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Independent Drug Testing to Ensure Drug Safety and Efficacy

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INDEPENDENT DRUG TESTING TO ENSURE DRUG SAFETY AND EFFICACY

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I. REGULATION OF PRESCRIPTION DRUGS AND MANUFACTURER CONFLICTS OF INTEREST

Drug manufacturers face a fundamental conflict of interest. Pursuit of profit compromises drug manufacturers' impartial assessment of the risks and benefit of their drugs.[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.[3]

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1. The conflicts of drug firms are, in part, conflicts of interest that affect medical practice in general. *See* MARC A. RODWIN, CONFLICTS OF INTEREST AND THE FUTURE OF MEDICINE: THE UNITED STATES, FRANCE AND JAPAN (Oxford University Press, 2011); MARC A. RODWIN, MEDICINE, MONEY, AND MORALS: PHYSICIANS' CONFLICTS OF INTEREST (Oxford University Press, 1993). For application of conflict of interest analysis in the pharmaceutical sectors, see Karine Morin et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 JOURNAL AM. MED. ASS'N 78, 80 (2002) (focusing on conflicts specifically between pharmaceutical companies and the testing of new drugs).

2. *See* Marc A. Rodwin, *Conflicts of Interest, Institutional Corruption, and Pharma: An Agenda for Reform*, 40 J.L. MED. & ETHICS 511, 511–12 (2012); Marc A. Rodwin, *Rooting Out Institutional Corruption to Manage Inappropriate Off-label Use*, 41 J.L. MED. & ETHICS 654 (2013); *see also*, Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1539 (2000) (highlighting several instances in which researchers have been more willing to promote a drug or claim that it was effective if they were funded by pharmaceutical companies).

3. *See e.g.*, Federal Food and Drugs Act of 1906, Pub. L. No. 59-384, § 8, 34 Stat. 768, 770 (1906) (repealed 1938) (representing the first major piece of reform). There is growing literature analyzing problems with drug safety and current practices in pharmaceutical industry research and marketing. *See generally* JOHN ABRAMSON, OVERDO$ED AMERICA: THE BROKEN PROMISE OF

Several policies counter this conflict of interest.[4] Nevertheless, when the Food and Drug Administration ("FDA") considers whether to approve sale of a drug, it relies upon clinical trials designed and controlled by the drug sponsor.[5] An ample record reveals that drug firms can design clinical trials in ways that bias the conclusions,[6] can misinterpret or misreport the trial data, or can engage in fraud.[7]

AMERICAN MEDICINE (HarperCollins, 2004); MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (paperback ed. 2005); JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS (Knopf, 2004); HOWARD BRODY, HOOKED: ETHICS, THE MEDICAL PROFESSION, AND THE PHARMACEUTICAL INDUSTRY (Rowman & Littlefield, 2007); MERRILL GOOZNER, THE $800 MILLION DOLLAR PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS (University of California Press, 2004); DAVID HEALY, PHARMAGEDDON (University of California Press, 2012); DONALD W. LIGHT, THE RISKS OF PRESCRIPTION DRUGS (Columbia University Press, 2010); THOMAS J. MOORE, PRESCRIPTION FOR DISASTER: THE HIDDEN DANGERS IN YOUR MEDICINE CABINET (Simon & Schuster, 1998); RAY MOYNIHAN & ALAN CASSELS, SELLING SICKNESS: HOW THE WORLD'S BIGGEST PHARMACEUTICAL COMPANIES ARE TURNING US ALL INTO PATIENTS (Nation Books, 2005); Marc-André Gagnon, *Corporate Influence Over Clinical Research: Considering the Alternatives*, 21 PRESCRIRE INT'L 191, 191–95 (2012) (comparing clinical research to a promotional campaign); Joel Lexchin, *The Medical Profession and the Pharmaceutical Industry: An Unhealthy Alliance*, 18 INT'L J. HEALTH SERVICES 603, 603–16 (1988) (highlighting how this problem is not just limited to the American medical industry by discussing the conflict between the Canadian Medical Association and the pharmaceutical industry); Sergio Sismondo, *Ghost Management: How Much of the Medical Literature Is Shaped Behind the Scenes by the Pharmaceutical Industry*?, 4 PLOS MED. 1429, 1429–33 (2007) (suggesting that drug companies often conduct and write studies and then pay academics to put their names on it very late in the process); Carl Elliott, *The Drug Pushers*, THE ATLANTIC (Apr. 1, 2006 12:00 PM), http://www.theatlantic.com/magazine/archive/2006/04/the-drug-pushers/304714/ (describing the conflict created by pharmaceutical reps influencing doctors' prescribing habits). *Contra* RICHARD A. EPSTEIN, OVERDOSE: HOW EXCESSIVE REGULATION STIFLES PHARMACEUTICAL INNOVATION (Yale University Press, 2006) (arguing that that the United States over-regulates the pharmaceutical industry).

4. *See, e.g.*, 21 C.F.R. § 54.1 (2013) (requiring clinicians involved in pharmaceutical research to disclose all financial connections to the sponsoring company, including payments and patents to try to reduce bias caused by financial ties); U.S. DEP'T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, CTR. FOR BIOLOGICS EVALUATION & RESEARCH, GUIDANCE FOR INDUSTRY: E9 STATISTICAL PRINCIPLES FOR CLINICAL TRIALS (1998), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf (detailing industry guidelines dedicated to reducing statistical bias or manipulation in research studies by pharmaceutical companies).

5. *See* Kristin Rising et al., *Reporting Bias in Drug Trails Submitted to the Food and Drug Administration: Review of Publication and Presentation*, 5 PLOS MED. 1561, 1567–68 (2008) (showing how common it is for drug trails to be manipulated or biased when run by drug companies).

6. *See* Marcia Angell, *Industry-Sponsored Clinical Research: A Broken System*, 300 JAMA 1069, 1069–71 (2008) (recalling particular issues when the drug company, Merck, had their own paid employees write studies regarding the effectiveness of one of their products, a practice that has also occurred at other companies); Harlan M. Krumholz & Joseph S. Ross, *A Model for Dissemination and Independent Analysis of Industry Data*, 306 JAMA 1593, 1593 (2011) (noting that public confidence in research had been shaken when companies have been shown to intentionally manipulate clinical research trials); Drummond Rennie, *When Evidence Isn't: Trials,*

Manufacturer bias can slant research when it is performed either in-house, or when manufacturers finance or manage external researchers.[8] Today, drug firms typically rely mainly on external researchers,[9] using Contract Research Organizations ("CROs"), or university-based researchers to carry out clinical trials and/or to perform some or all of the analysis.[10] Drug firms may also contract with specialists to design trials.[11] The corrupting influence persists because the drug sponsor chooses who will conduct the trials, and these researchers depend on the sponsor for their income;[12] additionally, researchers report to the drug sponsor, not to the FDA.[13] Researchers, therefore, have incentives to advance the goals of the drug sponsor and to follow the drug sponsor's directives.[14]

This Article explores a proposal that would preclude biased drug testing by removing all drug sponsor influence on the design and conduct of clinical trials for new drug applications ("NDAs"), a reform that would address the root of institutional corruption.[15] Recently advocated by leading

Drug Companies and the FDA, 15 J.L. & POL'Y 991, 998 (2007) (describing documented instances of physicians conducting studies on behalf of drug companies and intentionally administering competing drugs incorrectly to make the studied drug look more effective, or manipulating statistical analyses to show robust positive results).

7. *See, e.g.*, Rennie, *supra* note 6, at 995–96 (recounting a time when the author, as an editor of a major medical journal, realized that two authors had published dramatically conflicting results in different journals at the same time).

8. *See* Angell, *supra* note 6 (discussing how Contract Research Organizations ("CROs") are susceptible to bias by allowing manufactures near total control of study design and execution because drug companies are their only clients).

9. *See* Bodenheimer, *supra* note 2, at 1539–40 (2000) (observing how drug companies increasingly rely on CROs and site-management organizations ("SMOs") to conduct research instead of traditional academic institutions).

10. *Id.*

11. *Id.* (describing how companies will have an external investigator design the trial if they lack internal personnel with the needed expertise, or will design the trial in-house and then submit it to investigators for review).

12. *See* Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research*, 289 JAMA 454, 463 (2003) (discussing possible links between researchers in the biomedical field who are funded by drug sponsors and then achieve positive results in studies).

13. *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) (observing that drug companies often include confidentiality clauses in contracts made with external researchers to prevent public or even private discussion of results).

14. *See* Bodenheimer, *supra* note 2, at 1543 (noting that the pharmaceutical companies who provide all or some of a researcher's financial support use the money as leverage when being presented with potentially unfavorable results).

15. 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 231–34 (2011) (defining institutional corruption using examples from various governments around the world); DENNIS F. THOMPSON, ETHICS IN CONGRESS: FROM INDIVIDUAL TO INSTITUTIONAL CORRUPTION 37–43 (1995) (using the example

scholars, the idea has a long history, yet was neglected for over half a century due to pharmaceutical industry opposition.

A. The Origins of Contemporary Pharmaceutical Regulation

Before examining the oversight of clinical trials, let us briefly review the evolution of the pharmaceutical industry over the last century. In the beginning of the twentieth century, the drug market was premised on the doctrine of laissez-faire.[16] Manufacturers did not have to test their drugs or disclose the ingredients, could make any therapeutic claim, and could sell any product directly to consumers.[17]

Reformers and muckrakers—supported by the American Medical Association ("AMA")—spearheaded the fight for federal drug regulations.[18] 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.[19] The law presumed that, with accurate labeling, individuals

of five senators known as "The Keating Five" to describe institutional corruption); Dennis F. Thompson, *Two Concepts of Corruption: Making Campaigns Safe for Democracy*, 73 GEO. WASH. L. REV. 1036 (2005) (developing additional insight into institutional corruption in the political sphere via campaign laws). For a review of institutional corruption and the pharmaceutical industry, see the special issue (Volume 41, Issue 3) of the Journal of Law, Medicine and Ethics devoted to the Institutional Corruption and Pharmaceutical Industry. Symposium, *Institutional Corruption and the Pharmaceutical Industry*, 41 J.L. MED. & ETHICS 544 (2012). For discussion of institutional corruption, *see generally The Lab at Edmond J. Safra Center for Ethics*, HARVARD UNIV., http://www.ethics.harvard.edu/lab (last visited Oct. 26, 2014), which details the work of several researchers who are analyzing institutional corruption in the pharmaceutical economy and other areas of public life.

16. *See* HARRY F. DOWLING, MEDICINES FOR MAN: THE DEVELOPMENT, REGULATION, AND USE OF PRESCRIPTION DRUGS 187–212, 230–32 (1970) (discussing the history of food and drug law, and the Food and Drug Administration); PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION 11–94 (2003) (containing an overview of the history of Dr. Wiley, who developed the FDA); PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES 23 (1980) (illustrating that at the start of the 20th century, patients could go directly to the pharmacy to buy drugs without a prescription, and pharmacists could promote wares they chose to sell).

17. *See, e.g.*, Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1759 (1996) (noting that drug manufacturers in the early 20th century could claim that their product or an ingredient in it could cure cancer, even if there was no supporting evidence).

18. *See* DOWLING, *supra* note 16, at 155–56; *see also* HILTS, *supra* note 16, at 52 (describing how the American Medical Association forced congressional action by threatening their members' lobbying of the Senate if a bill was not passed).

19. Federal Food and Drug Act of 1906, Pub. L. No. 59-384, § 8, 34 Stat. 768, 770 (1906) (repealed 1938). *See also* Merrill, *supra* note 17, at 1758 (reviewing the content of the Pure Food and Drug Act and discussing its impact in court cases).

could safely choose drugs.[20] Advertising of therapeutic claims remained unregulated until the Shirley amendments in 1912 prohibited false and fraudulent statements regarding the curative or therapeutic effect of drugs.[21]

Industry opposition blocked enactment of the Roosevelt administration's 1933 bill to regulate drugs until a scandal in 1937. In order to improve the flavor of a sulfa-based drug called sulfanilamide, the Massengill Company added a chemical that was toxic, causing the rapid death of 106 people who had ingested the drug.[22] Congress then passed the Food, Drug, and Cosmetic Act of 1938 ("FDCA"), which required drug firms to seek FDA permission to market drugs, and which allowed the FDA 60 days to deny authorization if it found that the drug was dangerous or improperly labeled.[23]

Manufacturers then had incentives to conduct research and to evaluate their products.[24] The marketing of Thalidomide led to the birth of children with severe deformations in multiple countries, and created pressure for stronger regulation.[25] The 1962 amendments to the FDCA prohibited marketing of drugs unless the FDA granted approval, and the amendments removed the 60 day deadline for FDA review of new drugs.[26] The amendments required drug sponsors to demonstrate that drugs are effective—not only safe—for a designated use.[27] It also authorizes the FDA to withdraw its approval for drugs already on the market based on new evidence.[28] Manufacturers are required to track drug distribution to facilitate recalls of unsafe products, and to follow FDA standards for good manufacturing practices.[29] The law restricts promotion of drugs to

20. *See* TEMIN, *supra* note 16, at 4 (recalling that most consumers at the turn of the century chose drugs for themselves as opposed to a doctor choosing for them, so ensuring consumers knew what they were selecting and purchasing was a priority).

21. Pure Food Act Amendment of 1912, Pub. L. No. 62-301, 37 Stat. 416, 416–17 (1912).

22. *See* TEMIN, *supra* note 16, at 40–42 (providing more detail on the sulfanilamide scandal and how it was used to gain political support for drug regulation reform).

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

24. The 1938 Act did not require firms to show that their drugs were effective. *See* Federal Food, Drug, and Cosmetic Act § 505 (requiring evaluation of whether a drug is safe for use, but not requiring evidence that it is effective).

25. TEMIN, *supra* note 16, at 123–24.

26. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 104, 76 Stat. 780, 784 (1962) (codified as amended at 21 U.S.C. § 355 (2006)). For a history and analysis of the legislation, including how its development was impacted by tragic events, see Jerry Avorn, *Learning about the Safety of Drugs—A Half-Century of Evolution*, 36 NEW ENG. L. REV. 2151, 2151–53 (2011); Merrill, *supra* note 17, at 1764–65.

27. Drug Amendments of 1962 § 102(a)–(c) (codified as amended in scattered sections of 21 U.S.C. (2006)).

28. *Id.* § 102(d).

29. *Id.* §§ 101, 103.

therapeutic uses approved by the FDA.[30] Promotional materials must note risks, as well as benefits, and summarize side effects and contraindications.[31] The FDA specifies what information the label must include, and labels must state the generic name, as well as the brand name.[32]

In 1970, the FDA promulgated regulations that set standards for the evidence that manufacturers would have to submit in order to demonstrate that new drugs were safe and effective.[33] Since then, testing of drugs follow set stages.[34] After researchers have identified a potentially therapeutic molecule, they test its effects in laboratories on chemicals, cells, or tissues.[35] The FDA then requires firms to test its drugs for toxicity on animals.[36] Drug candidates that have not been ruled out due to toxicity or lack of efficacy can then be tested on humans in three phases.[37]

In Phase I, researchers test the drug on a small number of human subjects only to determine whether it is toxic in humans, and if so, at what doses.[38] Phase II testing consists of a clinical trial in a larger group of patients in order to measure its benefits and risks.[39] Drugs that are not highly toxic are tested in Phase III clinical trials on a large number of human research subjects, and researchers then compare its effect with a control group.[40] Typically, the control group uses a placebo or an

30. *See Promotion of Unapproved Drugs and Medical Devices*, News & Events, U.S. FOOD & DRUG ADMIN. (statement of William B. Schultz, Deputy Commissioner for Policy, FDA (Feb. 22, 1996)), http://www.fda.gov/NewsEvents/Testimony/ucm115098.htm (last updated Aug. 6, 2009).

31. Drug Amendments of 1962 § 131(a).

32. *Id.* §§ 112, 131.

33. *See* Suzanne White Junod, *FDA and Clinical Drug Trials: A Short History*, FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm (last visited Oct. 28, 2014) (providing a brief historical overview of legislative developments during the 1960s and 1970s and their corresponding impact on clinical drug trials).

34. *See* RICHARD E. ROWBERG, CONG. RESEARCH SERV., RL30913, PHARMACEUTICAL RESEARCH AND DEVELOPMENT: A DESCRIPTION AND ANALYSIS OF THE PROCESS 4–5 (2001) (discussing the phases of drug research).

35. For a description and history of the process used for drug development and testing drugs, see SUSAN ALDRIDGE, MAGIC MOLECULES: HOW DRUGS WORK (Cambridge University Press, 1998) and JÜRGEN DREWS, IN QUEST OF TOMORROW'S MEDICINES (Springer-Verlag, 2003).

36. *See* ROWBERG, *supra* note 34, at 8 (describing how animal testing provides information on the immediate impact of the drug, long term effects, and even how the drug might impact pregnancy).

37. 21 C.F.R. § 312.21 (2014).

38. *See* ROWBERG, *supra* note 34, at 9 (explaining how Phase I consists of 10 to 100 humans, and determining what range of dose concentrations do not produce unacceptable side effects). *See also* 21 C.F.R. § 312.21(a) (detailing Phase I of an investigation).

39. *See* ROWBERG, *supra* note 34, at 10 (explaining how Phase II trials include 50 to 500 humans to determine the effectiveness a drug). *See also* 21 C.F.R. § 312.21(b) (explaining Phase II of an investigation).

40. *See* ROWBERG, *supra* note 34, at 10–11; 21 C.F.R. § 312.21(c).

alternative therapy.[41] Human subjects are randomly assigned to either the test group or the control group.[42] It is a double blind study, which means that the medication must be coded so that neither the physician who administers the drug, nor the individual taking the drug, knows which individuals receive the test drug and which individuals receive the placebo (or the standard therapy to which it is compared) until the code is broken after collection of data.[43] To counter the risk of fraud or unreliable studies, regulations establish standards for research methods, record keeping, and data reporting.[44] The FDA also inspects toxicological laboratories and facilities that conduct clinical trials in order to monitor compliance.[45]

B. Options for Control of Clinical Trials

There are six options for addressing conflicts of interest in clinical trials, which are displayed in Table 1 below. At one extreme, the drug sponsor has complete control over clinical trials; at the other extreme, the federal government conducts the clinical trials. Between these two poles are four strategies that can be used individually or combined. The FDA relies mainly on the second strategy, which has been supplemented in recent years by the fourth strategy.

41. ROWBERG, *supra* note 34, at 10.

42. CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: E10 CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS 3 (2001), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073139.pdf.

43. *See id*. at 4 (explaining that the purpose of double blind studies is to minimize biases).

44. *See* 21 C.F.R. §§ 312.57, 314.126 (2010) (addressing recordkeeping, and adequate and well-controlled studies).

45. *See* OFFICE OF REGULATORY AFFAIRS, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD LABORATORY PRACTICES, QUESTIONS AND ANSWERS 7 (1981), *available at* http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133748.pdf; FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., INFORMATION SHEET GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS: FDA INSPECTIONS OF CLINICAL INVESTIGATORS 3 (2010), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf.

TABLE 1: STRATEGIES TO ADDRESS DRUG SPONSOR CONFLICTS OF INTEREST IN CLINICAL TRIALS

←Manufacturer Control					Government Control→
1	**2**	**3**	**4**	**5**	**6**
Drug firms conduct clinical trials with little regulation	FDA regulates and oversees clinical trials that drug firms conduct	Government or private entity certifies clinical researchers. Drug firms conduct clinical trials using certified researchers	Government promotes transparency by requiring: (1) registration of trials; (2) disclosure of clinical study reports; or (3) disclosure of patient level data	Government selects independent entities to conduct clinical trials	Government agency conducts clinical trials

The first option ignores the conflict of interest in allowing drug firms to oversee their own research, and permits the drug firm to conduct clinical trials without any oversight.[46] The second strategy has the FDA regulate clinical trials that are conducted by drug firms, using standards for research.[47] The third strategy requires that only certified research organizations and researchers conduct clinical trials.[48] The fourth strategy promotes transparency of drug firm-sponsored research (since 2007, the United States has required registration of clinical trials to promote transparency[49]).[50] The fifth strategy precludes drug firm bias by having the

46. *See supra* notes 1–14 and accompanying text (explaining the conflict of interest in allowing drug firms to oversee their own research).

47. *See supra* note 33 and accompanying text (explaining that this is the strategy that the FDA has taken).

48. *See* N.Y. Acad. of Med. Comm. on Pub. Health, *The Importance of Clinical Testing in Determining the Efficacy and Safety of Drugs*, 38 BULL. N.Y. ACAD. MED. 415, 420, 429 (1962) (explaining how there is no requirement for a tester to certify his professional qualifications, and articulating the need for establishing professional standards).

49. *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801(j)(2)(C), 121 Stat. 823, 907–08. The push for registration of clinical trials emerged after studies showed the presence of biased information in published literature evaluating drugs. *See* An-Wen Chan et al., *Empirical Evidence for Selective Reporting of Outcomes in Randomized*

federal government select independent researchers to design and conduct clinical trials.[51] The sixth strategy mandates that the government agency conduct clinical trials.

Until now, almost all regulations have employed the second strategy by setting technical standards for laboratory testing and clinical trials.[52] This strategy, however, could be further developed in new ways.[53] For example, regulations could oversee financial relations between the drug

Trials: Comparison of Protocols to Published Articles, 291 JAMA 2457, 2457–65 (2004) (explaining how drug firms published studies showing positive results but buried studies that show drugs' ineffectiveness or high risks, causing medical journal editors to promote clinical trial registration to increase access to data). In 2004, the International Committee of Medical Journal Editors agreed that their journals would not publish clinical trial results unless the trial was registered before patients enrolled. Catherine DeAngelis et al., Editorial, *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 351 NEW ENG. J. MED. 1250, 1250–51 (2004). The Committee of Editors decided that registries should include data specified by the World Health Organization ("WHO"). *See WHO Trial Registration Data Set*, International Clinical Trials Registry Platform ("ICTRP"), WORLD HEALTH ORGANIZATION, http://www.who.int/ictrp/network/trds/en/index.html (last visited Oct. 17, 2014) (setting forth the minimum amount of trial information required to appear for a trial to be considered fully registered by the WHO).

Current law requires registering certain trials on the ClinicalTrials.gov website if the trial is part of an FDA investigation of a new drug application, or if there is a trial site in the U.S. In addition, researchers must post key results within a year after collecting data. Researchers have up to three years, however, to post results for studies of off-label drug uses (i.e., uses other than those the FDA has approved). *See* 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, 2338–39 (2011) (stating that while the federal government mandates that clinical trials be registered, researchers are permitted to a three year delay). Nevertheless, registration practice falls short of what the law requires. *See id.* (finding that 39% of trials were registered late, while only 12% of completed studies registered their results within the year); Sylvain Mathieu et al., *Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials*, 302 JAMA 977, 977 (2009) (stating that registration requirements typically were ignored, and were the exception to the rule rather than the norm). Moreover, current law and policy impedes access to information on drug safety. 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, 487 (2007) (explaining how current law and policy impedes access to information on drug safety).

50. *See* Galbraith, *supra* note 13, at 768 (2009) (describing how increased transparency would help increase public trust and interest); Ida Sim et al., Comment, *Clinical Trial Registration: Transparency is the Watchword*, 367 LANCET 1631, 1631 (2006) ("Transparency [of clinical trials] is the best antidote to such free-floating distrust.").

51. *See* Rennie, *supra* note 6, at 1010 (arguing for a separate and independent entity of researchers to engage in trials, who would be prohibited from receiving funds from pharmaceutical companies as a way to preclude drug firm bias).

52. *See* Galbraith, *supra* note 13, at 713–14 (2009) (explaining the FDA's role in setting the prerequisites that pharmaceutical companies must substantiate in claiming that a drug is safe and effective); Rennie, *supra* note 6, at 1003 (2007) (describing the role of the FDA and the standards for trials).

53. *See infra* notes 59–64 and accompanying text.

sponsor and researchers.[54] Regulations could also preclude individuals and firms from conducting a clinical trial if either have significant financial conflicts of interest.[55]

Some reformers in the 1960s and 1970s advocated for certification of researchers (the third strategy),[56] but the United States has not pursued this approach.[57] Regulations could authorize the federal government or private organizations to certify researchers, and to require that only certified researchers and organizations conduct drug trials used to support NDAs.[58]

To strengthen the transparency strategy, regulations could require that drug sponsors and their researchers make the clinical study report public (which drug firms currently only supply to the FDA) in order to comply with the FDA rules and international standards.[59] Clinical study reports contain key information related to the clinical trial, including: the study protocol, the designated clinical end points, discussion of methods and statistical analysis, tabulated data, and analysis of data.[60] Regulations could also require disclosure of clinical trial patient level data.[61] Making detailed

54. *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., FINANCIAL RELATIONSHIPS AND INTERESTS IN RESEARCH INVOLVING HUMAN SUBJECTS: GUIDANCE FOR HUMAN SUBJECT PROTECTION 5–6 (2004), *available at* http://www.hhs.gov/ohrp/archive/humansubjects/finreltn/fguid.pdf (raising points to consider when determining whether specific financial interests in research affect human subjects' rights and welfare, and which approaches should subsequently be taken to protect those subjects).

55. *See id.* (explaining how conflicts of interest may be managed by eliminating or mitigating financial interests).

56. *See* N.Y. Acad. of Med. Comm. on Pub. Health, *supra* note 48, at 433–34 (urging that clinical testing be formally recognized as a medical specialty, and noting specific requirements for certification).

57. *See generally* 21 C.F.R. § 312.70 (2014) (describing the selection process of investigators and monitors). There is still no guidance on the certification of researchers, but the FDA can bar researchers from conducting clinical trials used to support new drug applications. *Id.*

58. *See* Rennie, *supra* note 6, at 1010.

59. *See* Guideline for Industry: Structure and Content of Clinical Study Reports, 61 Fed. Reg. 37,320, 37,322 (July 17, 1996) (stating that currently, requirements for data presentation vary widely); Peter Doshi et al., *The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience*, 10 PLOS MED. 1, 2 (2012) (explaining how the European Medicines Agency has recently started to make clinical trial reports available when they are requested under public disclosure statutes); Marc A. Rodwin & John D. Abramson, *Clinical Trial Data as a Public Good*, 308 JAMA 871, 871 (2012) (indicating that John Abramson and I have called for legislation to require mandatory disclosure of clinical study reports for FDA approved drugs); Press Release, European Meds. Agency, Medicines Agency Widens Public Access to Documents (Nov. 30, 2010) (on file with author), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/11/WC500099468.pdf.

60. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801, 121 Stat. 823, 904–22 (2007).

61. *See* Harlan M. Krumholz & Joseph S. Ross, *A Model for Dissemination and Independent Analysis of Industry Data*, 306 JAMA 1593, 1594 (2011) (stating that a complete release of

information public on clinical trials would allow independent researchers to review the analysis, or to perform their own evaluation. Proponents of this approach say that it would make it harder for drug sponsors to hide risks from the public, and that it would also help to hold the FDA accountable for its decisions.[62]

New regulations that advanced the second, third, and fourth strategies would not remove the drug sponsor bias. Consequently, some critics have proposed ending the drug sponsor's control over clinical trials that the FDA uses to evaluate drugs.[63] 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 sponsor would finance the drug testing, just as they currently do. Some proposals, however, would have the pharmaceutical industry collectively finance the testing; others propose that the federal government share the costs of drug testing with the pharmaceutical industry collectively, or with the drug sponsor.[64]

C. Contemporary Proposals for Independent Drug Testing

In the last two decades, several authors have called for independent drug testing. These proposals are supported by scholarly literature that documents publication bias as well as biased research design in drug company-controlled trials.[65] In 2004, Dr. Marcia Angell proposed the

patient-level data addresses industry and societal concerns, and that the "way forward" is to disclose clinical trial patient level data).

62. *See id*. at 1593–94 (proposing a model that emphasizes independence, transparency, fairness, and reproducibility, which would allow for the release and review of findings, and further instill confidence in the public that efforts are not being manipulated by funding or coordinating organizations).

63. *See* Sheldon Krimsky, *Publication Bias, Data Ownership, and the Funding Effect in Science: Threats to the Integrity of Biomedical Research*, RESCUING SCIENCE FROM POLITICS: REGULATION AND THE DISTORTION OF SCIENTIFIC RESEARCH 61, 81 (Wendy Wagner & Rena Steinzor eds., 2006) (proposing an independent institute that would contract with independent researchers and would not be controlled by the sponsoring company); Catherine D. DeAngelis, *Conflict of Interest and the Public Trust*, 284 JAMA 2237, 2238 (2000) ("When an investigator has a financial interest in or funding by a company with activities related to his or her research, the research is lower in quality, [and is] more likely to favor the sponsor's product . . . .").

64. *See infra* Parts II, III (discussing contemporary proposals).

65. *See* Lisa Bero & Drummond Rennie, *Influences on the Quality of Published Drug Studies*, 12 INT'L J. TECH. ASSESSMENT HEALTH CARE 209, 211 (1996) (stating that the most serious threat to the quality of drugs arise out of systematic bias introduced during the research process); 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, 51 (1989) (finding that hidden biases, which are difficult to detect, and overt biases existed in the design of clinical studies); P.C. Waller et al., *Review of Company*

creation of an Institute for Prescription Drug Trials within the National Institutes of Health ("NIH") that would oversee the clinical trials.[66] This proposal projected that the NIH would carry out the research through independent researchers at universities.[67] The data would belong to the institute and the researchers, and the results would be public.[68] The FDA would then rely on these studies to decide whether or not to authorize the marketing of the drug.[69] To fund the institute, drug firms would be assessed a percentage of their gross revenues.[70]

In 1993, Doctors Wayne Ray, Marie Griffin, and Jerry Avorn proposed creating a governmental center that would assess drug effectiveness and compare the costs and benefits of alternative drug therapies.[71] The center would fund and/or conduct studies of drugs already approved for sale, and coordinate drug research performed by government agencies.[72] The authors would finance the center through a tax on drug sales and third-party payer subscription fees.[73]

In 1996, Doctors Lisa Bero and Drummond Rennie advocated for legislation that would support independent studies of drug cost effectiveness and comparative effectiveness that would be funded by a user fee on pharmaceutical firms.[74] In 2007, Dr. Rennie argued that the United States should create a federally financed National Institute of Clinical Trials.[75] This institute would decide what trials to conduct and would make

Postmarketing Surveillance Studies, 304 BRIT. MED. J. 1470, 1470–71 (1992) (arguing that post-marketing studies have made a limited contribution to the assessment of drug safety overall).

66. ANGELL, *supra* note 3, at 244–45 (paperback ed. 2005).

67. *Id.* at 245.

68. *Id.*

69. *Id*. at 245–46 (explaining that the Institute for Prescription Drug Trials would oversee clinical trials before FDA approval, rather than after).

70. *Id*. at 245. Dr. Angell summarizes problems with industry sponsored clinical trials. *See generally* Angell, *supra* note 6, at 1070 (discussing conflicts of interest that exist within industry sponsored drug research). For a review of problems with industry funded trials, see Thomas Bodenheimer, *Uneasy Alliance*: *Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539 (2000).

71. Wayne A. Ray et al., *Sounding Board*: *Evaluating Drugs After Their Approval for Clinical Use*, 329 NEW ENG. J. MED. 2029, 2031 (1993). Their proposal incorporated parts of the FDCA amendments proposed in 1974 and 1978, the Joint Commission on Prescription Drug Use's 1980 recommendations, and Senator David Pryor's proposed Pharmaceutical Access and Prudent Purchasing Act of 1990. *Id*. at 1031.

72. *Id*. at 2030–31.

73. *Id*. at 2031.

74. Bero & Rennie, *supra* note 65, at 229. Several other physicians have called for increasing funding for clinical trials to improve pharmaceutical policy and clinical care. *See* Alastair J.J. Wood et al., *Sounding Board*: *Making Medicines Safer—The Need for an Independent Drug Safety Board*, 339 NEW ENG. MED. J. 1851, 1852 (1998) (proposing the creation of an independent drug safety board to evaluate drugs).

75. Rennie, *supra* note 6, at 1009–11.

grants to researchers.[76] Researchers would receive all of their funds through their institutions and would not be allowed to receive other funds.[77]

A group of scholars interested in public goods and intellectual property have also called for publicly funded clinical trials to ensure unbiased evaluation, and to reduce the cost of drug development.[78] They argue that if clinical trials were publicly funded, it would be unnecessary to grant patents or exclusive marketing periods to drug firms—at the very least, we could shorten the duration of the monopoly.[79] Additionally, these scholars note that lower prices would increase access to pharmaceuticals globally.[80]

Most contemporary proponents of independent testing, however, are either not aware, or have forgotten, that Congress considered similar proposals between the late 1950s and 1980.[81]

76. *Id*. at 1010–11.

77. *Id*. (arguing that such a system would allow for greater credibility).

78. *See e.g.*, Tracy R. Lewis et al., *The Case for Public Funding and Public Oversight of Clinical Trials*, THE ECONOMISTS' VOICE, Jan. 2007, at 1, 1–4 (arguing that independent drug testing conducted by the federal government would eliminate a conflict of interest, which exists between the drug manufacturers and drug testers).

79. *See* James Love & Tim Hubbard, *Prizes for Innovation of New Medicines and Vaccines*, 18 ANNALS HEALTH L. 155, 162–63 (2009) (stating that prizes could be a viable alternative to granted exclusive rights); Tracy R. Lewis et al., *Treating Clinical Trials as a Public Good: The Most Logical Reform* 3 (Sept. 1, 2006) (unpublished manuscript) (on file with the University of California Berkeley Law and Economics Workshop), *available at* http://escholarship.org/uc/item/3cn7258n (arguing that the elimination of drug production monopolies would benefit both health care providers and customers in terms of cost).

80. *See* Love & Hubbard, *supra* note 79, at 171–72 (stating that a drug price decrease of 95% to 99% is feasible if greater competition were allowed in the development of medicines, allowing for greater access to drugs, especially those used to treat serious conditions); James Love & Tim Hubbard, *A New Trade Framework for Global Healthcare R&D*, 2 PLOS BIOLOGY 147, 150 (2004) (arguing that greater competition in drug research and development will allow for new medical inventions at marginal costs, allowing resources to be allocated to those areas with the greatest needs); Comment to the World Health Org. Intergovernmental Working Grp. on Pub. Health, Innovation & Intellectual Prop., James Love, Knowledge Ecology Int'l (Sept. 30, 2007) (on file with the World Health Org.), *available at* http://www.who.int/phi/public_hearings/second/contributions_section2/Section2_JamesLove-KEI_prizes.pdf (eliminating market exclusivity for prescription drugs would create greater supply and access to medical devices and products, and could have a dramatic change on the global market for pharmaceutical drugs).

81. *See Administered Prices in the Drug Industry (Antibiotics), Part 24: Hearings Before the Subcomm. on Antitrust & Monopoly of the S. Comm. on the Judiciary*, 86th Cong. 13934–35 (1960) [hereinafter *Administered Prices Hearing, Part 24*] (indicating that Senator Kefauver had introduced the bill calling for drug testing to be conducted by the FDA); *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 Congress (1967–79); *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study, Part 3: Hearings Before the Subcomm. on Reorganization & Int'l Orgs. of the S. Comm. on Gov't Operations*, 88th Cong. 790 (1963) [hereinafter *Drug Research & Regulation Hearings, Part 3*]; *Preclinical and Clinical Testing by the Pharmaceutical Industry, Part 1*: *J. Hearings Before the Subcomm. on Health of the S. Comm.*

II. THE STALLED REFORM: PROPOSALS FOR INDEPENDENT DRUG TESTING FROM 1959–1980

Between 1959 and 1980, Congress, the FDA, industry advocates, and consumer advocates debated how drugs should be tested.[82] Hearings chaired by Senator Estes Kefauver (D-TN), Hubert H. Humphrey (D-WI), Gaylord Nelson (D-WI), and Ted Kennedy (D-MA) document their views.[83] The hearings revealed two main problems with relying on manufacturer testing: (1) the economic incentives of drug firms compromised their impartiality, biased the design of the clinical trials, and sometimes led to fraud;[84] and (2) testing laboratories and investigators performed shoddy work because they lacked training, and cut corners to boost income.[85] By 1960, the FDA found that many NDAs were based on poorly designed and implemented studies.[86] FDA investigations and congressional hearings revealed fraud by testing laboratories, physician investigators, and drug firms, finding quality problems that compromised the reliability of testing.[87] The FDA developed regulations to address these

on Labor & Pub. Welfare and the Subcomm. on Admin. Practice & Procedure of the S. Comm. on the Judiciary, 94th Cong. (1975) [hereinafter *Preclinical & Clinical Testing Hearings, Part 1*].

82. *See, e.g.*, *Administered Prices Hearing, Part 24*, *supra* note 81; *Drug Research & Regulation Hearings, Part 3*, *supra* note 81; *Preclinical & Clinical Testing Hearings, Part 1*, *supra* note 81.

83. *See* sources cited *supra* note 81.

84. 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 & Int'l Org. of the S. Comm. on Gov't Operations*, 87th Cong. 32 (1962) (statement of William S. Middleton, Chief Medical Director, Veterans' Administration); *Interagency Coordination in Drug Research and Regulation: Agency Coordination Study, Part 2: Hearings Before the Subcomm. on Reorganization & Int'l Org. of the S. Comm. on Gov't Operations*, 87th Cong. 373, 375 (1962) [hereinafter *Drug Research & Regulation Hearings, Part 2*] (statement of Mr. William Weiss, Bureau of Program Planning and Appraisal, Food and Drug Administration).

85. *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 (Houghton Mifflin, 1965); JOHN BRAITHWAITE, CORPORATE CRIME IN THE PHARMACEUTICAL INDUSTRY 105 (1984) (explaining that data could be fabricated both to meet particular deadlines as well as to produce results that were favorable to the manufacturer); MILTON SILVERMAN & PHILIP R. LEE, PILLS, PROFITS, AND POLITICS 137 (1974) (stating that there are few research workers with both the competence and motivation to properly conduct clinical tests).

86. *See Drug Research & Regulation Hearings, Part 3*, *supra* note 81, at 782 (finding that many new drugs did not have sufficient data to establish that the particular drug was both safe and effective).

87. *Id*. at 792 (illustrating expert testimony that revealed that approved drugs had been improperly investigated by investigators with questionable qualifications); *see also Drug*

problems.[88] The standards for drug testing became more rigorous and FDA oversight increased, but congressional hearings revealed that many problems still persisted.[89]

A. 1959–1961: The Kefauver Hearings and Other Proposals

Senator Estes Kefauver held hearings on the pharmaceutical industry from 1959 to 1961.[90] In testimony, Dr. Maxwell Finland, associate professor at Harvard Medical School, proposed having the NIH set up study sections to evaluate drugs.[91] That way, as Dr. Finland notes, "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."[92] Dr. Finland also warned of risks when university researchers depended on drug firm grants.[93] He said that "... departments of clinical pharmacology[ ] should not depend ... on funds that come from individual drugs, because ... some people cannot perhaps divorce their judgment from the sources of their

Research & Regulation Hearings, Part 2, *supra* note 84, at 375 (describing how in one expert's opinion, unconscious bias rather than overt fraud provides the greatest opportunity for poor testing of new drugs). These problems led many people to conclude that the federal government should either test drugs or contract with independent parties to design and carry out the clinical trials. *See Administered Prices Hearing, Part 24*, *supra* note 81, at 13933 (statement of Maxwell Finland, Associate Professor of Medicine, Harvard Medical School) (noting that the National Institutes of Health could oversee the testing of new drugs, ensuring a proper supply of materials and qualified staff to conduct studies).

88. *See, e.g.*, *Significant Dates in U.S. Food and Drug Law History*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm (last updated Mar. 25, 2014) (showing that in 1962, the FDA passed the Kefauver-Harris Drug Amendments to ensure drug efficacy and greater safety).

89. *See Preclinical & Clinical Testing Hearings, Part 1*, *supra* note 81, at 11–12 (discussing issues in scientific data retrieval, which existed within the FDA).

90. The hearing initially focused on market competition, but after the Thalidomide disaster, they focused on drug safety issues, including drug testing. *See Administered Prices Hearing, Part 24*, *supra* note 81, at 13609, 13943, 14041 (discussing the need for competent expert research into whether drugs are safe for the general public). The hearings and recommendations were summarized in SUBCOMM. ON ANTITRUST & MONOPOLY, ADMINISTERED PRICES: DRUGS, S. REP. NO. 87-448, at 245 (1961). For an engaging popular account of the hearings on the pharmaceutical industry chaired by Senator Estes Kefauver, see RICHARD HARRIS, THE REAL VOICE (Macmillan 1964).

91. *See Administered Prices Hearing, Part 24*, *supra* note 81, at 13933 (explaining that the National Institutes of Health would assign funds to testing centers with proper qualifications to conduct clinical tests). 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, *Clinical Investigation of New Antimicrobial Agents*, 120 J. INFECTIOUS DISEASES 620 (1969).

92. *Administered Prices Hearing, Part 24*, *supra* note 81, at 13933.

93. *Id*. at 13934.

support."[94] Senator Kefauver added that "the efficacy of drugs should be tested by the Food and Drug Administration."[95] Dr. Finland believed, however, that it would be preferable to have an independent entity carry out the study in order to avoid having an FDA scientist evaluate the agency's research.[96]

In 1960, Alek Rozental, an economics professor at Saint Louis University, published "The Strange Ethics of the Ethical Pharmaceutical Industry" in *Harper's Magazine*.[97] To ensure drug safety, Rozental wrote that the United States should follow the 1959 proposal of the United Kingdom's Hinchliffe committee on drug safety and cost.[98] Rozental recommended that "all new drugs . . . be subject to independent clinical trials preferably conducted by a central organization, to be financed by the industry."[99]

B. 1962–1963: The Humphrey Hearings

Senator Hubert Humphrey chaired hearings before the Subcommittee on Reorganization and International Organizations from August of 1962 through 1964.[100] The committee examined three key questions: (1) what

94. *Id.*

95. *Id.*

96. *Id.*

97. *See* Alek A. Rozental, *The Strange Ethics of the Ethical Drug Industry*, HARPER'S MAG., May 1960, at 73, 73 (discussing the need for reform of the drug industry to better serve doctors and patients in light of the large profits drug companies were making at the time).

98. *Id.* at 84.

99. *Id*. Rozental suggested that another option that might generate less political opposition would be to create an independent profession of clinical testers, akin to certified public accountants serving as independent auditors. *Id.*

100. *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 Governmental Operations*, 88th Cong. (1963) [hereinafter *Drug Research & Regulation Hearings, Part* 1 *(88th Cong.)*]; *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 Governmental Operations*, 88th Cong. (1963) [hereinafter *Drug Research & Regulation Hearings, Part 2 (88th Cong.)*]; *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 Governmental Operations*, 88th Cong. (1963) [hereinafter *Drug Research & Regulation Hearings, Part 3 (88th Cong.)*]; *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 Governmental Operations*, 88th Cong. (1963) [hereinafter *Drug Research & Regulation Hearings, Part 4 (88th Cong.)*]; *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 Governmental Operations*, 88th Cong. (1963) [*hereinafter Drug Research & Regulation Hearings, Part 5 (88th Cong.)*]. The Humphrey hearings began after the Kefauver hearings (1959–1961), but before Congress passed the 1962 FDA amendments.

role should the federal government play in testing drugs or setting standards for drug testing; (2) which organizations should conduct clinical tests; and (3) what qualifications should individuals have to conduct clinical trials?[101]

When the hearings began, the FDA had not yet developed regulations specifying how drugs should be tested under the 1962 FDA amendments.[102] The 1938 Food and Drug Act provided that manufacturers had to select reliable investigators, specifying that these reliable investigators needed to be experts qualified by scientific training."[103] The FDA declined to specify criteria that qualified individuals as experts, explaining that it was not authorized to control the practice of medicine.[104]

Prior to regulations in 1970, there was little distinction between physicians and investigators.[105] Drug firms would frequently give investigational drugs to several practitioners to test on their patients. Pharmaceutical firms would draw on their reports or testimonials when submitting NDAs. The FDA recommended that specialists test the drugs in the diseases for which that drug would be used, and that firms employ several investigators, each of which would work independently in different locations to ensure a balanced assessment.[106] Drug testing, however, was often not clearly separated from marketing.[107] In 1960, Dr. Mendel C. Sheps from the University of Pittsburgh School of Medicine wrote that "the scientific requirements for careful investigation . . . compete with high-pressure marketing demands."[108] In fact, he continued, "the responsibility for arranging . . . the first trials on human beings is at times given to detail men."[109]

101. *Drug Research & Regulation Hearings, Part 1 (88th Cong.)*, *supra* note 100, at 57–58.

102. The FDA proposed 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. 3073–74 (proposed Feb. 17, 1970) (to be codified at 21 C.F.R. §§ 130, 146).

103. Federal Food, Drug and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1053 (1938) (codified at 21 U.S.C. § 355 (2013).

104. N.Y. Acad. of Med. Comm. on Pub. Health, *supra* note 48, at 420.

105. *See id.* at 429 (noting that a physician "tacitly qualifies himself" as an investigator and that there is limited oversight of a physician's proper qualifications to be an investigator, thus blurring the line between physician and investigator).

106. *Id.* at 420.

107. *Drug Research & Regulations Hearings, Part 4 (88th Cong.)*, *supra* note 100, at 1590 (explaining that high-pressure marketing demands often influenced the clinical testing and perceived worthiness of drugs).

108. *Id.* (explaining that clinical studies served a dual purpose: not only were they arranged to gain scientific insight on the "clinical worthiness" of the said drug, but they also attempted to promote the drug to the medical profession to gain their acceptance and support).

109. *Id.*

The hearing record included the New York Academy of Medicine's 1962 report on drug testing, which found that many tests were substandard because investigators lacked training or experience in designing studies, or in recording and reporting results.[110] The record noted that neither the FDA, nor any other official or professional body, had set standards for clinical investigators.[111] The report recommended that investigators should have training in clinical research, that pharmaceutical firms' medical directors should have experience in clinical testing, and that the research should take place in hospitals.[112]

The report rejected two proposals, however, that would shift responsibility from drug firms to the federal government. The first proposal would establish a "national central office on testing . . . [that would] arrange to conduct and supervise the testing of all products."[113] The report argued that a national center would be overly bureaucratic, which would be unacceptable to pharmaceutical manufacturers and clinicians.[114] The second proposal, modeled on the AMA Committee on Therapeutic Trials, would establish a national referral agency for clinical investigators.[115] The report also did not support this idea due to the failure of the AMA's earlier testing plan.[116]

In 1963, Consumers Union, which had built its reputation as an independent tester of consumer products, evaluated the 1962 FDA amendments in its journal, *Consumer Reports*. Consumer Unions said that the "fundamental question" is this: "is it good public policy to permit the drug manufacturers to do or to supervise the clinical testing of their own products?"[117] Consumers Union argued that since the FDA relied on reports "procured by the manufacturers," the arrangement was an inadequate substitute for "an objective testing agency."[118] In Senate testimony, Consumers Union called for the creation of an independent government

110. *Drug Research & Regulation Hearings, Part 2 (88th Cong.), supra* note 100, at 528, 536.

111. *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 & Regulation Hearings, Part 4 (88th Cong.), supra* note 100, at 1607. The institution ultimately decided against it, however, concluding that a certification system for scientists' conduct of research had "no acceptable precedent." *Id.*

112. *Drug Research & Regulation Hearings, Part 2 (88th Cong.*), *supra* note 100, at 539–40.

113. *Id.* at 538.

114. *Id.*

115. *Id.*

116. *Id.*

117. *Drug Safety*, CONSUMER REPS., Mar. 1963, at 134, 136.

118. *Drug Research & Regulation Hearings, Part 3 (88th Cong.), supra* note 100, at 1052.

agency to test drugs that would produce all of the data that the FDA would use when deciding whether or not to approve new drugs for marketing.[119]

Dr. Charles May, professor of pediatrics at the New York University School of Medicine, called for increased clinical testing by publicly funded researchers.[120] Dr. May proposed the creation of publicly funded, autonomous drug testing centers located at medical-school-affiliated-hospitals,[121] where the facilities and core staff would be publicly funded.[122] In Dr. May's proposal, the FDA or other agencies would provide grants for individual research projects, and investigators would choose research projects based on scientific merit.[123]

Several other physicians suggested that there should be a separation between firms sponsoring a new drug and researchers testing the drug.[124] One idea was to have the industry pool funds for testing new drugs.[125] More frequently, physicians have proposed even greater separation.[126] Dr. George Baehr, Chair of the New York State Public Health Council, proposed testing drugs only in FDA-approved trial centers located in teaching hospitals.[127] Dr. M. Harold Book of Kings Park State Hospital wrote, "the preliminary testing on human patients . . . should be assigned to

119. *Id.*

120. *Id.* at 1034, 1053–54 (explaining that clinical testing should be conducted in New Treatment Centers by publically funded researchers such as clinicians, pharmacologists, or any specialists the studies required).

121. Dr. May summarized his ideas in a March 1963 memorandum and subsequent hearing testimony. *Id.* at 1044–45, 1053–54 (explaining that his proposal would be to create new centers for drug research in medical institutions, starting with a few, and expanding the program to other facilities if the launching of the program is successful).

122. *Id.* at 1054.

123. *Id.* (explaining that the choice, control, and initiative of choosing research projects would remain with the investigators who are supported by basic grants).

124. *Drug Research & Regulation Hearings, Part 4 (88th Cong.)*, *supra* note 100, at 1617–18, 1620, 1625–28, 1631–34, 1636, 1639 (highlighting a collection of correspondence from scientists and other sources that suggest sponsors of drugs should be separate from those researching the drugs).

125. 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. The president of the American Society for Clinical Investigation supported a proposal to replace the practice of having individual drug firms directly pay investigators; in its place, a board of impartial scientists and public and industry representatives should disburse payments to drug testers from a common fund supported by pharmaceutical firms. *Drug Research & Regulation Hearings, Part 5 (88th Cong.)*, *supra* note 100, at 2419–20 (statement of Irving M. London, President, Am. Society for Clinical Investigation).

126. *See Drug Research & Regulation Hearings, Part 4 (88th Cong.)*, *supra* note 100, at 1617–18, 1620, 1625–28, 1631–34, 1636, 1639 (addressing physicians' proposals to conduct clinical drug testing independent from manufacturer control).

127. *Id.* at 1641 (explaining that all drugs should be clinically tested in FDA-approved trial centers located at teaching hospitals of medical schools before being released for sale).

some independent noncommercial agency and not to any individuals or groups who are dependent . . . for financial support on pharmaceutical houses."[128] Doctors I.H. Page and Ray W. Gifford, Jr. of the Cleveland Clinic wrote that "an independent agency [should] be created to receive and administer funds to pay the costs of drug testing."[129]

During this period, there were numerous examples of fraud in pharmaceutical firm-sponsored testing.[130] In 1962, reports of harmful side effects from the use of MER/29 (triparanol), a drug marketed to reduce blood cholesterol, led the manufacturer, which was a subsidiary of Richardson-Merrell, to stop selling the drug.[131] Investigations later found fraudulent reporting of the toxicological studies.[132] Investigations by the FDA and other federal agencies revealed fraudulent reporting of the toxicological studies by university based researchers.[133] There were also reports of bias arising from drug company sponsorships of drug trials, and the trade press reported on "rigging" of research.[134] A 1963 *New England Journal of Medicine* editorial criticized firms that set unethical publication restrictions, specifically those who only permitted publication of positive results.[135]

In the 1964 hearings, Senator Humphrey reported the views of professionals on how drug firms' payments to clinical investigators might compromise their objectivity.[136] Dr. Edward Adelson, of the George Washington University School of Medicine, wrote that "an investigator who depends on drug funds . . . knows that if he hopes to get further grants[,] it would be better to obtain results proving [that] the drug . . . is a good one."[137] Dr. George E. Schreiner, head of the American Federation

128. *Drug Research & Regulation Hearings, Part 5 (88th Cong.)*, *supra* note 100, at 2285.

129. *Id.* at 2296.

130. *See* BRAITHWAITE, *supra* note 85, at 51–54 (illustrating the problem of dishonesty in the investigation of new drug usage through examples of fraudulent clinical trials).

131. *Id*. at 60 (emphasizing that this MER/29 case was one of the most shocking case of fraud in the area of safety testing of drugs).

132. *Id.* at 62 (noting that Richardson-Merrell's reports of a chronic toxicity study in monkeys was fraudulent, and served as count three in the charges against them and the eventual downfall of the MER/29 drug).

133. *Id.* at 58–59.

134. *See Drug Research & Regulation Hearings, Part 3 (88th Cong.)*, *supra* note 100, at 975–76 (Exhibit 137, excerpt from Drug Trade News) (explaining that many drug testers test with predetermined results to ensure a drug is permissible for consumption).

135. *Regarding the Clinical Test*, 268 NEW ENG. J. MED. 680, 680 (1963).

136. *Drug Research & Regulation Hearings, Part 4 (88th Cong.)*, *supra* note 100, at 1641–51 (Exhibit 206) (noting a variety of letters and comments from various medical professionals on their personal experience with bias in the drug testing profession).

137. *Id.* at 1647.

for Clinical Research, wrote "that when there is direct payment from drug firms, there may be too much temptation to turn in a favorable report."[138]

At the conclusion of the 1964 hearings, Senator Humphrey wrote a memo to his colleagues that outlined reform options.[139] In this memo, Senator Humphrey described one option, which was to ask the pharmaceutical industry to contribute funds to hire researchers who would be "entirely independent of [the] industry [and would] perform preclinical and clinical tests."[140] Another option, proposed by Dr. Harry Dowling, was to grant the FDA funds "to finance the testing of a drug by an independent agency . . . [when] the Administration was not satisfied with the evidence submitted by the manufacturer of the drug."[141]

The FDA was also worried about the quality of testing. Speaking before the Pharmaceutical Manufacturers Association in 1966, FDA Commissioner James L. Goddard stated that he was:

> 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.[142]

During this period, FDA officials met with industry representatives and specialists on research methodology to develop more rigorous testing procedures, which was followed by an FDA sponsored conference on drug

138. *Drug Research & Regulation Hearings, Part 5 (88th Cong.)*, *supra* note 100, at 2406 (Exhibit 273, Article by Joseph R. Hixson, Herald Tribune).

139. *See Drug Research & Regulation Hearings, Part 4 (88th Cong.)*, *supra* note 100, at 1668–69 (Exhibit 210) (explaining the history, past problems, current problems, and future problems in drug testing).

140. *See id.* at 1688 (Exhibit 210) (posing a number of reform options as questions, including whether the pharmaceutical industry should be asked to contribute funds to hire independent researchers).

141. *Id.*

142. BRAITHWAITE, *supra* note 85, at 51; *see also, Preclinical and Clinical Testing by the Pharmaceutical Industry, Part 2: J. Hearings Before the Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare and the Subcomm. on Admin. Practice & Procedure of the S. Comm. on the Judiciary*, 94th Cong. 157 (1976) [hereinafter *Preclinical & Clinical Testing Hearings, Part 2*] (statement of Sen. Gaylord Nelson, Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare) (summarizing the various problems in the drug industry and noting the need for reform in clinical testing).

testing.[143] In 1970, the FDA promulgated regulations, which required drug testing to demonstrate safety and efficacy.[144]

C. 1967–1979: The Nelson Hearings and Legislation

Senator Gaylord Nelson investigated clinical trials and other matters from 1967–1979 as part of the hearings that he chaired on Competitive Problems in the Pharmaceutical Industry.[145] Individuals who testified proposed various reforms, which included shifting the responsibility for testing drugs to the federal government.[146]

During the 1968–1969 hearings, several physicians advocated for the requirement of independent testing.[147] Dr. Paul Lowinger, from the Wayne State University School of Medicine, proposed the creation of a federal agency, which would be funded by the federal government and/or the pharmaceutical industry to supervise drug research.[148] This federal agency would test drugs, finance independent organizations to test drugs, or oversee drug trials.[149] Investigators would report their findings to the

143. *See 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.*, 92d Cong. 8527 (1972) [hereinafter *Present Status of Competition in the Pharm. Industry, Part 22*] (statement of Charles C. Edwards, Comm'r, Food and Drug Admin.) (explaining the various steps of progress made within the FDA and the drug testing industry to ensure better testing procedures).

144. 21 C.F.R. § 146 (1970); *see also Present Status of Competition in the Pharm. Industry, Part* 22, *supra* note 143 (explaining the various changes that the FDA made to its regulations in order to improve drug testing).

145. *See generally 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. (1967–1979) (discussing issues related to clinical trials and other issues in the pharmaceutical industry). These hearings, held from 1967 to 1979, are nicely summarized by two reports of the Congressional Research Service: CONGRESSIONAL RESEARCH SERV., 53-690 O, COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY: DRUG TESTING: SUMMARY AND ANALYSIS (1979) [hereinafter CONGRESSIONAL RESEARCH SERV., 1979 SUMMARY], and CONGRESSIONAL RESEARCH SERV., 56-036, COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY: DRUG TESTING: SUMMARY AND ANALYSIS (1972).

146. *See* CONGRESSIONAL RESEARCH SERV., 1979 SUMMARY, *supra* note 145, at 68–78.

147. *See id.* at 68 (explaining that various physicians/advocates for reform propose independent testing to ensure that drug testing is impartial and produces the fairest results possible).

148. *See id.*; *see also*, *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 *Present Status of Competition in the Pharm. Industry, Part 10*] (explaining the need for drug testing reform and the importance of government supervision).

149. *See* CONGRESSIONAL RESEARCH SERV., 1979 SUMMARY, *supra* note 145, at 68–69 (explaining that the agency would be created to supervise and approve research methods).

agency instead of the drug sponsor.[150] Dr. Dale Console, the former medical director of E. R. Squibb & Co., supported the creation of a central testing agency, which the federal government and pharmaceutical firms would jointly fund, and which would select investigators to conduct drug trials without the drug sponsors knowing their identity.[151]

In contrast, Dr. Franz Inglefinger, editor of the *New England Journal of Medicine*, testified that independent testing, overseen by a government agency, would reduce the risk of bias, but that it might not be worth the cost.[152] Dr. Inglefinger thought it was sufficient to require drug firms to contract with universities to perform clinical trials.[153]

Dr. Donald Mainland, who coordinated research for the American Rheumatism Association's Cooperating Clinics Committee, argued that drug firms could influence clinical trials when they were the intermediary between the FDA and researchers.[154] Congress, he said, should "take the evaluation of drugs entirely out of the producer's hands" after the completion of animal toxicological testing.[155] He favored the creation of an independent, not-for-profit drug testing agency that would provide research grants in a manner similar to the NIH, noting that 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 . . . with the trials."[156]

Dr. Paul Lowinger of the Wayne State University School of Medicine proposed that Congress should create a National Institute of Pharmacology that would "supervis[e] and approv[e] research protocols for [drug] investigations . . . [,]" and would require drug firms to finance the clinical trials.[157] Dr. George Nichols, of Harvard Medical School, also proposed the creation of a central agency to test drugs that drug firms and the federal

150. *See id.* at 69 (explaining that if results were reported to an independent agency, the impartiality of the testing would improve).

151. *See 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. 4478, 4481 (1969) (explaining that testing through a central agency that is jointly funded through the government and firms would increase the impartiality and fair results of testing).

152. *Present Status of Competition in the Pharm. Industry, Part 10*, *supra* note 148, at 4017, 4024.

153. *Id.* at 4017, 4025.

154. *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).

155. *Id.* (noting that the federal government is called upon to direct the impartiality of testing).

156. *Id.* at 2768–69.

157. *Present Status of Competition in the Pharm. Industry, Part 10*, *supra* note 148, at 3997, 4001–04.

government would jointly finance in order to eliminate "questionable practices revolving around payment to investigators."[158] Dr. William B. Bean, head of internal medicine at the University of Iowa College of Medicine, supported having drug testing conducted by "a neutral judging body, professional competent, and quite independent of any extraneous source of financial support or any hint of obligation or connection with the . . . promoters of the drug."[159]

In 1968, NIH director Dr. James Shannon called for having a federal agency evaluate drugs when the FDA deemed that the data it received from manufacturers were insufficient.[160] The agency would either conduct its own studies, or contract with independent institutions.[161] Conversely, Dr. Harry Dowling, an authority on drug safety, responded that it might be better instead for the FDA to develop an in-house capacity to evaluate drugs.[162]

In 1971, Senator Nelson introduced an omnibus drug bill that would create independent third-party drug testing.[163] He summarized the problem that the bill sought to remedy as follows:[164]

158. *Id.* at 3977, 3985.

159. *Id.* at 3919, 3920.

160. DOWLING, *supra* note 16, at 230–32.

161. *Id.*

162. *Id.* (commenting on the Shannon proposal, which was published in thei ha National Institutes of Health, "Drug Research Reports" (1968)).

163. S. 2812, 92d Cong. (1971).

164. The bill was included as part of an omnibus drug bill, S. 2812, in the 92d 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 Cong. (1975); National Drug Testing and Evaluation Act, S. 630, 95th Cong. (1977); National Drug Testing and Evaluation Act of 1979, S. 774, 96th Cong. (1979). Senator Nelson testified that he developed his proposal with FDA officials in 1969, while chairing the "Competitive Problems" hearings. *See Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 156–57. 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 on Nelson's third-party testing proposal as described in S. 966, see *Examination of the Pharmaceutical Industry: Legislation Amending the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, Parts 1, 5, 6, 7: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the S. Comm. on Labor & the Pub. Welfare*, 93d-94th Cong. (1973-1974). Also, see Sen. Nelson's statement before the Kennedy subcommittee, in which he outlines more than a decade of statements by the FDA indicating that the problems of fraud and poorly designed studies were a problem of the past, and that stronger monitoring and inspections have eliminated the problem, which is available at *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 156–60.

> 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 may 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, [and] who are not motivated even subconsciously by the desire to get anything but the truth.[165]

Senator Nelson introduced the omnibus 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.[166]

The Nelson bill vested the federal government with responsibility for all testing of NDA and FDA drug reviews.[167] The Nelson bill also authorized the creation of a National Drug Testing and Evaluation Center within the FDA to oversee clinical investigations of new drugs, which meant that the federal government would perform the tests either through

165. CONG. REC., *supra* note 164; *see also Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 156 (Sen. Nelson explaining several years later that the current system was "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").

166. Public Health Price Protection Act of 1972, S. 966, 93d Cong. (1973); National Drug Testing and Evaluation Act, S. 1321, 94th Cong. (1975); National Drug Testing and Evaluation Act, S. 630, 95th Cong. (1977); National Drug Testing and Evaluation Act of 1979, S. 774, 96th Cong. (1979). *See also Gaylord Nelson*, DISCOVER THE NETWORKS: A GUIDE TO THE POLITICAL LEFT, http://www.discoverthenetworks.org/individualProfile.asp?indid=1861 (last visited Nov. 7, 2014) (detailing the political career of Senator Gaylord Nelson and his work while in office).

167. *Examination of the Pharmaceutical Industry, Part 1: Hearings on S. 3441 and S. 966* § 102 *Before the Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare*, 93d Cong. 55–56 (1973) (examining the text of S. 966, 93d Cong. § 102 (1973)).

the testing center, or by contracting with independent organizations.[168] The Secretary of the Department of Health, Education, and Welfare ("HEW") would decide whether each drug would be tested through the national testing center or an independent organization.[169] Drug companies would finance the testing center and the clinical trials by paying into a common fund, which the Secretary of HEW would draw from to pay for testing.[170] The Secretary would publicize the "methodology, results, and conclusions."[171] Drug sponsors could still conduct their own clinical trials, but they were subject to HEW regulations and public disclosure of the testing methods and results.[172]

D. 1973–1980: The Kennedy Hearings

Senator Ted Kennedy chaired hearings entitled "Examination of the Pharmaceutical Industry" in 1973–1974,[173] as well as hearings entitled "Preclinical and Clinical Testing by the Pharmaceutical Industry" from 1975–1979.[174] Kennedy also examined the Nelson proposal for independent drug testing, among other issues.[175]

At the hearings in 1974 and 1976, which were held during the presidencies of Richard Nixon and Gerald Ford, Charles Edwards (HEW Assistant Secretary for Health) and Alexander Schmidt (FDA Commissioner) opposed Senator Nelson's proposed national drug-testing center.[176] Commissioner Schmidt argued that economic incentives and tort

168. *Id.* at 56–57.

169. *Id.* at 55–56.

170. *Id.* at 55.

171. *Id.* at 63 (text of S. 966, 93d Cong. §102 (1973)).

172. *Id.*

173. *Examination of the Pharmaceutical Industry: Legislation Amending the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, Parts 1, 2, 3, 4, 5, 6, 7: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the S. Comm. on Labor & the Pub. Welfare*, 93d-94th Cong. (1973–1974).

174. *Preclinical and Clinical Testing by the Pharmaceutical Industry, Part 1–3*: *J. Hearings Before the Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare and the Subcomm. on Admin. Practice & Procedure of the S. Comm. on the Judiciary*, 94th Cong. (1975–1976); *Preclinical and Clinical Testing by the Pharmaceutical Industry, Parts 4–5: Hearings Before the Subcomm. on Health & Scientific Research of the S. Comm. on Human Res.*, 95th Cong. (1977–1978); *Preclinical and Clinical Testing by the Pharmaceutical Industry: Hearing Before the Subcomm. on Health & Scientific Research of the S. Comm. on Labor & Human Res.*, 96th Cong. (1979) [hereinafter *Preclinical & Clinical Testing (1979)*].

175. *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 161.

176. *See Examination of the Pharmaceutical Industry, Part 5: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare*, 93d Cong. 2162 (1974) [hereinafter *Examination of the Pharm. Industry, Part 5*] (opposing the proposal for a National Drug-Testing center); *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 160 (proposing instead a progressive series of steps to evaluate and reform the existing system).

liability created an incentive for drug firms to carry out proper studies,[177] and that the "professional integrity of toxicologists in the industry" helped to assure high quality investigations.[178] Commissioner Schmidt noted that having the federal government or independent labs perform the work would not necessarily improve the quality of testing.[179] Furthermore, Commissioner Schmidt announced that the FDA would create regulations to assure "good laboratory practice[s]" in animal testing, would inspect animal testing facilities, and would audit or review any data where there was suspicion of falsification.[180]

Commissioner Schmidt also reported that the FDA had rejected the idea of drug testing under federal auspices,[181] as it was not feasible in the short term since the federal government lacked sufficient personnel and testing facilities.[182] Moreover, due to the dearth of independent laboratories, it was not possible to have independent third parties perform the tests.[183] Schmidt also argued that it would be too costly to have the federal government test drugs, as "there is no way that we can get the resources to put into this that drug companies do."[184] Furthermore, Schmidt argued that he believed "all monopolies, whether public or private, tend to stagnate, [so] the prospect of any single institution gaining such control over all preclinical drug investigation troubles me."[185]

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

177. *See Examination of the Pharm. Industry*, *Part* 5, *supra* note 176, at 2163 (statement of Alexander Schmidt, FDA Comm'r) ("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."). *See also Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 92–93 (statement of Alexander Schmidt, FDA Comm'r) (discussing economic incentives, such as the pharmaceutical industry's practice of cross-checking data with competitors, and liability implications stemming from marketing an unsafe product).

178. *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 45.

179. *Id.* at 103–04.

180. *Id.* at 47–48.

181. *Id.* at 103–04.

182. *Id.* at 104.

183. *See id.* (discussing challenges presented by the insufficiency of independent laboratories in number and capacity to handle large numbers of studies).

184. *Examination of the Pharm. Industry, Part 5*, *supra* note 176, at 2164–65.

185. *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 103.

ultimately evaluate the research performed under its aegis.[186] Edwards contended that "the public would be deprived of . . . FDA impartial review of clinical data."[187] Commissioner Schmidt claimed that all that was needed to ensure reliable trials was increased FDA oversight that is supported by FDA authority to issue subpoenas, examine records, and conduct investigations.[188] Edwards rebutted, however, with the opinion that a government center would not necessarily do a better job of testing than drug firms, and that industry bias could be countered through increased government surveillance.[189]

The Pharmaceutical Manufacturers Association ("PMA") and the AMA both opposed the creation of a national drug testing and evaluation center.[190] 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,"[191] and that creating the center would lead to a "drastic slowing down of drug research."[192] Speaking for the AMA, Dr. James Sammons argued that creating an FDA drug testing center would transform the FDA from a judge of research that was conducted by others into an organization that judged its own research.[193]

Meanwhile, further investigations and hearings found that many clinical trials did not comply with legal requirements or research norms.[194] The FDA investigations of G. D. Searle in the early 1970s revealed poor oversight, negligence, and fraud in the firm's toxicological drug testing.[195]

186. *Examination of the Pharm. Industry, Part 5*, *supra* note 176, at 2163–65 (statement of Charles C. Edwards, Assistant Secretary for Health, Department of Health, Education, and Welfare).

187. *Id.* at 2163.

188. *Id.* at 2164–65.

189. *Id.* at 2163 ("There is nothing wrong with the system. . . . [B]ut we have . . . done a very poor job of surveillance . . . .").

190. *Examination of the Pharmaceutical Industry, Part 6: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the S. Comm. on Labor & Public Welfare*, 93d Cong. 2419, 2535 (1974) [hereinafter *Examination of the Pharm. Industry, Part 6*].

191. *Id.* at 2526.

192. *Id.* at 2494.

193. *Id.* at 2545, 2572–73 (statement of James H. Sammons, Executive Vice President Designate, American Medical Association). 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. *Id.*

194. *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 337–39.

195. *See id.* at 24–42 (memorandum from Searle Investigation Task Force to Searle Investigation Steering Committee) (showing the results of the investigation dealing with the integrity of animal data, which G. D. Searle & Co. submitted to the FDA in support of the safety of its products, and highlighting issues such as inadequate training, delayed necropsy of animals, and unexplained alterations in records).

The FDA found "a pattern of conduct[,] which compromises the scientific integrity of the studies."[196] At the 1976 hearings, Gregory J. Ahart reported that a Government Accounting Office ("GAO") investigation concluded that there is "a lack of assurance that the data . . . upon which FDA bases its decision to approve a new drug . . . is accurate and reliable."[197]

Subsequently, the FDA developed regulations for Good Laboratory Practices ("GLP"),[198] and introduced bio-research monitoring and inspection.[199] A 1977 study found poor compliance with these standards;[200] by 1979, however, compliance had risen to 88%.[201]

Congressional testimony in 1976 made clear that there were then two types of problems with drug testing: first, manufacturers' bias compromised impartiality, and second, cost pressures led organizations to perform poor

196. *Preclinical and Clinical Testing by the Pharmaceutical Industry, Part 3: Joint Hearings Before the Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare and the Subcomm. on Admin. Practice & Procedure of the S. Comm. on the Judiciary*, 94th Cong. 4 (1976) [hereinafter *Preclinical & Clinical Testing Hearings, Part 3*]. An FDA survey of 155 clinical investigators between 1972 and 1974 found that 74% did not comply with one or more legal requirements, 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. *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 340.

197. *Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 335. Specifically, Mr. Ahart made the following points regarding the GAO's findings. Before 1974, there was no comprehensive monitoring plan. Since 1972, when the 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 a 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%; and 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, it 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.

198. Good Laboratory Practice for Nonclinical Laboratory Studies, 21 C.F.R. § 58 (2011).

199. *See* U.S. FOOD & DRUG ADMIN., CHAPTER 48–BIORESEARCH MONITORING, COMPLIANCE PROGRAM GUIDANCE MANUAL (2001), *available at* http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133765.pdf (providing guidance for nonclinical laboratories on compliance with Good Laboratory Practice requirements).

200. BRAITHWAITE, *supra* note 85, at 82–83.

201. *See* MARCEL DEKKER, INC., GOOD LABORATORY PRACTICE REGULATIONS 35 (Sandy Weinberg ed., 3d ed. 2003).

quality work.[202] Having a governmental agency rather than the manufacturer select the organization that performs the tests would eliminate bias.[203] Other measures were needed, however, to control for poor quality work due to economic pressures.[204] Officials from the National Cancer Institute described the procedures that they used to ensure that testing by outside firms was of high quality.[205] Dr. Sidney Wolfe of the Public Citizen's Health Research Group ("HRG") argued that "what we learn . . . is not to allow any more testing by industry or by companies, who owe their allegiance to industry," further explaining that "no kind of surveillance of any kind over conflicted and inadequate data is going to improve the quality of it."[206]

In 1978, Senator Kennedy renewed his hearings, and testimony and documents revealed continued negligence, fraud, and fabrication of data.[207] Another theme that the hearings explored concerned the dependence of toxicological laboratories on drug firms for their continued operation.[208] Would the toxicological laboratories' dependence induce these labs to engage in fraud due to fear that the drug firms would not renew the labs' contract if they reported unfavorable results? Some witnesses suggested that

202. *See generally Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 14 (statement of Sen. Edward M. Kennedy, Chairman, Subcomm. on Health of the S. Comm. on Labor & Pub. Welfare and the Subcomm. on Admin. Practice & Procedure of the S. Comm. on the Judiciary) ("Many decisions made in the course of designing, conducting and reporting studies tended to minimize the chances of discovering toxicity and to allay possible FDA concern."); *Preclinical & Clinical Testing Hearings, Part 3*, *supra* note 196, at 13 (statement of Alexander Schmidt, FDA Comm'r) (discussing various lapses in integrity, including instances where employees of laboratory subcontractors "were instructed to falsify data by their employer").

203. *See infra* Part III.A (addressing objections to independent testing).

204. *See infra* Part III.B (discussing approaches to eliminate economic pressures and conflicts of interests for research organizations selected by the federal government).

205. *See Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 147–55 (testimony of Frank J. Rauscher, Jr., Director, National Cancer Institute); *see also* BRAITHWAITE, *supra* note 85, at 104–06 (summarizing Dr. Schmidt's testimony, which reviews the points covered by Dr. Rauscher).

206. *Preclinical & Clinical Testing Hearings, Part 3*, *supra* note 196, at 691 (statement of Dr. Sidney Wolfe, Public Citizens Health Research Group).

207. *Preclinical and Clinical Testing by the Pharmaceutical Industry, Part 5: Hearings on Examination of The Process of Drug Testing and FDA's Role in the Regulation and Conditions Under Which Such Testing is Carried Out Before the Subcomm. on Health and Scientific Research of the Comm. on Human Res.*, 95th Cong. 7–8 (1978) (statement of Sen. Edward M. Kennedy) (discussing case reports on "fictitious subjects, and on subjects who were never administered the investigational drug they were supposed to have received," and case reports "containing the results of clinical laboratory work which was not actually performed").

208. *See Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 139 (statement of John R. Quarles, Deputy Administrator of the EPA) ("[A] laboratory might be so dependent upon a pesticide producer for contract work that its independent scientific judgment could be impaired by the close economic relationship."). *See also* BRAITHWAITE, *supra* note 85, at 80 ("One of the issues raised by the Searle investigations was the relationship between contract laboratories and large pharmaceutical companies.").

drug firms instructed laboratories to fabricate data, a practice called "dry-labeling."[209] Other witnesses and senators expressed concern that drug testers either failed to record data, or that drug testers fabricated data as a means to ensure that manufacturers would continue to employ them.[210]

E. The Carter Administration Report on New Drug Regulation

During the administration of President Jimmy Carter, the Department of Health and Human Services ("DHHS") Review Panel on New Drug Regulation concluded that the current system was flawed since the "FDA must rely almost exclusively on the accuracy and objectivity of industry-generated data[,] . . . [and b]ecause the company has a financial interest in successful test results, the present drug testing system contains an inherent bias."[211] The review panel 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."[212] The panel noted that the disadvantage of having the federal government conduct clinical trials was that "[i]f such testing were undertaken by the FDA, the agency would be in the untenable position of passing upon the result of its own research."[213] 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."[214]

209. *See Preclinical & Clinical Testing Hearings, Part 3*, *supra* note 196, at 13 (statement of Alexander Schmidt, FDA Comm'r) (noting that "[s]ome of the laboratory determinations alleged to have been carried out were found by the FDA investigators not to been carried out at all," otherwise "called 'dry-labeling' by some," which means "[t]hat data sheets are simply filled out by individuals who know the range of values to submit, and put out the data sheets"); BRAITHWAITE, *supra* note 85, at 80 ("[Can] pharmaceutical companies use their commercial power to impose a set of expectations on contract laboratories whereby unfavorable results cause the laboratory to believe that it will be unlikely to get future contracts?").

210. *See Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 139–42, 158–59 (noting that drug companies concealed information and made falsified statements to the FDA, and there are problems when self-interested industries control the studies).

211. NORMAN DORSEN ET AL., DEP'T OF HEALTH, EDUC., & WELFARE, FINAL REPORT OF THE REVIEW PANEL ON NEW DRUG REGULATION 83 (1977).

212. *Id.* at 85–86.

213. *Id.* at 88.

214. *Id.* at 89.

F. The Drug Regulation Reform Act of 1978

In 1978, the FDA and HEW supported the Drug Regulation Reform Act of 1978, sponsored by Senator Kennedy and nine other senators.[215] The bill would have reformed the drug review process, and created some governmental capacity to evaluate drugs.[216] The bill also would have increased the FDA's role in overseeing the design and implementation of testing protocols, while requiring increased disclosure of clinical trial data.[217]

The bill proposed a "National Center for Clinical Pharmacology" to conduct some intramural public clinical pharmacology research.[218] The Center's functions consisted of "conduct[ing] and support[ing] research in clinical pharmacology and clinical pharmacy, including investigations for: (1) the safety and effectiveness of existing and new uses of drug products, (2) the development of drug products for diseases and other conditions of low incidence, [and] (3) drug products of special significance or with respect to which there is substantial controversy as to safety and effectiveness."[219] The pharmaceutical industry, physicians, and some consumer advocates opposed the reform, and as a result, the bill was never reported out of the committee.[220]

215. 124 CONG. REC. 2,755 (1978) (statement of Sen. Edward M. Kennedy) (indicating nine co-sponsors: Cranston, Eagleton, Hathaway, Javits, Nelson, Pell, Randolph, Riegle, and Williams).

216. *See* JOSEPH A. CALIFANO, DEP'T OF HEALTH, EDUC., & WELFARE, DRUG REGULATION REFORM ACT OF 1978 SECTION-BY-SECTION ANALYSIS i–viii (1978) (indicating subparts of the bill governing approval of drug entities and drug products and noting the requirements for: dispensing, labeling, distribution, licensing, manufacturing, components, packaging, registration, investigation, exporting, practitioners, and standards for safety).

217. *See id.* at 97 ("Subsection (f) establishes the requirements for the conduct of a drug innovation investigation [including] (1) confining distribution of the drug to experts qualified to investigate the drug or the disease under [the] study; (2) preventing the drug from being dispensed by investigators other than those specified to conduct the investigation; (3) conducting the investigation in accordance with the protocol submitted in the registration; (4) maintaining records, and submitting reports to the Secretary, regarding the investigation so that the Secretary may determine whether the conditions of registration are being fulfilled; (5) reporting to the Secretary information of newly discovered risks so that the Secretary may determine whether participants are being subjected to an unreasonable and significant risk of illness or injury; (6) complying with the requirements in section 130 regarding protection of human subjects in research; and (7) not promoting or commercializing the drug product.").

218. *See id.* at 193–94 (noting that § 201 "amends the Public Health Service Act by . . . establish[ing] a National Center for Clinical Pharmacology. . . . [and] authoriz[ing] the Center to conduct and support research in clinical pharmacology . . . ").

219. *Id.*

220. *See Oversight: The Food and Drug Administration's Process for Approving New Drugs: Hearings on H.R. 37 Before the Subcomm. on Sci., Research, & Tech. of the Comm. on Sci. & Tech.*, 96th Cong. 315, 317, 389, 419, 564–65 (1979) (noting that the President of the Pharmaceutical Manufacturers Association on the Drug Approval Process of the FDA rejected the

Senator Kennedy's 1979 hearings documented continued problems with research fraud,[221] and FDA audits also revealed continued fraud and flawed research.[222] In the 1980 election where Ronald Reagan was elected President, Senator Gaylord Nelson lost his bid for re-election, and the Senate majority shifted from the Democratic Party to the Republican Party.[223] These changes ended the congressional proposals for independent drug testing.[224] Discussion of independent drug testing in medical and popular journals then virtually ceased until the 1990s.

III. REVISITING PROPOSALS FOR INDEPENDENT DRUG TESTING

A. Assessing the Arguments Against 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 additionally argued that the federal government lacked the capacity to perform this work.[225] These assertions assumed that private firms and the federal government could not expand their capacities to meet new demands.[226]

reform, that Dr. Moulton, advocate for the National Consumer League, disagreed with FDA reform, and that the Drug Regulation Reform Act of 1978 failed to secure congressional approval). *See also H.R. 12980 (95th): Drug Regulation Reform Act*, GOVTRACK.US, https://www.govtrack.us/congress/bills/95/hr12980 (last visited Nov. 9, 2014) ("This bill was introduced on June 5, 1978, in a previous session of Congress, but was not enacted.").

221. *Preclinical & Clinical Testing, (1979)*, *supra* note 174, at 12–13 (statement of Sherwin Gardner, Deputy Comm'r, FDA).

222. *See id.* at 10 (noting that the FDA "[found] a number of investigators whose work represents sloppy science, disregard for the rights of test subjects, and misrepresentation of test data").

223. *See* Peter Temin, *Government Actions in Times of Crisis: Lessons from the History of Drug Regulation*, 18 J. SOC. HIST. 433, 437 (noting that Ronald Regan was elected and the Democrats lost the Sentate); Demetrios Caraley, *Do Congressional Liberals Really Need to Tremble? A Quick Look at Some Hard Data*, 96 POL. SCI. Q. 27, 28 (1981) (noting that Gaylord Nelson lost in the Senate).

224. *See* Stuart J. Land, *Current Issues Relating to FDA Regulation of New Drugs*, 38 FOOD DRUG COSM. L.J. 29, 29–34 (1983) ("In a period of deregulation [and d]uring a time of personnel reductions," "the present policy is chilling the publication of clinical research results," as "progress is slow in the OTC Drug Review. . . . [T]he pace is glacier-like.").

225. *See, e.g.*, *Drug Research & Regulation Hearings, Part 3*, *supra* note 81, at 1053, 1060–61, 1261 (noting that a study for toxicological drug testing shows that drug testing is too complex, timely, costly, and energy-consuming, so it should be sufficient to have briefer and less thorough investigations; additionally, while the FDA needs greater competency, a national organization for the objective evaluation of drugs is not an easily attained goal).

226. *See id.* at 1041, 1060–61 ("Assuming the majority still believe[s] our Government should do only what cannot be, or is not, done by private agencies, the present situation and probable

The opponent's arguments were probably not correct then, and the arguments are certainly not true now. Today, rather than test drugs in-house, manufacturers contract out this work.[227] 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 constitutes a global industry.[228] Yet, testing by third parties still is not independent today.[229] Manufacturers either design the clinical trial or direct and oversee the researchers who do, and manufacturers also select the organization that conducts the research.[230] Researchers, whether in CROs or universities, depend on the drug manufacturer for their income and must follow the manufacturer's directions if they want to receive continued funding.[231]

Public policy could promote the independence of existing contract research organizations and universities if a governmental agency selected both the entity that performed the clinical trials and monitored its work.[232] Furthermore, by allocating funds for the research, the agency could spur the growth of organizations with high standards for integrity, quality, and independence.[233] For example, the internationally recognized Mario Negri Pharmacological Institute has performed independent clinical trials in Europe for nearly 50 years, has published more than 13,000 original scientific papers in scientific journals, and now conducts about 80 clinical trials a year.[234]

trends seem to call for a magnitude of resources and effort far beyond the capacities of any combination of private enterprises.").

227. *See* Maysoun D. Masri et al., *Contract Research Organizations: An Industry Analysis* 5 INT'L J. PHARMACEUTICAL HEALTHCARE MARKETING 2, 5 (2007) (noting that pharmaceutical and biotechnology manufacturers utilize CROs more and more to conduct research endeavors at a greater speed and less cost).

228. *See id.* at 12–13, 18 (noting a clear shift toward globalization of clinical trials); Richard A. Rettig, *The Industrialization of Clinical Research,* 19 HEALTH AFF. 129, 141 (2000) (noting a shift to CROs).

229. *See* Rettig, *supra* note 228, at 134 (noting that some firms manage their own trials, with most employing a hybrid form of internally and outsourced management, while drug firms usually recruit for and design trials followed by a NDA submission to the FDA).

230. *Id.*

231. *See* Jill A. Fisher & Corey A. Kalbaugh, *United States Private-Sector Physicians and Pharmaceutical Contract Research: A Qualitative* Study, 9 PLOS MED. 2, 4–6 (2012) (noting that sponsoring companies influence physicians' opinions and decisions through financial pressures).

232. *See supra* Part III.A (providing a solution to sever the CROs and universities' reliance on a manufacturer's directions).

233. *See supra* Part III.A (explaining how public policy separates the CROs and universities' dependence on a manufacturer's income and direction).

234. *See* MARIO NEGI INST. FOR PHARMACOLOGICAL RES., http://www.marionegri.it/mn/en (last visited Nov. 9, 2014) (describing the Institute as a "not-for-profit biomedical research organization. . . . [that] started work in Milan on 1 February 1963. . . . and 'has published more

Independent testing, its opponents also argued, would not ensure that clinical trials were well designed or conducted competently.[235] Even if a governmental agency selected the researchers, the researchers might perform sloppy work or engage in fraud.[236] No doubt, independent testing alone is not sufficient to ensure accurate results.[237] Nevertheless, independent testing eliminates the biggest problem: bias.[238] 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.[239]

Opponents also claimed that having the federal government test drugs would mire the FDA in conflicts of interest because the government would both conduct clinical trials and also evaluate those trials when deciding whether or not to approve drugs.[240] There is irony in opposing government drug testing as a means to avoid conflicts of interest. The rationale for government-sponsored testing is to remove the conflict of interest that is present when a firm evaluates its products.[241] The issue, therefore, is whether government-sponsored testing would result in evaluations that were more or less biased than when a manufacturer tested its own products. Drug manufactures have a systematic bias in favor of their products,[242] while governmental agencies do not have a bias in favor of or against any particular product.[243] Certainly, some individual governmental personnel might harbor a bias towards a firm or a product, but that would not systematically slant all testing.[244]

than 10,000 articles in prestigious international scientific journals and several books and congress proceedings'").

235. *See* Masri et al., *supra* note 227, at 2, 19 (noting that clinical trials present concerns of accuracy, quality, ethics, and safety).

236. *See, e.g.*, Rettig, *supra* note 228, at 130 (noting that the FDA halted FDA-regulated trials at the University of Colorado that were not reviewed by its IRB within the prior year).

237. *See id.* at 142 (noting concerns of suppression of research results by drug firms, bias in interpreting inconclusive research, and ghost authorship of articles).

238. *See* Joel Lexchin, *Those Who Have the Gold Make the Evidence: How the Pharmaceutical Industry Biases the Outcomes of Clinical Trials of Medications*, 18 SCI. & ENGINEERING ETHICS 248, 257 (2012) (noting that bias could be reduced if the industry left the planning and monitoring of the research design in the hands of the researchers).

239. *See Preclinical & Clinical Testing Hearings, Part 2*, *supra* note 142, at 144.

240. *See supra* text accompanying note 186.

241. *See supra* text accompanying note 206.

242. *See supra* text accompanying note 2.

243. *See supra* text accompanying note 241.

244. *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR CLINIC TRIAL SPONSORS, ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES 7 (2006) (highlighting how the current use of separate adjudication committees in clinical trials ensure data that is as accurate and bias-free as possible).

It is easy to avoid bias if a government agency evaluated the quality and results of its own work by simply having one government agency perform the clinical trials, and a separate and independent agency evaluating those trials.[245] In fact, government agencies frequently evaluate the work of other government programs.[246] For example, the Government Accountability Office ("GAO"), an independent agency, evaluates the performance of federal programs.[247] GAO reports are a model of objective evaluation, and are highly regarded.[248] It is also possible for the FDA to avoid evaluating any work performed by governmental employees or programs by having the NIH select independent contractors, who would then perform the clinical trials.[249] Then the FDA would evaluate the research performed in the private sector, just as it does today.[250] The key difference would be that the researchers would not be dependent on, influenced by, or chosen by the drug sponsor.

Currently, it requires about 15 years from the beginning of drug development until a drug can be marketed.[251] Phase I clinical trials in humans take about a year and a half, Phase II clinical trials typically take two years, and Phase III clinical trials take three to five years.[252] Opponents of independent testing also claim that independent testing would slow the

245. *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 244 (indicating that the current use of distinct adjudication committees in clinical trials is a successful mode of bias elimination).

246. *See* Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Republication, 67 Fed. Reg. 8452 (Feb. 22, 2002) (explaining that Congress directed the Office of Management and Budget to issue guidelines for governmental agencies that ensure quality, objectivity, utility, and integrity of information, and to require that these agencies implement administrative mechanisms permitting access to information about non-compliance with these guidelines).

247. *See* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-12-5SP, SUMMARY OF GAO'S PERFORMANCE AND ACCOUNTABILITY REPORT 1 (2011), *available at* http://www.gao.gov/assets/590/587949.pdf (describing the GAO's duties as including the examination of public funds, evaluating federal programs and policies, and providing analyses, recommendations, and other assistance to help Congress make informed decisions).

248. *See id.* at i (highlighting the integrity aspect of the agency by stating that they take an "objective, fact-based, nonpartisan, nonideological, fair, and balanced approach" to all of their activities); *see also* Noah B. Bleicher et al., *Accountability in Indefinite-Delivery/Indefinite-Quantity Contracting: The Multifaceted Work of the U.S. Government Accountability Office*, 37 PUB. CONT. L.J. 375, 413 (2008) (acknowledging the GAO's ability to provide objective, balanced analyses in the ID/IQ contracting field).

249. *See* ANGELL, *supra* note 3, at 245.

250. *See id.* (proposing having the FDA shift the responsibility for the conduct of clinical trials from sponsors to independent researchers and their institutions).

251. *See* ROWBERG, *supra* note 34, at 13 (providing a graph showing that the entire pharmaceutical drug process takes an average of 15 years from the inception of drug development to market approval).

252. *Id.* at 9–11.

introduction of new drugs,[253] but this assertion is unpersuasive. Independent testing is unlikely to cause much delay because there is no reason that researchers chosen by the NIH should perform work more slowly than researchers chosen by a pharmaceutical firm. It might take a governmental agency longer than a drug firm to select which researchers to employ, but not much.[254] If it takes more time in developing the research protocol to ensure that clinical trials are better designed and methodologically sound, then that would be time well spent. Moreover, there are ways to take care of the problems that any delay would cause for manufacturers.[255] The Hatch-Waxman Act already extends for up to five years the period of market exclusivity that manufacturers of new drugs receive, which compensates manufacturers for part of the time that it takes them to conduct clinical trials and for the FDA to review NDAs.[256] Regulations could increase the period of market exclusivity in order to account for any increased time taken to conduct clinical trials using the new process.

B. Controlling Conflicts of Interests of Research Organizations Engaged by the Government

Having a government agency select the private organization that conducts clinical trials would not necessarily remove all conflicts of interest. There exists potential bias if the researchers with which the federal government contracted with depended on drug manufacturers for most of their research income.[257] The manufacturer could cease to employ the researchers in the future, or retaliate in other ways if the researchers produced negative evaluations of the manufacturer's products for

253. *See Examination of the Pharm. Industry, Part 6*, *supra* note 190, at 2494 (criticizing an independent National Drug Testing and Evaluation Center because the drug progress would diminish since new products could not be approved unless it had a "significantly greater safety effectiveness" than current market-approved drugs).

254. *Present Status of Competition in the Pharm. Industry, Part 10*, *supra* note 148, at 4025 (statement of Dr. Franz Ingelfinger, editor of the New England Journal of Medicine) (arguing that a study with a potentially large financial gain would take time to pick from an extensive list of independent investigators, while a relatively dull study would also cause delay since it will be difficult to interest good researchers).

255. *See, e.g.*, 35 U.S.C. § 156(a)(4) (2012) (providing extensions for patents that were subject to regulatory review before they were commercially marketed).

256. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1602 (codified as amended in scattered sections of 15, 21, 28, 35 U.S.C.).

257. *See Administered Prices Hearing, Part 24*, *supra* note 81, at 13934.

government-sponsored testing.[258] Additionally, the risk of losing contracts from drug manufacturers could bias the evaluations of researchers.

The 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. Fewer research organizations could thrive without doing any work for drug firms, however, and adopting this rule would reduce the pool of organizations willing to accept federal drug contracts;[259] this might make it difficult for the federal government to find research organizations capable of performing high quality work.

An alternative strategy is to reduce the degree of financial dependence rather than eliminating it entirely. The agency awarding drug evaluation contracts could offer work only to CROs or universities that earned 40% or less of their research revenue from drug manufacturers. Regulations could also direct the agency to give preference in awarding contracts to well qualified organizations that received 10% or less of their revenue from drug manufacturers.

To further reduce the risk of bias while improving 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 makes sense to require public disclosure of the proposed research protocol and the review of experts that evaluated it, and to allow the public to comment on the proposed research protocol. Based on the expert evaluation and public comments, the government agency could ask the research organization to revise its trial design and research protocol as needed.

C. Begin Independent Testing With New Drugs

We can distinguish among three categories of drug trials: (1) those used to support NDAs; (2) post-marketing trials required by the FDA as a

258. 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, 519–20 (2011).

259. *See* Bekelman et al., *supra* note 12 (stating that approximately one-fourth of biomedical researchers at academic institutions receive funding from the drug industry, one-third of lead authors in published articles have financial interests, and two-thirds of academic institutions have financial interests in businesses that sponsor their faculty research).

condition for granting marketing approval; and (3) other post-marketing approval trials not required by the FDA.[260] Independent testing should start with clinical trials to support NDAs.[261]

Federal law already requires that drug companies submit evidence on drug safety and effectiveness, and to specify how to conduct these trials when the drug companies seek approval to market a new drug.[262] The FDA probably then has authority to promulgate regulations that require that such clinical trials be designed and conducted by an independent organization that is selected and supervised by a federal agency. Congress also could create this requirement by amending the FDCA, and firms would have to comply because with legislative change, they would have no alternative.

The FDA also has jurisdiction over certain post-marketing trials because regulations require that manufacturers monitor the risks of drugs that they market, and that manufacturers submit results from their post-marketing trials to the FDA.[263] Sometimes the FDA specifies the kind of post-marketing trials that a drug manufacturer must perform, particularly if the NDA revealed potential serious drug risks.[264] The FDA or Congress could require that drug firms finance independent clinical trials for those post-marketing studies. It is hard for the FDA to ensure that drug firms complete post-marketing studies because the FDA lacks the ability to routinely stop a manufacturer from marketing an approved drug.[265] In contrast, regulatory authorities in the European Union have such power

260. *See* 21 U.S.C. § 355-1 (2012) (indicating that the FDA requires premarketing strategies in addition to post-marketing strategies for an already approved drug if new safety information surfaces and the strategy is necessary to make sure the benefits of the product outweigh the risks). *See also* Lance L. Shea et al., *Cause and Effect? Assessing Postmarketing Safety Studies As Evidence of Causation in Products Liability Cases*, 62 FOOD & DRUG L.J. 445, 447 (2007) (stating that the FDA can request, without compelling by regulation, a sponsor to conduct post-marketing studies indicating that there are trials being conducted that are not FDA required).

261. *See* Finnuala Kelleher, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J.L. & SOC. PROBS. 67, 84 (2004) (indicating that current Institutional Review Boards have no external review after pre-trial protocol approval, and are not independent of the institutions they are reviewing, leading to a lack of accountability).

262. 21 U.S.C. § 355(b) (2012).

263. 21 U.S.C. § 355-1 (2012).

264. 21 C.F.R. §§ 314.80–.81 (2001).

265. Until enactment of the Food and Drug Administration Amendments Act of 2007, the FDA lacked the authority to compel drug firms to conduct post-marketing studies of approved drugs. *See* Peter Chang, *Reauthorization of Pdufa: An Exercise in Post-Market Drug Safety Reform*, 36 J.L. MED. & ETHICS 196, 197 (2008). Drug firms often did not complete or delayed conducting these studies. U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GEN., PUB'L NO. OEI-01-04-00390, FDA'S MONITORING OF POSTMARKETING STUDY COMMITMENTS 11 (2006), *available at* http://oig.hhs.gov/oei/reports/oei-01-04-00390.pdf. *See also* INSTITUTE OF MEDICINE, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 55, 155–57 (Alina Baciu et al. eds., The National Academies Press 2007).

because authorization to market a new drug expires after five years unless the European Medicine Agency approves a renewal application.[266] Therefore, the FDA would need Congress to grant the FDA new powers, which would be similar to the regulatory authorities in the European Union in order to ensure that firms carried out these trials.

Drug firms also conduct clinical trials for approved drugs that are not required by the FDA, and will often compare the efficacy of one drug to another to help market their products.[267] It will be much harder to require these trials to be independently conducted, because manufacturers are not required to conduct these clinical trials and they therefore have the option of not funding such clinical trials.[268] If Congress wants independent clinical trials to evaluate the comparative efficacy of approved drugs, then Congress will probably need to finance these studies. In the end, the best solution is for Congress to pass legislation that requires manufacturers to submit such data to the FDA, which would then give the FDA jurisdiction over such research.

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

267. Service of U.S. Nat'l Insts. of Health, *Learn About Clinical Studies*, CLINICALTRIALS.GOV, https://www.clinicaltrials.gov/ct2/about-studies/learn#ClinicalTrials (last reviewed Aug. 2012) (stating that some clinical trials compare new medical approaches to a standard one, or compare interventions that are already available to each other).

268. *See* Shea et al., *supra* note 260.