers are not required to act contrary to their values. *See* SUMMING UP, *supra*, at 68.

The principle of justice incorporates the concern that researchers treat patients in a fair and non-arbitrary manner. *Id.* at 70-71. Although in certain situations equity may require that researchers treat patients identically, other situations may require that patients be treated fairly. For example, health professionals must apply a uniform standard of death to all patients, but all patients are not equally entitled to scarce biomedical resources. *Id.* Justice requires that burdens and benefits be shared fairly and that distribution of benefits and burdens be based on morally sound criteria. *See* R. LEVINE, *supra*, at 17-18.

The principle of promoting well-being requires researchers to make all decisions in consideration of promoting the health and welfare of the patient, while considering the welfare of others, including the patient's family and future patients, who may benefit from knowledge gained from research. *Id.* at 67. "The principle of well-being also commands that the interests of incompetent patients be protected, according to the standards that a reasonable person would apply under the circumstances in weighing potential benefits and risks." SUMMING UP, *supra*, at 67.

4. Prior to the 1960s, the United States had very few laws governing medical research. *See* Curran, *Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies*, 98 DAEDALUS 542, 542-45 (1969). Under the auspices of the Department of Health, Education, and Welfare (HEW) (predecessor to the present Department of Health and Human Services (HHS)), the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) published the first federal guidelines for the ethical conduct of experimentation on humans. *See* SENATE COMM. ON LABOR AND PUBLIC WELFARE, 94TH CONG., 1ST SESS., FEDERAL REGULATION OF HUMAN EXPERIMENTATION, CRS-12 (Comm. Print 1975) (prepared by Staff of Science Policy Research Div. of Congressional Research Service) [hereinafter EXPERIMENTATION REPORT]. Although the NIH published guidelines in 1953 for research conducted at its Clinical Research Center in Bethesda, Maryland, these guidelines did not cover NIH-sponsored human experimentation at other locations. *See* Curran, *supra*, at 574-76. The Surgeon General subsequently published guidelines for NIH intramural research programs, PUBLIC HEALTH SERV., U.S. DEPT. OF HEALTH, EDUCATION, AND WELFARE, PROTECTION OF THE INDIVIDUAL AS A RESEARCH SUBJECT, (May 1, 1969), *reprinted in* EXPERIMENTATION REPORT, *supra*, at CRS-93, and the HEW codified regulations for HEW-sponsored research. Protection of Human Subjects, 39 Fed. Reg. 18,914 (1974).

In 1963, the FDA published regulations governing drug research on humans conducted at all public and private facilities. Procedural and Interpretive Regulations; Investigational Use, 28 Fed. Reg. 179 (1963) (current version at 21 CFR pt. 312) [hereinafter First Investigational Drug Regs.]. Both the FDA and HEW regulations provided for periodic ethical review of research involving human subjects, measuring the risks and benefits of the research, and obtaining the informed consent of the research subject.

5. Although the NIH issued the first guidelines governing research on human subjects, *see supra* note 4, these guidelines did not extend to research conducted by private clinics or

the rights and welfare of human test subjects by ensuring that the research is necessary, justified, and based on sound risk-benefit analysis.⁶

For over two decades, the FDA has carefully protected the rights of persons involved in experimental drug testing. Two regulatory provisions which have remained constant since the FDA first published regulations in 1963 are the requirements that both the evidentiary burden of proving the safety and effectiveness of the experimental drug and the economic burden of incurring the cost of drug development remain on the drug manufacturer.⁷

In the spring of 1987, however, the FDA published a proposal that would allow pharmaceutical companies to sell experimental drugs to terminally ill patients with practically no supervision from the FDA.⁸ The proposal not only allowed the drug company to shift a portion of its economic burden to

hospitals. *Id.* In 1963, the FDA published the first guidelines regulating private clinical research. First Investigational Drug Regs., *supra* note 4, at 179. Although the FDA's primary objective in drafting the regulations was to establish procedures for testing and approving new drugs, the regulations generally reflected the principles of the Nuremberg Code. *See* Curran, *supra* note 4, at 561-70. The regulations directed the drug manufacturer to provide the FDA with information regarding the nature of the experimental drug, the design of the clinical trial, and the training and experience of the persons conducting the research. First Investigational Drug Regs., *supra* note 4, at 179-80. Although the regulations directed that research could not proceed until the manufacturer had secured the consent of human research subjects, the FDA did not elaborate on either the procedures for obtaining such consent or the adequacy of such consent. *See id.* at 181. Thus, in 1966, the FDA published a formal statement detailing the nature and adequacy of the consent required of humans involved in experimental drug trials. Consent for Use of Investigational New Drugs on Humans; Statement of Policy, 31 Fed. Reg. 11,415 (1966). The FDA's most recent revision of its investigational drug regulations requires the clinical investigator to comply with FDA regulations governing the protection of human subjects and the ethical review of clinical trials. *See* 21 C.F.R. §§ 312.53(g)(vii), 312.60 (1988).

6. *See infra* text accompanying notes 39-41. In addition, the FDA regulations command that only qualified researchers conduct the clinical investigations and that the researchers obtain the informed consent of the human subject before commencing any research. *Id.*

7. Since the FDA first published investigational drug regulations in 1963, the burden has rested on the drug sponsor to justify the use of an experimental drug in clinical trials and ultimately to produce evidence that the drug is sufficiently safe and effective for marketing to the general public. *See* First Investigational Drug Regs., *supra* note 4, at 179. Although the regulations did not contain a blanket ban on the sale of investigational drugs, the FDA required a drug manufacturer seeking FDA permission to sell an investigational drug to justify the sale to the FDA. *Id.* at 180. This provision effectively compelled the drug manufacturer to shoulder the cost of drug development while the drug was under investigation. Once the FDA approved the drug, the manufacturer could recoup development costs.

The requirement that the drug manufacturer bear both the evidentiary burden of showing the safety and effectiveness of a drug and the financial burden of incurring development costs remained constant in the FDA regulations through 1986. *See* New Drugs for Investigational Use, 39 Fed. Reg. 11712 (1974) (current version at 21 C.F.R. pt. 312 (1988)).

8. The proposal was actually a repropounded section of a larger proposal to streamline regulations of the development and testing of new drugs. *See infra* text accompanying notes 124-27.

its human test subject,⁹ but also allowed the company to shift its evidentiary burden to the FDA.¹⁰ While the former provision ran contrary to historical FDA regulations,¹¹ the latter contradicted the agency's enabling act.¹²

Not surprisingly, the FDA proposal was the product of a convergence of forces which influenced the agency's rulemaking activity. First, public awareness of a lag in drug development caused by stringent regulations fueled pleas from terminally ill patients for early access to promising new drugs.¹³ Second, the Reagan administration, through the White House Office of Management and Budget (OMB), pushed its agenda of deregulation onto all administrative agencies,¹⁴ specifically targeting the FDA investigational drug regulations for major change.¹⁵ Third, a growing population of persons with AIDS increased the pressure on the FDA to relax restrictions on access to investigational drugs.¹⁶

During the past decade, OMB has risen to a powerful position in the agency rulemaking process. Pursuant to two executive orders,¹⁷ President Reagan has charged OMB with the task of reviewing all agency rules for consistency with his deregulatory agenda. Commentators have questioned both the authority for and the wisdom of the President's decision to grant

9. See *infra* notes 158-59 and accompanying text.

10. See *infra* text accompanying notes 141-45.

11. The first FDA regulations governing the use of experimental drugs in clinical trials contained a provision requiring drug sponsors seeking to sell investigational drugs during clinical trials to provide to the FDA "a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved." First Investigational Regs., *supra* note 4, at 180. This provision, which effectively precluded the sale of investigational drugs, remained constant in FDA regulations of treatment use and sale of investigational drugs until the publication of the new rule which is the subject of this Comment.

12. See *infra* text accompanying notes 146-47.

13. See *infra* text accompanying notes 55-63.

14. See OMB WATCH, THROUGH THE CORRIDORS OF POWER 11-12 (1987).

15. In its annual regulatory reform report, OMB tracks federal agency regulatory activity. In its 1985-86 report, the White House Office of Management and Budget (OMB) stated that certain FDA "classic" health and safety regulations "can be unnecessarily burdensome [and] interfere with consumer choices . . ." EXECUTIVE OFFICE OF THE PRESIDENT, OFFICE OF MANAGEMENT AND BUDGET, REGULATORY PROGRAM OF THE UNITED STATES GOVERNMENT: APRIL 1, 1985 - MARCH 31, 1986, at 73. In its 1987-88 report, OMB stated that the FDA regulatory reform program is "[d]esigned to prepare FDA for the challenges of today and of the 21st century." EXECUTIVE OFFICE OF THE PRESIDENT, OFFICE OF MANAGEMENT AND BUDGET, REGULATORY PROGRAM OF THE UNITED STATES GOVERNMENT: APRIL 1, 1987 - MARCH 31, 1988, at 87; see also *infra* text accompanying notes 64-67.

16. See *infra* text accompanying notes 72-77.

17. President Reagan issued Executive Order 12,291, 46 Fed. Reg. 13,193, reprinted in 5 U.S.C. § 601 (1982) [hereinafter First Reagan Order], in 1981, and Exec. Order No. 12,498, 50 Fed. Reg. 1036 (1985), reprinted in 5 U.S.C. § 601 (Supp. IV 1986) [hereinafter Second Reagan Order], in 1985.

such power to OMB.¹⁸ Moreover, the manner in which OMB has implemented the two executive orders has caused even greater concern.¹⁹ While the President may legitimately desire to coordinate national regulatory policy, the history of the FDA's new rule on the treatment use and sale of investigational drugs evidences the danger of allowing a small, non-expert staff at OMB to set the national agenda for drug regulations.

This Comment will explore the history of the FDA's proposed investigational drug rule and OMB's involvement in the rule. First, the Comment will set forth a brief history of the FDA and its regulations governing the drug development process. Next, the Comment will consider criticisms of the drug approval process and the mounting pressures on the FDA to revise its drug approval regulations. Third, the Comment will examine the emergence of OMB into the regulatory arena, its accelerated rise under the Reagan administration, and criticisms of OMB's involvement in the agency rulemaking process. The Comment will then explore and analyze OMB's role in the FDA's promulgation of the new rule allowing early access to investigational drugs. Finally, the Comment will discuss the implications of OMB's involvement in the FDA's promulgation of drug regulations and, more specifically, the dangers of allowing OMB to regulate federal regulators.

I. THE HISTORY OF THE FDA

A. Statutory History

Congress created the FDA to protect the public from unsafe drugs. The first act authorizing the FDA to regulate the drug market was the Federal Food and Drug Act of 1906.²⁰ This act authorized the FDA to recall a misbranded or adulterated drug only after the drug manufacturer had introduced the drug into the stream of commerce.²¹ In an effort to broaden the regulatory authority of the FDA, Congress enacted the Federal Food, Drug and Cosmetic Act of 1938 (the Act).²² The Act created a passive approval process whereby the FDA would automatically approve a new drug for marketing unless the FDA could show that the drug was unsafe for public consumption.²³

18. See *infra* text accompanying notes 104-12.

19. See *infra* text accompanying notes 113-23.

20. Ch. 3915, 34 Stat. 768 (also known as the Wiley or Heyburn Act), *repealed in part by* Federal Food, Drug and Cosmetic Act of 1938, ch. 675, 52 Stat. 1040 (1938) (current version at 21 U.S.C. §§ 301-392 (1982)).

21. *Id.*

22. Ch. 675, 52 Stat. 1040 (1938) (current version at 21 U.S.C. §§ 301-392 (1982)).

23. *Id.* Under the passive approval process, a drug manufacturer submitted a request to

In 1962, after the Thalidomide tragedy in Europe,²⁴ Congress amended the Act, requiring drug manufacturers to prove that a new drug is sufficiently safe and effective for intended patient populations before receiving FDA approval.²⁵ Congress thus shifted the burden of proving the safety and effectiveness of a new drug from the FDA to the drug manufacturer (the sponsor).²⁶

Congress further instructed the FDA to promulgate regulations permitting drug sponsors to ship investigational drugs to hospitals and clinics for the sole purpose of testing the drug in clinical studies.²⁷ The amended Act permits only a qualified expert (the investigator) to conduct such studies and requires the investigator to obtain the informed consent of human test sub-

the FDA to market a new drug. The FDA had no authority to deny the request unless the FDA could produce evidence that the drug was unsafe. Thus, the burden of showing that a new drug was not safe was placed on the FDA.

24. In 1961 and 1962, the treatment of pregnant women in Europe with Thalidomide resulted in the births of several thousand infants with defective limbs. Roberts & Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 584. Although the FDA never approved Thalidomide for marketing in the U.S., 2.5 million tablets of the drug were distributed to 1267 investigators. S. REP. NO. 1153, 89th Cong., 2d Sess. 8-25 (1966), reprinted in J. KATZ, *supra* note 1, at 921.

25. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C. §§ 321, 331, 332, 348, 351-53, 355, 357-60, 372, 374, 376, 381 (1982)) [hereinafter Drug Amendments]. Beginning in 1959, Senator Estes Kefauver initiated hearings on the Drug Amendments for the primary purpose of investigating profits and pricing in the drug industry. EXPERIMENTATION REPORT, *supra* note 4, at CRS-15. During the course of the hearings, the Thalidomide tragedy occurred, shifting the central focus of the hearings from economic issues to the safety and effectiveness of drugs on the U.S. market. *See id.* at CRS-15-16. Thus, the Drug Amendments originated in the Senate subcommittee on Antitrust and Monopoly. *See* 108 CONG. REC. 22,037 (1962), reprinted in 23 LEGISLATIVE HISTORY OF THE FOOD, DRUG & COSMETIC ACT 188 (1979). The Senate Judiciary Committee subsequently revised the bill. *Id.* After the Thalidomide tragedy in Europe, President Kennedy urged James Eastland, Chairman of the Senate Judiciary Committee to strengthen the bill by giving the FDA greater authority to regulate the drug development process. *Id.* The final bill contained strong measures to enhance standards of drug manufacturing, to ensure the accuracy of drug advertising, and to empower the FDA to approve only those drugs which the manufacturer has shown to be both safe and effective. *Id.* at 22,041, reprinted in 23 LEGISLATIVE HISTORY OF THE FOOD, DRUG & COSMETIC ACT 192 (1979).

26. Section 355 of the Federal Food, Drug, and Cosmetics Act (the Act) now requires a drug manufacturer to submit "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1) (1982). Before the FDA will approve the new drug for marketing, the drug manufacturer must submit "substantial evidence," *id.* § 355(d), to the FDA to show "whether or not such drug is safe for use and whether such drug is effective in use." *Id.* § 355(b)(1); *see also infra* note 29. The FDA may also deny the request if test results are inadequate to show that the drug is safe, 21 U.S.C. § 355(d)(1), if the drug is manufactured under unsafe conditions, *id.* § 355(d)(3), if the FDA has independent evidence that the drug is unsafe, *id.* § 355(d)(4), or if the proposed labeling is false or misleading. *Id.* § 355(d)(6).

27. 21 U.S.C. § 355(i).

jects before beginning the study.²⁸ The amended Act suggests that the FDA should approve clinical studies of new drugs only if the drug's sponsor submits drug research results to the FDA showing that drug research on animals justifies commencing drug tests on human beings.²⁹ By carving out a narrow and guarded investigational drug exemption to the prohibition against distributing unapproved new drugs, Congress intended to place the burden of justifying clinical studies, and subsequently proving the safety and effectiveness of a new drug, on the drug sponsor.³⁰

B. Development of FDA Drug Regulations

In 1963, shortly after Congress passed the Drug Amendments,³¹ the FDA published a set of new drug regulations creating an investigational new drug application (IND) and a new drug application (NDA).³² The regulations require a drug sponsor to file an IND to obtain FDA approval before testing an investigational drug on human subjects.³³ After completing clinical trials, the sponsor must file an NDA to obtain FDA approval before distributing and marketing the new drug.³⁴ The FDA may deny either application.

The section of the amended Act authorizing clinical drug research on

28. *Id.*

29. The amended Act states that the FDA may use its discretion in promulgating regulations which require drug manufacturers seeking FDA approval to begin testing investigational drugs on humans, and suggests that the FDA require such manufacturers to submit "reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing" before the commencement of any investigation. *Id.* § 355(i)(1).

30. One commentator, discussing the Drug Amendments, remarked:

As may well be imagined, there was opposition to the requirement that manufacturers prove the efficacy of their drugs. This meant a fundamental change in the philosophy of public regulation of the drug industry. From a policeman of safety, the FDA was transformed into an arbiter of value, quality, and success in scientific achievement.

Curran, *supra* note 4, at 552.

31. See *supra* note 25 and accompanying text.

32. The FDA published the investigational new drug application (IND) regulations on January 8, 1963, First Investigational Drug Regs., *supra* note 4, at 179, and the new drug application (NDA) regulations on June 20, 1963, 28 Fed. Reg. 6375 (1963) (current version at 21 C.F.R. pt. 314 (1988)).

33. The IND regulations set forth the information that the FDA requires of the drug sponsor prior to commencement of drug testing on humans. 21 C.F.R. § 312.23 (1988). The sponsor must justify the clinical trials by producing results of preclinical trials. *Id.* The sponsor must also set forth the exact nature of the trials, the names and qualifications of the investigators performing the research, the expected results of the trials, and the expected duration of the trials. *Id.*

34. *Id.* § 314. The NDA regulations set forth the information which the drug sponsor must submit to the FDA in order to obtain marketing approval for the new drug. *Id.*

humans³⁵ incorporates the ethical principles found in the Nuremberg Code. The amended Act requires that the sponsor must justify the research with results of prior animal studies,³⁶ that only expert investigators conduct the research,³⁷ and that the investigator obtain the prior informed consent of each human test subject.³⁸

The IND regulations also incorporate the Nuremberg Code's ethical principles. The regulations charge the sponsor with the responsibility of selecting qualified investigators, monitoring the progress of the clinical trials, and ensuring that the trials do not deviate from the planned investigation submitted to the FDA in the IND.³⁹ The investigator is responsible for obtaining the informed consent of each research subject, keeping accurate records of data collected during the investigation, and ensuring that an institutional review board⁴⁰ approves and continues to review the progress of the investigation.⁴¹ Thus, the IND regulations ensure that researchers will treat human subjects with respect, justice and beneficence.

C. The Drug Approval Process

To meet its statutory burden of proving to the FDA that an investigational drug is both safe and effective for its intended use, a drug sponsor must submit the new drug to a myriad of tests during the investigational process.⁴² Typically, the process begins with preclinical studies in which the

35. 21 U.S.C. § 355(i) (1982).

36. *Id.* § 355(i)(1).

37. *Id.* § 355(i).

38. *Id.*

39. 21 C.F.R. § 312 (1988).

40. Each research hospital has an institutional review board (IRB) composed of medical, ethical and lay professionals which is charged by the FDA with the responsibility of monitoring the day-to-day progress of the clinical trial and of ensuring the rights of human test subjects. *Id.* § 56. The IRB ensures that the patient is aware of the investigational nature of the drug, understands the risks and benefits of taking the drug, and gives his or her informed consent to treatment. *Id.* The IRB further ensures that ethical guidelines are followed in all clinical trials including trials in which placebos are administered. See R. LEVINE, *supra* note 3, at 325-28.

The IND regulations require that the investigator ensure that the IRB fulfills its duties as set forth in § 56 of the FDA drug regulations. 21 C.F.R. § 312.66 (1988). Section 56 charges IRBs with the responsibility of ensuring that clinical investigations involving human research subjects are conducted in accordance with medical ethics. *Id.* § 56. Since medical ethics dictate that placebos cannot be used if a known drug is effective in treating a disease, it is the responsibility of the IRB to monitor the clinical tests to determine whether testing shows any drug to be effective in treating the disease. *Id.*

41. 21 C.F.R. §§ 312.60, 312.61, 312.62, 312.64, 312.66, 312.68 (1988).

42. To obtain FDA approval to distribute and market a new drug, a sponsor must submit "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1) (1982). The FDA

investigator conducts drug tests in vitro and administers the drug to laboratory animals.⁴³ Once the results of the in vitro and animal studies show that the drug is sufficiently safe, the sponsor submits an IND application to the FDA for approval to begin clinical testing of the drug on human subjects.⁴⁴

The IND regulations separate clinical testing into three phases.⁴⁵ In Phase 1, the investigator administers the drug to a small group of healthy subjects to gather preliminary information about the drug's relative safety for humans.⁴⁶ In Phase 2, the investigator administers the drug, in controlled clinical trials, to a small group of patients suffering from the disease for which the drug was developed.⁴⁷

Whereas Phase 1 primarily focuses on whether the drug is safe for humans, Phase 2 begins to focus on whether the drug is effective in the patient population for which the drug is intended.⁴⁸ If the drug shows promise in the Phase 2 trials, the investigator begins Phase 3 of the drug testing process. Based on the data obtained in the earlier phases, the investigator ex-

may deny a sponsor's application if the FDA finds a "lack of substantial evidence 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 proposed labeling thereof." *Id.* § 355(d)(5). The amended Act defines "substantial evidence" as:

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 thereof.

Id. § 355(d).

43. See Preamble to Proposed IND Rewrite, 48 Fed. Reg. 26,720, 26,726 (1983) (codified at 21 C.F.R. pt. 312) (proposed June 9, 1983). For an overview of the drug development process see *id.* at 26,723.

44. 21 C.F.R. § 312.23 (1988).

45. *Id.* § 312.21; see also Hurley, *Planning Research and Development of New Drugs to Assure Regulatory Approval*, 39 FOOD DRUG COSM. L.J. 312, 313 (1984).

46. 21 C.F.R. § 312.21(a) (1988). Phase 1 testing is generally conducted on healthy volunteers, although patients may be enrolled in the study. *Id.* Phase 1 focuses on the pharmacological action of the drug, the side effects of the drug and the ideal dosage and method of administration in humans. *Id.* Phase 1 trials typically involve between 20 and 80 volunteers. *Id.*; see also *AIDS Drug Development and Related Issues: Hearing Before the Subcomm. on Intergovernmental Relations and Human Resources of the House Comm. on Government Operations*, 99th Cong., 2d Sess. 80-82 (1986) [hereinafter *AIDS Hearing*] (testimony of Walter R. Dowdle, Ph.D., AIDS Coordinator, Public Health Service, HHS).

47. 21 C.F.R. § 312.21(b) (1988). Phase 2 trials typically involve several hundred subjects. *Id.*

48. The regulations state that "Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug." *Id.*

pands the trials in Phase 3 to include a much larger group of patients.⁴⁹ The objective of Phase 3 trials is to assess the safety and effectiveness of the drug in diagnosing and treating the intended patient population.⁵⁰ Phase 2 and 3 trials often involve double blind tests in which certain patients receive placebos while others receive the active drug.⁵¹

The IND regulations, promulgated by the FDA pursuant to the amended Act, have protected human research subjects from abusive research and have protected American consumers against a Thalidomide-type tragedy. Commentators argue, however, that by increasing regulation of drug testing and development, Congress and the FDA have traded an efficient drug market for a safe one. While acknowledging that the investigational drug regulations have effectively prevented drug manufacturers from introducing unsafe and ineffective drugs in the market, these commentators argue that the regulations have also prevented desperately ill patients from gaining access to promising drugs.

II. CURRENTS OF CHANGE AT THE FDA

Approximately fifteen years after Congress enacted the Drug Amendments, several independent forces began churning and then converged to pressure the FDA to revise its drug regulations. First, statistics produced by critics of the Drug Amendments, which revealed a substantial increase in drug development time, fueled increasingly louder cries from terminally ill patients for access to investigational drugs.⁵² Second, the Reagan adminis-

49. Phase 3 trials typically involve between several hundred to several thousand patients. *Id.* § 312.21(c).

50. *Id.*

51. Because Phase 1 of a clinical drug test focuses on safety and not on effectiveness, each subject in Phase 1 will receive the active drug. Investigators only use placebos in Phase 2 and Phase 3 trials, where the investigators require a standard against which the effectiveness of a new drug can be measured. *AIDS Hearing, supra* note 46, at 81-82 (testimony of Walter R. Dowdle, Ph.D., AIDS Coordinator, Public Health Service, HHS). Investigators use placebos in controlled clinical trials where there exists no known standard therapy for the disease. In order to ethically justify using a placebo on a human test subject, there must exist a valid null hypothesis which states that no treatment is any better than any other treatment. Hence, the investigator must believe that the new drug being tested will provide no greater benefit to the patient than the inert placebo. *Id.* at 56-57 (testimony of Robert J. Levine, M.D., Professor of Medicine, Yale Univ. School of Medicine). Obviously, the investigator's goal is to disprove the null hypothesis. Once the investigator has reason to believe that one treatment provides better results than any other treatment, the investigator can no longer justify the placebo-controlled trial. *Id.* For example, since certain treatments are relatively effective in treating cancer, it would be unethical to test a new cancer treatment against a placebo control. Therefore, new cancer treatments must be tested against existing cancer treatments. *Id.* at 69. For a thorough discussion of the ethics of using placebos in clinical trials, see Rosner, *The Ethics of Randomized Clinical Trials*, 82 AM. J. MED. 283 (1987).

52. See *infra* text accompanying notes 55-63.

tration's agenda to ease regulation in various sectors of the economy included a plan to relax regulations of investigational drugs.⁵³ Third, the AIDS virus, a fatal disease which swiftly struck thousands of young Americans, became the final impetus for streamlining the FDA's drug regulations.⁵⁴

A. *Slow Drug Development and the Drug Lag*

Soon after the FDA published its first regulations governing investigational drugs, critics began voicing concern that the amended Act increased the time in which the FDA approved a new drug for marketing and created a drug lag in the United States as compared to other countries.⁵⁵ Because of the exacting safety and efficacy requirements set forth in the IND regulations, only an approximate twenty percent of INDs are approved for marketing.⁵⁶ The elapsed time from identification of a new chemical entity to drug approval by the FDA is estimated at eleven years, and the cost approaches \$65,000,000 per drug.⁵⁷ Prior to the enactment of the Drug Amendments, the time frame from identification to approval spanned approximately two and a half years,⁵⁸ and the monetary cost was three to four times less than the current cost.⁵⁹

The lag time for drug approval in the United States has caused desperately

53. See *infra* text accompanying notes 64-67.

54. See *infra* text accompanying notes 72-77.

55. For an extensive discussion of the delayed availability of new drugs within the United States, see Roberts & Bodenheimer, *supra* note 24. These critics argue: "[F]irst, the additional testing requirements stemming from the 1962 Amendments and subsequent regulations delay the availability of important new drugs. Second, the increased costs of regulatory compliance reduce the incentive for research and innovation. Third, the 1962 Amendments fail to reduce the percentage of ineffective drugs on the market." *Id.* at 586.

For a review of the research conducted on the drug lag in the United States vis-a-vis other countries, see Schiffrin, *Lessons from the Drug Lag: A Retrospective Analysis of the 1962 Drug Regulations*, 5 HARV. J.L. & PUB. POL'Y 91 (1982). One study, cited by Schiffrin, compares the United States drug market with that of Britain and concludes:

[D]rug availability is more constrained in the United States in three respects: there are more drugs available in Britain that are not available in the United States than vice versa; drugs that are available in both countries are more often introduced in Britain before being introduced in the United States; and drugs that are available in both countries are more likely to be approved for a wider range of indications in Britain than in the United States.

Id. at 95.

56. In the preamble to the proposed IND Rewrite, the FDA acknowledged that "only 20 percent of new chemical entities studied under an IND ever reach the NDA stage." Proposed IND Rewrite, *supra* note 43, at 26,720; see also Hurley, *supra* note 45, at 312.

57. Hurley, *supra* note 45, at 312.

58. Roberts & Bodenheimer, *supra* note 24, at 586.

59. See Schiffrin, *supra* note 55, at 103.

ill patients to petition the FDA for early access to promising investigational drugs.⁶⁰ The drug lag vis-a-vis foreign drug markets has sent some of these patients to foreign countries in search of a cure or treatment.⁶¹

In response to pleas from desperate patients and physicians for pre-marketing access to investigational drugs, the FDA developed ad hoc, uncodified procedures for granting early access. The "compassionate use" exemption allows drug companies, under strict agency supervision, to provide promising investigational drugs to terminally ill patients before the FDA approves the drug for marketing.⁶² Because the FDA had never codified the exemption, however, and because patients and physicians experienced difficulty in obtaining information regarding access to investigational drugs under the compassionate use exemption,⁶³ advocates of drug regulation reform continued to pressure the FDA for easier access to promising new drugs.

B. *The Reagan Administration's Regulatory Agenda*

President Reagan entered office promising to ease government regulation in various sectors of the economy.⁶⁴ The President appointed Vice President Bush to head the Task Force on Regulatory Relief. The task force's vehicle for revising selected regulations was OMB.

OMB assumed a leading role in the struggle to reform the FDA's drug regulations.⁶⁵ As the enforcer of President Reagan's national deregulation

60. See Preamble to Proposed IND Rewrite, *supra* note 43, at 26,728.

61. See *AIDS Hearing*, *supra* note 46 at 5-8 (testimony of Paul Popham and John Smith, two AIDS patients).

62. See *id.* at 58-60 (testimony of Robert J. Levine, Professor of Medicine, Yale Univ. School of Medicine); *id.* at 101 (testimony of Dr. Harry Meyer, Director, Center for Drugs and Biologics, FDA).

63. The "compassionate use" exemption was seen by many as an inadequate solution, since patients and physicians experienced great difficulty obtaining information regarding access to the drug. *Id.* at 5-11 (testimony of Paul Popham and John Smith, two AIDS patients). Historically, drug companies have performed research on investigational new drugs in a rather secretive manner. Preferring to shield investigatory research from public scrutiny so that news of early success does not feed false hope to desperately ill patients, drug companies traditionally maintain a low profile until a new drug is certain to be approved. Consequently, patients and their physicians have extreme difficulty obtaining information regarding the discovery of promising new drugs, the existence of clinical trials, and the qualifications necessary to be accepted into clinical trials. *Id.* The FDA recognized the need for increased information to the medical community regarding the availability of investigational drugs and cited this lack of information as one of the reasons for its attempt to codify the "compassionate use" exemption in the IND Rewrite. See Preamble to Proposed IND Rewrite, *supra* note 43, at 26,728-29.

64. See OMB WATCH, *supra* note 14, at 11.

65. Shortly after the FDA published repropoed regulations for treatment use and sale of investigational drugs, see *Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale*, 52 Fed. Reg. 8850 (1987) (proposed Mar. 19, 1987) [hereinafter *Reproposal*], Ted Weiss, chairman of the House subcommittee responsible for

program, OMB targeted the drug development and approval process for regulatory reform.⁶⁶ Certain OMB staffers believed that the federal government should not interfere with a physician's right to prescribe experimental drugs to desperately ill patients.⁶⁷

Although the FDA had begun to revise its drug regulations before the Reagan administration entered office,⁶⁸ OMB expedited the publication of proposed rules designed to streamline the drug development and approval process. In October 1982, the FDA published a proposed "NDA Rewrite" which addressed the drug approval process.⁶⁹ The proposed "IND Rewrite," published in June 1983,⁷⁰ focused on the drug development process. Included in the IND Rewrite was a provision which essentially codified the ad hoc compassionate use procedures for allowing terminally ill patients access to promising new drugs.⁷¹

C. The AIDS Epidemic

The proposed IND and NDA Rewrites represented a significant effort on the part of the FDA to streamline the drug development and approval

FDA oversight, held a hearing on the regulations. Representative Weiss noted that one of the objectives of the hearing was to "examine the decisionmaking process that led to the proposal and, in particular, the pivotal role played by political appointees in the Office of Management and Budget (OMB)." *FDA Proposal to Ease Restrictions on the Use and Sale of Experimental Drugs: Hearing before the Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Government Operations, 99th Cong., 1st Sess. 3 (1987) [hereinafter Drug Hearing]* (testimony of Rep. Ted Weiss).

66. See *Experimental Drugs, Power and the Limits of Deregulation*, Wash. Post, July 15, 1987, at A21, col. 1. At the congressional oversight hearing on the FDA's Reproposal regarding early access to investigational drugs, see *supra* note 65, Representative Weiss produced a document showing that certain staffers at OMB believed that the FDA should not have the authority to deny a patient access to an investigational drug. *Drug Hearing, supra* note 65, at 280-83. Representative Weiss expressed grave concern over "OMB's position that physicians should be allowed to do whatever they think is best under the circumstances, irrespective of what FDA concludes about the safety or efficacy of a new drug." *Id.* at 129.

67. See *id.*; see also *infra* note 134.

68. In the preamble to the final IND Rewrite, the FDA explains that it first published "concept papers" on drug regulation reform in 1979. See *New Drug, Antibiotic, and Biologic Drug Product Regulations*, 52 Fed. Reg. 8798 (1987) (codified at 21 C.F.R. pt. 312) (proposed June 9, 1983) [hereinafter Final IND Rewrite].

69. *New Drug and Antibiotic Regulations*, 47 Fed. Reg. 46,622 (1982) (codified at 21 C.F.R. pt. 314) (proposed Oct. 19, 1982) [hereinafter Proposed NDA Rewrite].

70. Proposed IND Rewrite, *supra* note 43, at 26,720.

71. At a congressional oversight hearing to investigate the history of the investigational drug regulations, see *infra* text accompanying note 165, FDA Commissioner Frank Young testified that the 1983 proposed IND Rewrite "merely codified the agency's current unwritten criteria for granting treatment IND requests." See *Drug Hearing, supra* note 65, at 94 (testimony of FDA Commissioner Frank Young).

processes.⁷² In the early 1980's, however, the deadly AIDS virus emerged on the national health scene, fueling a demand for new drugs to treat and cure patients afflicted with the disease.⁷³

In September 1981, the Centers for Disease Control reported 129 AIDS cases in the United States.⁷⁴ The number of cases began to increase dramatically. The Centers for Disease Control reported 257 AIDS cases by February 1982; 1,029 cases by January 1983; 4,115 cases by April 1984; 8,229 cases by February 1985; and 16,458 cases by January 1986.⁷⁵ The Surgeon General reports that health officials expect 179,000 AIDS-related deaths by 1989 and 270,000 reported cases by the end of 1991.⁷⁶

The alarming rise in the number of AIDS victims increased the pressure on the FDA to drastically ease access to investigational drugs.⁷⁷ This pressure, combined with pressure from other terminally ill patients, provided OMB with the justification it needed to impose its drug regulation reform agenda on the FDA.

While the FDA sought to ease restrictions on experimental drugs intended for desperately ill patients, OMB sought to eliminate such restrictions. The power play which ensued between the agency and the administration over the investigational drug regulations resulted in large part from the emergence of OMB as the regulator of agency rulemaking.

72. In the proposed IND Rewrite, the FDA indicated that the modifications were intended to streamline the IND process while upholding high standards to protect human test subjects. Proposed IND Rewrite, *supra* note 43, at 26,720.

73. At a 1986 congressional hearing, two AIDS patients testified that AIDS victims are desperate for drugs to treat the AIDS virus. See *AIDS Hearing*, *supra* note 46, at 5-13 (testimony of Paul Popham and John Smith, two AIDS patients). The AIDS patients also testified that AIDS victims and their physicians often are unable to obtain information concerning new AIDS drugs because drug manufacturers typically do not disclose such information until the drug is nearing the approval stage. *Id.* One patient testified that AIDS patients are "so desperate to find something" that they are spending large sums of money and traveling to foreign countries in search of a treatment or cure. *Id.* at 7.

74. See 35 CENTERS FOR DISEASE CONTROL, MORBIDITY AND MORTALITY WEEKLY REPORT 17-21 (Jan. 17, 1986).

75. *Id.*

76. See U.S. DEPT. OF HEALTH AND HUMAN SERVICES, SURGEON GENERAL'S REPORT ON ACQUIRED IMMUNE DEFICIENCY SYNDROME 6 (1986).

77. At the congressional oversight hearing to explore the history of the investigational drug regulations, FDA Commissioner Frank Young presented written testimony confirming that AIDS patients played a major role in the FDA's attempt to ease restrictions on investigational drugs. Commissioner Young wrote that "[a]lthough the issue of early availability of breakthrough drugs clearly applies to a wide number of serious and life-threatening disease categories, the current AIDS epidemic has focused attention on the early availability of experimental drugs as never before, and rightly so." *Drug Hearing*, *supra* note 65, at 77.

III. EMERGENCE OF OMB AS THE REGULATOR OF REGULATORS

A. *The Rise of OMB*

OMB's role in agency rulemaking has grown steadily over the past several decades.⁷⁸ In 1971, President Nixon instituted a review process requiring administrative agencies to circulate proposed rules to OMB and other agencies for comment before final publication.⁷⁹ Later, President Ford instructed agencies to prepare and submit to OMB an economic impact statement for every major rule.⁸⁰ In 1978, President Carter implemented a regulatory reform program, designating OMB as official overseer.⁸¹ Carter required agencies to prepare a regulatory analysis for each significant regulation and to submit the analysis to a central committee which would identify and eliminate duplicative regulatory efforts.⁸²

During the Nixon, Ford, and Carter administrations, OMB enjoyed an active role in agency rulemaking. OMB had very little power, however, to actually sway an agency rule.⁸³ Thus, while OMB's visibility in agency rulemaking increased during earlier administrations, not until the Reagan

78. In large part, the growth of OMB's role in rulemaking procedures is in direct response to the growth of administrative agencies in the 1960s and 1970s. See Morrison, *OMB Interference with Agency Rulemaking: The Wrong Way to Write a Regulation*, 99 HARV. L. REV. 1059, 1060-63 (1986). One commentator observed that the "shift in the center of gravity of lawmaking" from Congress to the agencies is in large part "due to the increasing complexity of modern society." Rosenberg, *Beyond the Limits of Executive Power: Presidential Control of Agency Rulemaking Under Executive Order 12,291*, 80 MICH. L. REV. 193, 209 (1981).

Observers of OMB's expanded role point to a number of reasons for this expansion, including the fact that agencies, pursuant to congressional instruction but with little coordination between themselves, began drafting extensive and costly regulations without considering the economic effects of the regulations on industries struggling in a depressed economy. Morrison, *supra*, at 1060-62.

79. See OMB WATCH, *supra* note 14, at 10; Morrison, *supra* note 78, at 1060-63; Rosenberg, *supra* note 78, at 222-25.

80. OMB WATCH, *supra* note 14, at 10. President Ford sought to sensitize regulators to the consequential costs of regulations. *Id.*; see also Morrison, *supra* note 78, at 1061.

81. OMB WATCH, *supra* note 14, at 10-11; see also OMB WATCH, OMB CONTROL OF RULEMAKING: THE END OF PUBLIC ACCESS, 4 (1985) [hereinafter CONTROL OF RULEMAKING]; Morrison, *supra* note 78, at 1061.

82. OMB WATCH, *supra* note 14, at 11; CONTROL OF RULEMAKING, *supra* note 81, at 5; Morrison, *supra* note 78, at 1060-63.

83. One observer commented that "[t]he Carter program, like its predecessors, has been judged a failure by some because it lacked a formal enforcement mechanism." CONTROL OF RULEMAKING, *supra* note 81, at 5. Another observer remarked that prior to the Reagan administration, each change in the rulemaking process "was a step toward greater centralization and particularly toward insuring a greater decisional role of persons outside the agency including various economic advisers in the White House. Yet with very few exceptions . . . the ultimate policy decisions remained both legally and practically in the hands of the individual agencies." Morrison, *supra* note 78, at 1062.

administration's arrival did OMB experience a marked growth in its power to influence specific agency rules.

B. OMB Under the Reagan Administration

OMB secured a prominent position in the agency rulemaking process under the Reagan administration. In 1980, Congress passed the Paperwork Reduction Act⁸⁴ to cut federal information-collecting activities.⁸⁵ The statute authorizes OMB to review proposed agency rules to determine whether an agency information collection request is "necessary for the proper performance of the functions of the agency"⁸⁶ and to ensure that the "information will have practical utility for the agency."⁸⁷

In 1981, President Reagan broadened OMB's authority by issuing Executive Order 12,291 (First Reagan Order).⁸⁸ Pursuant to the First Reagan Order, an agency seeking to promulgate a rule must submit the rule to OMB before publication, and must justify the economic cost of the new regulation.⁸⁹ Upon review of the rule, OMB may make comments on the rule to which the agency must respond, "to the extent permitted by law,"⁹⁰ before issuing the rule.⁹¹

President Reagan issued Executive Order 12,498 (Second Reagan Order) in 1985, which further expanded OMB's rulemaking authority.⁹² The Second Reagan Order requires agency heads to ensure that agency regulations conform with the regulatory goals of the President,⁹³ and to submit regula-

84. Pub. L. No. 96-511, 94 Stat. 2812 (1980) (codified as amended at 44 U.S.C. §§ 3501-3520 (1982)).

85. The stated goal of the Paperwork Reduction Act is to minimize record keeping and reporting requirements. 44 U.S.C. § 3501 (1982).

86. *Id.* § 3504(c)(2).

87. *Id.*

88. First Reagan Order, *supra* note 17.

89. The First Reagan Order provides that major rules must be sent to the OMB accompanied by a Regulatory Impact Analysis which sets forth the costs and benefits of the proposed rule and explains the reasons for not selecting alternative regulatory approaches. *Id.* at 13,194, reprinted in 5 U.S.C. § 601(3)(d) (1982). Major rules are defined as rules which will have an annual economic impact of \$100 million or more, a major economic impact on a certain sector of the economy or an adverse impact on an industry's ability to compete abroad. *Id.* at 13,193, reprinted in 5 U.S.C. § 601(1)(b).

90. *Id.* at 13,196, reprinted in 5 U.S.C. § 601(2).

91. OMB may delay comment on the rule indefinitely, thereby exercising a "pocket veto." Raven-Hansen, *Making Agencies Follow Orders: Judicial Review of Agency Violations of Executive Order 12,291*, 1983 DUKE L.J. 285, 294-95 (1983). If OMB transmits comments to the agency, the agency may decide to withdraw the rule if the agency cannot adequately modify the rule to satisfy OMB comments. Rosenfield, *Presidential Policy Management of Agency Rules Under Reagan Order 12,498*, 38 ADMIN. L. REV. 63, 76 & n.80 (1986).

92. Second Reagan Order, *supra* note 17.

93. *Id.* at 1036, reprinted in 5 U.S.C. § 601(3)(a).

tory objectives to OMB for annual review prior to taking any regulatory actions, including fact-finding investigations.⁹⁴

C. Criticisms of OMB's Influence On Agency Rulemaking

The Paperwork Reduction Act and the two Reagan Executive Orders purportedly were designed to alleviate recordkeeping and reporting burdens on the public,⁹⁵ to ensure that agency rules are cost-sensitive,⁹⁶ and to effectively allocate resources in light of the administration's agenda.⁹⁷ Commentators have noted, however, that the statute and the two orders have given OMB a "regulatory 'pocket veto'"⁹⁸ and that the Reagan administration has effectively substituted OMB's discretion for agency discretion.⁹⁹ By giving OMB authority to review agency rules and by obligating agencies to respond to OMB's comments, the First Reagan Order enables OMB to coerce agencies into fashioning rules which reflect the President's deregulatory agenda.¹⁰⁰ Because OMB conducts its review and comment process in secrecy,¹⁰¹ the regulatory history of a rule is often unknown to Congress and to the public.¹⁰² Critics of the Second Reagan Order argue that it not only entitles OMB to bar individual agency rules, but that it also empowers OMB to meddle in every aspect of an agency's rulemaking activity.¹⁰³

1. Constitutional Concerns

Observers of OMB's emergence as regulator of the regulators have raised constitutional concerns regarding the President's authority to empower

94. *Id.* at 1036-37, reprinted in 5 U.S.C. § 601(2)(a).

95. See 44 U.S.C. § 3501 (1982).

96. See *supra* text accompanying notes 88-91.

97. See *supra* text accompanying notes 92-94.

98. Raven-Hansen, *supra* note 91, at 295.

99. See Morrison, *supra* note 78, at 1063; Rosenberg, *supra* note 78, at 214-16.

100. For interesting illustrations and analyses of OMB's coercive tactics, see Rosenfield, *supra* note 91, at 97-101. Rosenfield documents how OMB, in 1983, forced the Environmental Protection Agency (EPA) to radically modify a regulation proposed under the Clean Water Act. *Id.* at 97-98.

101. See *infra* note 117.

102. For example, the role which OMB played in the FDA's new drug regulations was not clear. See *infra* text accompanying notes 217-19. Congress held a subcommittee hearing to uncover the extent of OMB's involvement in the FDA's rulemaking process. See *infra* notes 165-83 and accompanying text; see also *infra* notes 120-23.

One commentator observed that the Reagan regulatory reform process "alters the assumptions Congress and the public can make about agency decisions since it is no longer clear to what extent regulatory decisions reflect OMB or agency policy." OMB WATCH, *supra* note 14, at 11.

103. The Second Reagan Order seeks to force agencies to apply the President's regulatory policies not only to individual regulations, but also to the broad goals and objectives of the agency. See Rosenfield, *supra* note 91, at 71-72.

OMB to regulate agency rulemaking.¹⁰⁴ Article II of the United States Constitution, which vests executive power in the President, does not address the President's role in administrative decisionmaking. Article II empowers the President to appoint¹⁰⁵ and commission¹⁰⁶ officers of the United States and to "require the Opinion, in writing, of the principal Officer in each of the Executive Departments, upon any Subject relating to the Duties of their respective Offices."¹⁰⁷ Article II further instructs the President to "take Care that the Laws be faithfully executed."¹⁰⁸

Because the Constitution does not expressly authorize the President to oversee agency rulemaking, the central question is whether article II implicitly gives the President such power. Most legal commentators argue that because the framers divided federal power between three separate branches and expressly vested legislative power in Congress, the framers did not intend for the President to supervise the substance of agency rules.¹⁰⁹ The President is subject to the laws enacted by Congress, which have delegated rulemaking authority to respective agency heads by enacting various agency enabling statutes.¹¹⁰ Thus, any inherent power which the President may have over agency rulemaking activity is necessarily limited by the power delegated to the agency heads.

The consensus is that while the President may have inherent constitutional authority to issue executive orders designed to facilitate and coordinate the operation of the executive branch, the agency head's congressionally delegated discretionary authority limits the President's power to influence agency rulemaking.¹¹¹ Moreover, beyond the constitutional question, Congress and legal commentators are growing increasingly concerned over the practices OMB has adopted to implement the Reagan Orders.¹¹²

104. See, e.g., *Oversight of the Office of Management and Budget Regulatory Review and Planning Process: Hearing Before the Subcomm. on Intergovernmental Relations of the Senate Comm. on Governmental Affairs*, 99th Cong., 2d Sess. 43 (1986) [hereinafter *OMB Hearing*] (Sen. Gore states: "I have felt since the inception of Executive Order 12,291 that it was simply unconstitutional and that it was only a matter of time before that conclusion was reached in the courts.").

105. U.S. CONST. art. II, § 2, cl. 2.

106. *Id.* at cl. 3.

107. *Id.* at cl. 1.

108. *Id.* at § 3.

109. Morton Rosenberg, a specialist in American public law with the Congressional Research Service, argues that "[t]he idea that power over administrative decision-making derives from the President's role as head of the executive branch or inheres in the concept of 'executive power', . . . is inconsistent with a written Constitution establishing divided, limited government." Rosenberg, *supra* note 78, at 197; see also Rosenfield, *supra* note 91, at 78-79.

110. Rosenberg, *supra* note 78, at 202-06.

111. *Id.* at 209-12.

112. See, e.g., *OMB Hearing*, *supra* note 104, at 56-58. In an OMB oversight hearing,

2. Policy Concerns

The emergence of OMB as the regulator of agency rulemaking raises important policy questions. The central policy questions concern whether and to what extent the President should oversee agency rulemaking, regardless of whether the Constitution authorizes executive oversight. While some commentators argue that executive supervision of agency rulemaking brings consistency,¹¹³ coordination,¹¹⁴ and accountability¹¹⁵ to federal regulatory policy, the recent track record reveals that OMB, operating in a secretive

Senator Carl Levin stated that although he is an advocate of executive coordination of agency rulemaking, "the OMB is undermining the genuine support for the concept of Executive oversight . . . by the high-handed and strong-arm manner in which it is implementing the concept." *Id.* at 57; see also *infra* text accompanying notes 117-23.

113. Some commentators argue that the President should coordinate conflicting rulemaking activity caused by broad enabling statutes that grant several agencies regulatory authority over the same industry. Proponents argue that the President, as chief executive, should balance and coordinate national regulatory policy. See DeMuth & Ginsburg, *White House Review of Agency Rulemaking*, 99 HARV. L. REV. 1075, 1079 (1986). For instance, in the late 1970s, the nuclear technology industry was regulated by the Nuclear Regulatory Commission, the EPA, and the Department of Energy. The regulation of hazardous chemicals was controlled by the EPA, the FDA, the Federal Aviation Administration, the Department of Transportation, the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission. Today, recombinant DNA research is regulated by the EPA, OSHA, FDA, NIH and the Department of Agriculture. *Id.*

114. Proponents of executive management of agency rulemaking have argued that OMB can facilitate the flow of information between agencies and thereby reduce the amount of time required to promulgate a new rule. See DeMuth & Ginsburg, *supra* note 113, at 1080-82; Strauss & Sunstein, *The Role of the President and OMB in Informal Rulemaking*, 38 ADMIN. L. REV. 181, 188-94 (1986). OMB's involvement in the rulemaking process, however, tends instead to drag out the rulemaking process and cause lengthy delays. Under the First Reagan Order, OMB has 60 days to respond to a proposed rule and 30 days to respond to a final rule. First Reagan Order, *supra* note 88, at 13,195, reprinted in 5 U.S.C. § 601(3)(e)(2) (1982). If the OMB Director disagrees or disapproves of any portion of the proposal or rule, the Director may stop progress on the proposal or rule until it has been revised. *Id.* at 13,195, reprinted in 5 U.S.C. § 601(3)(f)(1). It is this latter provision which has caused delay in agency rulemaking.

At a recent OMB oversight hearing, two witnesses testified that OMB successfully delays rules which are not popular with OMB staff. In one instance, OMB delayed OSHA's efforts to promulgate regulations of grain elevators for over three years. See *OMB Hearing, supra* note 104, at 47-51 (testimony of Deborah Berkowitz, Director, Safety and Health, Food and Allied Service Trades Dept., AFL-CIO). In another instance, OMB ignored a congressional deadline by which EPA was to promulgate regulations for hazardous waste in underground storage tanks. Although the agency was required to publish regulations by March 1, 1985, OMB delayed promulgation of a final rule until June 26, 1985. *Id.* at 76-77 (testimony of Robert V. Percival, Senior Attorney, Environmental Defense Fund).

115. Proponents of executive oversight of agency rulemaking argue that rulemakers should be accountable to the President, who is accountable to a national constituency. "[T]he President is electorally accountable. Equally important, he is the only official in government with a national constituency. These characteristics make him uniquely well-situated to design regulatory policy in a way that is responsive to the interests of the public as a whole." Strauss & Sunstein, *supra* note 114, at 190; see also DeMuth & Ginsburg, *supra* note 113, at 1080-82.

manner, attempts to dictate policy positions to agencies without justifying its position to either the agency, the public, or Congress.¹¹⁶

In fact, OMB's review practices have led to increasing concern that OMB, rather than injecting a higher level of consistency, coordination, and accountability into the rulemaking process, has transformed the rulemaking process into a secretive, coercive, and off-the-record power struggle between OMB and the agencies.¹¹⁷ In recent congressional oversight hearings, congressmen characterized OMB as a "swamp"¹¹⁸ and a "black hole,"¹¹⁹ because once an agency transmits a proposed rule to OMB for review, the agency loses track of the proposal's whereabouts.

While most agencies adhere to the notice, comment, and recordkeeping procedures set forth in the Administrative Procedure Act,¹²⁰ OMB shuns public and congressional inquiry and avoids making a record on which it could be held accountable. OMB comments are virtually never transmitted

116. One critic wrote:

[U]nder the present system, OMB can simply refuse to approve a regulation without giving any reason, and an agency head is left the job of devising an acceptable explanation for refusing to proceed or for deleting a particularly offensive requirement. And, because this process operates in secret, there is no way for the public, the Congress, or the courts to know precisely what OMB has done and what the real basis is for decisions issued under the nominal signature of the agency head.

Morrison, *supra* note 78, at 1067-68; *see also* Rosenfield, *supra* note 91, at 97-101.

117. Many observers have expressed alarm at OMB's refusal to conduct its review process in an open manner. One commentator observes that "[s]ecrecy pervades virtually all OMB review." Rosenfield, *supra* note 91, at 97. At a recent OMB oversight hearing, one senator expressed frustration with OMB's refusal to open its records to public scrutiny. Emphasizing the importance of the EPA's grain dust regulations, Senator Levin stated:

The identity of the persons who have been making these decisions has been hidden from the public. OMB's role in this whole rulemaking process has been hidden. We have made efforts over the years to try to bring this to public light so that people will be accountable for those decisions, but we have so far not succeeded, and OMB has not complied with what is [sic] obviously strong signals coming from the public and from the Congress.

OMB Hearing, supra note 104, at 2-3 (testimony of Sen. Carl Levin).

118. *Drug Hearing, supra* note 65, at 98 (testimony of Rep. Ted Weiss).

119. *OMB Hearing, supra* note 104, at 99 (testimony of Sen. Durenberger). Senator Durenberger supports the role of OMB as the "voice of efficiency and coordination" in agency rulemaking. *Id.* Like other watchful observers of OMB's increasing involvement in agency rulemaking, however, Senator Durenberger expresses growing concern over the methods OMB chooses to implement its supervisory powers.

OMB continues to keep its oversight role both secret and one-sided. Under the current process, OMB can delay proposed rules for any length of time, it can interfere with statutory deadlines for regulations, it can serve as a secret conduit for industry opposition to rules and it can impose its own limited interpretation of cost-benefit analysis to the exclusion of other relevant considerations. And, in fact, OMB has done all of these things.

Id.

120. 5 U.S.C. § 553 (1982).

in writing to the agency, but instead are conveyed over the telephone.¹²¹ Because of the secretive nature of OMB's review, agency heads are often unaware of the status of a rule or proposal once it has been transmitted to OMB.¹²² Although it may appear from the public record that an agency has drafted and promulgated a new rule, in fact OMB may have played a major role in fashioning the rule without ever accounting for its role.¹²³ Rather than make the executive agencies more accountable to the public, OMB has merely ensured that the agencies are more accountable to OMB.

IV. OMB'S ROLE IN THE FDA'S INVESTIGATIONAL DRUG REGULATIONS: THE LANGUAGE, THE STRUGGLE AND THE RESOLUTION

The history of the FDA's new investigational drug regulations clearly demonstrates the secretive manner in which OMB has chosen to influence agency regulations. After the FDA submitted its proposal to OMB, OMB reviewed the substantive provisions of the proposal and proceeded to badger the FDA into adopting key provisions drafted by OMB staff. A subsequent congressional hearing exposed OMB's role in drafting the regulations and the FDA, thereafter, revised its regulations before final publication.

In 1985, the FDA submitted revised IND regulations governing the drug development process to OMB for approval before publication.¹²⁴ The IND

121. See Rosenfield, *supra* note 91, at 96-97. One example of the extent of the secrecy was uncovered at a recent OMB oversight hearing. OMB, refusing to transmit written comments to OSHA, dictated its comments over the phone, which an OSHA staffer then transcribed. Because certain agency staffers were concerned over the implications of OMB's comments, "[t]his paper was leaked out of OSHA. There was an exchange in a men's room between a staff [member] of the House and some OSHA staff people to leak this out. It was typed up and released to the Washington Post." *OMB Hearing, supra* note 104, at 10 (testimony of Deborah Berkowitz, Director of Safety and Health, Food and Allied Services Trade Dept., AFL-CIO). This type of behavior is a far cry from the accountability and openness which proponents of executive oversight might envision.

122. In fact, the director of OMB and members of Congress may be unaware of which OMB staff members rejected or approved an agency rule. At a recent Senate oversight hearing, OMB Director James C. Miller could not identify the OMB staffer responsible for rejecting an agency's technical analysis which justified the agency's proposed rule. *OMB Hearing, supra* note 104, at 179; see also *infra* note 175 and accompanying text.

123. One Senator recently opined:

[W]e should make sure that the decisionmakers are held accountable for their decisions . . . [b]ecause OMB is working in the dark, and not in the daylight, because there is no requirement in the law that OMB's input be made public so that we know who is making these decisions. Right now the decisionmaker is not held accountable for his decisions.

OMB Hearing, supra note 104, at 11 (testimony of Sen. Levin).

124. The preamble to the proposed IND Rewrite indicates that the FDA submitted the proposal to OMB in 1983. See Preamble to Proposed IND Rewrite, *supra* note 43, at 26,735.

Rewrite proposal contained provisions to streamline the IND process¹²⁵ and to codify the compassionate use exemption which the FDA had developed to allow terminally ill patients access to investigational drugs.¹²⁶ The FDA defined the section that codified the compassionate use exemption as "treatment use of an investigational new drug."¹²⁷

Seven months later,¹²⁸ OMB transmitted its unwritten comments to the FDA, suggesting revisions to two sections of the proposed IND Rewrite. First, OMB sought revised language in the treatment use section of the proposal, effectively limiting the FDA's capacity to deny requests for investigational drugs.¹²⁹ Second, OMB wanted to delete the section prohibiting sale of investigational drugs and to substitute it with a section allowing such sale.¹³⁰ Because the FDA was reluctant to accept OMB's changes, a power play ensued. Over a year later, the FDA simultaneously published the final IND Rewrite,¹³¹ without OMB's changes,¹³² and a reproposal incorporating OMB's desired language in the two controversial sections.¹³³

A. *The Language: OMB's Proposed Changes to the Rule*

The Reproposal, containing OMB's desired changes to the treatment use and sale sections of the IND Rewrite, represented a drastic change in the FDA's investigational drug regulations. The changes sought by OMB to the treatment use section of the regulations conflicted with the statutory lan-

However, at the congressional oversight hearing to examine the history of the investigational drug regulations, *see infra* text accompanying notes 165-66, FDA Commissioner Frank Young testified that the FDA submitted the IND Rewrite proposal to OMB on July 25, 1985. *See Drug Hearing, supra* note 65, at 95.

125. In the preamble to the proposed IND Rewrite, the FDA stated that the regulations reflect the FDA's commitment to "facilitate the development, evaluation, and approval of safe and effective new therapies without compromising the underlying standards of safety and effectiveness upon which the American public has come to depend." Preamble to Proposed IND Rewrite, *supra* note 43, at 26,720.

126. In the preamble to the proposed IND Rewrite, the FDA acknowledged its historical policy of allowing seriously ill patients access to investigational drugs through a compassionate use exemption. *Id.* at 26,728-29. The FDA explained that the proposed IND Rewrite merely codified the compassionate use exemption. *Id.* The FDA specifically stated that the IND Rewrite would retain the agency's current policy prohibiting the unapproved sale of investigational drugs. *Id.* at 26,734.

127. *Id.* at 26,742.

128. The proposed IND Rewrite was submitted to OMB on July 25, 1985. *Drug Hearing, supra* note 65, at 95. OMB responded to the FDA in February 1986. *Id.*

129. *See infra* text accompanying notes 141-45.

130. *See infra* text accompanying notes 152-60.

131. Final IND Rewrite, *supra* note 68, at 8798.

132. The final IND Rewrite retained a modified prohibition against sale, *id.* at 8833, and reserved the section regarding treatment use. *Id.* at 8838.

133. Reproposal, *supra* note 65, at 8850.

guage of the amended Act. In addition, OMB's proposed changes to the sale provision of the IND regulations ran contrary to historical FDA principles.

First, OMB sought to allow patients with immediately life-threatening diseases easy access to investigational drugs. Certain staff members at OMB held the opinion that "it is not a Federal responsibility to second-guess a licensed medical practitioner [sic] judgment that his patient will benefit from the use of a particular drug."¹³⁴ Accordingly, OMB's changes would have allowed patients with an immediately life-threatening disease to obtain investigational drugs without requiring the drug sponsor to prove the safety and effectiveness of the drug.¹³⁵

As originally proposed by the FDA, the regulations would allow patients with a "serious" disease¹³⁶ to obtain access to an investigational drug¹³⁷ after the drug had completed Phase 2 trials¹³⁸ and after the sponsor had gathered "sufficient evidence of the drug's safety and effectiveness" to warrant its use.¹³⁹ The FDA could deny a request for treatment use if it found that the risk to the patient outweighed the potential benefit or if the FDA found insufficient evidence to prove the safety and effectiveness of the drug.¹⁴⁰

134. See *Drug Hearing*, *supra* note 65, at 282 (memo authored by OMB staff member Bruce Artim discussing the differences between OMB and FDA positions on the treatment use and sale of investigational drugs). The internal OMB strategy memo states: "FDA refuses to budge [from its position on treatment use which] places total discretion [in] the agency. Essentially, our position takes the view that it is not a Federal responsibility to second-guess a licensed medical practitioner [sic] judgment that his patient will benefit from the use of a particular drug." *Id.*

135. See *infra* text accompanying notes 141-45. The Reproposal did contain certain restrictions on the type of drugs available for access. The Reproposal required that the drug must be "intended to treat [an] . . . immediately life-threatening disease" for which "no satisfactory alternative drug or other therapy" is available, and that the drug sponsor is investigating the drug in controlled clinical trials while "pursuing marketing approval of the drug with due diligence." Reproposal, *supra* note 65, at 8856.

136. The IND Rewrite proposal identified only one patient group — those with a "serious disease condition . . . for whom no satisfactory alternative drug or other therapy is available." Proposed IND Rewrite, *supra* note 43 at 26,742. The Reproposal created two patient groups. See *infra* note 141.

137. Section 312.34 of the IND Rewrite proposal provided that pre-marketing FDA approval for treatment use of an investigational new drug could be obtained in two ways. First, a patient could request the drug sponsor to submit a treatment protocol to the FDA, or if the sponsor did not want to submit a treatment protocol, the patient's physician could submit a treatment IND to the FDA. Proposed IND Rewrite, *supra* note 43, at 26,742.

138. Section 312.34(a) of the proposed IND Rewrite leaves open the possibility that access may be granted during Phase 2 or earlier, but only "if compelling circumstances warrant [such use]." *Id.*

139. *Id.*

140. Section 312.34(d) of the IND Rewrite proposal provided that the FDA could deny a treatment protocol or treatment IND if it found that "[t]he potential risks outweigh the potential benefits of the drug in the treatment of patients," or if "[t]here is not sufficient evidence of the drug's safety and effectiveness to justify its intended treatment use." *Id.* at 26,743.

As repropoed pursuant to OMB's changes, the regulations would allow patients with an "immediately life-threatening disease"¹⁴¹ access to an investigational drug prior to the completion of Phase 2 trials.¹⁴² Under the Reproposal, the FDA would have no authority to deny a request for treatment use of an investigational drug unless the FDA could produce evidence to show that "the drug clearly does not provide a therapeutic benefit" or that the drug would expose the patient to "an unreasonable and significant additional risk of illness or injury."¹⁴³ Thus, the Reproposal shifted the burden of proof, requiring the FDA to disprove the safety and effectiveness of a new drug. Many experts, considering this burden insurmountable,¹⁴⁴ argued that the Reproposal would effectively deregulate investigational drugs intended for patients with immediately life-threatening diseases.¹⁴⁵

As repropoed, the rule contradicted the amended Act, which instructed the FDA to regulate the distribution of investigational drugs. The amended Act directs the FDA to exempt investigational drugs from the prohibition against pre-approval distribution.¹⁴⁶ The statute authorizes the FDA, in its discretion, to base such exemptions on "conditions relating to the protection of the public health," including the sponsor's submission to the FDA of re-

141. Reproposed § 312.34(b) separated the patient population into two groups: patients with a "serious disease" and patients with an "immediately life-threatening disease." Reproposal, *supra* note 65, at 8856. The Reproposal did not define "serious disease" or "immediately life-threatening disease." The final rule on treatment use defines "immediately life-threatening disease." See *infra* note 195.

142. Section 312.34(a) of the Reproposal states that investigational drugs intended for patients with a serious disease would ordinarily be made available after Phase 2 trials. Reproposal, *supra* note 65, at 8856. Investigational drugs intended for patients with an immediately life-threatening disease, however, would be made available "earlier in the investigational process" as FDA may permit. *Id.*

143. *Id.*

144. See *Drug Hearing*, *supra* note 65, at 7-11 (letter to FDA regarding the Reproposal signed by five former commissioners of FDA and four former chief counsels of FDA).

145. See *infra* note 160. Upon publication of the Reproposal, the FDA received hundreds of letters from prominent physicians, researchers, and ethicists, urging the FDA to reconsider its authority under the Reproposal to protect deathly ill patients from harmful drugs. See Letter from John E. Jones, Vice President for Health Affairs, Medical Center, West Virginia University 1 (Apr. 30, 1987) (FDA Docket No. 82N-0394, vol. 10, comment C00196) (burden of proving safety and efficacy should remain with drug sponsor); Letter from Susan E. Krown, M.D., Head of the AIDS Clinical Group, Sloan-Kettering Cancer Center (Apr. 15, 1987) (FDA Docket No. 82N-0394, vol. 8, comment C00103) (any attempt by FDA to prove that a drug is ineffective would be virtually impossible); Memorandum from the Pharmacology Subcom. of the AIDS Treatment Evaluation Unit, Dep't of Health and Human Services 2 (Apr. 16, 1987) (FDA Docket No. 82N-0394, vol. 8, comment C00087) (FDA would have no basis for denying access to ineffective drugs such as "sugar pills"); Comments of the Pharmaceutical Mfrs. Ass'n 8 (May 4, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00229) (the FDA's burden of proving that a drug is not safe is "virtually impossible").

146. See *supra* text accompanying notes 27-30.

ports of preclinical tests, the results of which are "adequate to justify the proposed clinical testing."¹⁴⁷

Interpreting the statute in *United States v. Rutherford*,¹⁴⁸ the United States Supreme Court held that drugs intended for terminally ill patients were not exempt from the requirement of the FDA's pre-marketing approval.¹⁴⁹ The Court found specific congressional intent to protect all persons, including those who are terminally ill, from unsafe or ineffective drugs.¹⁵⁰ Thus, although OMB staff viewed the regulation of investigational drugs as an interference with the physician's right to practice medicine,¹⁵¹ Congress viewed such regulation as a necessary safeguard to protect the rights and welfare of human beings involved in the testing of experimental drugs.

The second major change that OMB sought to the IND regulations concerned the sale of investigational drugs. As originally proposed by the FDA, the rule provided that drug sponsors could not promote,¹⁵² commercially distribute,¹⁵³ or sell¹⁵⁴ investigational drugs without prior agency approval. Nor could sponsors prolong clinical testing of a new drug once the drug showed promise.¹⁵⁵ Under the Reproposal, the sponsor could sell an investigational drug to patients who received the drug under a "treatment protocol"¹⁵⁶ or "treatment IND"¹⁵⁷ without prior, written agency consent as long as the sale did not constitute commercial marketing, promotion, or advertising and as long as the sponsor actively pursued marketing approval.¹⁵⁸

This revision represented a major change in traditional FDA practices and procedures.¹⁵⁹ By coupling the reproposed provision on treatment use,

147. 21 U.S.C. § 355(i) (1982).

148. 442 U.S. 544 (1979).

149. *Id.* at 560.

150. *Id.* at 552-54.

151. *See supra* note 134.

152. Proposed IND Rewrite, *supra* note 43, at 26,737.

153. *Id.*

154. *Id.*

155. *Id.*

156. *See supra* note 137.

157. *Id.*

158. Reproposal, *supra* note 65, at 8850. The Reproposal provided that a drug sponsor could not sell an investigational new drug to patients involved in clinical trials without the prior written consent of the FDA. Such consent would be based on the sponsor's explanation of the need to sell the drug to human test subjects in order to continue the clinical trial. *Id.*

159. Beginning with its first investigational drug use regulations, the FDA assumed that the cost of developing new drugs would be incurred by the pharmaceutical company and not by the human test subject. *See supra* note 7. The OMB staff was aware of the fact that the FDA historically denied requests to sell investigational drugs. *See Drug Hearing, supra* note 65, at 281 (memo prepared by OMB staff member Bruce Artim to compare the FDA's position

which severely limited the FDA's authority to deny access to investigational drugs, with the repropoed provision allowing sale of investigational drugs, the Reproposal represented a substantial deviation from traditional agency practice. Thus, some FDA experts suggested that the combination of these repropoed sections might prevent the FDA from regulating "quack" drugs.¹⁶⁰

B. *The Struggle: The Politics Behind the Changes*

Upon repropoing the regulations governing treatment use and sale of investigational new drugs, the FDA sparked congressional and public interest. Over 300 public comments poured into the FDA.¹⁶¹ Although the public generally supported the concept of granting early access to investigational drugs,¹⁶² the comments focused on two concerns. First, the public ques-

on the treatment use and sale of investigational drugs with OMB's position). After the FDA published the Reproposal, hundreds of comments poured into the FDA questioning the ethics of allowing pharmaceutical companies to charge for investigational drugs. *See infra* note 164.

160. *Drug Hearing, supra* note 65, at 10-11. A letter commenting on the Reproposal, authored by five former commissioners and four former chief counsels of the FDA, *infra* note 171, urged the FDA to add language to the Reproposal stating that the FDA could deny access to investigational drugs unless the FDA had some evidence on which it could rationally decide that the drug was safe and effective.

[W]e want to call attention to the interplay of [re]proposed § 312.34 and [re]proposed § 312.7(d). We have no general objection to the sale of drugs administered under an IND. If there were no requirement for some rational basis for believing an investigational drug may be effective, however, the permission to sell it pursuant to § 312.7(d) could provide an unintended opportunity for the marketing of governmentally legitimized quack drugs to those suffering from immediately life-threatening diseases for which no satisfactory treatment is available.

Drug Hearing, supra note 65, at 10-11.

161. Preamble to Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale; Final Rule, 52 Fed. Reg. 19,466 (1987) (codified at 21 C.F.R. pt. 312) (proposed March 19, 1987) [hereinafter Final Rule].

162. The FDA received comments from individual patients, ethical organizations, research hospitals, medical associations and pharmaceutical companies. The comments generally supported the concept of allowing desperately ill patients access to promising new drugs. *See, e.g.*, Letter from R.E. Henkin, M.D., Chairman, Institutional Review Bd. for the Protection of Human Subjects, Loyola Univ. of Chicago (Apr. 3, 1987) (FDA Docket No. 82N-0394, vol. 6, comment C00065); Letter from American Psychological Ass'n (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00245); Letter from American Medical Ass'n (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00236); Letter from American Pharm. Ass'n (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00237); Dep't of Health and Human Services, Memorandum of Meeting between FDA and Health Professional Groups (Mar. 27, 1987) (FDA Docket No. 82N-0394, vol. 6, memorandum MM 00002); Letter from Johns Hopkins University (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00260). Private patients suffering from terminal illnesses, however, did not share the medical community's concerns regarding the FDA's diminished authority to regulate investigational drugs or the sale of investigational drugs. To these patients, the repropoed regulations represented new hope for a treatment or cure for their illnesses, and they pleaded

tioned whether the FDA retained sufficient authority to deny requests for investigational drugs which had not been shown to be sufficiently safe or effective.¹⁶³ Second, many comments addressed whether allowing the sale of investigational drugs would create problems of equal access or would allow pharmaceutical companies to profit from drugs which had not been shown to be sufficiently safe or effective.¹⁶⁴

The publication of the Reproposal also sparked congressional interest. Representative Ted Weiss promptly scheduled an oversight hearing by a

with the FDA to ease access to investigational drugs. *See, e.g.*, Comment C00101 (June 10, 1987) (FDA Docket No. 82N-0394, vol. 8) (husband of woman with Alzheimer's disease urges FDA to test new drugs); Comment C00323 (May 21, 1987) (FDA Docket No. 82N-0394, vol. 12) (AIDS patient supports increased access to investigational drugs); Comment C00298 (May 5, 1987) (FDA Docket No. 82N-0394, vol. 12) (son of man stricken with cancer urges increased access to investigational drugs); Comment C00069 (Apr. 14, 1987) (FDA Docket No. 82N-0394, vol. 6) (AIDS Related Complex patient supports availability of experimental treatments); Comment C00278 (May 6, 1987) (FDA Docket No. 82N-0394, vol. 11) (patient with metastatic disease supports access to investigational drugs).

163. *See, e.g.*, Dep't of Health and Human Services, Memorandum from Pharmacology Subcom. of the AIDS Treatment Evaluation Unit at 2 (Apr. 16, 1987) (FDA Docket No. 82N-0394, vol. 8, comment C00087) (under the reproposed regulations, the FDA would not have the authority to deny access to ineffective drugs if there is no alternative drug or therapy available); Letter from Susan E. Krown, M.D., Head of the AIDS Clinical Group, Sloan-Kettering Cancer Center 2 (Apr. 15, 1987) (FDA Docket No. 82N-0394, vol. 8, comment C00103) (FDA's burden under the Reproposal of proving lack of effectiveness of new drug is "virtually impossible" for drugs that have recently entered the testing process); Comments of NIH staff 3-4 (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00247) (under the Reproposal, the FDA would rarely have grounds to deny access to investigational drugs); Dep't of Health and Human Service Memorandum of Meeting between FDA and Consumer Groups and Orphan Drug Groups (Mar. 27, 1987) (FDA Docket No. 82N-0394, vol. 6, memorandum MM 00002) (Reproposal weakens the safety and efficacy provisions of the drug approval process by shifting the burden of proof from the sponsor to the FDA).

164. *See, e.g.*, Letter from Donald Abrams, M.D., Assistant Director, AIDS Clinic, San Francisco General Hospital 2 (Apr. 29, 1987) (FDA Docket No. 82N-0394, vol. 10, comment C00188) (decision to allow drug companies to sell unproven drugs is ethically questionable); Comments of the American Medical Ass'n 5 (Apr. 30, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00236) (raises question of possible discrimination against patient unable to pay for investigational drugs, since insurance companies rarely reimburse patients for investigational treatments); Comments of Pharmaceutical Mfrs. Ass'n 9-10 (May 4, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00229) (FDA should protect patients from drugs whose effectiveness is questionable); Letter from Ada Sue Selwitz, President, Applied Research Ethics Nat'l Ass'n 2 (Apr. 17, 1987) (FDA Docket No. 82N-0394, vol. 9, comment C00113) (questions ethics of selling unproven drugs to desperate patients); Letter from Sheila C. Mitchell, M.D., Director, Medical Research Office, Baystate Medical Center, Springfield, Mass. 2 (Apr. 29, 1987) (FDA Docket No. 82N-0394, vol. 10, comment C00197) (questions the ethical basis of allowing desperately ill patients to exhaust their financial resources on untested and potentially unsafe drugs); Letter from Nat'l Multiple Sclerosis Soc'y 2-3 (April 10, 1987) (FDA Docket No. 82N-0394, vol. 8, comment C00084) (Reproposal would allow "profit-making" drug companies to shift development costs onto seriously ill individuals before showing that the drug is safe and effective).

House subcommittee and invited both the FDA and OMB.¹⁶⁵ Representative Weiss proposed to examine both the effect of the repropoed regulations on the FDA's regulatory authority and the decisionmaking process which led to the regulations.¹⁶⁶ OMB not only declined the subcommittee's invitation to attend the hearing,¹⁶⁷ but also refused to produce several documents regarding the decisionmaking process which the subcommittee staff had requested.¹⁶⁸

The hearing focused on both the treatment use provision¹⁶⁹ and the sale provision of the Reproposal.¹⁷⁰ At the hearing, a former chief counsel of the

165. *Drug Hearing, supra* note 65, at 3. Representative Weiss chairs the Human Resources and Intergovernmental Relations Subcommittee of the House Committee on Government Operations. The subcommittee oversees FDA drug regulations.

166. *Id.* at 2-3.

167. *Id.* Wendy Gramm, OMB Administrator for Information and Regulatory Affairs, declined the subcommittee's request to testify at the hearing because of a "conflicting engagement." *Id.* at 145.

168. *Id.* at 3. The subcommittee sent OMB three letters requesting "all records—including, but not necessarily limited to, notes, memoranda, correspondence, and drafts—written or received by OMB personnel in any way related" to the Reproposal. *Id.* at 146, 147-48. OMB responded one month after the first subcommittee letter and 15 days after the hearing, stating that "[w]hile we have every desire to be responsive to the legitimate needs of Congress, none of your three letters sent to OMB refers to any legal authority to support the proposition that the OMB is compelled by law to produce internal documents of the type currently sought." *Id.* at 150. In fact, OMB did not produce all the requested documents until the subcommittee threatened OMB with a subpoena. Off-the-record telephone interview with staff member of House Human Resources and Intergovernmental Relations Subcom. (Nov. 19, 1987).

169. *Drug Hearing, supra* note 65, at 1-3 (testimony Rep. Weiss). One prominent researcher warned that modern drugs are becoming increasingly more potent as a result of synthesizing technologies and recombinant DNA. *Id.* at 37 (testimony of Dr. Charles G. Moertel, Purvis and Roberta Tabor Professor of Oncology, Mayo Clinic and Mayo Medical School, and Chairman, North Central Cancer Treatment Group). He cautioned that a disaster similar to the Thalidomide disaster is more probable today than it was in 1962 and that the American public would be exposed to the risk of a national tragedy if the proposed regulations were implemented. *Id.* at 37.

Another distinguished researcher testified that the Reproposal would effectively prohibit the FDA from denying a premature request for access to an investigational drug, precisely because insufficient evidence would have been gathered on the drug's safety and effectiveness. Because the regulations would place the burden of proving that a drug is not safe and effective on the FDA, the FDA would be unable to deny access to a drug which had not been sufficiently tested because the FDA would have no evidence to support its contention that the drug is not safe or effective. *Id.* at 64-65 (testimony of Dr. Martin S. Hirsch, Infectious Disease Unit, Dep't of Medicine, Massachusetts General Hospital and Harvard Medical School, and Chairman, Steering Committee, AIDS Treatment Evaluation Program).

170. *Id.* at 1-3 (testimony Rep. Weiss). One respected researcher testified that because the proposed regulations would allow patients to purchase promising investigational drugs, the patient would have no incentive to enroll in a clinical trial where test subjects may be administered a placebo rather than the active drug. *Id.* at 61 (testimony of Dr. Itzhak Brooks, Professor of Pediatrics and Surgery, Uniformed Services Univ. of the Health Sciences, and Chairman, Anti-Infective Drugs Advisory Committee, FDA). Because it would be more desir-

FDA testified on behalf of himself, three other former chief counsels and five former commissioners of the FDA, that the repropoed regulations might allow the marketing of worthless drugs to patients with life-threatening diseases.¹⁷¹ The former chief counsel testified to his personal belief that the regulations were not consistent with the language of the amended Act.¹⁷²

Four officials from the National Institutes of Health testified that a number of its departments were not consulted on the language of the Reproposal and that as published, the regulations would adversely affect its ability to continue AIDS research.¹⁷³

The present commissioner of the FDA, Frank Young, made a futile attempt to justify the language of the repropoed regulations during the oversight hearing.¹⁷⁴ The correspondence that the subcommittee received from the FDA, however, clearly shows that OMB rejected the Commissioner's attempts to compromise and forced the FDA to accept OMB's language.¹⁷⁵

able to receive the drug outside a clinical trial, the researcher cautioned that the repropoed regulations might create a situation in which wealthy patients would purchase the drug outside of a clinical trial, thereby delegating the role of human test subject to those patients who could not afford to purchase the drug. *Id.* This warning is supported by the fact that most insurance companies will not reimburse patients for investigational drugs. *See* Letter from American Medical Ass'n 6 (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00236); Letter from Johns Hopkins Univ. 2 (May 5, 1987) (FDA Docket No. 82N-0394, vol. 11, comment C00260); Letter from Health Insurance Ass'n of Am. 1 (Apr. 30, 1987) (FDA Docket No. 82N-0394, vol. 10, comment C00203).

At the hearing, Congressman Weiss questioned the FDA's current general counsel on whether the Reproposal's language allowing the sale of investigational drugs conflicted with the language in the amended Act which prohibits drug companies from commercializing unapproved drugs. *Drug Hearing, supra* note 65, at 123. The general counsel did not believe that the regulation conflicted with the amended Act. *Id.*

171. *Drug Hearing, supra* note 65, at 4. Richard M. Cooper, Chief Counsel of the FDA from 1977-79 testified on behalf of himself and former Comm'r Charles Edwards, former Comm'r Alexander Schmidt, former Comm'r Donald Kennedy, former Comm'r Jere Goyan, former Comm'r Arthur Hull Hayes, Jr., former Chief Counsel Peter Barton Hutt, former Chief Counsel Richard Merrill and former Chief Counsel Nancy Buc.

172. *Id.* at 13. In addition, William W. Goodrich, who served as chief counsel of the FDA for nearly 20 years, sent written comments to the subcommittee strongly objecting to the Reproposal. *Id.* at 15.

173. Dr. William F. Raub, Deputy Director, NIH; Dr. William Friedewald, Associate Director for Disease Prevention, Office of the Director, NIH; Dr. Maureen W. Myers, Chief, AIDS Treatment Branch, National Institute for Allergy and Infectious Diseases; and Dr. Charles R. McCarthy, Office for Protection from Research Risks, Office of the Director, testified before the subcommittee. *Id.* at 16. Dr. McCarthy testified that within the health organizations, an agency desiring to propose regulations which would affect another agency customarily circulates the proposed regulations to those agencies. *Id.* Dr. McCarthy further testified that the FDA did not circulate the Reproposal among any of the affected agencies. *Id.*

174. *See id.* at 66-73.

175. The Commissioner twice submitted revised language to OMB regarding the evidentiary standard for FDA denial of treatment use of an investigational drug. *See generally id.* at 276-79 (copies of memoranda discussing proposed language). In fact, Commissioner Young

The evidence suggests that OMB staff forced Commissioner Young to accept OMB's proposed changes despite the commissioner's initial reservations and against the better judgment of his staff¹⁷⁶ and the associated medical research community.¹⁷⁷

After struggling with OMB for over a year,¹⁷⁸ FDA Commissioner Young relented and accepted OMB's language, despite the objections of the medical community and the FDA staff. Commissioner Young instead decided to insert restrictive language into the preamble to the regulations.¹⁷⁹ The Commissioner believed that restrictive language in the preamble would take precedence over less restrictive language in the regulation.¹⁸⁰ At the hearing, however, a former FDA chief counsel testified that language in the regulation controls language in the preamble.¹⁸¹

Thus, the oversight hearing transcript reveals that after a year-long strug-

preferred to "essentially preserv[e] the status quo" on the investigational drug regulations. *Id.* at 99. OMB rejected both of the Commissioner's drafts, complaining that the "FDA refus[e]d to budge from its proposal." *Id.* Remarkably, Commissioner Young was unable to identify the OMB staff person responsible for rejecting the FDA's version of the Reproposal. *Id.* at 97. Congressman Weiss expressed concern that neither Congress nor the FDA could identify "who in OMB made a major decision on health policy that overrode [FDA] recommendations, even though [the FDA is] supposed to be in charge of making such decisions." *Id.*

176. In preparation for the hearing, the subcommittee staff learned that no one in the Center for Drugs and Biologics, the FDA office responsible for monitoring the IND process, was in support of the repropose rule. *Id.* at 100. In addition, the current chief counsel of the FDA warned Commissioner Young in November 1986 that the more far-reaching changes in the Reproposal "could be challenged as inconsistent with existing statutory authority." *Id.* at 296; see also *supra* text accompanying notes 146-51.

177. Numerous directors from research departments at NIH were wary of the proposed rule. See *supra* note 173 and accompanying text. In addition, three prominent medical researchers testified about their concerns regarding the proposed rule. See *supra* notes 169-70.

178. The FDA transmitted the proposed IND Rewrite to OMB in July 1985. See *supra* note 124. Memoranda submitted to the subcommittee show that the battle continued into January 1987. *Drug Hearing, supra* note 65, at 272-79. The date of the final resolution is not on record.

179. Commissioner Young testified that he was concerned about the language that OMB sought regarding treatment use and sale of investigational drugs. *Drug Hearing, supra* note 65, at 98-101. After OMB rejected several FDA versions of alternative language, see *supra* note 175, the Commissioner decided to accept strong language in the preamble in lieu of strong language in the regulation, hoping that the preamble language would counterbalance OMB's language in the repropose rule. *Drug Hearing, supra* note 65, at 98-101.

180. See generally *Drug Hearing, supra* note 65, at 100-12 (discussing weight to be accorded preamble language). The Commissioner testified that by inserting interpretive language into the preamble, he believed that he would have the ability to require sufficient data from drug sponsors on which to make a determination of the safety and effectiveness of an investigational drug. *Id.* at 112. The preamble to the repropose rule states that the FDA would base its decision to allow a request for an investigational drug on "sufficient information" that the FDA expected would be provided. Preamble to Reproposal, *supra* note 65, at 8852.

181. *Drug Hearing, supra* note 65, at 13 (testimony of Richard M. Cooper, Esq.).

gle with OMB over language in the proposed investigational drug regulations, the FDA accepted OMB's version, opting to insert restrictive language in the preamble.¹⁸² At the hearing, however, the FDA learned that the language in a regulation prevails over language in the regulation's preamble, and thus decided to redraft the Reproposal before publishing a final rule.¹⁸³

C. The Resolution: The Final Rule

The FDA published the final rule on May 22, 1987.¹⁸⁴ In its final form the rule strikes a compromise between the proposal and the Reproposal. First, the FDA revised the provisions of the rule relating to sale. The FDA changed the term describing drug pricing for investigational drugs distributed for treatment use from "sale" of a drug, which was used in the Reproposal,¹⁸⁵ to "charging for" a drug.¹⁸⁶ The FDA wanted to make clear that drug companies are authorized to recoup certain costs,¹⁸⁷ but are not allowed to sell investigational drugs for a profit.¹⁸⁸ In addition, the FDA lengthened the reporting period before charging from ten to thirty days after the FDA receives notice of the drug sponsor's intent to charge.¹⁸⁹ The regulations also prohibit drug sponsors from charging for treatment use of an investigational drug unless and until there is adequate enrollment in ongoing clinical trials for that drug.¹⁹⁰

Second, the FDA clarified its intentions regarding the stage of the investigational process at which the FDA will grant patient requests for investigational drugs. In the final rule, the FDA emphasized its intent to grant desperately ill patients access to investigational drugs early in the investigational process.¹⁹¹ The treatment use section of the final rule, however, indicates that the FDA will grant access to investigational drugs later in the

182. See *supra* notes 179-80 and accompanying text.

183. *Drug Hearing*, *supra* note 65, at 13 (testimony of Richard M. Cooper, Esq.) Commissioner Young testified that he believed he had sufficient authority under the preamble to deny access to drugs which sponsors had not sufficiently tested. *Id.* at 112. He promised to reconsider whether the regulation authorized him to make decisions regarding the relative safety and effectiveness of an investigational drug. *Id.* at 108. Commissioner Young testified: "I thought I had that judgment, but if I don't have that judgment, then I've got to go back and look at the rule." *Id.* at 112.

184. Final Rule, *supra* note 161, at 19,466.

185. Reproposal, *supra* note 65, at 8855.

186. 21 C.F.R. § 312.7(d) (1988).

187. See Preamble to Final Rule, *supra* note 161, at 19,473.

188. Drug companies are specifically allowed to recover the "costs of manufacture, research, development, and handling of the investigational drug." 21 C.F.R. § 312.7(d)(3) (1988).

189. *Id.* § 312.7(d)(2).

190. *Id.* § 312.7(d)(2)(i).

191. Section 312.34(a) states: "The purpose of this section is to facilitate the availability of

investigational process than the Reproposal had indicated. The Reproposal had stated that the FDA ordinarily would grant seriously ill patients access after Phase 2 trials had been completed, or earlier if appropriate.¹⁹² The final rule, however, states that seriously ill patients ordinarily may access investigational drugs during Phase 3 trials or later.¹⁹³ While the final rule's provision regarding access for patients with an immediately life-threatening disease does not substantially differ from that of the Reproposal, the final rule provides that such patients ordinarily may not access investigational drugs until the drug enters Phase 2 trials.¹⁹⁴

The major change in the treatment use section of the final rule is the standard that the FDA will employ in determining whether to grant patients with an immediately life-threatening disease access to investigational drugs. The final rule shifts back to the drug sponsor the burden of showing evidence sufficient to provide a reasonable basis for granting access.¹⁹⁵ While the burden on the sponsor under the final rule is lighter than the burden historically imposed on drug sponsors,¹⁹⁶ the final rule relieves the FDA of the burden of producing any evidence of the safety and efficacy of a drug.

V. IMPLICATIONS OF OMB'S INVOLVEMENT IN THE FDA'S DRUG REGULATION

OMB's involvement in the FDA's promulgation of the investigational drug regulations causes concern for several reasons. First, the substantive changes which OMB compelled the FDA to accept in the Reproposal highlight the insensitivity of OMB to historical FDA regulations and the judgment of the FDA staff. Second, the changes demonstrate the ignorance of

promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins" *Id.* § 312.34(a).

192. Reproposal, *supra* note 65, at 8856.

193. 21 C.F.R. § 312.34(a) (1988).

194. *Id.* § 312.34(a).

195. The regulations state that the FDA may deny access:

if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug: (A) May be effective for its intended use in its intended patient population; or (B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

Id. § 312.34(b)(3)(i).

The final rule defined an "immediately life-threatening disease" as "a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment." *Id.* § 312.34(b)(3)(ii).

196. Historically, a drug sponsor seeking to release an investigational drug under a compassionate use exemption, had the burden of producing "sufficient evidence of the drug's safety and effectiveness . . . to justify its intended treatment use." *See* Preamble to Proposed IND Rewrite, *supra* note 43, at 26,729. The compassionate use exemption was codified in the original IND Rewrite proposal. *Id.* at 26,742.

the non-expert OMB staff to fundamental principles of medical ethics. Third, OMB's language in the Reproposal runs contrary to the amended Act. Finally, the manner in which OMB conducted its review illuminates the danger of allowing OMB to secretly coerce an agency to adopt regulations which subvert the will of Congress.

Historically, FDA regulations have placed both the financial and the evidentiary burden of proving the safety and effectiveness of a new drug on the drug sponsor.¹⁹⁷ These two requirements have remained static since the FDA first published investigational drug regulations twenty-five years ago. OMB, pursuant to the President's deregulatory agenda, sought changes in the investigational drug regulations which would shift the financial burden of drug development onto the desperately ill patient¹⁹⁸ and the evidentiary burden onto the FDA.¹⁹⁹ OMB imposed its changes on the FDA despite the fact that not a single staff person within the FDA's Center for Drugs and Biologics supported the Reproposal.²⁰⁰ Thus, OMB single-handedly forced the FDA to adopt repropounded regulations which contravened both historical FDA regulations and the judgment of an agency staff comprised of highly qualified medical experts.

Second, the history of the investigational drug regulations demonstrates OMB's ignorance of certain fundamental principles of medical ethics. The politically appointed budget staff at OMB fashioned changes to the investigational drug regulations which reflected the President's policy of deregulation but which contravened ethical norms of medical research. Ethical principles governing modern medical research dictate that researchers should treat human test subjects with respect, justice and beneficence.²⁰¹ The Reproposal conflicts with these principles.

The principle of respect requires society to protect those patients with diminished autonomy.²⁰² Patients with life-threatening diseases are especially vulnerable because they face imminent death and are desperate for a cure.²⁰³ By allowing drug companies to sell typically expensive, unproven drugs; to

197. See *supra* note 7 and accompanying text.

198. See *supra* note 158 and accompanying text.

199. See *supra* text accompanying notes 143-45.

200. See *supra* note 176.

201. See *supra* text accompanying note 3.

202. See R. LEVINE, *supra* note 3, at 15-16. While society benefits from the data gained from human research, the principle of respect requires society to give patients information about alternative health care choices, honor those choices where possible, protect the privacy rights of patients, and ensure that researchers are allowed to act in accordance with their consciences or values. SUMMING UP, *supra* note 3, at 68.

203. See *AIDS Hearing*, *supra* note 46, at 7 (testimony of Paul Popham, AIDS patient).

desperately ill patients, the Reproposal fails to adequately protect the autonomy of these patients.

The principle of justice requires society to distribute benefits and burdens equally throughout society.²⁰⁴ The Reproposal would have produced several unjust results. First, it would have unjustly permitted society to reap the benefit of medical research without incurring the cost of drug development. Second, it would have imposed on the desperately ill patient the burden of paying for an unproven treatment. Third, it would have discriminated against those patients who are not independently wealthy enough to afford the cost of the drug.²⁰⁵

The principle of beneficence requires drug sponsors to promote the well-being of human test subjects.²⁰⁶ The Reproposal ran contrary to this principle in several ways. First, it would have forced the FDA to allow the distribution of a drug on which it had insufficient evidence to determine whether the drug was relatively safe or effective.²⁰⁷ Second, the risk of harm to the patient, had the Reproposal been adopted, would have far outweighed any unsubstantiated and speculative benefit. Third, by allowing the sale of investigational drugs, the risk of economic harm coupled with the physical risk to the patient would have produced an unacceptable risk/benefit ratio.²⁰⁸

The history of the FDA's investigational drug regulations also demon-

204. See R. LEVINE, *supra* note 3, at 17. Justice dictates that researchers treat patients in a fair and non-arbitrary manner. Society, as the prime beneficiary of drug research has traditionally incurred the cost of such research, by allowing pharmaceutical companies to recapture development costs in the marketplace once the sponsor has received FDA approval to market the drug. Insurance companies and health plans assist patients in paying for approved drug treatment, thereby distributing the cost of such treatment equitably to society.

205. The Reproposal would have allowed society to shift the cost of drug development to the patient involved in the research by authorizing drug companies to sell the drug to patients while the drug is still in the investigational stage. Most insurance companies will not assist patients in paying for drugs which have not been approved by the FDA. Thus, the patient must personally finance the cost of treatment use of investigational drugs. See *supra* note 170.

While the final rule also allows drug companies to charge desperately ill patients for investigational drugs, the language of the final rule does not produce results as unjust as does the language in the Reproposal. The final rule places the burden of proving safety and effectiveness on the drug company and allows the FDA discretion in determining whether to permit the sale of an investigational drug. Therefore, the likelihood that an investigational drug will be both effective and safe is much greater in the final rule.

206. Beneficence requires researchers to exercise great care, to make all decisions with the aim of promoting the health of the individual patient, and to consider the welfare of others, including future patients who may benefit from knowledge gained from research. SUMMING UP, *supra* note 3, at 67.

207. See *supra* text accompanying notes 141-43.

208. *Id.* See, e.g., AIDS Hearing, *supra* note 46, at 25 (testimony of Matilde Krim, Ph.D., Cochair of the American Foundation for AIDS Research). When research first began on the drug AZT, the cost of supplying the drug to a single patient exceeded \$10,000 per year.

strates OMB's indifference to the will of Congress. In the amended Act, Congress specifically directed the FDA to regulate investigational drugs.²⁰⁹ Furthermore, the Supreme Court has ruled that drugs intended to treat deathly ill patients are not exempt from FDA regulations.²¹⁰ Nonetheless, OMB, motivated by a general bias against regulation,²¹¹ sought to curtail the FDA's power to prohibit the distribution of investigational drugs.

Essentially, the OMB staff that reviewed the Reproposal contended that medical doctors should have the right to prescribe investigational drugs to desperately ill patients without the interference of the federal government.²¹² OMB staff failed to comprehend the difference between a physician's right to practice medicine and an investigator's right to conduct research.²¹³ Whereas the FDA does not have the authority to regulate the former, Congress has expressly mandated the FDA to regulate the latter.²¹⁴ The amended Act directs the FDA to regulate the distribution and use of investigational drugs in order to protect the rights and welfare of patients.²¹⁵ Aware of the FDA staff's concern that the language in the Reproposal conflicted with the language in the amended Act,²¹⁶ OMB nonetheless compelled the FDA to publish the Reproposal.

Perhaps the greatest danger to the regulatory process is illuminated by the procedures that OMB chose to review the FDA's investigational drug rules. The tactics employed by OMB during its review illustrate how OMB has

209. See *supra* text accompanying notes 24-30.

210. See *United States v. Rutherford*, 442 U.S. 544 (1979). In *Rutherford*, Justice Marshall wrote:

Nothing in the history of the 1938 Food, Drug, and Cosmetic Act, which first established procedures for review of drug safety, or of the 1962 Amendment, which added the current safety and effectiveness standards. . . suggests that Congress intended protection only for persons suffering from curable diseases. To the contrary, in deliberations preceding the 1938 Act, Congress expressed concern that individuals with fatal illnesses, such as cancer, should be shielded from fraudulent cures.

Id. at 553; see also *supra* text accompanying notes 148-51.

211. See *supra* note 66.

212. See *supra* text accompanying note 67.

213. Robert Levine, Professor of Medicine at Yale University, defines research as "a class of activities designed to develop or contribute to generalizable knowledge," whereas practice is "a class of activities designed solely to enhance the well-being of an individual patient or client." R. LEVINE, *supra* note 3, at 3.

214. See *supra* notes 27-29 and accompanying text.

215. See 21 U.S.C. § 355(i)(1982).

216. FDA Commissioner Frank Young fought with OMB over the language in the Reproposal for over a year. See *supra* text accompanying note 178. Commissioner Young was aware of the agency staff's concerns about the rule. See *supra* note 176. Although no public record exists which summarizes the discussions between Commissioner Young and OMB, Commissioner Young testified that he expressed his concerns to OMB. See *Drug Hearing*, *supra* note 65, at 98.

transformed the national regulatory process into a coercive and secretive operation. Setting its sights on the FDA's investigational drug regulations, OMB fashioned language which it forced the FDA to accept.²¹⁷ Moreover, OMB's entire review process was shrouded in secrecy. Because OMB refused to submit its comments to the FDA in writing, produce documents to a congressional oversight subcommittee, or answer legislators' questions regarding its involvement in the formulation of the FDA regulations, OMB remains largely unaccountable for its role in the FDA's rulemaking process. Neither the preamble to the Reproposal nor the preamble to the final rule indicates OMB's involvement in the redrafting of the regulations. The preambles merely indicate that the FDA sent the proposal and Reproposal to OMB, pursuant to the Paperwork Reduction Act, for review of the FDA's compliance with the recordkeeping and reporting requirements.²¹⁸ In fact, the single document which details OMB's involvement in the formulation of the investigational drug regulations is the transcript of the congressional oversight hearing.²¹⁹ Had Representative Weiss not had the foresight to summon FDA Commissioner Young before the subcommittee to detail OMB's involvement in the Reproposal, the FDA may have published the Reproposal as a final rule and the public would have had no indication of OMB's influence in formulating the FDA's investigational drug regulations.

OMB's attempt to secretly compel the FDA to adopt final regulations substantially easing restrictions on investigational drugs demonstrates the danger of allowing a small non-expert staff to set national drug policy. Society takes great risks by allowing a politically appointed budget staff to single-handedly force the FDA to adopt drug regulations which run contrary to historical agency regulations, fundamental ethical norms, the better judgment of the expert agency staff, and the agency's congressional mandate. Not only does society risk subverting the will of Congress by allowing OMB to fashion regulations contrary to the FDA's enabling act, but it runs a greater risk of restricting the FDA's authority to stop drug manufacturers from distributing unsafe drugs to desperate patients.²²⁰

217. See *supra* text accompanying notes 176-77.

218. See Preamble to Final IND Rewrite, *supra* note 68, at 8855; Preamble to Final Rule, *supra* note 161, at 19,476.

219. See *supra* text accompanying notes 165-66.

220. These risks are more than hypothetical possibilities. In fact, a recent report indicates that the executive branch, undeterred by critics of OMB's role in the investigational drug regulations, currently has plans to further revise the drug approval process. See *The Sun*, (Baltimore, Md.) Aug. 7, 1988, at 3A, col. 4. The administration's plans include lowering the standard for approval of drugs intended for life-threatening diseases. A staff person of the Vice President's deregulatory task force explained: "We want to vary the regulatory hurdles depending on the seriousness of the disease. Maybe you should lower your standards if you're dealing with a disease that's certain to result in death." *Id.*

Moreover, because OMB reviews all administrative agency rules, OMB's heavy-handed review procedures threaten the entire federal regulatory process. The secretive, coercive tactics employed by OMB during its review of the investigational drug regulations have become standard operating procedure at OMB,²²¹ undermining fundamental principles of agency rulemaking. First, OMB, operating in a secretive manner, refuses to allow public participation in the formulation of rules which affect public rights. Second, because OMB imposes its regulatory program on administrative agencies, agency rules may be the product of a small staff of OMB budget experts rather than the result of reasoned decisionmaking through public participation. Ultimately, regulations formulated in a vacuum by a small staff which is unaccountable to the public will not reflect the larger societal values which ought to shape federal regulatory policy. Thus, the history of the FDA's investigational drug regulations illustrates not only the danger of allowing OMB to regulate national drug policy, but also the peril of permitting OMB to undermine public participation and reasoned decisionmaking in the federal regulatory arena.

VI. CONCLUSION

The history of the FDA's investigational drug regulations illustrates OMB's recent attempts to control the national regulatory arena. Heeding the President's deregulatory agenda, OMB sought changes in the FDA's investigational drug regulations which ran contrary to both historical FDA drug regulations and established principles of medical ethics. Moreover, OMB ignored the mandate of Congress that drug manufacturers prove the safety and effectiveness of a new drug before receiving FDA approval to distribute it. Despite a year-long struggle over the language in the rule, OMB prevailed and the FDA published the Reproposal.

OMB's involvement in the formulation of the investigational drug regulations remained obscure until Congress, at an oversight hearing, exposed OMB's role in secretly coercing the FDA to repropose changes to the regulations. As a result of the oversight hearing, the FDA commissioner revised the Reproposal and subsequently published modified regulations. The secretive manner in which OMB chose to review the FDA's proposed regulations, however, highlights the danger of permitting a small budget staff to formulate national regulatory policy, regardless of whether the agency, Congress, or the public supports the rule. By permitting OMB staff to isolate itself from the public and to conduct its regulatory review process in secret, society tacitly approves the formulation of rules which are indifferent to basic

221. See *supra* notes 116-23 and accompanying text.

societal values. Although the final FDA investigational drug rule substantially retreats from OMB's version, the history of the rule demonstrates the danger of allowing OMB to regulate the regulators.

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