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INDEPENDENT CLINICAL TRIALS TO TEST DRUGS: THE NEGLECTED REFORM

MARC A. RODWIN*

I. DRUG MANUFACTURER CONFLICTS OF INTEREST

Drug manufacturers face a fundamental conflict of interest. Pursuit of profit compromises their impartial assessment of their drugs' benefits and risks.¹ Their biased evaluation can corrupt public knowledge of drugs, lead to marketing unsafe and/or ineffective drugs, and undermine rational physician prescribing.² Over the last century, federal regulation has mitigated but not eliminated this problem, which corrupts drug therapy and medical practice.³

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1. The conflicts of drug firms are part conflicts of interest that affect medical practice in general. See MARC A. RODWIN, *MEDICINE, MONEY, AND MORALS; PHYSICIANS' CONFLICTS OF INTEREST* (1993); MARC A. RODWIN, *CONFLICTS OF INTEREST AND THE FUTURE OF MEDICINE: THE UNITED STATES, FRANCE AND JAPAN* (2011) [hereinafter RODWIN, *CONFLICTS OF INTEREST AND THE FUTURE OF MEDICINE*].

2. Marc A. Rodwin, *Conflicts of Interest, Institutional Corruption, and Pharma: An Agenda for Reform*, 40 J.L. MED. & ETHICS 511, 511 (2012) [hereinafter Rodwin, *Institutional Corruption and Pharma*].

3. There is a growing literature analyzing problems with drug safety and current practices in pharmaceutical industry research and marketing. See generally JOHN ABRAMSON, *OVERDOSED AMERICA: THE BROKEN PROMISE OF AMERICAN MEDICINE* (2004); MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (2004); JERRY AVORN, *POWERFUL MEDICINES: THE BENEFITS, RISKS AND COSTS OF PRESCRIPTION DRUGS* (2004); HOWARD BRODY, *HOOKED: ETHICS, THE MEDICAL PROFESSION, AND THE PHARMACEUTICAL INDUSTRY* (2007); Carl Elliott, *The Drug Pushers*, ATLANTIC, April 2006, <http://www.theatlantic.com/magazine/print/2006/04/the-drug-pushers/304714/>; Marc-André Gagnon, *Corporate Influence Over Clinical Research: Considering the Alternatives*, 21 *PREScrire INT'L* 191 (2012); MERRILL GOOZNER, *THE \$800 MILLION PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS* (2004); DAVID HEALY, *PHARMAGEDDON* (2012); Joel Lexchin, *The Medical Profession and the Pharmaceutical Industry: An Unhealthy Alliance*, 18 *INT'L J. HEALTH SERVICES* 603 (1988); DONALD W. LIGHT, *THE RISKS OF PRESCRIPTION DRUGS* (2010); THOMAS J. MOORE,

Today, the federal government counters this conflict of interest in several ways. First, legislation precludes introducing drugs in interstate commerce unless the Food and Drug Administration (FDA) finds that the drug's sponsor has demonstrated that the drug is safe and effective for a designated use.⁴ It prohibits the firm from marketing the drug for any other use.

Second, the FDA requires that drug sponsors demonstrate safety and efficacy by submitting data from clinical trials on human research subjects.⁵ Typically, in the trial, one group of individuals is treated with the test drug and a control group is treated with a placebo or an alternative drug therapy.⁶

The FDA also oversees the conduct of clinical research used to support applications to market a drug referred to as new drug applications or NDAs. Regulations counter the risk of fraud and unreliable research. They establish standards for research methods, record keeping, and data reporting.⁷ In addition, the FDA inspects toxicological laboratories and facilities that conduct clinical trials to monitor compliance with these standards.⁸

Nevertheless, the conflicts of interest persist because the firm that seeks to market a drug designs and controls the clinical trials used to test its safety and efficacy. The FDA relies upon these trials when it evaluates whether or not to authorize marketing the drug. An ample record reveals that drug firms can design clinical trials in ways that bias the conclusions.⁹ They can also misinterpret or misreport the trial data, or engage in fraud.¹⁰

PRESCRIPTION FOR DISASTER: THE HIDDEN DANGERS IN YOUR MEDICINE CABINET (1998); RAY MOYNIHAN & ALAN CASSELS, *SELLING SICKNESS: HOW THE WORLD'S BIGGEST PHARMACEUTICAL COMPANIES ARE TURNING US ALL INTO PATIENTS* (2005); Sergio Sismondo, *Ghost Management: How Much of the Medical Literature Is Shaped Behind the Scenes by the Pharmaceutical Industry?*, 4 PLOS MED. 1429 (2007). Some scholars, however, argue that the United States overregulates the pharmaceutical industry. See RICHARD A. EPSTEIN, *OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION* (2006).

4. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(a)-(b) (2006). This Act, the FDCA, regulates the sale of drugs in interstate commerce. *Id.* § 355(a). In theory, a physician, other individual, or firm could market a drug in only one state and avoid federal regulation under the FDCA. For the most in depth study of the FDA, see DANIEL CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* (2010).

5. 21 C.F.R. § 312.58(a) (2012).

6. 21 C.F.R. § 314.126(a)(2).

7. 21 C.F.R. §§ 312.57, 314.126.

8. U.S. FOOD & DRUG ADMIN., *GUIDANCE FOR INDUSTRY: GOOD LABORATORY PRACTICES, QUESTIONS AND ANSWERS 7* (2007), available at <http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133748.pdf>; U.S. FOOD & DRUG ADMIN., *INFORMATION SHEET GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS: FDA INSPECTIONS OF CLINICAL INVESTIGATORS 2* (2010), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf>.

9. Dummond Rennie, *When Evidence Isn't: Trials, Drug Companies and the FDA*, 15 J.L. & POL'Y 991, 1007-08 (2007). See also Harlan M. Krumholz & Joseph S. Ross, *A Model for*

Drug firm bias can slant research performed in house and also the clinical research conducted by external researchers that drug firms finance or manage. In fact, today to conduct clinical research drug firms typically rely mainly on researchers who are not full time company employees.¹¹ They engage Contract Research Organizations (CROs) or university-based researchers to carry out clinical trials and/or to perform some or all of the analysis.¹² They may also contract with specialists to design trials.¹³ Having third parties conduct the research does not eliminate corrupting influences for a simple reason. The drug sponsor chooses who will conduct the trials and these researchers depend on sponsoring firm for their income; they therefore have incentives to advance the goals of the drug firm that employs them and to follow its directives.¹⁴ In addition, these researchers report to the drug sponsor, not to the FDA or the equivalent regulatory authority in other countries.¹⁵ They cannot report their results or their analysis separately to governmental authorities.¹⁶

This article explores a reform proposal that precludes bias in clinical trials used to test drugs. Simply stated, it removes all drug firm influence on the design and conduct of clinical trials used to decide whether to allow marketing of a drug. Recently advocated by several leaders in drug policy and research, this reform proposal has a long history, but was neglected for over half a century due to pharmaceutical industry opposition, and so the federal government pursued alternative strategies to counter bias, which proved ineffective.¹⁷ When regulation of manufacturer controlled clinical trials failed to eliminate bias, flawed practice, and fraud, public officials increased oversight relying on the same flawed approach.¹⁸

It would not be surprising if contemporary scandals galvanize support for a new round of reforms. Neither would it be remarkable if responsible pharmaceutical industry leaders and public officials supported stricter

Dissemination and Independent Analysis of Industry Data, 306 JAMA 1593, 1593-94 (2011); see also Marcia Angell, *Industry-Sponsored Clinical Research: A Broken System*, 300 JAMA 1069, 1069-71 (2008).

10. Rennie, *supra* note 9, at 994-96.

11. See Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1539-40 (2000).

12. *Id.*

13. *Id.* at 1541.

14. *Id.* at 1543.

15. See Christine D. Galbraith, *Dying to Know: A Demand for Genuine Public Access to Clinical Trial Results Data*, 78 MISS. L.J. 705, 754 (2009).

16. See *id.*

17. *Id.* at 712; Angell, *supra* note 9, at 1071; PETER TEMIN, *TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES* 2-5 (1980).

18. TEMIN, *supra* note 17, at 29.

oversight using the same paradigm. Nor will it be unexpected when the next generation of halfway reforms yields only minor improvements while drug firms develop new means to influence clinical trials. The corruption lies at the root: drug firm control over clinical trials, and so to be effective, reforms need to eliminate this problem.¹⁹

A. *Options for Control of Clinical Trials*

The chart below displays a typology of six key options for addressing conflicts of interest in clinical trials. The left end of the spectrum grants the drug sponsor complete control and ignores its conflict of interest. At the right end of the spectrum, the federal government conducts the clinical trials. Between these two poles are four strategies that public policy can employ individually or in various combinations. The FDA's regulatory regime has evolved over time, but it relies on the second strategy, supplemented in recent years by the fourth strategy.

STRATEGIES TO ADDRESS DRUG SPONSOR CONFLICTS OF INTEREST IN CLINICAL TRIALS

←Maximum Manufacturer Control

Maximum Government Control→

1	2	3	4	5	6
Drug firms conduct clinical trials with little regulation.	FDA regulates and oversees clinical trials conducted by drug firms.	Government or private entity certifies clinical researchers. Drug firms conduct clinical trials using certified researchers.	Government promotes transparency by requiring: <ul style="list-style-type: none"> • Registration of trials; • Disclosure of clinical study reports; or • Disclosure of patient level data. 	Government selects independent entities to conduct clinical trials.	Government agency conducts clinical trials.

19. The concept of institutional corruption has been developed by Lawrence Lessig and Dennis Thompson. See LAWRENCE LESSIG, *REPUBLIC, LOST: HOW MONEY CORRUPTS CONGRESS – AND A PLAN TO STOP IT* 226-47 (2011); Dennis F. Thompson, *Two Concepts of Corruption: Making Campaigns Safe for Democracy*, 73 GEO. WASH. L. REV. 1036 (2005); DENNIS F. THOMPSON, *ETHICS IN CONGRESS: FROM INDIVIDUAL TO INSTITUTIONAL CORRUPTION* (1995). For a review of institutional corruption and the pharmaceutical industry, see generally Rodwin, *Institutional Corruption and Pharma*, *supra* note 2. Several researchers at the Edmond J. Safra Center, Harvard University, are analyzing institutional corruption in the pharmaceutical economy and other areas of public life. See *The Lab at Edmond J. Safra Center for Ethics*, HARVARD UNIV., <http://www.ethics.harvard.edu/lab> (last visited Dec. 20, 2012).

The first option — really the absence of a strategy — allows the drug firm to conduct clinical trials without interference. It refrains from addressing its conflict of interest. The second strategy — the main one used today — has the FDA regulate and oversee clinical trials conducted by drug firms. The regulations set standards to promote reliable research.

A third strategy requires that only certified research organizations and researchers conduct clinical trials. A fourth strategy requires transparency to facilitate public review of clinical trial methods, analysis, and results. Since 2007, the United States has required registration of clinical trials to promote transparency.²⁰

A fifth strategy removes drug firm bias by having the federal government select independent organizations and researchers to design and conduct clinical trials. Researchers would not depend on drug firms to select them and so would lack incentives to favor the drug firm. A sixth strategy has a governmental institution or agency design and conduct clinical trials.

20. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801(a), 121 Stat. 823, 905-08 (codified as amended at 42 U.S.C. 282 (2006)). The push for registration of clinical trials emerged after studies showed the presence of biased information in the published literature evaluating drugs, resulting from bias in the clinical studies that were published. See An-Wen Chan et al., *Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to Published Articles*, 291 JAMA 2457 (2004). Drug firms published studies with positive results in several forms but buried studies with results that showed drugs were not very effective or that they posed high risks. This led medical journal editors to promote registration of clinical trials to increase access to data from unpublished clinical trials. *Id.* at 2462. In 2004, the International Committee of Medical Journal Editors agreed that their journals would not publish clinical trial results unless the researchers had registered the trial before patients enrolled in the trial. See Kay Dickersin & Drummond Rennie, *Registering Clinical Trials*, 290 JAMA 516 (2003); Editorial, *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 351 NEW ENG. J. MED. 1250 (2004). The committee of editors decided that registries should include data specified by the World Health Organization. *International Clinical Trials Registry Platform (ICTRP)*, WORLD HEALTH ORG. (2012), <http://www.who.int/ictcp/network/trds/en/index.html>. Current law requires registering Phase 2 and higher trials of drugs and biologicals on the ClinicalTrials.gov website if the trial is part of an FDA investigational new drug application, or if there is a trial site in the United States. Researchers must post key results within a year after the completion of collecting data. However, they have up to three years to post results for studies of off-label drug uses (i.e., uses other than those the FDA has approved). Nevertheless, registration practice falls short of what the law requires. Sylvain Mathieu et al., *Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials*, 302 JAMA 977 (2009); Michael R. Law et al., *Despite Law, Fewer Than One in Eight Completed Studies Of Drugs and Biologics are Reported on Time on ClinicalTrials.gov*, 30 HEALTH AFF. 2338 (2011). Moreover, current law and policy impedes access to information on drug safety. See Aaron S. Kesselheim & Michelle M. Mello, *Confidentiality Laws and Secrecy in Medical Research: Improving Public Access to Data on Drug Safety*, 26 HEALTH AFF. 483 (2007).

Until now, almost all efforts to address the drug sponsor's conflict of interest employed the second strategy and set standards for the conduct of laboratory testing and clinical trials.²¹ The federal government could bolster the second strategy with different kinds of rules. Regulations could that the drug sponsor's proposed protocol and research design be reviewed by independent experts selected by the FDA. Based on the peer review, the FDA could then require that the sponsor revise the protocol and research design. Other regulations could oversee financial relations between the drug sponsor and researchers. They could preclude individuals and firms from conducting a trial if they have significant conflicts of interest arising from other financial ties with the drug company. They could also set standards for compensation of firms and individuals.

Some reformers in the 1960s and 1970s advocated certification of researchers — the third strategy — but the United States has not pursued this approach.²² Regulations could require that only certified individual researchers and organizations conduct drug trials used to support NDAs. They could authorize the federal government or private organizations to certify researchers. Regulations could require training, experience, and other qualifications for certification. They could create a system to revoke certification from individuals and firms that engaged in misconduct or violated rules. They could preclude individuals and firms from conducting trials when they have designated conflicts of interest such as financial ties with pharmaceutical firms whose products they test.

To strengthen the transparency strategy, regulations could require that drug sponsors and their researchers make public the clinical study report, which drug firms now produce to comply with international standards and FDA rules.²³ Clinical study reports contain key information related to the

21. See Tomas J. Philipson & Eric Sun, *Is the Food and Drug Administration Safe and Effective?* 6 (Nat'l Bureau of Econ. Research, Working Paper No. 13561, 2007).

22. See, e.g., Committee on Public Health, *The Importance of Clinical Testing in Determining the Efficacy and Safety of Drugs*, 38 BULL. N.Y. ACAD. MED. 415, 433-34 (1962). Although the United States does not certify researchers for drug testing, the FDA can bar researchers from conducting clinical trials used to support new drug applications. 21 C.F.R. § 312.70 (2012).

23. See INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, GUIDELINE FOR INDUSTRY: STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS; see also International Conference on Harmonisation: Guideline on Structure and Content of Clinical Study Reports; Availability, 61 Fed. Reg. 37,320 (July 17, 1996). John Abramson and I have called for legislation to require mandatory disclosure of clinical study reports for FDA approved drugs. See Marc A. Rodwin & John D. Abramson, *Clinical Trial Data as a Public Good*, 308 JAMA 871 (2012). See also Peter Doshi et al., *The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience*, 9 PLOS MED. e1001201 (2012). Recently, the European Medicines Agency has started to make clinical trial reports available when they are requested under

clinical trial, including: the study protocol, the designated clinical end points, discussion of methods and statistical analysis, tabulated data, and analysis of data. Regulations could also require disclosure of clinical trial patient level data. Making public detailed information on clinical trials would allow independent researchers to review the analysis or to perform their own evaluation. Proponents of this approach say it would make it harder for drug sponsors to hide risks from the public and also help hold the FDA accountable for its decisions.²⁴

New regulations that advanced the second, third, and fourth strategies could reduce the risk of fraud or bias and improve the design and implementation of clinical trials. However they would not remove the bias inherent in drug sponsor influence over the trials. Consequently, some critics have proposed ending the drug sponsor's control over clinical trials used by the FDA to evaluate drugs.²⁵ This reform can be implemented through the fifth strategy, having the federal government contract with independent organizations to design and conduct clinical trials, or through the sixth strategy, having the federal government conduct the clinical trials. Under most formulations of these proposals, the drug firm that wishes to market the drug pays the cost of the trials, just as they currently do. Some people, however, propose that the pharmaceutical industry collectively finance the trials;²⁶ others propose that the federal government share the costs of testing a drug either with the pharmaceutical industry collectively or with the sponsor of the drug.²⁷

Governmental oversight of clinical trials is part of broader regulation of pharmaceutical firms to manage their conflicts of interest. To understand proposals to reform the conduct of clinical trials, it will help to review how public authorities have regulated drug firms over the last century.

public disclosure statutes. See Press Release, Eur. Meds. Agency, European Medicines Agency Widens Public Access to Documents, (Nov. 30, 2010), available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/11/news_detail_001158.jsp&mid=WC0b01ac058004d5c1 (2010). See also Peter Doshi & Tom Jefferson, *The First 2 Years of the European Medicines Agency's Policy on Access to Documents: Secret No Longer*, ARCHIVES INTERNAL MED., Dec. 19, 2012, at E1 (reviewing data from the first 2 years of the EMA's access policy and finding diversity in the requestor affiliation).

24. See Krumholz & Ross, *supra* note 9, at 1593-94.

25. See a discussion of contemporary proposals *infra* Part III. Angell, *supra* note 9, at 1071; Marcia Angell & Arnold S. Relman, *Patents, Profits & American Medicine: Conflicts of Interest in the Testing & Marketing of New Drugs*, DAEDALUS, Spring 2002, at 102, 111; ANGELL, *supra* note 3, at 245.

26. *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study, Part 4: Hearings Before the Subcomm. On Reorganization and Int'l Org. of the S. Comm. on Government Operations*, 88th Cong. 1620 (1963) [hereinafter *Drug Research and Regulation Hearings, Part 4*]; ANGELL, *supra* note 3, at 245.

27. See *infra* Part II, III (discussing contemporary proposals).

II. COPING WITH DRUG FIRM CONFLICTS OF INTEREST: A HISTORY OF U.S. DRUG REGULATION

In the beginning of the twentieth century, there were no effective institutional means to control pharmaceutical firm conflicts of interest. The law allowed a drug market premised on *laissez-faire*.²⁸ Manufacturers could sell directly to consumers any product and make any therapeutic claim. Manufacturers were not required to test their drugs for safety or efficacy, or even to disclose the ingredients. Many products marketed as medicines lacked active ingredients. Other products, sold without prescriptions and often without the contents being disclosed, included narcotics, alcohol, or other dangerous substances.²⁹ Patients and physicians lacked the ability to evaluate drugs or choose among them. Firms did not engage in anything similar to contemporary drug development or clinical trials.

There were two categories of drugs. The first, referred to as *ethical drugs*, were listed in the U.S. Pharmacopeia or in the National Formulary, and consisted of drugs that the physicians and pharmacists considered reliable.³⁰ In practice, these drugs were substances that were in the public domain, and hence not patented, although there was no reason why an individual or firm that invented a new drug could not patent it.³¹ Multiple firms produced and sold them to physicians and pharmacists in a form ready for use.³² In addition, pharmacists and physicians often obtained the raw ingredients and compounded these medicines.³³ Among the approximately 200 drugs in these formularies, about a dozen are considered valuable today, most notably: morphine, digitalis, quinine, diphtheria antitoxin, aspirin, and ether.³⁴

28. For a history of food and drug law and the FDA see PHILIP J. HILTS, *PROTECTING AMERICA'S HEALTH; THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION* 11-94 (2003); see HARRY F. DOWLING, *MEDICINES FOR MAN: THE DEVELOPMENT, REGULATION, AND USE OF PRESCRIPTION DRUGS* 187-212, 230-32 (1970); see also TEMIN, *supra* note 17, at 23.

29. TEMIN, *supra* note 17, at 23-25, 32-33.

30. *Id.* at 24; James L.J. Nuzzo, *Independent Prescribing Authority of Advanced Practice Nurses: A Threat to the Public Health?*, 53 *FOOD & DRUG L.J.* 35, 36 (1998).

31. Nuzzo, *supra* note 30, at 36.

32. *Id.*; Glenn Sonnedecker, *Contribution of the Pharmaceutical Profession Toward Controlling the Quality of Drugs in the Nineteenth Century*, in *SAFEGUARDING THE PUBLIC: HISTORICAL ASPECTS OF MEDICINAL DRUG CONTROL* 97, 108 (John B. Blake ed., 1970).

33. Sonnedecker, *supra* note 32, at 99.

34. TEMIN, *supra* note 17, at 24, 59. All of these drugs, with the exception of Aspirin, were added to the Pharmacopeia in the early 20th century. Aspirin was added at a later date. UNITED STATES PHARMACOPEIAL CONVENTION, *THE PHARMACOPEIA OF THE UNITED STATES OF AMERICA* 122-24, 393 (1905). Morphine was added in 1907. UNITED STATES PHARMACOPEIAL CONVENTION, *THE PHARMACOPEIA OF THE UNITED STATES OF AMERICA* 293 (1907).

The second category of drugs was proprietary medicines, often referred to as *patent medicines* or *secret nostrums*.³⁵ These were actually not patented but branded products, and the brand name was protected as a trademark.³⁶ Ingredients and production methods were secret. Later analysis revealed that many consisted mainly of water or alcohol. Some contained morphine or opium.³⁷ Firms marketed these drugs directly to consumers, typically through newspaper advertising, and also to pharmacies and physicians who resold them to patients.³⁸

A. *The Rise of Drug Regulation*

Reform came slowly. The American Medical Association (AMA) had opposed the sale of patent remedies/secret nostrums since its founding in 1847.³⁹ The AMA Code declared it unethical for doctors to use or vouch for such drugs.⁴⁰ Not until 1905, however, did the AMA have sufficient resources to cease advertising patent medicines in its medical journal and to institute a private system of drug regulation.⁴¹ Then, the AMA decided to advertise only drugs that it approved.⁴² It approved only drugs marketed exclusively to physicians that listed all active ingredients on the label but that did not include information that would allow patients to medicate themselves. The AMA analyzed these drugs to confirm that the label listed the contents accurately.⁴³

Reformers and muckrakers — supported by the AMA — spearheaded federal drug regulation.⁴⁴ In 1906, Congress passed the Pure Food and Drug Act, which required manufacturers to disclose therapeutic ingredients on the drug label and prohibited the sale of adulterated, misbranded, or deleterious products.⁴⁵ The presumption was that with accurate labeling,

35. The leading study of the proprietary medicine market prior to the 1938 FDCA is JAMES HARVEY YOUNG, *THE TOADSTOOL MILLIONAIRES: A SOCIAL HISTORY OF PATENT MEDICINES IN AMERICA BEFORE FEDERAL REGULATION* (1961).

36. Nuzzo, *supra* note 30, at 36.

37. TEMIN, *supra* note 17, at 25.

38. *Id.* at 25-26; see, e.g., Peter Temin, *Technology, Regulation, and Market Structure in the Modern Pharmaceutical Industry*, 10 BELL J. ECON. 429, 441 (1979).

39. Nuzzo, *supra* note 30, at 36.

40. *Id.*

41. See TEMIN, *supra* note 17, at 29.

42. For a history of the AMA regulation of drugs see DOWLING, *supra* note 28, at 153-185. See also, RODWIN, *CONFLICTS OF INTEREST AND THE FUTURE OF MEDICINE*, *supra* note 1, at 85-90, 102-06.

43. Marc A. Rodwin, *Drug Advertising, Continuing Medical Education, and Physician Prescribing: A Historical Review and Reform Proposal*, 38 J.L. MED. & ETHICS 807, 808 (2010).

44. See DOWLING, *supra* note 28, at 155-56; see also HILTS, *supra* note 28, at 52.

45. Pure Food and Drug Act of 1906, Pub. L. No. 59-384, § 8, 34 Stat. 768, 770. For a review of the history and analysis of the Food, Drug and Cosmetic Act see Richard A. Merrill,

individuals could safely choose drugs. Advertising of therapeutic claims remained unregulated until amendments in 1912 prohibited false and fraudulent statements regarding the curative or therapeutic effect.⁴⁶

Despite these reforms, in 1929, proprietary medicines accounted for half of drug sales, and patients could purchase drugs without prescriptions, except for narcotics.⁴⁷ At the end of the 1930s, only a handful of companies produced drugs that had any therapeutic value.⁴⁸ They had not invested in or discovered these drugs and they did not conduct any research to develop and test new products. Henry Gadsden testified before Congress that when he joined Merck in 1937, "you could count the basic medicines on the fingers of your two hands. Our own . . . catalog did not carry a single exclusive prescription medicine Most of our products were sold without a prescription. And 43 percent of the prescription medicines were compounded by the pharmacist" ⁴⁹

The Roosevelt administration sponsored legislation to regulate drugs in 1933, but industry opposition blocked its enactment until a scandal galvanized popular support. In 1937, the Massengill Company added a chemical to improve the flavor of a sulfa-based drug called sulfanilamide. The chemical proved toxic and killed at least 106 people who ingested the drug.⁵⁰ Congress then ended the laissez-faire drug regime by passing the Food, Drug, and Cosmetic Act (FDCA).

The legislation required firms to seek permission to market drugs in interstate commerce from the FDA and allowed the FDA 60 days to deny authorization if it found that the drug was dangerous or improperly labeled.⁵¹ Manufacturers no longer had unchecked authority to sell drugs.⁵²

The Architecture of Government Regulation of Medical Products, 82 VA. L. REV. 1753 (1996); see also Peter Barton Hutt, *The Regulation of Drug Products by the United States Food and Drug Administration*, in *THE TEXTBOOK OF PHARMACEUTICAL MEDICINE* 565-601 (John P. Griffin & John O'Grady eds., 5th ed. 2006).

46. Pure Food Act Amendment of 1912, Pub. L. No. 62-301, 37 Stat. 416, 416-17.

47. TEMIN, *supra* note 17, at 38, 46.

48. See Peter Temin, *The Origin of Compulsory Drug Prescriptions*, 22 J.L. & ECON. 91, 105 (1979); see *1920s and 1930s: Salving with Science*, AM. CHEM. SOC'Y (2000), <http://www2.uah.es/farmamol/The%20Pharmaceutical%20Century/Ch2.html>.

49. TEMIN, *supra* note 17, at 59.

50. *Id.* at 40-42.

51. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938).

52. See TEMIN, *supra* note 17, at 42. The 1938 Act did not regulate drug advertising, but other legislation granted the Federal Trade Commission power to stop firms from making false claims in advertising if they could show intent to defraud or mislead. *Id.*

These changes created incentives for drug firms to conduct research and to evaluate their products.⁵³

B. 1962 FDCA Amendments Standards for Clinical Trials

The marketing of Thalidomide led to the birth of children with severe deformations in multiple countries and created pressure for Congress to pass the 1962 Kefauver-Harris Amendments to the FDCA.⁵⁴ The legislation removed the deadline for the FDA to review marketing applications; since then, firms cannot market drugs unless the FDA grants approval.⁵⁵

The 1962 amendments require drug sponsors to demonstrate that drugs are *effective*, not only *safe*.⁵⁶ It authorizes the FDA to withdraw its approval for drugs already on the market based on new evidence;⁵⁷ manufacturers are required to track drug distribution to facilitate recalls of unsafe products and to follow FDA standards for good manufacturing practices.⁵⁸

The law restricts promotion to therapeutic uses approved by the FDA. Promotional materials must note risks, as well as benefits, and summarize side effects and contraindications.⁵⁹ The FDA specifies what information the label must include and labels must state the generic as well as the brand name.⁶⁰

The law requires that manufacturers receive FDA permission to use new drugs in experiments before they begin tests for a NDA.⁶¹ It empowers the FDA to require a manufacturer to carry out follow-up safety studies after it grants marketing approval;⁶² it requires that manufacturers report to the FDA any information they receive on suspected adverse drug events.⁶³

53. The 1938 Act did not state that firms had to show their drugs were effective. See generally Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938). However, the FDA's view was that in order to decide whether a drug was safe it needed to consider its therapeutic benefits. Temin, *supra* note 48, at 103-04. FDA scientists believed they should tolerate a higher level of risks for drugs that would alleviate a serious medical problem than for a drug that produced little or no therapeutic benefit. See TEMIN, *supra* note 17, 48-49.

54. Jerry Avorn, *Learning about the Safety of Drugs – A Half-Century of Evolution*, 365 NEW ENG. J. MED. 2151, 2151-52 (2011); see also Merrill, *supra* note 45, at 1764; HILTS, *supra* note 28, at 144-65; Hutt, *supra* note 45, at 569.

55. Drug Amendments of 1962, Pub. L. No. 87-781, § 104, 76 Stat. 780, 784.

56. *Id.* § 102(a).

57. *Id.* § 102(e).

58. *Id.* §§ 101, 103.

59. *Id.* § 131(a).

60. Drug Amendments of 1962, Pub. L. No. 87-781, §§ 112, 131, 76 Stat. 780, 790, 791.

61. *Id.* § 103(b).

62. See *id.* § 102(d).

63. See *id.* § 102(d).

The law and subsequent regulations set a new standard to demonstrate safety and effectiveness and this created the contemporary system used to conduct clinical trials. These rules replaced a haphazard system of testing that often consisted of testimonials based on the clinical experience of researchers or the experience and opinions of physicians whom drug firms deemed to be experts. In its place, the regulations require drug firms to submit "substantial evidence" based on "adequate and well controlled" scientific experiments carried out by "experts qualified by scientific training."⁶⁴ The FDA worked with the pharmaceutical industry and clinical researchers to create standards for testing drugs, and in 1970, issued regulations on the conduct of clinical trials used to evaluate drugs.⁶⁵

Before beginning clinical trials, researchers identify potentially therapeutic molecules and conduct pre-clinical research.⁶⁶ Typically they are guided by information and theories, which suggest that changing a biological process might alleviate a medical problem. Based on this groundwork, researchers search for molecules that affect these biological processes.⁶⁷ They test the molecules that are the active ingredients in medicines in a laboratory to identify their effects on chemicals, cells, or tissues.⁶⁸

After the researchers identify a promising molecule, the FDA requires firms to test drugs, initially in animals and then in humans. First, researchers

64. *Id.*

[T]he term 'substantial evidence' means 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.*

65. Hearing Regulations and Regulations Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations, 35 Fed. Reg. 7250, 7250 (May 8, 1970) (codified at 21 C.F.R. 146). For a careful study of the how clinical trials and clinical research developed, see HARRY M. MARKS, *THE PROGRESS OF EXPERIMENT: SCIENCE AND THERAPEUTIC REFORM IN THE UNITED STATES, 1900-1990* (2000).

66. For a description and history of the process used for drug development and testing drugs, see SUSAN ALDRIDGE, *MAGIC MOLECULES: HOW DRUGS WORK* 23-52 (1998); see JÜRGEN DREWS, *IN QUEST OF TOMORROW'S MEDICINES* 71-115 (2003). For a succinct review, see Richard E. Rowberg, CONG. RESEARCH SERV., RL 30913, *PHARMACEUTICAL RESEARCH AND DEVELOPMENT: A DESCRIPTION AND ANALYSIS OF THE PROCESS* (2001). See also, *Science & Research: Proposed New Drug, Antibiotic, and Biological Product Regulations*, U.S. FOOD & DRUG ADMIN. (1983), www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119443.htm [hereinafter FDA, *Proposed New Regulations*].

67. See FDA, *Proposed New Regulations*, *supra* note 66.

68. See PACIFIC BIOLABS, *PRECLINICAL TOXICOLOGY, GUIDANCE FOR THE INDUSTRY* 5-6, 20 (1997), available at <http://www.pacificbiolabs.com/downloads/booklet%20preclinical%20tox%20guidance.pdf>.

test the drug in animals at various doses to identify whether it is toxic.⁶⁹ They also may note its potential therapeutic effects.⁷⁰ If a molecule is not highly toxic in animals, researchers can proceed to test the drug in humans in clinical trials divided into three phases.⁷¹ In the first phase of clinical trials researchers test the drug to a small number of human subjects to determine whether it is toxic in humans, and if so at what doses. Those studies yield information about what does human can tolerate the drug without immediate health risks. If the drug appears safe enough to continue testing, researchers conduct a second phase clinical trial in a larger group of patients to measure its benefits and risk.⁷² If a molecule still shows promise, researchers can proceed to the third phase, a controlled clinical trial that tests a drug's safety and effectiveness in a larger number of human research subjects.⁷³

Phase three clinical trials evaluate a drug by comparing its use in test subjects with a control group. Typically, the control group uses a placebo or an alternative therapy.⁷⁴ Protocols specify a process for randomly assigning subjects to test and control groups in order to preclude bias in assignment of individuals among the groups.⁷⁵ The study must generally be double blind.⁷⁶ That is, the medication must be coded so that neither the physician administering it nor the test subject knows which individuals receive the test drug or the placebo or standard therapy to which it is compared until the code is broken after collection of the data.⁷⁷ The protocols must specify methods for making and recording observations and methods for statistical analysis.⁷⁸ Firms must provide extensive documentation and submit raw data and analysis as well as the results.⁷⁹

These regulations greatly improved the quality of drug testing. It spurred the development of new research methods and a clinical research industry.⁸⁰

69. Investigational New Drug Application, 21 C.F.R. §§ 312.22, 312.23 (2012).

70. *Id.* § 312.23.

71. *Id.* § 312.21(a).

72. *Id.*

73. *Id.* § 312.21(c).

74. See 21 C.F.R. § 312.23(a). In some situations the control group could be patients that receive no treatment or historical data on the progress of an illness. *Id.* § 312.32(c)(1)(i)(C).

75. *Id.* § 312.23(a)(5)(iii).

76. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: E9 STATISTICAL PRINCIPLES FOR CLINICAL TRIALS 11 (1998).

77. *Id.*

78. 21 C.F.R. § 312.23(a)(6)(iii)(f).

79. See *id.* § 312.23(a)(8).

80. Margaret Hamburg, *50 Years after Thalidomide: Why Regulation Matters*, U.S. FOOD & DRUG ADMIN. VOICE (Feb. 7, 2012), <http://blogs.fda.gov/fdavoices/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters/>.

Market analysts estimated the CRO market to be \$24 billion in 2010 and growing by 15%.⁸¹ Nevertheless, since the 1970 regulations went into effect, there have been three sorts of problems: fraud, poor quality, and bias.⁸² Therefore, several contemporary researchers, physicians, and advocates contend that drug-firm control over clinical research compromises our knowledge and public safety.

III. CONTEMPORARY PROPOSALS FOR INDEPENDENT DRUG TESTING

In the last two decades, several authors have called for having an independent entity, rather than drug manufacturers, design and conduct clinical trials to test drugs. Dr. Marcia Angell argues that we should not permit drug firms to control tests of their products.⁸³ She proposes the creation of an Institute for Prescription Drug Trials within the National Institutes of Health (NIH) that would oversee the clinical trials.⁸⁴ NIH would contract with independent researchers at universities to carry out the research.⁸⁵ The data would belong to the institute and the researchers, and the results would be made public.⁸⁶ Researchers would be permitted to use the data for publications.⁸⁷ The FDA would rely on these studies to decide whether to authorize marketing of the drug.⁸⁸ Drug firms would be assessed a percentage of their gross revenues to fund the institute.⁸⁹

In a similar vein, doctors Wayne Ray, Marie Griffin, and Jerry Avorn proposed creating a governmental center to assess drug effectiveness and compare the costs and benefits of alternative drug therapies.⁹⁰ They argue

81. See MAYSOUN DIMACHKIE MASRI ET AL., CONTRACT RESEARCH ORGANIZATIONS: AN INDUSTRY ANALYSIS 5 (2012), available at <http://www.guidestarclinical.com/whitepapers/CONTRACT%20RESEARCH%20ORGANIZATIONS%20AN%20INDUSTRY%20ANALYSIS.pdf> (citing BIOPHARM RESEARCH PUBL'G, CONTRACT RESEARCH ANNUAL REVIEW 2011 (2011)). For analysis of the forces creating this industry, see generally Richard A. Rettig, *The Industrialization of Clinical Research*, HEALTH AFF., Mar. – Apr. 2000, at 129.

82. See Sidney Shapiro, *Divorcing Profit Motivation from New Drug Research: A Consideration of Proposals to Provide the FDA with Reliable Test Data*, 1978 DUKE L.J. 155, 181; see Sean R. Tunis et al., *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1624 (2003).

83. ANGELL, *supra* note 3, at 245.

84. *Id.*

85. *Id.*

86. *Id.* at 245, 247.

87. *Id.* at 245.

88. See ANGELL, *supra* note 3, at 246.

89. *Id.* at 245. Dr. Angell nicely summarizes problems with industry sponsored clinical trials in an article. See generally Angell, *supra* note 9. For a review of problems with industry funded trials, see generally Bodenheimer, *supra* note 11.

90. Wayne A. Ray et al., *Evaluating Drugs After Their Approval for Clinical Use*, 329 NEW ENG. J. MED. 2029, 2031 (1993).

that pharmaceutical-industry-sponsored studies do not answer key questions about risks and benefits necessary for clinicians to make therapeutic choices, particularly among alternative drug therapies.⁹¹ Nor do drug firms have incentives to study the cost effectiveness of alternative therapies.⁹² The center would fund and/or conduct studies of drugs already approved for sale and coordinate drug research performed by government agencies.⁹³ Dr. Ray and his colleagues propose to finance the center through a tax on drug sales and third-party payer subscription fees.⁹⁴

Dr. Drummond Rennie argues that the United States should create a National Institute of Clinical Trials, financed with federal funds and a budget separate from that of the NIH.⁹⁵ The institute would decide what trials to conduct and make grants to researchers to carry out the studies.⁹⁶ Researchers would receive all their funds through their institutions and not be allowed to receive other funds.⁹⁷ In a variation of this plan, doctors Lisa Bero and Rennie have proposed legislation to finance independent studies of the cost effectiveness and comparative effectiveness of drugs by having the FDA charge drug firms a user fee.⁹⁸

A group of scholars interested in public goods and intellectual property have also called for having publicly funded independent clinical trials.⁹⁹ They note that in addition to ensuring unbiased evaluation, public funding would reduce the cost of drug development now borne by individual firms.¹⁰⁰ If clinical trials to test drugs were publicly funded, they argue, it would be unnecessary to grant drug firms patents or exclusive marketing

91. *Id.* at 2029-30. The article notes that there were several proposals for Congress to create a national evaluative body for drugs. *Id.* at 2031. FDCA amendments proposed in 1974, 1978, and by the Joint Commission on Prescription Drug Use in 1980, and by Senator David Pryor's proposed Pharmaceutical Access and Prudent Purchasing Act of 1990. *Id.*

92. *Id.* at 2030.

93. *Id.* at 2031.

94. *Id.*

95. Rennie, *supra* note 9, at 1010.

96. *Id.*

97. *Id.*

98. Lisa A. Bero & Drummond Rennie, *Influences on the Quality of Published Drug Studies*, 12 INT'L J. TECH. ASSESSMENT HEALTH CARE 209, 229 (1996). Several other physicians have called for increasing funding for clinical trials to improve pharmaceutical policy and clinical care. See Tunis et al., *supra* note 82, at 1631. Dr. A. J. Wood proposed the creation of an independent drug safety board to evaluate drugs. See Alastair J.J. Wood et al., *Making Medicines Safer – The Need for an Independent Drug Safety Board*, 339 NEW ENG. J. MED. 1851, 1852 (1998).

99. E.g., Tracy R. Lewis et al., *The Case for Public Funding and Public Oversight of Clinical Trials*, ECONOMIST'S VOICE, Jan. 2007, at 1 [hereinafter Lewis et al., *The Case for Public Funding*], available at <http://www.duke.edu/~ab389/PubList/LewisReichmanPDF.pdf>.

100. *Id.* at 1-2.

periods to spur their investment, or at least we could shorten the duration of the monopoly.¹⁰¹ Drug prices would fall, which would increase access by individuals with low income, particularly in third-world countries, and improve health care globally.¹⁰²

These reform proposals are supported by scholarly literature and case studies that document publication bias, biased research design, and other problems in drug company-controlled trials. Dr. Joel Lexchin and his colleagues reviewed medical literature on drug-company-sponsored clinical trials and found that company-sponsored research was more likely to draw conclusions favorable to the sponsor than studies funded by other sources.¹⁰³ Of 16 studies that examine funding sources and outcomes of

101. See James Love & Tim Hubbard, *Prizes for Innovation of New Medicines and Vaccines*, 18 ANNALS HEALTH L. 155, 178 (2009); see Tracy R. Lewis et al., Univ. of Cal. Berkeley Law and Economics Workshop: Treating Clinical Trials as a Public Good: The Most Logical Reform 4 (Sept. 1, 2006) [hereinafter Lewis et al., *Treating Clinical Trials as a Public Good*], available at <http://escholarship.org/uc/item/3cn7258n>.

102. For discussion of public funding of clinical trials in particular, see Lewis et al., *The Case for Public Funding*, *supra* note 99; Lewis et al., *Treating Clinical Trials as a Public Good*, *supra* note 101; Love & Hubbard, *supra* note 101, at 159, 177-79. For one of the intellectual leaders in the public goods approach to intellectual property and drug development, see the work of James Love, Director of Knowledge Ecology International. James Love, Director, KNOWLEDGE ECOLOGY INT'L (Aug. 12, 2009), <http://keionline.org/jamie>. For some of his key articles, see James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519, 1528-34 (2007); Tim Hubbard & James Love, *A New Trade Framework for Global R&D*, 2 PLOS BIOLOGY 0147, 0150 (2004); Comment from James Love, Knowledge Ecology Int'l, to the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, World Health Organization, *The Role of Prizes in Stimulating R&D* (Sept. 30, 2007), available at http://www.who.int/phi/public_hearings/second/contributions_section2/Section2_JamesLove-KEI_prizes.pdf; JAMES LOVE, CONSUMER PROJECT ON TECH., EVIDENCE REGARDING RESEARCH AND DEVELOPMENT INVESTMENTS IN INNOVATIVE AND NON-INNOVATIVE MEDICINES (2003). See generally DEAN BAKER, CTR. FOR ECON. & POLICY RESEARCH, THE BENEFITS AND SAVINGS FROM PUBLICLY- FUNDED CLINICAL TRIALS OF PRESCRIPTION DRUGS (2008). See generally THOMAS POGGE, AUSTL. NAT'L UNIV., CRAWFORD SCH. OF PUB. POLICY, DEV. POLICY CTR., DISCUSSION PAPER #7, THE HEALTH IMPACT FUND: MORE JUSTICE AND EFFICIENCY IN GLOBAL HEALTH (2011). See generally Thomas Pogge, *The Health Impact Fund: Boosting Pharmaceutical Innovation Without Obstructing Free Access*, 18 CAMBRIDGE Q. HEALTHCARE ETHICS 78 (2009). In a similar vein, some authors have suggested that the data from clinical trials should be a public good, and that we should revise treaties and laws that confer drug companies data exclusivity from their trials for several years. See Jerome H. Reichman, *Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for a Public Goods Approach*, 13 MARQ. INTELL. PROP. L. REV. 1, 9 (2009).

103. Joel Lexchin et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167, 1167 (2003).

clinical trials and meta-analyses, 13 studies found that drug-company-funded studies favored the sponsor's product.¹⁰⁴

Studies may favor the sponsor's product due to publication bias.¹⁰⁵ Drug firms typically do not seek to publish studies unless it helps market their product.¹⁰⁶ As a result, published literature is a biased sample of the studies that have been conducted.¹⁰⁷ Indeed, sometimes drug firms even try to stop researchers from independently publishing articles on clinical trials that yield unfavorable results.¹⁰⁸ Pharmaceutical firm funding, furthermore, also skews what kinds of studies are conducted. Manufacturers, notes Dr. Wayne Ray, "would not benefit from studies to determine whether inexpensive off-patent drugs or non-pharmaceutical interventions could replace profitable, single-source products or from studies to determine the rates of adverse reactions to approved products."¹⁰⁹

A growing literature also documents various sources of bias in trial outcomes including the questions posed, the study design, its methodology, and the way it is conducted or reported.¹¹⁰ Even well-designed studies may slant results due to flaws in how they were conducted. Researchers might not follow the protocol, not report all the data, incorrectly report the data, or fabricate the data.¹¹¹

The choice of research subjects can also skew outcomes. Individuals should be randomly assigned among the test and control groups and neither clinician nor research subject should know in which group they are placed. However, researchers sometimes use flawed randomization methods

104. *Id.* at 1168.

105. P.C. Gøtzsche, *Multiple Publication of Reports of Drug Trials*, 36 *EUR. J. CLINICAL PHARMACOLOGY* 429, 431-32 (1989); Patricia Huston & David Moher, *Redundancy, Disaggregation, and the Integrity of Medical Research*, 347 *LANCET* 1024, 1025 (1996); Martin R. Tramèr et al., *Impact of Covert Duplicate Publication on Meta-Analysis: A Case Study*, 315 *BRIT. MED. J.* 635, 635 (1997).

106. See Bero & Rennie, *supra* note 98, at 209; see Huston & Moher, *supra* note 105, at 1025.

107. Tramèr et al., *supra* note 105, at 638.

108. Michael McCarthy, *Company Sought to Block Paper's Publication*, 356 *LANCET* 1659, 1659 (2000); David G. Nathan & David J. Weatherall, *Academic Freedom in Clinical Research*, 347 *NEW ENG. J. MED.* 1368, 1369 (2002); Drummond Rennie, Editorial, *Thyroid Storm*, 277 *JAMA* 1238, 1238 (1997) (describing Boots Pharmaceuticals' attempt to discredit and prevent the publication by claiming the study was flawed).

109. Ray et al., *supra* note 90, at 2030.

110. Bero & Rennie, *supra* note 98, at 211; P.C. Waller et al., *Review of Company Post-Marketing Surveillance Studies*, 304 *BRIT. MED. J.* 1470, 1471 (1992); Peter C. Gøtzsche, *Methodology and Overt and Hidden Bias in Reports of 196 Double-Blind Trials of Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis*, 10 *CONTROLLED CLINICAL TRIALS* 31, 31-32 (1989).

111. Bero & Rennie, *supra* note 98, at 219, 222.

so patients are not actually randomly assigned or either the clinician or research subject knows whether the individual receives the test drug or the alternative.¹¹² Also, sometimes drugs are tested on individuals who are not typical of patients who will use the drug; for example, they may be healthier than intended patients.¹¹³

Often drug studies measure a surrogate endpoint rather than the desired effect. Rather than testing the extent to which a drug reduces heart attacks, strokes, or mortality due to coronary artery disease, for example, the trial measures its effect on the research subject's cholesterol level.¹¹⁴ The presumption is that reducing blood cholesterol will decrease cardiac morbidity and mortality, but that might not actually be so.

Ideally, drug trials should evaluate the drug's effectiveness, toxicity and other risks, treatment costs, and its ease of use.¹¹⁵ In fact, they often do not study all these variables: they measure effectiveness or risk, not both.¹¹⁶ Frequently they do not measure how the drug's effect varies as the dose changes, so we do not know the trade-offs between positive benefits and toxicity as the drug dose increases.¹¹⁷ Furthermore, many trials compare a drug to a placebo rather than to the standard drug therapy or other treatments and therefore do not help clinicians decide whether to use one drug rather than another, or a non-drug therapy.¹¹⁸ And comparative studies are often flawed because they do not evaluate differences in effect as the drug dose changes. Studies that compare two drugs with a fixed dose are often biased because the choice of dose favors one drug over the other, but the drug's apparent superiority ends when the dose is changed.¹¹⁹

IV. THE STALLED REFORM: PROPOSALS FOR INDEPENDENT DRUG TESTING 1960-1980

The question of how to test drugs and who should do the testing surfaced before Congress enacted the 1962 FDCA Amendments that empowered the FDA to oversee drug testing used by the firms to support their application to market new drugs.¹²⁰ Moreover, debates over how to test drugs to ensure they are safe and effective persisted even after Congress

112. *Id.* at 216, 218.

113. *Id.* at 213.

114. *See id.* at 219.

115. *See* Tunis et al., *supra* note 82, at 1626-27.

116. Bero & Rennie, *supra* note 98, at 218.

117. *See id.*

118. Tunis et al., *supra* note 82, at 1629.

119. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: E 10 CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS 7-8 (2001).

120. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781 (codified as amended in scattered sections of 21 U.S.C. (2006)).

enacted the 1962 FDCA Amendments. A review of United States Senate hearings and other documents reveals a persistent debate between 1959 and 1980 in Congress, the FDA, and among industry and consumer representatives over what a drug-testing regime should look like. In hearings chaired by Senators Estes Kefauver (D-TN), Hubert Humphrey (D-WI), Gaylord Nelson (D-WI) and Ted Kennedy (D-MA), witnesses proposed and debated the merits of alternative approaches.¹²¹

One problem noted with having drug firms test drugs was that the economic incentives of drug firms compromised their impartiality, biased the design of clinical trials, and sometimes led to fraud.¹²² A second problem noted was that testing laboratories and physician investigators performed shoddy work because of their lack of training and their desire to boost income by cutting corners.¹²³ In order to resolve these problems, many observers suggested that Congress should enact legislation to prevent drug

121. *Administered Prices in the Drug Industry (Antibiotics)*, Part 24: Hearings Before the Subcomm. On Antitrust and Monopoly of the S. Comm. on the Judiciary, 86th Cong. (1960) [hereinafter *Administered Prices Hearing, Part 24*]; *Preclinical and Clinical Testing by the Pharmaceutical Industry*, 1975, Part 1: Joint Hearings before the Subcomm. on Health of the S. Comm. On Labor and Public Welfare and the Subcomm. on Administrative Practice and Procedure of the S. Comm. on the Judiciary, 94th Cong. (1975) [hereinafter *Preclinical and Clinical Testing Hearings, Part 1*]; *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study*, Part 3: Hearings Before the Subcomm. on Reorganization and Int'l Org. of the S. Comm. on Government Operations, 88th Cong. (1963) [hereinafter *Drug Research and Regulation Hearings, Part 3*]; *Competitive Problems in the Drug Industry*, Parts 1-34: Hearings Before the Subcomm. on Monopoly of the S. Select Comm. on Small Bus., 90-96th Cong. (1967-79) [hereinafter *Competitive Problems in the Drug Industry Hearings, Parts 1-34*].

122. The FDA had noted problems with fraud, bias, and poor study design even before 1961. See *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study*, Part 1: Hearings Before the Subcomm. On Reorganization and Int'l Org. of the S. Comm. on Government Operations, 87th Cong. 32 (1962) [hereinafter *Drug Research and Regulation Hearings, Part 1*] (statement of William S. Middleton, Chief Medical Director, Veterans' Administration). See *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study*, Part 2: Hearings Before the Subcomm. on Reorganization and Int'l Org. of the S. Comm. on Government Operations, 87th Cong. 373, 375 (1962) [hereinafter *Drug Research and Regulation Hearings, Part 2*] (statement of Mr. William Weiss, Bureau of Program Planning and Appraisal, Food and Drug Administration).

123. These problems were analyzed by several people. See MORTON MINTZ, *THE THERAPEUTIC NIGHTMARE: A REPORT ON THE ROLES OF THE UNITED STATES FOOD AND DRUG ADMINISTRATION, THE AMERICAN MEDICAL ASSOCIATION, PHARMACEUTICAL MANUFACTURERS, AND OTHERS IN CONNECTION WITH THE IRRATIONAL AND MASSIVE USE OF PRESCRIPTION DRUGS THAT MAY BE WORTHLESS, INJURIOUS, OR EVEN LETHAL* (1965), reprinted in MORTON MINTZ, *BY PRESCRIPTION ONLY* 331-34 (1967); see JOHN BRAITHWAITE, *CORPORATE CRIME IN THE PHARMACEUTICAL INDUSTRY* 105 (1984); see MILTON SILVERMAN & PHILIP R. LEE, *PILLS, PROFITS, AND POLITICS* 137 (1974).

firms from controlling the evaluation of drugs.¹²⁴ They argued that in order to ensure the integrity and quality of testing, the federal government should either perform the testing itself, or contract with independent parties to design and carry out the clinical trials.¹²⁵

By 1960, the FDA found that many applications for drug approval were based on poorly designed and implemented studies.¹²⁶ FDA investigations and congressional hearings revealed fraud by testing laboratories, physician investigators, and drug firms, as well as quality problems that compromised the reliability of results.¹²⁷ Between 1960 and 1980, the FDA developed regulations to address these problems.¹²⁸ The standards for drug testing became more rigorous and FDA oversight increased, but congressional hearings revealed that many problems still persisted.¹²⁹

A. 1960-1961: *The Kefauver Hearings and Other Proposals for Independent Testing*

Senator Estes Kefauver held hearings on the pharmaceutical industry from 1959 to 1961. The hearing initially focused on market competition, but after the Thalidomide disaster they focused on drug safety issues, including drug testing.¹³⁰ At those hearings Dr. Maxwell Finland, who was associate director of the Thorndike Memorial Laboratory, associate professor of medicine at Harvard Medical School, and a physician at the Boston City Hospital, testified in support of creating a system of independent drug testing.¹³¹ The federal government, he noted, had generously funded basic scientific and medical research but had neglected applied research,

124. See *Administered Prices Hearing, Part 24*, *supra* note 121, at 13,933 (statement of Maxwell Finland, Associate Professor of Medicine, Harvard Medical School).

125. *Id.* at 13,932-33; BRAITHWAITE, *supra* note 123, at 104.

126. See *Drug Research and Regulation Hearings, Part 3*, *supra* note 121, at 782.

127. *Id.* at 792; See *Drug Research and Regulation Hearings, Part 2*, *supra* note 122, at 375.

128. *Significant Dates in U.S. Food and Drug Law History*, U.S. FOOD & DRUG ADMIN. (Nov. 6, 2012), <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm>.

129. *Preclinical and Clinical Testing Hearings, Part 1*, *supra* note 121, at 8-9.

130. *Administered Prices Hearing, Part 24*, *supra* note 121, at 13,609, 13,943, 14,017, 14,041. The hearings and recommendations were summarized in ADMINISTERED PRICES: DRUGS, S. REP. NO. 87-448 (1961). For an engaging popular account of the hearings on the pharmaceutical industry chaired by Senator Estes Kefauver, see RICHARD HARRIS, *THE REAL VOICE* (1964).

131. *Administered Prices Hearing, Part 24*, *supra* note 121, at 13,923. Dr. Finland discusses this proposal and other issues in an article that appeared while Senators Gaylord Nelson and Ted Kennedy were investigating the pharmaceutical industry. See Maxwell Finland, Editorial, *Clinical Investigation of New Antimicrobial Agents*, 120 J. INFECTIOUS DISEASES 620, 629 (1969).

particularly the clinical evaluation of new drugs.¹³² Dr. Finland recounted his previous efforts

to interest the National Research Council and also the drug industry to set up subcommittees or panels in different medical areas for the independent evaluation of drugs, supported from funds provided either by the pharmaceutical industry as a whole, or by governmental or other nonprofit agencies but not tied to individual products or firms.¹³³

Now Dr. Finland suggested an alternative: having the NIH set up study sections to evaluate drugs.¹³⁴ With independent testing he argued, “the endorsement of inferior products that are not in the best interest of the public, is much less likely to occur than when the support for testing the product is furnished by the individual producer.”¹³⁵ Dr. Finland noted that it would require legislation or regulation “in order to get the products tested in this unbiased manner before approval, licensing or certification.”¹³⁶ In response, Senator Kefauver said that his legislation included “a suggestion that the efficacy of drugs should also be tested by the Food and Drug Administration.”¹³⁷ Dr. Finland replied that it would be preferable for the evaluation to be carried out by an independent entity rather than FDA scientists, who would later have to evaluate the results of the research.¹³⁸

Dr. Finland also specified problems arising from financial dependency of university researchers on grants from drug firms. He said, “. . . departments of clinical pharmacology — should not depend on their continuing work . . . on funds that come from individual drugs, because it is obvious that some people cannot perhaps divorce their judgment from the sources of their support.”¹³⁹

In 1960, Alek Rozental, an economics professor at Saint Louis University, published his article, *The Strange Ethics of the Ethical Pharmaceutical Industry*, in *Harper's Magazine*.¹⁴⁰ Rozental explained that to ensure drug safety, the United States should follow the 1959 proposal of the Hinchliffe Committee, a blue ribbon advisory committee in the United Kingdom that studied drug safety and cost.¹⁴¹ The Hinchliffe proposal recommended that “all new drugs. . . be subject to independent clinical

132. *Administered Prices Hearing, Part 24, supra note 121, at 13,932.*

133. *Id.* See generally Finland, *supra* note 131.

134. *Administered Prices Hearing, Part 24, supra note 121, at 13,933.*

135. *Id.*

136. *Id.*

137. *Id.* at 13,934.

138. *Id.*

139. *Administered Prices Hearing, Part 24, supra note 121, at 13,934.*

140. Alek A. Rozental, *The Strange Ethics of the Ethical Drug Industry*, *HARPER'S MAG.*, May 1960, at 73.

141. *Id.* at 82, 84.

trials preferably conducted by a central organization, to be financed by the industry.¹⁴² Rozental contended that new drugs should be tested to determine if they are safe and effective, and to compare their performance and price to existing alternative drugs.¹⁴³ He acknowledged that political constraints might preclude the United States from adopting a centralized testing agency, but suggested that there would be less opposition to something similar: the creation of an independent profession of clinical testers akin to certified public accountants serving as independent auditors.¹⁴⁴

B. 1962-1963: *The Humphrey Hearings*

Senator Hubert Humphrey chaired hearings before the Subcommittee on Reorganization and International Organizations from August 1962 through 1964.¹⁴⁵ His hearings began after the Kefauver hearings (1959-1961), but before Congress passed the 1962 FDA amendments.¹⁴⁶ The committee examined three important questions: (1) What role should the federal government play in testing drugs or setting standards for drug testing? (2) Which organizations should conduct clinical tests? (3) What qualifications should individuals have to conduct clinical trials?¹⁴⁷

When the Humphrey hearings began, the FDA had not yet developed regulations specifying how drugs should be tested, or what evidence would be necessary to demonstrate safety and efficacy under the 1962 FDA amendments.¹⁴⁸ The 1938 Food and Drug Act included guidelines for designing and conducting tests on humans. It provided that manufacturers had to select reliable investigators with appropriate experience to test drugs, in particular, "experts qualified by scientific training."¹⁴⁹ But the FDA

142. *Id.* at 84.

143. *Id.*

144. *Id.*

145. *Drug Research and Regulation Hearings, Part 1*, *supra* note 122; *Drug Research and Regulation Hearings, Part 2*, *supra* note 122; *Drug Research and Regulation Hearings, Part 3*, *supra* note 121; *Drug Research and Regulation Hearings, Part 4*, *supra* note 26; *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study, Part 5: Hearings Before the Subcomm. On Reorganization and Int'l Org. of the S. Comm. on Government Operations*, 88th Cong. (1963) [hereinafter *Drug Research and Regulation Hearings, Part 5*].

146. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

147. *Drug Research and Regulation Hearings, Part 1*, *supra* note 122, at 2, 58.

148. The FDA promulgated regulations setting standards for conducting clinical trials in 1970. *Hearing Requests on Refusal or Withdrawal of New Drug Applications and Issuance, Amendment or Repeal of Antibiotic Drug Regulations and Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations*, 35 Fed. Reg. 3073, 3073-74 (Feb. 17, 1970) (codified at 21 C.F.R. § 146 (1970)).

149. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1053 (1938).

declined to specify criteria that qualified individuals as experts, explaining that it was not authorized to control the practice of medicine.¹⁵⁰

Prior to the 1970 regulations that implemented the 1962 amendments, there was little distinction between physicians and investigators. Drug firms would frequently give investigational drugs to a number of practitioners to test on their patients.¹⁵¹ Pharmaceutical firms would draw on the reports or testimonials of these physician investigators as evidence of safety when submitting NDAs.¹⁵² The FDA recommended that drugs be tested by specialists in the diseases for which that drug would be used.¹⁵³ It recommended that firms employ several investigators, each working independently in different locations, to ensure a more balanced assessment of the drugs' effects.¹⁵⁴

However, drug testing was not always clearly separated from marketing. In 1960, Dr. Mendel C. Sheps from the University of Pittsburgh School of Medicine wrote, "although some . . . studies are of high quality, the scientific requirements for careful investigation . . . compete with high-pressure marketing demands."¹⁵⁵ In fact, he continued, "the responsibility for arranging with physicians to make the first trials on human beings is at times given to detail men."¹⁵⁶

At the 1963 hearings, Senator Karl Mundt (R-SD) asked FDA Commissioner George P. Larrick to clarify who determined whether investigators were experts.¹⁵⁷ He asked, "Expertise is determined by the firm trying to sell the goods, rather than by the organization trying to protect the public health; is that right?"¹⁵⁸ Larrick explained that although the FDA lacked a legal standard for expertise in testing drugs, it took investigators' backgrounds into account when assessing NDAs.¹⁵⁹ It checked "whether or not this man who did the work [has] . . . scientific experience, education and whatnot . . . [that are] qualifications to do that job."¹⁶⁰ Draft regulations, Larrick noted, allowed the FDA to require companies to submit information

150. New York Academy of Medicine, Committee on Public Health, *The Importance of Clinical Testing in Determining the Efficacy and Safety of Drugs*, 38 BULL. N.Y. ACAD. MED. 415, 420 (1962).

151. See *id.*

152. See *id.* at 419.

153. *Id.* at 420.

154. *Id.*

155. *Drug Research and Regulation Hearings, Part 4*, *supra* note 26, at 1589-90.

156. *Id.* at 1590.

157. *Drug Research and Regulation Hearings, Part 1*, *supra* note 122, at 40.

158. *Id.*

159. *Id.* at 200.

160. *Id.* at 195-96.

on the professional qualifications of proposed investigators, along with their plans for testing.¹⁶¹

The hearing record included a 1962 report on the clinical testing of drugs by the New York Academy of Medicine, which found that many tests were substandard due to the shortcomings of the investigators who lacked training or experience in designing studies, or recording and reporting results.¹⁶² The New York Academy recommended that investigators should have training in clinical research, that pharmaceutical firms' medical directors should have experience in clinical testing, and that investigations should take place in hospitals.¹⁶³ The report also noted that the FDA had refrained from issuing standards for clinical investigators because it did not want to interfere with the practice of medicine and that no other official or professional body had undertaken this task.¹⁶⁴

Regarding the respective roles of the federal government and the pharmaceutical industry, Dr. Burroughs Mider, Director of Laboratories and Clinics at the NIH, explained to Senator Karl Mundt that his understanding was that drug manufacturers bore primary responsibility for the research that supported drug development and licensing.¹⁶⁵ Senator Mundt responded that this arrangement, ". . . is not quite adequate to serve the public interest."¹⁶⁶

At the time, the FDA could not conduct any of its own clinical tests.¹⁶⁷ Paul L. Day, then the Scientific Director of FDA's scientific program, reported that the FDA needed to engage in more basic research, noting that without it, the agency's emphasis on dealing with short-term regulatory problems would leave it ill-prepared for future developments.¹⁶⁸ Mr. Day said, "We are so busy putting out fires that we don't have time to do any fire prevention."¹⁶⁹ The lack of a substantial FDA scientific program not only

161. *Id.* at 197-98.

162. *Drug Research and Regulation Hearings, Part 2, supra* note 122, at 528-41.

163. *Id.* at 531, 539-40.

164. *Id.* at 531. Note that professional organizations did ultimately consider establishing their own guidelines. The American Society for Pharmacology and Experimental Therapeutics, for example, considered the question of whether qualifying boards should be established in clinical pharmacology. *Drug Research and Regulation Hearings, Part 4, supra* note 26, at 1607. However, concluding that a certification system for scientists' conduction research had "no acceptable precedent," it decided against it. *Id.*

165. *Drug Research and Regulation Hearings, Part 1, supra* note 122, at 215.

166. *Id.*

167. *Id.* at 175 (article by Ralph G. Smith, Director, Division of New Drugs, Food and Drug Administration).

168. *Drug Research and Regulation Hearings, Part 2, supra* note 122, at 325-26.

169. *Id.* at 325; see also *id.* at 342 (report based on a 1960 survey of employee attitudes at FDA concluded that the agency should be "strongly supported in its effort to maintain a

corroded employee morale and retention, but also weakened the FDA, which needed qualified scientists to review NDAs, which were often flawed due to poor study design, bias, and sometimes even fraud.¹⁷⁰

The 1962 hearings examined the federal government's intramural clinical research programs. William Middleton, Chief Medical Director of the Veterans' Administration (VA) Department of Medicine and Surgery, informed the Committee that the VA had been conducting limited clinical trials in its facilities since 1947, beginning with tuberculosis drugs.¹⁷¹ In all, the VA had conducted 29 "cooperative studies" (clinical investigations).¹⁷² Dr. Burroughs Mider reported on the intramural testing capacity of the NIH, including facilities for the study of approximately 420 patients, most of whom suffered from diseases with no known cures.¹⁷³

The New York Academy of Medicine report outlined but rejected two reform proposals that would have shifted responsibility from drug firms to the federal government. The first proposal was to establish a "national central office on testing . . . [that would] arrange to conduct and supervise the testing of all products."¹⁷⁴ The report argued that a national center would be overly bureaucratic, and would be unacceptable to pharmaceutical manufacturers and clinicians.¹⁷⁵ The second proposal, modeled on the AMA Committee on Therapeutic Trials, would establish a national referral agency for clinical investigators.¹⁷⁶ The report found that the idea had merit, but ultimately did not support it due to the failure of the AMA's earlier plan.¹⁷⁷

In 1963, Consumers Union, which had built its reputation as an independent tester of consumer products, and had long advocated for the enactment of food and drug safety legislation, evaluated the 1962 FDA amendments in its journal, *Consumer Reports*.¹⁷⁸ "At the core of the problem" of drug safety, it said, "lies that most fundamental question:

research program of high quality on methodology and standardization of drug testing and related areas of science.").

170. *Id.* at 375 (statement of Shelby T. Grey, Director, Bureau of Program Planning and Appraisal, Food and Drug Administration).

171. *Drug Research and Regulation Hearings, Part 1*, *supra* note 122, at 32-33.

172. *Id.* at 33.

173. *Id.* at 213-14.

174. *Drug Research and Regulation Hearings, Part 2*, *supra* note 122, at 538.

175. *Id.*

176. *Id.*

177. *Id.*

178. *Drug Safety: The Basic Question is Whether Control of Clinical Testing Should Be Left to Manufacturers. At a Time of Worldwide Concern over Dangerous Drugs, a "Citizen's Committee" Proposes Surrender of Public Responsibility*, CONSUMER REP., Mar. 1963, at 134 [hereinafter CONSUMER REPORTS].

namely, is it good public policy to permit the drug manufacturers to do or to supervise the clinical testing of their own products?"¹⁷⁹

The article acknowledged that the 1962 amendments authorized the FDA to oversee drug testing, but noted, "the drug maker remains responsible for drug testing."¹⁸⁰ It argued that since the FDA was handling test reports that have been "procured by the manufacturers," the arrangement was an inadequate substitute for "an objective testing agency."¹⁸¹ The article supported Senator Hubert Humphrey's call for having the World Health Organization (WHO) oversee a network of drug evaluation centers.¹⁸² In Senate testimony, Consumers Union called for the creation of an independent government agency to test drugs that would produce all of the data that the FDA would use in deciding whether to approve marketing for drugs.¹⁸³ It envisioned this agency as a public-private partnership.¹⁸⁴ There would be no parallel testing by drug firms.¹⁸⁵

Dr. Charles May, professor of pediatrics at New York University School of Medicine, called for increasing the amount of clinical testing conducted by publicly funded researchers in universities and at the FDA. He proposed the creation of publicly funded, autonomous drug testing centers located at medical-school-affiliated hospitals.¹⁸⁶ The facilities and core staff would be publicly funded.¹⁸⁷ The FDA or other agencies would provide grants for individual research projects.¹⁸⁸ Investigators would choose research projects based on scientific merit.¹⁸⁹

In correspondence with the Congressional Committee, several other physicians suggested that there should be a separation between firms sponsoring an application to approve a new drug and researchers testing

179. CONSUMER REPORTS, *supra* note 178, at 136.

180. *Id.*

181. *Drug Research and Regulation Hearings, Part 3*, *supra* note 121, at 1051-52.

182. *Id.* at 1052.

183. *Id.*

184. *Id.*

185. *See id.*

186. Dr. May summarized his ideas in a March 1963 memorandum and subsequent hearing testimony. *Drug Research and Regulation Hearings, Part 3*, *supra* note 121, at 1042-46, 1053-54.

187. *Id.* at 1054.

188. *See id.* Note how this differs from the current system for NIH research grants. Rather than directly subsidizing facilities and staff at dedicated facilities, NIH grants support these costs through an indirect cost ratio built into grant awards. *See Circular A-21, Cost Principles for Educational Institutions*, THE WHITE HOUSE OFFICE OF MGMT. & BUDGET (May 10, 2004), http://www.whitehouse.gov/omb/circulars_a021_2004.

189. *Drug Research and Regulation Hearings, Part 3*, *supra* note 121, at 1054.

the drug.¹⁹⁰ One idea was to have the industry pool research funds. In September 1962, Dr. Keith J.B. Wightman of the University of Toronto proposed that pharmaceutical manufacturers create and collectively fund a foundation that would help design studies, identify investigators and facilities, and publish the results.¹⁹¹ In April 1964, the president of the American Society for Clinical Investigation supported a proposal to replace the practice of having individual drug firms directly pay investigators.¹⁹² The proposal suggested instead that a board of impartial scientists, and public and industry representatives, should disburse payments to drug testers from a common fund supported by pharmaceutical firms.¹⁹³

More frequently, physicians suggested placing even greater distance between drug manufacturers and those who conducted clinical trials. In December 1963, Dr. George Baehr, Chair of the New York State Public Health Council, proposed conducting drug testing only in FDA-approved trial centers located in teaching hospitals.¹⁹⁴ Dr. M.F. Murnaghan of the University of Ottawa explained that when the FDA was unsatisfied with manufacturer testing, it “either will have to set up facilities to check such testing or have the tests repeated by a neutral body at the expense of the manufacturer.”¹⁹⁵ In January 1964, Dr. M. Harold Book of Kings Park State Hospital wrote, “the preliminary testing on human patients . . . should be assigned to some independent noncommercial agency and not to any individuals or groups who are dependent in any way for financial support on pharmaceutical houses”¹⁹⁶ He suggested several options. “It might be a . . . branch of the Food and Drug Administration . . . a panel of experts chosen from universities and research institutions . . . the United Nations or possibly a new agency”¹⁹⁷ In March 1964, Drs. I.H. Page and Ray W. Gifford, Jr. of the Cleveland Clinic concurred, stating, “We have repeatedly suggested that an independent agency be created to receive and administer funds to pay the cost of drug testing. . . .”¹⁹⁸

During this period, there were increasing reports of fraud in pharmaceutical firm — sponsored testing. In 1962, reports of harmful side effects from the use of MER/29 (triparanol), a drug marketed to reduce

190. *Drug Research and Regulation Hearings, Part 4*, *supra* note 26, at 1617-41 (Exhibit 205, Clinical Testing: Letters to Subcomm. on Safety & Efficacy).

191. *Id.* at 1600.

192. *Drug Research and Regulation Hearings, Part 5*, *supra* note 145, at 2419-20 (statement of Irving M. London, President, American Society for Clinical Investigation).

193. *Id.*

194. *Drug Research and Regulation Hearings, Part 4*, *supra* note 26, at 1641.

195. *Drug Research and Regulation Hearings, Part 5*, *supra* note 145, at 2284.

196. *Id.* at 2285.

197. *Id.*

198. *Id.* at 2296.

blood cholesterol, led the manufacturer, William S. Merrell, a subsidiary of Richardson-Merrell, to stop selling the drug.¹⁹⁹ Subsequent investigations found widespread fraud in the reporting of their toxicological studies.²⁰⁰ Merrell's director of biological sciences not only substituted healthy animals for ones that had been tested with the drug and became sick, but also falsified data on the dosages of the drug that animals had received, and their responses.²⁰¹

An FDA investigation revealed that Dr. Kathleen E. Roberts had fabricated at least 57 charts, which purported to indicate how patients responded to the drug Regimen, prescribed to help reduce weight.²⁰² Another investigation in 1964 revealed that Dr. Bennett A. Robin submitted fraudulent clinical data.²⁰³ Robin was considered a reputable researcher and had been involved in the testing of 45 different drugs.²⁰⁴

There were also reports of bias arising from drug company sponsorships of drug trials. The trade press reported on "rigging" of research.²⁰⁵ A 1963 editorial in the *New England Journal of Medicine* criticized firms that set unethical publication conditions, specifically, permitting publication only if the research produced positive results.²⁰⁶

In the 1964 hearing record, Senator Hubert H. Humphrey included the views of professionals about how drug firms' payments to clinical investigators might affect the investigators' objectivity. Dr. Edward Adelson, of the George Washington University School of Medicine, wrote

a drug manufacturer who is anxious to obtain data to support the value of one of his drugs will be tempted to choose investigators who are more likely to give him the data he wants. Therefore, an investigator who depends on drug funds for his income knows that if he hopes to get further grants it would be better to obtain results proving the drug he is testing is a good one.²⁰⁷

Dr. George E. Schreiner, of Georgetown University Hospital and head of the American Federation for Clinical Research, indicated, "that when there is

199. BRAITHWAITE, *supra* note 123, at 60.

200. *Id.* at 61-64.

201. *Id.* at 61-62.

202. *Id.* at 57.

203. *Id.* at 58.

204. BRAITHWAITE, *supra* note 123, at 58.

205. *Drug Research and Regulation Hearings, Part 3*, *supra* note 121, at 975-76 (Exhibit 137, Excerpt From Drug Trade News).

206. *Id.* at 1018 (Exhibit 143, Editorial from the *New England Journal of Medicine*, March 21, 1963).

207. *Drug Research and Regulation Hearings, Part 4*, *supra* note 26, at 1647.

direct payment from drug firms, there may be too much temptation to turn in a favorable report”²⁰⁸

In a memo to his committee colleagues at the conclusion of the 1964 hearings, Senator Humphrey framed key questions that the Congress faced:

Should the auspices for present testing be changed or, more likely, supplemented? Should, as some sources contend, the pharmaceutical industry be asked by the profession to contribute to a “central pool” of funds to be administered by the profession and from which private laboratories and clinics, entirely independent of industry, could perform preclinical and clinical tests? Should the Food and Drug Administration be given the funds for a comprehensive supplementary testing program? . . . Among the relatively few expert observers who have submitted proposals is . . . Dr. [Harry] Dowling. In 1961, he wrote: “as an aid to the clinical testing of drugs, the [FDA] should have funds at its disposal to finance the testing of a drug by an independent agency (which would usually be a medical school or hospital) in cases in which the Administration was not satisfied with the evidence submitted by the manufacturer of the drug.”²⁰⁹

The implementations of the 1962 FDA amendments did not put an end to poor quality clinical trials or fraud. Speaking before the Pharmaceutical Manufacturers Association in 1966, FDA Commissioner James L. Goddard said

I have been shocked at the materials that come in. In addition to the problem of quality, there is the problem of dishonesty in the investigational new drug stage[,] [including] . . . the conscious withholding of unfavorable animal clinical data[,] [and] . . . [t]he deliberate choice of clinical investigators known to be more concerned about industry friendships than in developing good data . . .²¹⁰

A 1966 FDA investigation found that Dr. Leo J. Cass, a physician employed by the Harvard Law School Health Service, who had helped evaluate over 84 investigational drugs, had reported data on patients who had never been treated with the drug.²¹¹ These kind of problems continued throughout the late 1960s.

208. *Drug Research and Regulation Hearings, Part 5*, *supra* note 145, at 2406 (Exhibit 273, Article by Joseph R. Hixson, Herald Tribune).

209. *Drug Research and Regulation Hearings, Part 4*, *supra* note 26, at 1688 (Exhibit 210).

210. BRAITHWAITE, *supra* note 123, at 51; *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2: Joint Hearings Before the Subcomm. on Health of the S. Comm. On Labor and Public Welfare and the Subcomm. on Administrative Practice and Procedure of the S. Comm. on the Judiciary, 94th Cong. 157 (1976)* [hereinafter *Preclinical and Clinical Testing Hearings, Part 2*] (statement of Sen. Gaylord Nelson, Subcomm. on Health of the S. Comm. on Labor and Public Welfare).

211. BRAITHWAITE, *supra* note 123, at 58-59.

During this period, FDA officials met with industry officials and specialists on research methodology and drug trials to develop more rigorous drug testing procedures.²¹² These efforts culminated in the FDA sponsoring a conference on drug testing after which the FDA promulgated regulations on the evidence that the FDA would require to demonstrate drug safety and efficacy.²¹³

C. 1967-1979: *The Nelson Proposal and Hearings*

Senator Gaylord Nelson chaired congressional hearings on Competitive Problems in the Pharmaceutical Industry from 1967 to 1979.²¹⁴ The committee investigated clinical trials and other matters.²¹⁵ It heard testimony from individuals proposing reforms that spanned a continuum from modest changes in current arrangements, to shifting the responsibility for testing drugs' safety and efficacy from drug firms to the federal government.²¹⁶ Other witnesses made proposals between these two poles. These included proposals to have an independent agency contract with independent third parties to perform the research.²¹⁷

During the 1968-69 hearings, several physicians advocated on behalf of requiring independent drug testing. Dr. Paul Lowinger, Associate Professor of Psychiatry at Wayne State University School of Medicine and Chief of Outpatient Services at the Lafayette Clinic in Detroit, Michigan, proposed the creation of a federal agency, separate from the FDA, funded

212. *Competitive Problems in the Drug Industry: Present Status of Competition in the Pharmaceutical Industry, Part 22: Hearings Before the Subcomm. on Monopoly of the S. Select Comm. on Small Bus.*, 92nd Cong. 8527 (1972) [hereinafter *Competitive Problems in the Drug Industry Hearings, Part 22*] (statement of Charles C. Edwards, Comm'r, Food and Drug Administration).

213. See *id.* Hearing Requests on Refusal or Withdrawal of New Drug Applications and Issuance, Amendment or Repeal of Antibiotic Drug Regulations and Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations, 35 Fed. Reg. 3073, 3073-74 (Feb. 17, 1970) (codified at 21 C.F.R. § 146 (1970)).

214. See generally *Competitive Problems in the Drug Industry Hearings, Parts 1-34*, *supra* note 121. These hearings, held from 1967 to 1979, are nicely summarized by two reports of the Congressional Research Services. CONG. RESEARCH SERV., COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY: DRUG TESTING, SUMMARY AND ANALYSIS (1979) [hereinafter CONG. RESEARCH SERV., 1979 SUMMARY] (providing "a summary analysis and discussion of the issues highlighted during the 1968 and 1969 hearings on drug testing with a review of more recent findings and government actions relating to FDA testing requirements"); CONG. RESEARCH SERV., COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY: DRUG TESTING, SUMMARY AND ANALYSIS (1972).

215. See generally *Competitive Problems in the Drug Industry Hearings, Parts 1-34*, *supra* note 121 (discussing issues related to clinical trials and other issues in the pharmaceutical industry).

216. See generally *id.* (testimony from various individuals in the industry proposing drug testing reform).

217. See *id.*

by the federal government and/or the pharmaceutical industry, to supervise drug research.²¹⁸ The agency would test drugs, finance independent organizations to test drugs, or oversee drug trials.²¹⁹ Investigators would report their findings to the agency, instead of the drug sponsor.²²⁰ Dr. Dale Console, former medical director of E. R. Squibb & Co., supported the idea of creating a central testing agency that would select investigators to conduct drug trials, without the drug sponsors knowing their identity.²²¹ He suggested that the agency be supported by the federal government, and that fees be paid by drug firms.²²²

In contrast, Dr. Franz Ingelfinger, editor of the *New England Journal of Medicine*, testified that independent testing, overseen by a government agency, would reduce the risk of bias, but might not be worth the cost.²²³ He thought it was probably sufficient to require drug firms to contract with universities to perform clinical trials.²²⁴ Universities, he said, could assume responsibility for the trustworthiness of the clinical research.²²⁵ He argued that if drug firms paid universities, rather than directly paying clinical researchers, improper financial influence upon investigators would be eliminated.²²⁶ If Congress chose to have an independent organization oversee these drug trials used to support applications to market drugs, Dr. Ingelfinger suggested that the medical profession, the pharmaceutical industry, and the federal government should jointly manage the organization.²²⁷

Dr. Donald Mainland, who coordinated research for the American Rheumatism Association's Cooperating Clinics Committee, testified that it was current practice for the drug firm seeking marketing approval to act as

218. *Competitive Problems in the Drug Industry: Present Status of Competition in the Pharmaceutical Industry, Part 10: Hearings Before the Subcomm. on Monopoly of the S. Select Comm. on Small Bus., 90th-91st Cong. 3997, 4001 (1969)* [hereinafter *Competitive Problems in the Drug Industry Hearings, Part 10*].

219. *Id.* at 4001-02.

220. *Id.* at 4002; CONG. RESEARCH SERV., 1979 SUMMARY, *supra* note 214, at 68-69.

221. *Competitive Problems in the Drug Industry: Present Status of Competition in the Pharmaceutical Industry, Part 11: Hearings Before the Subcomm. on Monopoly of the S. Select Comm. on Small Bus., 91st Cong. 4481 (1969)* [hereinafter *Competitive Problems in the Drug Industry Hearings, Part 11*].

222. *Id.*

223. *Competitive Problems in the Drug Industry Hearings, Part 10, supra* note 218, at 4017, 4024-25.

224. *Id.* at 4025.

225. *Id.*

226. *Id.* at 4019.

227. *Id.* at 4024.

an intermediary between the FDA staff and third-party testers.²²⁸ This arrangement allowed drug firms to influence the trials as well as the communication between testers and the FDA. Dr. Mainland suggested that Congress, “take the evaluation of drugs entirely out of the producer’s hands,” after the completion of toxicological testing on animals, in order to remove the possibility of the producer biasing the process.²²⁹ Dr. Mainland proposed the creation of an independent, not-for-profit drug-testing agency that would provide grants for research in a manner roughly analogous to the NIH.²³⁰ He suggested that a council of experts from universities and research institutions should invite senior investigators to form “working parties” for individual drugs.²³¹ These “working parties” would then choose teams of suitable investigators to conduct the safety and efficacy studies.²³² The agency should be funded largely by the pharmaceutical industry in a manner that did not allow it to “influence the disposal of the money or interfere in any way with the trials or the results.”²³³

Dr. Paul Lowinger, of Wayne State University School of Medicine, proposed that Congress should create a National Institute of Pharmacology, “to supervis[e] and approv[e] research protocols for [drug] investigations . . .” and require drug firms to shoulder the financial responsibility for clinical trials.²³⁴ Under his proposal, investigators would report their results to both the institute and the firm sponsoring the drug.²³⁵ Dr. George Nichols, of Harvard Medical School, proposed the creation of a central agency to test drugs, jointly financed by drug firms and the federal government.²³⁶ He said that this arrangement would eliminate, “questionable practices revolving around payment to investigators”²³⁷

Dr. William B. Bean, head of internal medicine at the University of Iowa College of Medicine, testified that third-party testing was not a new idea.²³⁸ He explained that the AMA had tried to operate an independent testing

228. *Competitive Problems in the Drug Industry: Present Status of Competition in the Pharmaceutical Industry, Part 7: Hearings Before the Subcomm. on Monopoly of the S. Select Comm. on Small Bus.*, 90th Cong. 2775, 2777 (1968) [hereinafter *Competitive Problems in the Drug Industry Hearings, Part 7*].

229. *Id.*

230. *Id.* at 2768.

231. *Id.*

232. *Id.*

233. *Competitive Problems in the Drug Industry Hearings, Part 7*, *supra* note 228, at 2769.

234. *Competitive Problems in the Drug Industry Hearings, Part 10*, *supra* note 218, at 4002.

235. *Id.* at 4002-03.

236. *Id.* at 3985.

237. *Id.*

238. *See id.* at 3916-21.

system, but had given up because they found it was “far too extensive and expensive.”²³⁹ Dr. Bean supported having drug testing conducted by, “a neutral judging body professionally competent, and quite independent of any extraneous force of financial support or any hint of obligation or connection with the . . . promoters of the drug.”²⁴⁰ He favored having medical schools and departments of clinical pharmacology perform drug testing, supervised by a central drug panel.²⁴¹ In questioning Dr. Bean about his proposal, Senator Nelson suggested that one option to organize the trials would be to place independent groups in control of the process, while charging drug companies the costs.²⁴² Dr. Bean concurred that in his view, this was “the proper direction” for reforms.²⁴³

In 1968, the director of the NIH, Dr. James Shannon, called for having the NIH or another federal agency help evaluate drugs. When data that the FDA received from studies by manufacturers were insufficient or were questioned, the agency would conduct its own studies or contract with independent institutions to conduct studies. Dr. Harry Dowling, a leading authority on drug safety responded by suggesting it might be better for the FDA to develop in house capacity to evaluate drugs.²⁴⁴

In 1971, Senator Nelson introduced legislation to create a system of independent third-party drug testing as part of an omnibus drug bill. He summarized the problem the bill sought to remedy as follows.²⁴⁵

239. *Competitive Problems in the Drug Industry Hearings, Part 10*, *supra* note 218, at 3920.

240. *Id.* at 3919.

241. *Id.* at 3920.

242. *Id.*

243. *Id.*

244. See DOWLING, *supra* note 28, at 230-32 (commenting on the Shannon proposal published in NAT'L INSTS. OF HEALTH, DRUG RESEARCH REPORTS 4 (1968)).

245. The bill was included as part of an omnibus drug bill, S. 2812, in the 92nd Congress. It was introduced as stand-alone legislation thereafter. Public Health Price Protection Act of 1972, S. 966, 93d Cong. (1973) (a bill “[t]o amend the Federal Food, Drug, and Cosmetic Act, as amended, to provide for the establishment of a national drug testing and evaluation center); National Drug Testing and Evaluation Act, S. 1321, 94th Congress (1975); National Drug Testing and Evaluation Act, S. 630, 95th Congress (1977); National Drug Testing and Evaluation Act of 1979, S.774, 96th Congress (1979). Senator Nelson testified that he developed his proposal with FDA officials in 1969 while chairing the “Competitive Problems” hearings. See *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 157. In addition to creating a system for independent drug testing S. 2812 would require that “in order for a new drug to be approved, it must be demonstrated that the new drug is safer or more effective than a drug already on the market. 117 CONG. REC. 39,204-09 (1971) (statement of Sen. Gaylord Nelson). For exposition and discussion of Nelson’s third-party testing proposal as described in S. 966, see the hearings chaired by Senator Ted Kennedy, *Examination of the Pharmaceutical Industry, 1973-74: Legislation Amending the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, Parts 1, 5, 6, 7: Hearings on S.*

As the law reads at present, the FDA determines the safety and efficacy of a drug solely on the basis of information supplied by the drug company making the application. The dangers involved in the dependence on drug firms to perform, direct, or arrange for the testing of drugs in which they have a financial interest is obvious [T]here is an inevitable tendency—no matter how conscientious the firm—to emphasize the positive features and deemphasize the negative. Many of the people they engage to do their testing are equally anxious to secure additional contracts for drug testing. . . . A physician who turns in unfavorable reports on the drugs he is testing may not have his contract renewed [S]ome firms have been guilty of misrepresenting, distorting, and even withholding information developed in their testing of drugs which might in any way retard or prevent an approval to market. Injury and death have resulted from such actions.

Testing of drugs should be done by specialists who have no direct relationship with the manufacturer, who cannot benefit financially from the results, who are not motivated even subconsciously by the desire to get anything but the truth. We must remove the responsibility for testing drugs from the applicant who has a financial interest in the drug.²⁴⁶

As he explained several years later, the current system is, “inherently defective in that the promoter and beneficiary of the product which needs to be licensed and marketed controls all the studies that are made to prove its safety and its efficacy.”²⁴⁷ Senator Nelson introduced the omnibus drug bill again in 1973, and sponsored stand-alone bills for independent drug testing in each Congress until he lost his re-election bid in 1980.²⁴⁸

Under Nelson’s proposed legislation, the federal government would be responsible for all testing for NDAs and reviews of drugs.²⁴⁹ The federal government would either perform the tests, or contract with independent organizations to perform them.²⁵⁰ The legislation authorized the creation of

3441 and S. 966 *Before the Subcomm. On Health of the S. Comm. on Labor and the Public Welfare*, 93d-94th Cong. (1973-74). See also Senator Nelson’s statement before the Kennedy subcommittee in which he outlines more than a decade of statements by the FDA indicating the problems of fraud and poorly designed studies were a problem of the past and that stronger monitoring and inspections have eliminated the problem. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 156-60.

246. 117 CONG. REC. 39,204-09 (1971).

247. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 156.

248. Public Health Price Protection Act of 1972, S. 966, 93d Cong. (1973); National Drug Testing and Evaluation Act, S. 1321, 94th Congress (1975); National Drug Testing and Evaluation Act, S. 630, 95th Congress (1977); National Drug Testing and Evaluation Act of 1979, S.774, 96th Congress (1979).

249. *Examination of the Pharmaceutical Industry, 1973-74, Part 1: Hearings on S. 3441 and S. 966 Before the Subcomm. On Health of the S. Comm. on Labor and Public Welfare*, 93d Cong. 55-56 (1973) [hereinafter *Examination of the Pharmaceutical Industry Hearings, Part 1*] (text of S. 966, 93d Cong. § 102 (1973)).

250. *Id.* at 56.

a National Drug Testing and Evaluation Center within the FDA to oversee intramural clinical investigations of new drugs.²⁵¹ The Secretary of the Department of Health, Education, and Welfare (HEW) would decide whether the drug would be tested by the National Drug Testing and Evaluation Center, or by a qualified independent organization staffed by experts that the Secretary engaged.²⁵² Drug companies would finance the establishment and maintenance of the Center, and the expenses for conducting the clinical trials by paying into a common fund, from which the Secretary would draw to pay for drug testing costs.²⁵³ The Secretary of HEW would publicize the “methodology, results, and conclusions of all tests and investigations.”²⁵⁴ Drug sponsors could still conduct their own clinical trials, subject to regulation by HEW and public disclosure of the testing methods and results.²⁵⁵

D. 1973-1980: The Kennedy Hearings

Senator Ted Kennedy chaired hearings entitled, *Examination of the Pharmaceutical Industry* in 1973-74,²⁵⁶ and hearings entitled, *Preclinical and Clinical Testing by the Pharmaceutical Industry* from 1975 through 1979.²⁵⁷ Kennedy examined the Nelson proposal for independent drug testing, among other issues.²⁵⁸

During the presidencies of Richard Nixon and Gerald Ford, at the hearings in 1974 and 1976, Charles Edwards, HEW Assistant Secretary for Health, and FDA Commissioner Alexander Schmidt, opposed Senator

251. *Id.*

252. *Id.* at 55-56.

253. *Id.* at 60-61.

254. *Examination of the Pharmaceutical Industry Hearings, Part 1, supra* note 249, at 63 (text of S. 966, at § 102).

255. *Id.*

256. *Examination of the Pharmaceutical Industry, 1973-74: Legislation Amending the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, Parts 1-7: Hearings on S. 3441 and S. 966 Before the Subcomm. On Health of the S. Comm. on Labor and the Public Welfare, 93d Cong. (1973-74).*

257. *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1975-76, Parts 1-3: Joint Hearings Before the Subcomm. on Health of the S. Comm. On Labor and Public Welfare and the Subcomm. on Administrative Practice and Procedure of the S. Comm. on the Judiciary, 94th Cong. (1975-76); Preclinical and Clinical Testing by the Pharmaceutical Industry, 1977-78, Parts 4-5: Hearings Before the Subcomm. On Health and Scientific Research of the S. Comm. on Human Res., 95th Cong. (1977-78); Preclinical and Clinical Testing by the Pharmaceutical Industry, 1979: Hearing Before the Subcomm. On Health and Scientific Research of the S. Comm. on Labor & Human Res., 96th Cong. (1979) [hereinafter *Preclinical and Clinical Testing, 1979*].*

258. See *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 161.

Nelson's proposal to create a national drug-testing center.²⁵⁹ FDA Commissioner Schmidt acknowledged that some investigators made questionable decisions about their study design, controls, and reporting that minimized the chance of discovering toxicity.²⁶⁰ However, he argued, economic incentives and tort liability made it good business for drug firms to carry out proper studies.²⁶¹ Further, the "professional integrity of toxicologists in the industry" helped to assure overall high quality investigations.²⁶² Schmidt admitted that there would be no bias if the federal government tested drugs.²⁶³ But, he argued, having the federal government or independent labs perform the work would not necessarily improve the quality of testing.²⁶⁴ In order to improve the quality of drug testing, he announced that the FDA would create regulations for assuring "good laboratory practice" (GLPs) in animal testing, including the inspection of animal testing facilities, and auditing or reviewing any data where there is suspicion of falsification.²⁶⁵ Additionally, Schmidt said the FDA would consider the feasibility of instituting federal certification for testing laboratories.²⁶⁶

259. *Examination of the Pharmaceutical Industry, 1973-74, Part 5: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the S. Comm. on Labor and Public Welfare*, 93d Cong. 2162-63, 2282-83 (1974) [hereinafter *Examination of the Pharmaceutical Industry Hearings, Part 5*]. *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1975, Part 1: Joint Hearings Before the Subcomm. on Health of the S. Comm. On Labor and Public Welfare and the Subcomm. on Administrative Practice and Procedure of the S. Comm. on the Judiciary*, 94th Cong. 24, 29-30, (1975) [hereinafter *Preclinical and Clinical Testing Hearings, Part 1*]. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 81-82. "Senator, you are assuming that we could do it better than industry, and I have some disagreement with that. I think the problem is not the system per se, but in the monitoring that we carry on of the system. We have underway at FDA, and have had for a couple of years an improved surveillance system of these clinical investigations that are being carried on behalf of the manufacturer. . . There is nothing wrong with the system. It is good, but we have over the years done a very poor job of surveillance, if you will, but I think first of all there is not enough talent to go around in terms of having the drug industry involved in clinical testing along with the Federal Government." *Examination of the Pharmaceutical Industry Hearings, Part 5, supra* at 2163 (emphasis added).

260. *Preclinical and Clinical Testing Hearings, Part 1, supra* note 259, at 24, 29-30; *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 81-82.

261. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 92-93.

262. *Id.* at 45.

263. *Id.* at 103.

264. *Id.* at 104.

265. *Id.* at 47.

266. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 48. Specifically, see Commissioner Schmidt's discussion of Good Laboratory Practices, *id.* at 47, 98-99; site inspection and monitoring, *id.* at 48, 99-100, 105; and retrospective review of data *id.* at 48, 100. In response to Commissioner Schmidt's testimony, Senator Nelson argued that even with

Commissioner Schmidt reported that the FDA had rejected the idea of having the federal government conduct drug testing.²⁶⁷ Instituting federal testing was not feasible in the short term, he said, because the federal government lacked sufficient personnel and testing facilities.²⁶⁸ Moreover, due to the dearth of independent laboratories at the time, it was not possible to have independent third parties perform the testing.²⁶⁹ Schmidt also argued that it would be too costly to have the federal government conduct drug testing. “[T]here is no way that we can get the resources to put into this that drug companies do.”²⁷⁰ It would be hard to justify federal spending, he said, unless the government controlled how the resources were used, which would result in the government setting research priorities.²⁷¹ Furthermore, he argued, because “I believe that all monopolies, whether public or private, tend to stagnate, the prospect of any single institution gaining such control over all preclinical drug investigation troubles me.”²⁷²

Both Commissioner Schmidt and HEW Assistant Secretary Edwards testified that having the FDA engage in or select firms to perform drug testing would mire the FDA in conflicting roles, because the FDA would ultimately be the party to evaluate the research performed under its aegis.²⁷³

increased FDA oversight, the same problems would continue, and so there was a need for the reforms of drug testing that he proposed.

What disturbs me about this presentation today is not the facts that we were presented, Dr. Schmidt. It is the fact that it is an old, old, old case. Dr. Goddard said the same thing 10, 12, 14 years ago. Dr. Ley, who succeeded Dr. Goddard, said the same thing. Dr. Edwards succeeded Dr. Ley and he said the same thing. Now Dr. Schmidt is before us laying down the same case. In 1966, the then FDA Commissioner Dr. James Goddard gave a speech on this issue Nothing really of significance has been done since then In 1969, seven years ago, I went to the FDA, and we sat down with the FDA employees and drafted a third party testing bill. We introduced it 7 years ago in 1969. We introduced it in 1971. We introduced it in 1973. We introduced it in 1975. I have not seen a single agency thus far endorse the concept or the idea or be excited or interested in it So it ends up languishing here.

He later continued, “[I] would hate to be sitting here 6 years from now with the next Commissioner coming in with another case so we can say, now, 14 years or 15 years have gone by, 16 years, instead of 10, since Goddard, who was not the first one to raise the issue.” *Id.* at 157-158.

267. *Id.* at 103.

268. *Id.* at 104.

269. *Id.*

270. *Examination of the Pharmaceutical Industry Hearings, Part 5, supra* note 259, at 2164-65.

271. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 103.

272. *Id.*

273. *Examination of the Pharmaceutical Industry Hearings, Part 5, supra* note 259, at 2163-65 (statement of Charles C. Edwards, Assistant Secretary for Health, Department of Health, Education, and Welfare).

Edwards contended, "the public would be deprived of . . . FDA impartial review of clinical data."²⁷⁴ Senator Nelson replied that, unlike the FDA, drug sponsors had an economic bias in having drugs approved.²⁷⁵ Commissioner Schmidt claimed that all that was needed to ensure reliable trials was increased FDA oversight, but that this required granting the FDA authority to issue subpoenas, examine records, and conduct investigations.²⁷⁶ Edwards said that a government center would not necessarily do a better job of testing drugs than drug firms, and that countering industry bias could be achieved through better government surveillance.²⁷⁷

Both the Pharmaceutical Manufacturers Association (PMA) and the AMA opposed the creation of a national drug testing and evaluation center. PMA president Joseph Stetler argued that the proposal incorrectly assumed, "that scientists will somehow be more objective if their work is done under government rather than private aegis."²⁷⁸ He also argued that creating the center would lead to a "drastic slowing down of drug research."²⁷⁹ Speaking for the AMA, Dr. James Sammons argued that operating a drug testing center under the FDA's aegis would transform the FDA from a judge of research conducted by others, into an organization that judged its own research.²⁸⁰ Both the PMA and AMA opposed another aspect of the proposal, the idea that drug trials should compare the effectiveness of new drugs to those on the market, and that the FDA should consider comparative effectiveness when deciding whether to authorize the sale of a new drug.²⁸¹

Meanwhile, evidence continued to accrue showing that many clinical trials did not comply with legal requirements or clinical investigation norms.²⁸² Congressional committee hearings continued to report these findings. The FDA investigations of G. D. Searle in the early 1970s revealed poor oversight, negligence and fraud in the firm's toxicological drug

274. *Id.* at 2163.

275. *Id.*

276. *Id.* at 2164-65.

277. *Id.* at 2163 ("There is nothing wrong with the system . . . but we have . . . done a very poor job of surveillance . . .").

278. *Examination of the Pharmaceutical Industry, 1973-74, Part 6: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the S. Comm. on Labor and Public Welfare, 93d Cong. 2526 (1974)* [hereinafter *Examination of the Pharmaceutical Industry Hearings, Part 6*].

279. *Id.* at 2494.

280. *Id.* at 2545 (statement of James H. Sammons, Executive Vice President Designate, American Medical Association).

281. *Id.* at 2525, 2572-73.

282. See *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 337-39 (statement of Gregory J. Ahart, Director, Manpower and Welfare Division, U.S. General Accounting Office).

testing.²⁸³ The FDA found multiple examples in which the laboratory not only failed to conduct biopsies when it should have, but it also failed to report the presence of lesions discovered in animal subjects.²⁸⁴

Typically, the Searle lab employed two different pathologists to examine tissue.²⁸⁵ In cases where one pathologist identified a lesion and the other did not, rather than report both findings or have a third pathologist review the slides, the lab did not report the presence of a lesion.²⁸⁶ The company did not require its reports to be signed or dated, and did not have clear procedures for recording important information, or for editing reported data.²⁸⁷ Sometimes, the pathologists' reports were edited in order to make the findings appear more favorable in terms of safety.²⁸⁸ The company was unable to account for discrepancies between its reports and the raw data.²⁸⁹ In some studies, animals listed as alive were dead, and animals listed as dead were often listed as alive later.²⁹⁰ The FDA investigation found that, "the cumulative findings of problems within and across the studies . . . reveal a pattern of conduct which compromises the scientific integrity of the studies."²⁹¹

An FDA survey of 155 clinical investigators between 1972 and 1974 found that 74% did not comply with one or more legal requirements.²⁹² 28% did not adhere to the study protocol, 23% did not keep accurate records of the patients' condition before, during, and after trial, and 22% did not retain case records.²⁹³ These kinds of problems were not new. They had been documented in numerous congressional hearings throughout the 1960s and 1970s.²⁹⁴

283. See *id.* at 1, 24-129 (memorandum from Searle Investigation Task Force to Searle Investigation Steering Committee).

284. *Id.* at 36, 66, 76.

285. *Id.* at 118.

286. *Id.* at 69.

287. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 118.

288. *Id.* at 76.

289. *Id.* at 13-15.

290. *Id.* at 20-22.

291. *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 3: Joint Hearings Before the Subcomm. on Health of the S. Comm. On Labor and Public Welfare and the Subcomm. on Administrative Practice and Procedure of the S. Comm. on the Judiciary, 94th Cong. 4 (1976)* [hereinafter *Preclinical and Clinical Testing Hearings, Part 3*].

292. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 338-39; BRAITHWAITE, *supra* note 123, at 84.

293. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 340.

294. These problems were analyzed in newspaper articles, by Morton Mintz, many of which were later published as a book on the FDA and the pharmaceutical industry. MINTZ, *supra* note 123. These issues were later analyzed by John Braithwaite's study of white collar crime in the pharmaceutical industry. BRAITHWAITE, *supra* note 123.

At the 1976 hearings, Gregory J. Ahart, of the U.S. Government Accounting Office (GAO), summarized the GAO's investigation into FDA drug testing. The GAO concluded that there is, "a lack of assurance that the data which is finally submitted with the drug applications and upon which FDA bases its decision to approve a new drug for marketing is accurate and reliable."²⁹⁵

Testimonies in 1976 made clear that there were then two types of problems with drug testing: first, manufacturers' bias compromised impartiality, and second, cost pressures lead organization that performed tests to cut corners and produce poor quality work.²⁹⁶ Having a governmental agency, rather than the manufacturer, select the organization that performs the tests would eliminate bias. However, other measures were needed to control for poor quality work due to economic pressures.

Frank Rauscher, Jr. testified that the National Cancer Institute (NCI) had addressed both problems in ways that could serve as a model for a government-supervised program of independent drug testing.²⁹⁷ To control for bias, the NCI and its outside peer-review committees designed the research protocol.²⁹⁸ It awarded contracts through competitive bidding, but

295. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 335. Specifically, Mr. Ahart made the following points regarding the GAO's findings. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 335. Before 1974 there was no comprehensive monitoring plan. Since 1972, when FDA began a special survey of clinical investigators, it found that most clinical investigators were not fully compliant, and that most sponsors were not adequately monitoring their investigators. *Id.* at 364-65. In the survey conducted from 1972-74 the FDA found significant (74%) noncompliance with a number of requirements. *Id.* at 365. It identified failure in: obtaining patient consent – 35%; keeping accurate records of the amount of drugs received from sponsors and distributed to subjects – 50%; adhering to study protocol – 28%; maintaining accurate records reflecting the condition of the patient before, during, and after the study, and the nature of the laboratory work done and other therapy administered during the study – 23%; retaining case records as required – 22%; properly supervising the study – 12%. *Id.* FDA inspections of sample groups of clinical investigations under the Bureau of Drugs, the Bureau of Biologics, and of federally sponsored clinical investigations all reviewed the same types of deficiencies. *Id.* at 366-67. The FDA did develop a "comprehensive plan for clinical investigation evaluation" in 1975 that was intended to enhance/remedy the monitoring efforts, but as of January 1976, was not yet fully implemented. The FDA made only sparing use of its enforcement tools to improve clinical investigations. In the period following the '62 amendments, there were only two criminal prosecutions, regulatory letters have been used only once by the Bureau of Biologics and not at all by the Bureau of Drugs, and the two bureaus combined disqualified only 30 investigators. *Id.* at 368-69.

296. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 1-3.

297. See *id.* at 145, 148-50 (testimony of Frank J. Rauscher, Jr., Director, National Cancer Institute); see also BRAITHWAITE, *supra* note 123, at 104-06 (summarizing Dr. Schmidt's testimony which reviews the points covered by Dr. Rauscher).

298. *Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 150.

only considered laboratories that had no connection to the firms manufacturing the drugs being tested.²⁹⁹

The NCI used several strategies to counter the risk of contract laboratories cutting costs in ways that compromised the integrity and quality of testing. The NCI coded the compounds it sent for testing.³⁰⁰ Therefore, the tester did not know which chemical it was testing.³⁰¹ Periodically, the NCI sent testing labs a compound that it knew had certain carcinogenic or other effects as a means of ascertaining whether the laboratory performed tests accurately.³⁰² Moreover, the NCI awarded contracts to multiple toxicological laboratories as a means of checking the quality of the work, and to spur quality competition among laboratories.³⁰³ The NCI staff monitored the studies on a nearly day-to-day basis.³⁰⁴ Additionally, the NCI divided its testing into two separate parts, each of which could be evaluated. One organization performed the toxicological test and generated the data, while the second organization performed the data processing and statistical analysis.³⁰⁵

Following the FDA, GAO, and Senate investigations, the FDA developed regulations for GLPs for drug testers.³⁰⁶ The FDA also created a system of bio-research monitoring and inspection.³⁰⁷ However, a 1977 study of 39 laboratories performing toxicology studies found that their compliance with the GLPs varied between 32% and 98%.³⁰⁸ Surprisingly, university laboratories had worse records than the commercial laboratories.³⁰⁹ The FDA monitoring program was well in place by the time of the 1979 study of 28 laboratories, which found that the average compliance rate with GLPs was only 88%.³¹⁰ That study found nine examples of inaccurate reporting of test results from five laboratories.³¹¹

Throughout this period, consumer advocates continued to argue that the government should require independent testing. For example, in 1976, Dr.

299. *Id.* at 149-50.

300. *Id.* at 144.

301. *See id.*

302. *Id.* at 150.

303. *See Preclinical and Clinical Testing Hearings, Part 2, supra* note 210, at 149-50.

304. *Id.* at 144.

305. *Id.* at 148.

306. 21 C.F.R. § 58 (2011).

307. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, CHAPTER 48 – BIORESEARCH MONITORING (2001).

308. BRAITHWAITE, *supra* note 123, at 82.

309. *Id.*

310. JONATHAN D. COOK, FOOD & DRUG ADMIN., RESULTS OF THE TOXICOLOGY LABORATORY INSPECTION PROGRAM (JANUARY – MARCH 1979) 9 (1979).

311. *Id.* at 19.

Sydney Wolfe, of Public Citizen's Health Research Group (HRG), discussed the issue of drug testing at the Environmental Protection Agency and at the FDA, and argued that no amount of government surveillance could solve the fundamental problem of interested parties conducting or overseeing drug testing.³¹²

I think what we learn . . . is not to allow any more testing by industry or by companies, who owe their allegiance to industry. This has got to stop. No kind of surveillance of any kind over conflicted and inadequate data is going to improve the quality of it. The Government has to step in. It will be far cheaper for the Government, particularly if we use industry funds, to funnel out the testing money to reliable companies than to have to expend \$25 million, as you have proposed for FDA, to catch up with lousy industry data.³¹³

FDA Commissioner Schmidt acknowledged that the relationship between drug firms and testing laboratories required close scrutiny, but he opposed the proposals that Dr. Wolfe and others advocated.³¹⁴

In 1978, Senator Kennedy expressed "serious reservations about the adequacy" of the FDA's new monitoring program, and renewed his hearings.³¹⁵ Testimony and documents revealed continued negligence and fraud in drug testing.³¹⁶ The hearings documented examples of investigators fabricating data.³¹⁷ Some investigators submitted case reports providing results for patients who had not even been research subjects for the investigational drug.³¹⁸ Others wrote reports for laboratory work that had not been performed, or for human research subjects that did not exist.³¹⁹ Sometimes, investigators submitted data generated for the testing of one drug in place of data for an entirely different product.³²⁰

Another theme the hearings explored concerned the dependence of some toxicological laboratories on drug firms for their continued operation,

312. *Preclinical and Clinical Testing Hearings, Part 3, supra* note 291, at 686; CONG. RESEARCH SERV., 1979 SUMMARY, *supra* note 214, at 77 (citing *Drugs: A Consumer Advocate's View*, FDA CONSUMER, Dec. 1978 – Jan. 1979, at 10, 13).

313. *Preclinical and Clinical Testing Hearings, Part 3, supra* note 291, at 691.

314. *See id.* at 732.

315. *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1978, Part 5: Hearings Before the Subcomm. On Health and Scientific Research of the S. Comm. on Human Res., 95th Cong. 1 (1978)* [hereinafter *Preclinical and Clinical Testing Hearings, Part 5*].

316. *Id.* at 1-2.

317. *Id.*

318. *Id.* at 7.

319. *Id.* at 7-8.

320. *Preclinical and Clinical Testing Hearings, Part 5, supra* note 315, at 42.

and the employment of their staff.³²¹ Would their dependency induce these labs to engage in fraud due to fear that the drug firms would not renew their contracts if they reported unfavorable results? Some witnesses suggested that drug firms instructed laboratories to fabricate data, a practice that they called “dry-labeling.”³²² Other witnesses and senators expressed concern that drug testers failed to record data, or would fabricate data, in order to produce favorable results as a means of ensuring that drug firms would hire them for subsequent studies.³²³

E. *The Carter Administration Report on New Drug Regulation*

The administration of President Jimmy Carter also reviewed proposals to reform drug testing and the FDA. The final report of the Department of Health and Human Services Review Panel on New Drug Regulation, issued in 1977, discussed numerous issues, including clinical trials.³²⁴ It noted:

One of the most troublesome aspects of the present system...is that FDA must rely almost exclusively on the accuracy and objectivity of industry-generated data [B]ecause the company has a financial interest in successful test results, the present drug testing system contains an inherent bias which adversely affects the accuracy and acceptability of drug research.³²⁵

The panel distinguished between the risk of fraud and manufacturer bias, and said that, “present safeguards against the submission of fraudulent test data appear inadequate to detect and minimize this type of bias.”³²⁶ It explained, that “[t]he most direct means of minimizing the bias in testing is to have research conducted by investigators who are financially independent of the drug sponsor.”³²⁷

The key options, the panel concluded, were to institute “limited third-party testing, complete government testing, or government contracting of testing.”³²⁸ It disfavored limited third-party testing since that would subject

321. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 139; BRAITHWAITE, *supra* note 123, at 80.

322. *Preclinical and Clinical Testing Hearings, Part 3*, *supra* note 291, at 13; BRAITHWAITE, *supra* note 123, at 80.

323. *Preclinical and Clinical Testing Hearings, Part 2*, *supra* note 210, at 139-42, 158-159.

324. DEP’T OF HEALTH, EDUC., AND WELFARE, FINAL REPORT OF THE REVIEW PANEL ON NEW DRUG REGULATION (1977) [hereinafter REVIEW PANEL ON NEW DRUG REGULATION]. The report is summarized and discussed in CONG. RESEARCH SERV., 1979 SUMMARY, *supra* note 214, at 76-77.

325. REVIEW PANEL ON NEW DRUG REGULATION, *supra* note 324, at 83.

326. *Id.* at 84-85.

327. *Id.* at 85-86.

328. *Id.* at 88.

more human subjects to tests and would be more expensive than third-party testing alone.³²⁹ The disadvantage of having the federal government conduct clinical trials, said the panel, was that it “would require that the government evaluate the results of its own tests . . .” and also “require a sizable government bureaucracy.”³³⁰ Furthermore, it reported, the “FDA believes that if the government were the only drug tester, it inevitably would begin to set research priorities and would be in the position of determining the directions of drug innovation.”³³¹ In contrast, “independent contracting . . . would constitute a lesser regulatory intrusion . . .”³³² The panel, therefore, preferred a system under which “the government would be responsible for hiring and paying independent researchers, with the cost of research assessed to the sponsor,” and where “[t]he information produced would be given to both the pharmaceutical sponsor and the FDA for analysis.”³³³ It recommended that the FDA institute a pilot program to “contract with independent parties on behalf of the drug sponsor for the clinical testing of selected class of drugs,” and that it then “assess the feasibility . . . of introducing independent contract of clinical testing on a larger scale.”³³⁴

F. *The Drug Regulation Reform Act of 1978*

In January 1976, a frustrated Senator Nelson complained that meaningful drug testing reform would never occur unless the FDA supported sensible legislative proposals.³³⁵ In 1978, the FDA and HEW accepted this challenge, and supported legislation sponsored by Senator Kennedy and nine other senators.³³⁶ The legislation did not propose full-scale independent drug testing, but it did propose reforms of the drug review process, and create some governmental capacity to evaluate drugs.

The Drug Regulation Reform Act of 1978 proposed major restructuring of the drug approval process.³³⁷ It also reduced FDA control over initial

329. *Id.*

330. REVIEW PANEL ON NEW DRUG REGULATION, *supra* note 324, at 88-89.

331. *Id.* at 89.

332. *Id.*

333. *Id.*

334. *Id.* at 7-8, 90.

335. *Id.* at 157-60.

336. *Drug Regulation Reform Act of 1978: Hearings on S. 2755 Before the Subcomm. on Health and Scientific Research of the S. Comm. on Human Res., 95th Cong. 1-3 (1978)* [hereinafter *Drug Regulation Reform Act of 1978 Hearings*] (indicating the nine co-sponsors: Sens. Alan Cranston (CA), Thomas F. Eagleton (MO), William D. Hathaway (ME), Jacob K. Javits (NY), Gaylord Nelson (WI), Claiborne Pell (RI), Jennings Randolph (WV), Donald W. Riegle, Jr. (MI), and Harrison A. Williams, Jr. (NJ)).

337. *Id.* at 2-3.

clinical testing in humans, while increasing its oversight in the later phases.³³⁸ The Act increased the FDA's role in overseeing the design and implementation of testing protocols, and expanded the disclosure requirements for clinical trial data.³³⁹ Section 132 authorized the Secretary to write guidelines for later phases of drug trials.³⁴⁰ The Secretary could deny applications for drug testing on numerous grounds, including when "[T]he proposed plan for the development of the drug product is not adequate to meet its stated objectives," and when "[T]he proposed investigations are inadequate to meet their stated objectives."³⁴¹

The bill created a "National Center for Clinical Pharmacology" within HEW, separate from the FDA, to conduct some intramural public clinical pharmacology research.³⁴² The Center would publish an annual Drug Experience Assessment Report, based on its ongoing review and analysis of the use of drug products in the United States, including a qualitative analysis of the use of currently available drug products, and the adverse effects and other unanticipated reactions from such products.³⁴³ The Center's functions included:

[C]onduct[ing] and support[ing] research in clinical pharmacology and clinical pharmacy, including investigations (1) of the safety and effectiveness

338. Briefly, § 127 of the bill established "Drug Innovation Investigations," defined as investigations using "small numbers of human participants. . .intended to examine the clinical pharmacology of a drug entity or drug product in humans, to assess preliminarily its risks and effectiveness, or. . .biological mechanisms in humans." *Id.* at 98-99 (text of Senate Bill 2755). Under this section, applicants to conduct such innovations submit an application to FDA, including a description of the product, reports of previous investigations, and the proposed protocol for the investigation, including *inter alia* the maximum number of humans to be included, the names of the investigators, and any other information that is "necessary for the Secretary" to make a determination. *Id.* at 101-102. The applications would presumptively be accepted unless the Secretary concluded within thirty days that the proposed investigation would subject human participants to "unreasonable and significant risk," or that it would fail to satisfy the requirements of subsection (f). *Id.* at 97-98. Subsection (f) in turn required that the investigation registrant, among other things: distribute the drug product only to "experts who are qualified by scientific training and experience to investigate the drug . . . in humans . . ." (*id.* at 102) (note that the testing firm still retains control over who the investigators are, though they must disclose the investigators' names with the initial application"); "establish and maintain records, and submit reports to the Secretary, regarding the investigation to enable the Secretary to determine whether the conditions of registration are being fulfilled" (*id.*); and report to the Secretary "information regarding newly discovered risks of the drug product to enable the Secretary to determine whether human participants are being subjected to an unreasonable and significant risk of illness or injury" (*id.* at 102-103).

339. *Id.* at 105, 109-110.

340. *Id.* at 122-23 (§ 132).

341. *Drug Regulation Reform Act of 1978 Hearings, supra* note 336, at 107.

342. *Id.* at 227.

343. *Id.* at 228-29.

of existing and new uses of drug products, (2) for the development of drug products for diseases and other conditions of low incidence, (3) of drug products of special significance or with respect to which there is substantial controversy as to safety and effectiveness and for which there have been either no or minimal investigations, and (4) to otherwise facilitate breakthroughs in research on drug products.³⁴⁴

Several controversial provisions of the bill provoked opposition from the pharmaceutical industry, physicians, and some consumer advocates.³⁴⁵ The bill was never reported out of committee.³⁴⁶

By October 1979, FDA regulations regarding clinical investigations had not been finalized, and acting FDA commissioner Sherwin Gardner was reciting the same old sponsor-responsibility catechism: that the FDA neither could nor should oversee drug trials used for approving drugs.³⁴⁷

Senator Kennedy's 1979 hearings documented 31 cases of flawed clinical trials due to individual investigators engaging in fraud, falsifying patient records, misrepresenting medical histories of research subjects, violating trial protocols, and breaching numerous other FDA rules.³⁴⁸ Acting FDA Commissioner Sherwin Gardner reported that the FDA had audited trials to detect poor quality and fraud.³⁴⁹ The FDA found the bulk of research acceptable, but revealed that the work of some investigators "represent[ed] sloppy science, disregard for the rights of test subjects, and misrepresentations of test data."³⁵⁰ To address these problems, Gardner reported that the FDA was exploring several options. These included disqualifying misbehaving investigators from conducting trials, referring cases of misconduct for criminal prosecution, and developing new regulations.³⁵¹ Simultaneously, and much to Senator Kennedy's chagrin, the FDA was contemplating the elimination of requirements for drug sponsors to check their investigators' raw data.³⁵²

In the 1980 election, Ronald Reagan was elected President of the United States, Senator Gaylord Nelson lost his bid for re-election to the Senate, and Senate majority shifted from the Democratic to the Republican

344. *Id.* at 228.

345. *Id.* at 956-61 (statement of Barbara Moulton, National Consumers League).

346. *Drug Regulation Reform Act of 1978 Hearings*, *supra* note 336, at 956-1015 (statement of Barbara Moulton, National Consumers League).

347. *Preclinical and Clinical Testing*, 1979, *supra* note 257, at 13.

348. *See generally id.*

349. *Id.* at 9-10.

350. *Id.* at 10.

351. *Id.* at 10, 14.

352. *Preclinical and Clinical Testing*, 1979, *supra* note 257, at 13.

party.³⁵³ This change ended Congressional proposals for independent drug testing. Discussion of independent drug testing in medical and popular journals then virtually ceased until the 1990s.

V. REVISITING PROPOSALS FOR INDEPENDENT DRUG TESTING

A. *Alternative Approaches to Ensure the Integrity of Drug Testing*

Since the FDA promulgated regulations in 1970 that specified the evidence it would use to evaluate drug safety and effectiveness, it has either ignored or opposed proposals for independent testing. To counter problems of fraud, bias and poorly designed trials conducted by drug firms, it developed extensive regulations on how to conduct toxicological tests and clinical trials. It also monitored clinical research used to support NDAs. Nevertheless, over the last quarter century, governmental evaluations, studies on medical research, civil and criminal investigations, and tort suits have continued to reveal bias and fraud in drug-firm sponsored research. The FDA could increase its regulation and oversight of manufacturer-sponsored drug testing, yet there are limits on what that can accomplish because such regulation does not remove the source of compromising influences.

Having the federal government contract with organizations to test drugs would be a significant change but constitutes a more modest alteration than another reform proposal: public financing of clinical trials to test drugs.³⁵⁴ Proponents of public financing argue that it would curb research bias and fraud and ensure public access to clinical trial data, thereby improving our knowledge of drug risks and benefits. Even more important, they say, public funding could reduce spending on pharmaceuticals and increase access to drug therapy. Current policies grant drug firms a time-limited monopoly through patents and marketing exclusivity as an incentive to invest the funds needed to bring new drugs to market, about half of which pays to conduct clinical trials.³⁵⁵ If these clinical trials were publicly funded, the cost to drug

353. Peter Temin, *Government Actions In Times Of Crisis: Lessons From The History Of Drug Regulation*, 18 J. SOC. HIST. 433, 437 (1985); Nelson, Gaylord Anton, BIOGRAPHICAL DIRECTORY OF THE U.S. CONG., <http://bioguide.congress.gov/scripts/biodisplay.pl?index=n000033> (last visited Nov. 17, 2012).

354. See Part III, *Contemporary Proposals for Independent Drug Testing*, particularly notes 101 through 102 and accompanying text.

355. See WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RL 30756, PATENT LAW AND ITS APPLICATION TO THE PHARMACEUTICAL INDUSTRY: AN EXAMINATION OF THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984 ("THE HATCH-WAXMAN ACT") (2005). See also U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, POSTMARKETING STUDIES AND CLINICAL TRIALS – IMPLEMENTATION OF SECTION 505(O)(3) OF THE FEDERAL FOOD,

firms of bringing drugs to market would be cut in half. Consequently, legislation could also reduce the duration of drug patents and market exclusivity, and that would lower the amount that the federal government spends to purchase drugs for Medicare, Medicaid, the Veteran's Administration and the Department of Defense. Those savings could pay for the cost of funding the clinical trials.³⁵⁶

Despite the significant potential benefits of publicly funded trials, Congress is unlikely to enact this reform in the short term because it would require major changes in financing and patent policy. In contrast, independent drug testing would also improve the integrity of research and ensure public access to clinical trial data without the federal government incurring up-front expenses or changes in intellectual property law, making it an easier reform to enact.

B. Assessing the Arguments Against Independent Testing

Let us review the key arguments used to oppose proposals for independent drug testing.

In the 1960s and 1970s, opponents argued that independent drug testing was not feasible because there were insufficient independent private organizations to conduct toxicological tests and clinical trials, and the federal government also lacked the capacity to perform this work.³⁵⁷ These assertions assumed that private firms and the federal government could not expand their capacities to meet new demands. That was probably not correct in the early 1960s and 1970s, and it is certainly not true now. Today, rather than test drugs in-house, drug firms contract out this work to third parties. Initially, universities performed most of this research but over the last quarter century drug firms shifted most of their clinical trials to for-profit CROs, which now constitute a global industry.³⁵⁸ However, testing by third parties is not independent today. The drug manufacturer either designs the clinical trial or directs and oversees researchers who do, and it selects the organization that conducts the research. Contract researchers, whether

DRUG, AND COSMETIC ACT (2011), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

356. See, e.g., BAKER, *supra* note 102. Some public funding proposals would have the federal government directly fund the clinical trials. See, e.g., Lewis et al., *supra* note 101. Other proposals would have drug firms obtain research funds and conduct trials in the same manner they do now but instead of rewarding firms that develop innovative drugs by granting patents and market exclusivity, the federal government would award a monetary prize to the innovator, obtain rights to the drug, and then allow multiple firms to manufacture and market the drugs. Love & Hubbard, *supra* note 101; Pogge, *supra* note 102.

357. See Part IV.D, particularly notes 257, 265-267 and accompanying text.

358. See MASRI ET AL., *supra* note 81; see Rettig, *supra* note 81; see also Part II, notes 11-12 and accompanying text.

in CROs or universities, depend on the drug manufacturer for their income and must follow its directions if they want to receive contracts in the future.

Public policy could promote the independence of existing contract research organizations and universities if a governmental agency selected the entity that performed the clinical trials and monitored its work, either directly or through an intermediary. Furthermore, by allocating funds for the research, the agency could spur the growth of organizations that met high standards for integrity, excellence, and independence. Through contracts, it could encourage the growth of organizations such as the internationally recognized Mario Negri Pharmacological Institute, which has performed independent clinical trials in Europe for nearly 50 years, published more than 13,000 original scientific papers in scientific journals and now conducts about 80 clinical trials a year.³⁵⁹

Independent testing, its opponents also argued, would not ensure that clinical trials were well designed, free of methodological flaws, or conducted competently. Even if a governmental agency selected the researchers, opponents argued, researchers might perform sloppy work or engage in fraud. They suggested that it was therefore not important or valuable to ensure independent testing.³⁶⁰ No doubt, independent testing does not guarantee that drug evaluation will be performed well. However, that only shows that independence is not sufficient to ensure accurate drug testing. It does not show that independence is not an important factor or a necessary condition for accurate drug testing. Moreover, the National Cancer Institute's experience in contracting with laboratories to test chemicals demonstrates that regulators can monitor and control the quality of contracted testing.³⁶¹

Opponents also claimed that having the federal government test drugs would create a conflict of interest that would compromise FDA drug approval decisions because the government would then both conduct clinical trials and evaluate those trials when it decided whether or not to grant marketing approval. The federal government should not conduct clinical trials, they argued, because it should not be in the position of evaluating its own work.³⁶²

359. See Donald W. Light, *Trustworthiness and Integrity in Pharmaceutical Research: What can we learn from the Anti-Corruption Practices of the Mario Negri Institute of Pharmaceutical Research?* (Sept. 13, 2012) (unpublished manuscript) (on file with author). See also Home, ISTITUTO DI RICERCA FARMACOLOGICHE MARRIO NEGRI (Dec. 19, 2012), <http://www.marionegri.it/mn/en/>.

360. See Part IV.D, particularly note 262 and accompanying text.

361. See Part IV.D, particularly notes 297-305 and accompanying text.

362. See Part IV.D, particularly notes 230-233, 273-281 and accompanying text.

There is irony in opposing government drug testing on the grounds that it is mired by conflicts of interest. The impetus for government-sponsored testing — performed either by public employees or through contracts with researchers in the private sector — is to remove the conflict of interest present when a firm evaluates its products. The issue, therefore, is whether government-sponsored testing creates more or less bias than when drug firms test their own products. Drug manufacturers have a systemic bias in favor of their products while governmental agencies do not have a systemic bias in favor of or against any particular product. Certainly, some individual governmental personnel might harbor a bias toward a firm or a product. But that is unlikely to systematically slant all testing.

Granted, a governmental agency that conducts clinical trials may not objectively evaluate its own trials. However, government testing is possible without having the same agency both conduct clinical trials and evaluate the quality of those trials. Simply have one governmental agency conduct clinical trials and designate another agency to evaluate the research. The NIH could conduct clinical trials and the FDA could evaluate those trials, just as it currently evaluates clinical trials conducted by drug firms. In fact, government agencies frequently evaluate the work of other government programs. For example, the Government Accountability Office provides independent evaluation of federal programs. And the Congressional Research Service provides impartial evaluations of legislative proposals and legislative history. Furthermore, it is easy to eliminate the problem of having government agencies evaluate the work of government employees. Simply have the governmental agency evaluate clinical trials performed by private contractors. Most of the proposals for independent drug testing, in fact, have the FDA evaluate research conducted by private contractors and they also have a separate agency select the contract researchers.

Another drawback of independent testing, opponents claim, is that it would further slow the introduction of new drugs. This assertion is unpersuasive. Currently it requires about 15 years from the beginning of drug development until a drug can be tested and marketed.³⁶³ Phase I clinical trials in humans take about a year and a half.³⁶⁴ Phase II clinical trials typically take two years;³⁶⁵ and phase III clinical trials take three to five years. Review by the FDA can take up to two years but in recent years the FDA drug review, on average, has been completed in just over a year.³⁶⁶ Independent testing is unlikely to cause much delay and there are ways to take care of problems any delay would cause for manufacturers.

363. ROWBERG, *supra* note 66, at 9.

364. *Id.*

365. *Id.* at 10.

366. *Id.* at 14.

In principle, it should not take longer for contract researchers to conduct a clinical trial merely because a governmental agency hires it, rather than a drug firm. It might take a governmental agency longer than a drug firm to select which researchers to employ, but not much. And if ensuring that clinical trials are better designed and methodologically sound extends the time to develop the research protocol, that would be time well spent. Furthermore, the Hatch-Waxman Act already extends for up to five years the period of market exclusivity for manufacturers of new drugs to compensate them for part of the time it takes to conduct clinical trials and for the FDA to review NDAs.³⁶⁷ Regulations could increase the period of market exclusivity to account for any increased time taken to conduct clinical trials using the new process.

C. *Challenges to Controlling Private Research Organization Conflicts of Interest*

Having a government agency select the private organizations that conduct clinical trials would not necessarily remove all conflicts of interest. Presumably CROs or universities might earn only part of their income from federal government contracts and, therefore, they might also earn most of their income from work from drug manufacturers. If organizations selected by government agencies depended on receiving discretionary contracts from drug manufacturers for most of their income, such dependence would create a significant conflict of interest.³⁶⁸ The drug manufacturer could retaliate against researchers that produced negative evaluations of their products for government-sponsored testing by ceasing to employ them in the future. The risk of losing contracts from drug manufacturers could lead researchers and research organizations to conduct their government testing in ways that favored the manufacturer of drugs they test.

The simplest and most effective way to address this problem is to prohibit all firms and organizations that accept federal contracts for drug evaluation from performing any direct work for drug manufacturers. However, fewer research organizations could thrive without doing any work

367. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 15, 21, 28, 35 U.S.C. (2006)). See ROWBERG, *supra* note 66.

368. This sort of conflict of interest also occurs when independent medical review organizations evaluate decisions of insurers to deny medical services. Even when public authorities select the review organization, the review organizations often depend on the insurer whose decisions they assess. Typically these review organizations earn much of their income from performing other work for insurers. Insurers that are displeased with a decision of an independent review organization can select another organization to employ for this work. See Marc A. Rodwin, *New Standards for Medical Review Organizations: Holding Them and Health Plans Accountable For Their Decisions*, 30 HEALTH AFF. 519, 520 (2011).

for drug firms and so adopting that rule would reduce the pool of organizations willing to accept federal drug testing contracts. With fewer research organizations from which to choose, the federal government might have more difficulty finding organizations capable of performing high quality work.

An alternative strategy is to reduce the prevalence of conflicts of interest rather than preclude them. The agency awarding drug evaluation contracts could offer work only to CROs that earned 40 percent or less of their revenue from drug manufacturers. Regulations could also direct the agency to give preference in awarding contracts to organizations that received ten percent or less of their revenue from drug manufacturers, when such organizations were available and well qualified.

To further reduce the risk from conflicts of interest and improve the quality of clinical trials, the federal government could also contract with experts to evaluate the proposed research design and protocol before authorizing the start of the clinical trial. It probably makes sense to require public disclosure of the proposed research protocol and the comments of experts that evaluated it and to allow the public to comment on the proposed research protocol. Based on the expert evaluation and public comment, the government agency could ask the research organization to revise its trial design and research protocol.

D. Implementing Independent Drug Testing: Begin with New Drugs

We can distinguish three categories of drug trials: (1) those used to support an application to market a new drug; (2) post-marketing trials required by the FDA as a condition for granting marketing approval; (3) other post marketing approval trials not required by the FDA. Independent testing could be used for all three categories, but reform should start with independent testing to support NDAs.

Federal law already requires that drug companies submit evidence on drug safety and effectiveness when they seek approval to market a new drug. Moreover, FDA regulations specify how drug firms must conduct these trials. Since the FDA already sets standards for clinical trials used for drug approval, it probably has authority to promulgate regulations that require such clinical trials be designed and conducted by an independent organization selected and supervised by a federal agency. In any event, Congress could implement this policy by amending the FDCA without regulating other clinical trials for drugs.

The FDA also has jurisdiction over certain post-marketing trials because FDA regulations require that drug manufacturers monitor the risks of drugs they market. Manufacturers must submit to the FDA results from their post-marketing trials but often the FDA does not specify what manufacturers must do to fulfill their post-marketing commitments. Sometimes, however, the

FDA specifies the kind of post-marketing trial that a drug manufacturer must perform, particularly if the NDA revealed evidence of potential serious drug risks.³⁶⁹

In principle, the FDA or Congress could require that drug firms finance independent clinical trials for these post-marketing studies. However, ensuring that these trials are carried out would require an expansion of FDA authority. Until enactment of the Food and Drug Administration Amendments Act of 2007, the FDA lacked authority to compel drug firms to conduct post-marketing studies of approved drugs.³⁷⁰ Drug firms often did not complete or delayed conducting these studies.³⁷¹ One reason for this is that the FDA lacks the ability to routinely stop a manufacturer from marketing an approved drug. In contrast, regulatory authorities in the European Union have such power because authorization to market a new drug expires after five years unless the European Medicine Agency approves a renewal application.³⁷²

Drug firms also conduct clinical trials for approved drugs that are not require by the FDA. Typically they conduct such studies to help market their products. They may design these trials to demonstrate that a drug is more effective, safer, or more cost-effective than competing drugs or non-drug therapies, or to explore an approved drug's potential benefits for new uses. It will be much harder to require that these trials be funded by drug firms but conducted independently.

The federal government lacks leverage to require independent testing for these studies because federal law does not require drug manufacturers to supply the FDA evidence that these studies are designed to produce. Manufacturers therefore have the option of not funding such clinical trials and that makes it harder for the FDA to regulate how such studies must be conducted. If Congress wants independent clinical trials to evaluate the comparative efficacy of approved drugs it will probably have to finance these studies. Alternatively, Congress could pass legislation that requires manufacturers to submit such data to the FDA, which would then give the FDA jurisdiction over such research.

369. 21 C.F.R. § 314.80-.81 (2012).

370. Peter P. Chang, *Reauthorization of PDUFA: An Exercise in Post-Market Drug Safety Reform*, 36 J.L. MED. & ETHICS 196 (2008).

371. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GENERAL, OEI-01-04-00390, *FDA'S MONITORING OF POSTMARKETING STUDY COMMITMENTS* (2006). For a discussion of this problem and attempts to address it, see INST. OF MED., COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYSTEM, *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 55, 155-57 (2007).

372. Commission Regulation 726/2004, 2004 O.J. (L 136) 35.

