FDA Enforcement of Criminal Liability for Clinical Investigator Fraud

BY VANDYA SWAMINATHAN AND MATTHEW AVERY*

> Historically medicine is the only science that conducts life threatening experiments on human subjects in order to advance its knowledge base in the name of progress. When progress and commercialism coincide the potential for abuse is very great.
>
> – Theresa Richardson**

I. Introduction

During the mid-1990s, Dr. Robert Fiddes was a well-known and respected clinician.[1] He was the lead clinical investigator on over 170 clinical trials, where he oversaw the testing of new drugs on patients.[2] Pharmaceutical companies paid him well to test their drugs, and he was known for his ability to get and keep patients, and for generating thorough results.[3] However, Dr. Fiddes maintained his successful practice with lies and fraud.[4] For example, Dr. Fiddes often admitted

* Ms. Swaminathan is a J.D. Candidate at the University of California, Hastings College of the Law, 2012. Mr. Avery is an Associate at Baker Botts LLP in Palo Alto, California. The Authors would like to thank Professors Robin Feldman and Marsha Cohen of U.C. Hastings for advising them on this Article as part of the U.C. Hastings Law and Biosciences (LAB) Project.

** Theresa Richardson, Book Review, 36 CANADIAN J. HIST. 184, 184 (2001) (reviewing ALLEN M. HORNBLUM, ACRES OF SKIN: HUMAN EXPERIMENTS AT HOLMESBURG PRISON, A TRUE STORY OF ABUSE AND EXPLOITATION IN THE NAME OF MEDICAL SCIENCE (1998)).

1. Kurt Eichenwald & Gina Kolata, *A Doctor's Drug Trials Turn Into Fraud* N.Y. TIMES, May 17, 1999, at 1, *available at* http://www.nytimes.com/1999/05/17/business/a-doctor-s-drug-trials-turn-into-fraud.html?src=pm.

2. *Id.*

3. *Id.*

4. *Id.*

patients into clinical trials who had inappropriate medical profiles.[5] He paid an employee for a jug of her urine and passed it off as multiple patient samples.[6] He had employees run EKGs on each other to generate false patient data.[7] There are numerous additional examples of Dr. Fiddes's fraud, and he was able to maintain this scam for over a decade.[8] Although government auditors visited Dr. Fiddes' clinical sites and were told by employees about their suspicions of fraud, the government auditors were reluctant to challenge such a prominent figure.[9] But eventually one of Dr. Fiddes' employees blew the whistle on the doctor and brought the fraud to the attention of the Food and Drug Administration (FDA).[10] In September 1997, Dr. Fiddes pled guilty to fraud charges and was sentenced to fifteen months in prison.[11]

Pharmaceutical researchers arguably have many incentives to commit fraud due to the unique challenges they face bringing their products to market. Before a pharmaceutical company can sell a single pill, it must first spend hundreds of millions of dollars showing that what is inside the pill is safe for a patient to take and effective at treating a particular disease.[12] To show that a new drug is safe and effective, drug companies typically hire medical doctors to conduct clinical drug trials, in which these so-called clinical investigators oversee the testing of the new drug on hundreds to thousands of patients.[13] However, the drug discovery process has a high failure rate,[14] and enormous costs are associated with the identification, development, and testing of new drug candidates.[15] Because of the

5. *Id.* at 6.

6. *Id.* at 7.

7. *Id.*

8. *Id.* at 12.

9. *Id.* at 11.

10. *Id.* at 12.

11. *Id.* at 14.

12. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. OF HEALTH ECONOMICS 151, 165 (2003).

13. DAVID G. ADAMS ET AL., FOOD AND DRUG LAW AND REGULATION 330 (Food and Drug Law Institute eds. 2008).

14. *See* J.F. Pritchard et al., *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, 2 NATURE REV. DRUG DISCOVERY 542, 542 (2003) (describing failure risks associated with drug discovery).

15. *See* Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 477 (2007) (calculating average research and development costs of $1.32 billion per new molecule approved by the Food and Drug Administration).

huge investments involved, many drug researchers are under intense pressure to achieve positive results during clinical trials.[16] Furthermore, drug researchers face additional pressure to achieve positive results as quickly as possible. The initial investment for drug trials is very high and, as fewer research dollars become available, drug researchers find themselves in stiff competition with other researchers to get and keep these dollars based on initial results.[17] These scenarios can lead to a conflict of interest for drug researchers, where the goal of accurately measuring the safety and efficacy of a drug is at odds with the need to show positive results in order to keep the money from grants flowing in.[18] Unfortunately, some clinical investigators succumb to these pressures by falsifying the results of their studies and submitting fraudulent data to FDA. By hiding data that shows that a drug is unsafe or ineffective, a clinical investigator may be able to convince his industry sponsor, and ultimately FDA, to allow the sale of a potentially dangerous product. Consequently, it is important that FDA be able to deter such conduct by prosecuting clinical investigators who submit fraudulent data to the Agency.

However, FDA faces major challenges in bringing criminal charges against clinical investigators who have allegedly committed fraud because it is not clear whether the Agency has the authority to actually bring such charges.[19] The federal circuit courts of appeal have split on the issue and the United States Supreme Court has not yet stepped in to resolve the issue.[20] While there are alternate ways to indict clinical investigator misconduct, including using the mail fraud and false statements statutes, these alternatives are limited.[21] First, the statute of limitations for both false statements and mail fraud is only five years.[22] Often by the time FDA becomes aware of the fraud, the statute of limitations for mail fraud and false statements has passed.

16. Sandy Kline, *Scientific Misconduct: A Form of White Coat Crime*, 2 J. PHARMACY & LAW 15, 16 (1995).

17. *Id.* at 15.

18. *Id.* at 16.

19. *See* United States v. Smith, 740 F.2d 734 (9th Cir. 1984); *see also* United States v. Garfinkel, 29 F.3d 451 (8th Cir. 1994). The Department of Justice will file the actual criminal indictment against a clinical investigator accused of fraud based on the recommendation of FDA's Office of Criminal Investigations. *See* Part 1.3, *infra*. However, for the sake of convenience, this Article will refer to FDA bringing criminal charge against clinical investigators.

20. *Id.*

21. *See, e.g.*, United States v. Smith, 740 F.2d at 736.

22. 18 U.S.C § 3282 (2010).

Second, a physician convicted under either statute may be able to keep his medical license, which means he may be able to reoffend.[23]

This Article shows how FDA can use various provisions in the Food, Drug, and Cosmetic Act (FDCA) to seek criminal liability against clinical investigators who commit fraud. Part 1 of this Article provides a brief overview of the clinical trial process and the regulatory and economic factors that may incentivize investigator fraud. Part 2 reviews FDA's authority to pursue criminal liability for investigator fraud under section 355(i) of the FDCA. Part 3 then analyzes FDA's ability to seek criminal liability against fraudulent investigators as responsible corporate officers under the *Park* Doctrine. These analyses show how FDA uses the current regulations to address investigator fraud and how FDA's authority is insufficient to address fraud where the drug sponsors are entirely unaware of the conduct of the clinical investigators. Finally, Part 4 proposes improving regulatory enforcement to discourage investigator fraud by either: (1) increasing FDA's usage of section 355(i) and the *Park* Doctrine; (2) improving clinical investigator fraud reporting; or (3) enacting a criminal statute that explicitly penalizes any person who submits false data to FDA.[24]

23. Medical licensure varies between states. For example, in California, a doctor will have his license revoked if his crime is "substantially related" to his medical duties. *See* CALIF. BUS. & PROF. CODE § 2236 ("The conviction of any offense substantially related to the qualifications, functions, or duties of a physician and surgeon constitutes unprofessional conduct within the meaning of this chapter. The record of conviction shall be conclusive evidence only of the fact that the conviction occurred."). It is possible that a mail fraud conviction would not be considered "substantially related" to medical duties, while a FDCA conviction would be.

24. It is beyond the scope of this Article to analyze the following issues related to clinical investigator fraud: (1) criminal liability for investigator fraud under non-FDCA statutes, including criminal conspiracy, mail fraud, wire fraud, false statements to Government, and obstruction of justice; (2) civil liability for committing investigator fraud; and (3) liability for the sponsors and manufacturers administering the drug trials. For a discussion of criminal liability for investigator fraud under non-FDCA statutes, see generally Pamela H. Bucy, *Symposium: The Path From Regulator to Hunter: The Exercise of Prosecutorial Discretion in the Investigation of Physicians at Teaching Hospitals*, 44 ST. LOUIS L.J. 3 (2000). For a discussion of civil liability for committing investigator fraud, see generally E. Haavi Morreim *Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve*, 4 HOUS. J. HEALTH L. & POL'Y 1 (2003). For a discussion of liability for the sponsors and manufacturers administering the drug trials, see generally John W. Lundquist & Sandra L. Conroy, *Defending Against Food and Drug Law Prosecutions*, 21 CHAMPION 20 (1997).

II. Clinical Trials and Incentives for Fraud

A. FDA Regulation of Drugs

In order to market a new prescription drug, a pharmaceutical sponsor must first obtain regulatory approval from the Food and Drug Administration.[25] A new drug cannot be marketed until FDA approves the drug as safe, effective, and properly labeled.[26] To obtain FDA marketing approval, the sponsoring pharmaceutical company must perform extensive testing and analysis on the new drug in order to provide the Agency with data on the drug's safety, efficacy, pharmacology, and toxicology.[27] With this data, the sponsor must demonstrate: (1) that the drug is safe and effective for the use in the proposed labeling; and (2) that the benefits of the drug outweigh its risks.[28]

Before human clinical testing can begin on a drug candidate, the sponsor must complete substantial preclinical testing, which involves laboratory and animal tests.[29] After preclinical testing is complete, the sponsor can proceed through the investigational new drug (IND) process. During the IND process, the sponsor must conduct human clinical studies designed to demonstrate that the drug is safe and effective.[30] The process usually begins with Phase I clinical studies,[31]

25. *See* 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug."). Medical devices and biological products are subject to similar regulations. For purposes of this Article, discussion of clinical investigator fraud in the drug context is also applicable in the medical device and biological product contexts.

26. FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, INFORMATION FOR CONSUMERS (DRUGS) (2009), *available at* http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143462.htm.

27. 21 C.F.R. § 312.23.

28. FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, THE CDER HANDBOOK 7 (1998) [hereinafter FDA, THE CDER HANDBOOK], *available at* http://www.fda.gov/cder/handbook/handbook.pdf.

29. During pre-clinical testing, the sponsor must obtain toxicological and pharmacological information on the drugs. *See* 21 C.F.R. 312.23(a)(8); FDA, THE CDER HANDBOOK, *supra* note 28, at 5. In practice, however, most IND applicants only submit toxicology data. Interview with Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, in Wash., D.C. (Feb. 13, 2009). While FDA does not directly regulate preclinical testing, the Agency indirectly regulates how preclinical testing is conducted because it uses the results of these tests to determine whether to allow human clinical trials. Consequently, as part of preclinical testing, the sponsor must develop a "pharmacological profile" of the new drug to allow FDA to determine whether "it is reasonably safe to proceed with human trials of the drug." FDA, THE CDER HANDBOOK, *supra* note 28, at 5, 7.

30. *See* 21 U.S.C. § 355(d); 21 C.F.R. § 312.23.

which are generally conducted in twenty to eighty healthy volunteer subjects.[32] These studies are designed primarily to evaluate the safety of the drug,[33] though the sponsor must also obtain sufficient data about the drug's pharmacokinetic and pharmacological effects to permit the design of Phase II studies.[34] In Phase II clinical studies, the drug is generally tested on several hundred patients with the disease.[35] Phase II studies are conducted to obtain preliminary data on the drug's effectiveness.[36] If the preliminary evidence from the Phase II trials suggests the drug is effective, the sponsor may proceed to Phase III trials.[37] Finally, the pivotal Phase III trials are conducted to gather sufficient information about the drug's safety and efficacy to extrapolate the results to the general population.[38] Phase III studies are the most important and expensive trials, generally involving several thousand patients and costing hundreds of millions of dollars.[39]

Phase II and III studies are usually double-blind and placebo-controlled, with various fixed doses administered to random

31. Alternatively, the IND process can begin with exploratory IND studies (so-called "Phase Zero" studies), which involve administering the drug to a very limited number of healthy human volunteers for a limited duration (e.g., one week). Phase Zero studies are optional, and generally used to gather preliminary pharmacokinetic and pharmacodynamics data on multiple drug candidates to identify the best compound(s) to advance to full-scale clinical trials. Draft Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies, 70 Fed. Reg. 19,764 (Apr. 14, 2005).

32. FDA, THE CDER HANDBOOK, *supra* note 28.

33. *See* 21 C.F.R. 312.21(a) (stating that Phase I studies are "designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. . . . Phase I studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes); PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 630 (3d ed. 2007).

34. FDA, THE CDER HANDBOOK, *supra* note 28, at 8.

35. *Id.*

36. *Id.*; *see also* 21 C.F.R. § 312.21(b). Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is designed to assess dosing requirements and Phase IIB is designed to study efficacy. *See* SHEIN-CHUNG CHOW & JEN-PEI LIU, DESIGN AND ANALYSIS OF CLINICAL TRIALS: CONCEPTS AND METHODOLOGIES 16 (Wiley-Interscience 2nd ed. 2003).

37. FDA, THE CDER HANDBOOK, *supra* note 28, at 8.

38. *Id.*; *see also* 21 C.F.R. § 312.21(c).

39. *See* Gen Li, *Site Activation: The Key to More Efficient Clinical Trials*, PHARM. EXEC., Dec. 12, 2008 (reporting that single clinical trial can involve up to 50,000 patients, last five years or longer, and cost up to $500 million), THE CDER HANDBOOK, *supra* note 28, at 9.

patients.[40] Placebo-controlled means that there is also a patient population that randomly receives a placebo, which serves as a control against which safety and efficacy in the active group can be determined. Double-blind means that neither the physicians nor the patients know who is receiving placebos—only the clinical investigators overseeing the study know which patients are receiving actual treatment. This randomized fixed-dose design allows investigators to study the patients' responses to the various doses.[41]

Clinical investigators are in charge of running these clinical studies. The investigator's responsibilities include supervising the clinical study and protecting the rights, safety, and welfare of the test subjects.[42] While investigators often delegate study-related tasks to other employees, it is ultimately the investigator's responsibility to supervise the employees and to ensure their work is done in accordance with FDA regulations.[43] Prior to beginning human clinical trials, as part of the IND application, a pharmaceutical sponsor is required to submit information about the clinical investigator who will run the sponsor's clinical trial, including the investigator's name and curriculum vitae.[44] While the sponsor does not have to get direct approval for the clinical investigator, FDA can disapprove of the investigator due to prior malfeasance.[45] Additionally, the IND application must include a set of comprehensive investigator protocols that include the clinical procedures, lab tests, maximum dosage, and other information regarding the administration of the clinical trial.[46]

Once human clinical trials are complete, the sponsor may file a New Drug Application (NDA),[47] which requires the sponsor to

40. S.-M. Huang & R. Temple, *Is This the Drug or Dose for You?: Impact and Consideration of Ethnic Factors in Global Drug Development, Regulatory Review, and Clinical Practice*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 287, 288 (2008); *see also* 21 C.F.R. § 314.126.

41. Huang & Temple, *supra* note 40, at 288.

42. FDA, GUIDANCE FOR INDUSTRY: INVESTIGATOR RESPONSIBILITIES – PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF STUDY SUBJECTS 2 (2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM187772.pdf.

43. *Id.*

44. 21 C.F.R. § 312.53(c).

45. 21 C.F.R. § 312.70(b).

46. 21 C.F.R. § 312.23.

47. This Article refers to NDAs. Developers of biological products file Biologicals License Applications (BLAs) rather than NDAs. For purposes of this Article, any discussion of NDAs is also applicable to BLAs.

provide, among other things, detailed reports of the clinical trials conducted by the investigators.[48] FDA will then review the application—relying on the data to be accurate—to determine if the drug is "safe and effective" to treat the targeted disease state.[49] If the Agency approves the NDA, the sponsor may begin marketing its new drug immediately.[50]

B. The Economics of Clinical Trials and Fraud

Drug development is an extremely risky and expensive endeavor. The drug discovery process has a high failure rate[51] and enormous costs are associated with the identification, development, and testing of new drug candidates.[52] Fewer than 20% of drugs that begin human clinical trials are approved for marketing by FDA.[53] The remaining 80%+ usually fail to demonstrate adequate safety and efficacy in the general patient population.[54] Even if a drug candidate makes it to the

48. Pennington Parker Landen, *Federal Preemption and the Drug Industry: Can Courts Co-Regulate?*, 43 FOOD DRUG COSM. L.J. 85, 100 (1988); *see also* 21 U.S.C. § 355(a)–(b). In general, the NDA should contain reports on the following: (1) chemistry, manufacturing, and control; (2) nonclinical pharmacology and toxicology; (3) human pharmacokinetics and bioavailability; (4) clinical efficacy and safety data (both generally and by gender, age, and race); and (5) proposed labeling that describes, among other things, information concerning dosages, directions for administration, conditions for which the drug is effective, contraindications, and warnings about known or suspected side effects and adverse reactions. *See* 21 C.F.R. § 314.50; 21 U.S.C. §§ 321(m), 352(f)(1)–(2); Richard A. Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1 (1973); *see also* FDA, THE CDER HANDBOOK, *supra* note 28, at 21.

49. *See* 21 U.S.C. § 355(d). After reviewing the application, FDA may take one of three actions: (1) send a "not approvable" letter stating that the drug cannot be approved; (2) send an "approvable" letter indicating that the drug could be approved if certain changes are made; or (3) send an "approval" letter stating that the drug is approved as it stands. *See* FDA, THE CDER HANDBOOK, *supra* note 28, at 24; *see also* 21 C.F.R. §§ 314.105, 314.110, 314.120.

50. *See* 21 U.S.C. § 355(a).

51. *See* J.F. Pritchard et al., *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, 2 NATURE REV. DRUG DISCOVERY 542, 542 (2003) (describing failure risks associated with drug discovery).

52. *See supra* text accompanying note 53.

53. TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, IMPACT REPORT 2009: LARGE PHARMA SUCCESS RATE FOR DRUGS ENTERING CLINICAL TRIALS IN 1993–04: 16% (K.I. Kaitin ed., 2009); HUTT ET AL., *supra* note 33, at 624.

54. Lawrence J. Lesko & Janet Woodcock, *Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective*, 3 NATURE REV. DRUG DISCOVERY 763, 764 (2004); HUTT ET AL., *supra* note 33, at 624. In addition to safety and efficacy, a drug candidate might fail to make it to market because of commercialization issues. Lesko & Wookcock, *supra*. Note that this Article uses "efficacy" and "effectiveness" interchangeably, though the Author acknowledges that "effectiveness" is the preferred term of art. Interview with Peter Barton Hutt, Senior Counsel, Covington & Burling LLP,

final phase of clinical trials, success is still far from assured. Approximately 50% of drugs in Phase III clinical trials fail to obtain FDA marketing approval,[55] and in most cases the trials fail because the drugs have some safety or efficacy issue.[56] Almost half of all R&D costs are spent on performing Phase II and III clinical trials.[57]

There is concern that the increasingly challenging and inefficient regulatory regime, combined with an ever-more-costly drug development process, is preventing pharmaceutical pioneers from fully realizing the benefits of many scientific discoveries made in recent years.[58] Since peaking in 1996, when FDA approved fifty-three new drugs, the annual number of new drugs approved for marketing has steadily declined.[59] In 2011, only thirty new drugs were approved.[60] This declining product pipeline can be partially attributed to increased regulatory caution caused by recent high-profile safety issues.[61] As a result of the heightened bar to obtaining FDA approval,

in Wash., D.C. (Feb. 13, 2009); *see also* DEP'T OF HEALTH & HUMAN SERVICES, SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH & SOC'Y, REALIZING THE POTENTIAL OF PHARMACOGENOMICS 34 n.234 (2008) [hereinafter SACGHS PHARMACOGENOMICS REPORT] ("[T]he term 'effectiveness' is used as a measure of how well the test performs in 'real-world' clinical settings, and 'efficacy' is used for outcomes seen in controlled research settings.").

55. Lesko & Woodcock, *supra* note 54, at 764.

56. L.J. Lesko, *Personalized Medicine: Elusive Dream or Imminent Reality?*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 807, 810 (2007).

57. *See* ACCENTURE, IN PURSUIT OF HIGH PERFORMANCE: UNDERSTANDING PHARMACEUTICAL RESEARCH AND DEVELOPMENT COST DRIVERS 6 (2007), *available at* http://www.accenture.com/Global/Research_and_Insights/By_Industry/Life-Sciences/PharmaceuticalCostDrivers.htm.

58. *See* FDA, INNOVATION OR STAGNATION?: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS, at i (2004) [hereinafter FDA, INNOVATION OR STAGNATION].

59. BURRILL & CO., BIOTECH 2008 LIFE SCIENCES: A 20/20 VISION TO 2030, at 43 (2008).

60. *See* Anna Edney, *Drug Approvals Hit a Seven-Year High in 2011 on Improved Data*, BLOOMBERG (Jan. 5, 2012, 8:37 AM), http://www.bloomberg.com/news/2012-01-05/drug-approvals-in-u-s-reached-a-seven-year-high-in-2011-on-improved-data.html. Interestingly, the number of applications filed to investigate new drugs (INDs) has varied little since 1996, with approximately 1700 INDs filed per year. FDA, NUMBER OF INDS RECEIVED: CALENDAR YEARS 1986–2006, http://www.fda.gov/cder/rdmt/Cyindrec.htm. However, over the same period, the number of applications filed to market new molecular entities and biologics (i.e., NDAs and BLAs for NMEs) dropped almost 50%. FDA, INNOVATION OR STAGNATION, *supra* note 58, at 2 fig. 2.

61. Bethan Hughes, *2007 FDA Drug Approvals: A Year of Flux*, 7 NATURE REV. DRUG DISCOVERY 107, 107 (2008); *see also* HUTT ET AL., *supra* note 33, at 714. In the past decade, the pharmaceutical industry has found that FDA is "requesting more nonclinical studies and more clinical trials, of longer duration, with more subjects, containing more arms for additional dosage levels, with more diverse subjects, and longer

drug manufacturers have been plagued by a dearth of new product flow.[62]

At the same time that the number of new drug approvals is declining, research and development costs continue to rise. Since 1996, research and development spending by pharmaceutical manufacturers has nearly quadrupled, from $16.9 billion to $67.4 billion.[63] Recent estimates calculate that average R&D costs are now $1.32 billion per new molecule approved by FDA.[64] Overall, this means that more money is being spent on a product pipeline that brings fewer therapies to patients.

Because of the enormous financial risks associated with clinical trials, pharmaceutical companies take great pains to ensure that their drugs reach the market.[65] And while it is unlikely that a sponsor would directly instruct a clinical investigator to generate fraudulent data, investigators are incentivized to do whatever is necessary to generate positive results. Money appears to be the primary motive for clinical investigator fraud.[66] The major issue is how clinical investigators are paid, which is typically based on the number of patients enrolled in a study and the length of time these patients are retained. Also, if a patient drops out of a study early, the investigator usually only gets paid a portion of the full amount.[67] Thus, in order to maximize their paycheck, clinical investigators may invent fictional patients, purposely enroll ineligible participants, and falsify medical

follow up. The result [is] a significant reduction in NDAs submitted to the agency and an approximate doubling of the average cost of an NDA." *Id.*

62. FDA, INNOVATION OR STAGNATION, *supra* note 58, at 3.

63. *See* Matthew Avery, *Personalized Medicine and Rescuing "Unsafe" Drugs with Pharmacogenomics: A Regulatory Perspective*, 65 FOOD & DRUG L.J. 37, 38 (2010); *2011 Profile: Pharmaceutical Industry*, PHRMA, http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf (last visited Jan. 14, 2012).

64. *See* Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 477 (2007). *But see* Matthew Herper, *The Truly Staggering Cost of Inventing New Drugs*, FORBES, Feb. 10, 2012, http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/ (estimating that pharmaceutical companies actually spend between $4 billion and $11 billion on research and development for each new drug approved by FDA).

65. Richard A. Rettig, *The Industrialization of Clinical Research*, 19 HEALTH AFFAIRS 129 (2000) (describing expenditures made in drug development and the growth in pharmaceutical research).

66. Cullen T. Vogelson, *Investigators Gone Bad*, MODERN DRUG DISCOVERY, Apr. 1, 2001, at 27, *available at* http://pubs.acs.org/subscribe/archive/mdd/v04/i04/html/MDD04DeptRules.html. However, sometimes the motive for fraud is found in career advancement. *Id.*

67. *Id.*

assessments to prevent patients from withdrawing from a study. Additionally, investigators may purposely omit adverse events in order to ensure the study continues until its conclusion and is not cancelled early due to safety issues. A successful clinical investigation will not only result in a larger paycheck, but will also result in a higher likelihood of being hired for future clinical investigations as the investigator builds a reputation for getting clinical trials done.[68] Part of Dr. Fiddes' success as a clinical investigator was the phenomenal results he reported, which encouraged drug sponsors to hire him for additional clinical investigations.[69]

Obviously, certain factors may deter clinical investigators from committing fraud. By allowing a sponsor to rely on fraudulent data, the clinical investigator risks facilitating the market entry of a drug that may be dangerous or ineffective. If such a drug enters the marketplace, consumers may be harmed and the clinical investigator may find himself the subject of a criminal investigation.[70] Furthermore, the clinical investigator may have exposed his sponsor to product liability for any harm caused to patients by taking the unsafe and ineffective drug.

However, notwithstanding these moral and ethical dilemmas, clinical investigators may find reasons to commit fraud. Fraudulent documents can be used to remove outlier cases that make a drug appear unsafe. If only a few patients respond with adverse reactions, then an investigator may view this as an acceptable risk and attempt to hide data from these outliers to ensure that the clinical study is a success. Similarly, if the drug studies are not showing an effectiveness ratio as high as a company would like, an investigator may be tempted to manipulate the statistics by concealing data from non-responders. In this way, the investigator can ensure that the drug he is researching gains FDA approval, which then ensures that the investigator will get his full paycheck.

C. The Challenges to Discovering and Regulating Fraud

There are three mechanisms in place that should theoretically allow sponsors or FDA to discover any clinical investigator fraud: site monitoring, sponsor auditing, and FDA auditing. For site monitoring,

68. *Id.*

69. Eichenwald & Kolata, *supra* note 1, at 1.

70. Richard A. Epstein, *How Safe and Effective is the FDA?* MEDICAL PROGRESS TODAY, June 30, 2006, http://www.medicalprogresstoday.com/spotlight/spotlight_indarchive.php?id=1290.

the sponsor usually selects an appropriately trained individual to monitor the progress of the clinical investigation.[71] Because the sponsor is responsible for ensuring that the clinical investigators' obligations are being fulfilled, FDA recommends that the monitor periodically visit the clinical site to ensure the investigator is adequately performing his duties.[72] Site monitors are supposed to review every piece of data generated by a clinical study and are considered the best line of defense against clinical investigator fraud.[73] Sponsor auditing involves the sponsor of a clinical trial sending its own personnel to make sure an investigator is conducting a clinical trial in compliance with good clinical practice standards and other FDA regulations.[74] Sponsors usually only conduct their own audits for larger clinical trials.[75] Finally, FDA auditing is when the Agency sends its own monitors to inspect a clinical site and review data generated there. However, because of the FDA's budgetary constraints, these audits are relatively sporadic and are typically reserved for pivotal Phase III trials.

Reviewing clinical data to discover a protocol violation is a fairly simple process for most auditors.[76] However, it can be difficult to determine whether these protocol violations are due to mere carelessness or due to intentional fraud. Some warning signs of fraudulent behavior include, for example, data from patient visits on holidays or separate case report forms spanning a long period of time being written by the same pen.[77] Unfortunately, FDA does not have the resources needed to audit even a significant fraction of clinical trial sites. For example, FDA only inspected 1% of clinical trial sites between 2000 and 2005.[78] This leaves the brunt of fraud discoveries to site monitors and sponsor monitors. But these monitors are not always effective. Take the case of Dr. Fiddes—when an outside site monitor complained about Dr. Fiddes' suspicious conduct, Dr. Fiddes

71. *See* Vogelson, *supra* note 66, at 29.

72. FDA, 82D-0322, GUIDANCE FOR INDUSTRY, GUIDELINE FOR THE MONITORING OF CLINICAL INVESTIGATIONS 2-3 (1988) *available at* http://researchcompliance.uc.edu/FDA/FDAGuide_for_monitoring.pdf.

73. *See* Vogelson, *supra* note 66, at 29.

74. *Id.*

75. *Id.*

76. *Id.*

77. *Id.* at 30.

78. U.S. DEP'T OF HEALTH AND HUMAN SERVICES OFFICE OF INSPECTOR GENERAL, OEI-01-06-00160, THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL TRIALS, at 4 (2007).

complained to Pfizer and argued that the site monitor's outrageous demands were injuring Dr. Fiddes' integrity and reputation.[79] In response, the sponsor transferred the site monitor to a different location.[80]

If a site monitor's inspection report contains allegations of fraud, the report will then be routed through numerous governmental agencies to determine whether criminal sanctions should be filed. After an inspection is completed, the monitor sends an establishment inspection report to his contact in the Bioresearch Monitoring Program within FDA's Center for Drug Evaluation and Research.[81] The Bioresearch Monitoring Program may then refer the matter to FDA's Office of Criminal Investigations, if appropriate.[82] If the Office of Criminal Investigations believes criminal sanctions are warranted, then the matter is turned over the Department of Justice, which can file a criminal indictment against the clinical investigators for committing fraud.[83] However, the question remains whether FDA and the Department of Justice actually have the authority under the Food, Drug, and Cosmetic Act to bring these criminal sanctions.

III. Section 355(i): Failure to Prepare and Maintain Accurate Clinical Trial Data

Currently, the government primarily relies on section 355(i) of the FDCA when pursuing criminal charges against clinical investigators who commit fraud. However, nothing in section 355(i) expressly imposes an obligation on clinical investigators, and, in fact, that part of the statute specifically states that "[n]othing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs." Notwithstanding this seemingly clear statutory language, two Courts of Appeal have upheld criminal charges under section 355(i) against constitutional challenges, while a third appellate court has held that the government lacks the power to bring such charges.

79. Eichenwald & Kolata, *supra* note 1, at 10.

80. *Id.*

81. FDA, Program 7348.811, COMPLIANCE PROGRAM GUIDANCE MANUAL, CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS, (Dec. 2008) *available at* http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf.

82. John W. Lundquist & Sandra L. Conroy, *Defending Against Food and Drug Law Prosecutions*, 21 Champion 20, 21 (1997).

83. John R. Fleder, *Who Decides Your Fate in FDA Enforcement Matters?*, UPDATE MAGAZINE, 2007 at 40.

In light of the circuit split and the lack of a direct statutory basis for criminal liability under the FDCA, it is not obvious how FDA will pursue prosecution of investigator fraud. Parts 2.1 through 2.5, *infra*, attempt to clarify the scope of FDA's power and the current state of the Agency's approach by analyzing the three appellate cases where FDA attempted to bring criminal liability against clinical investigators for fraud.

A. Section 355(i)

Section 355(i) of the FDCA requires that the sponsor of a new drug establish records and make reports of clinical data directly to FDA.[84] However, as discussed above, the statute also explicitly disallows requiring a clinical investigator to submit such reports to FDA.[85] Thus, clinical investigators cannot be forced to undermine sponsors by bypassing them and reporting clinical results directly to FDA. Furthermore, if clinical investigators were forced to directly report to FDA, any employees of the sponsor supervised by the investigator may be hesitant to reveal too much information to the investigator, since even baseless suspicions could be reported to FDA.

FDA regulations promulgated under section 355(i) state that a clinical investigator "is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation."[86] In other words, the Agency imposes a duty on clinical investigators via this regulation to maintain accurate records of their clinical trials. However, section 355(i) has no provisions specifying what happens if it is violated. So FDA has looked to other sections of the FDCA to determine what happens if a clinical investigator fails to maintain

84. *See* 21 U.S.C. § 355(i)(1)(C) ("the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) . . . "); *see also* 21 U.S.C. § 355(i)(1)(D) ("…the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.").

85. 21 U.S.C. § 355(i)(4) ("Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs . . . .").

86. 21 C.F.R. § 312.62(b).

accurate records. Under section 331(e) of the FDCA, the "failure to establish or maintain and record, or make any report" under section 355(i) is a prohibited act and a violation of section 331.[87] And then section 333(a)(1) of the FDCA states that "[a]ny person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both."[88] Thus, by piecing these disparate portions of the FDCA together, the Agency can argue that clinical investigator fraud is a violation of section 355(i), which itself is a violation of section 331(e), which in turn is a violation of 333(a)(1), which allows for criminal liability. However, the courts disagree on whether this tenuous chain of statutes was intended to grant FDA authority to bring criminal charges against a clinical investigator who committed fraud.

B. Smith and the Rule of Lenity

One of the earliest attempts to convict a clinical investigator for fraudulent behavior occurred in the late 1970s. At the time, Dr. Ronald Smith was running a clinical trial for the Sterling-Winthrop pharmaceutical company, which was sponsoring the trial to investigate the safety and efficacy of one of its experimental drugs.[89] But in order to bolster the results of his trial, Dr. Smith forged documents for imaginary patients to make it look like they had enrolled in the trial and had positive results.[90] Sterling-Winthrop unknowingly submitted the fraudulent data generated by Dr. Smith to FDA. After the Agency discovered the fraud, the government indicted Dr. Smith under section 355(i) for failure to maintain accurate records.[91] However, the district court dismissed the charges, finding that the statute only applied to sponsors and did not apply to clinical investigators.[92]

The government appealed and argued that FDA's regulations created a duty under the statute that applied to clinical investigators.[93] The government's primary argument was that section 355 required sponsors to obtain documents from clinical investigators where the investigators state that they will maintain accurate records, and that

87. *See* 21 U.S.C. § 331(e).

88. *See id.* at § 333(a)(1).

89. United States v. Smith, 740 F.2d 734, 736 (9th Cir. 1984).

90. *Id.*

91. *Id.*

92. *Id.*

93. *Id.* at 737; *see also* 21 CFR §§ 312.1(a)(2) and (13).

requirement created the duty for investigators to maintain such records.[94]

But the Ninth Circuit disagreed with the government and affirmed the judgment of the district court, finding that section 355(i) neither expressly nor impliedly imposed a duty on clinical investigators to keep accurate records.[95] The court based its decision on the rule of lenity, which holds that courts should construe ambiguous criminal statutes in favor of defendants.[96]

The rule of lenity is based on due process and separation of powers concerns.[97] Essentially, the due process concern ensures that criminal defendants have a fair warning that they may be breaking the law.[98] Also, it ensures that a criminal defendant is aware of the punishment for his crime.[99] The separation of powers concern ensures that criminal penalties are created by the legislature.[100] Since criminal punishments are so severe and represent the moral condemnation of society, elected legislators, as opposed to individual judges, should define the nature of criminal activity.[101]

Applying the rule of lenity to Dr. Smith's case, the Ninth Circuit held that section 355(i) only imposed a duty on the manufacturers and sponsors of clinical trials.[102] Since section 355(i) was silent on the duties of clinical investigators, it could not be used to support criminal charges against investigators for failing to maintain accurate records.[103] Furthermore, the court held that FDA may not use regulations based on section 355(i) to independently create criminal liability for investigators.[104] Instead, the court noted that FDA's recourse was limited to holding an administrative hearing to ban the fraudulent investigator from working on clinical trials in the future.[105]

94. *Smith*, 740 F.2d at 737.

95. *Id.*

96. *Id.* at 738 ("When a criminal statute is ambiguous, courts are reluctant to find criminal liability for those activities which are questionably within its ambit.").

97. *Id.*

98. *Id.*

99. *Id.*

100. *Id.*

101. *Id.*

102. *Id.* at 739.

103. *Id.* at 738.

104. *Id.*

105. *Id.* at 739.

C. Garfinkel and Statutory Construction

In the 1990s, the government again tried to convict a clinical investigator for fraudulent behavior under section 355(i)—this time with better success. Dr. Barry Garfinkel was the principal clinical investigator for the experimental drug Anafranil (clomipramine), an antidepressant developed by Ciba-Geigy Ltd.[106] Dr. Garfinkel not only failed to follow the drug-protocol requirements, but also falsified data to conceal that failure.[107] After Dr. Garfinkel's fraudulent activity was revealed, the government indicted him under section 355(i) for failing to maintain accurate records.[108]

The district court dismissed the indictment based on the Ninth Circuit's decision in *Smith*.[109] The court concurred that Congress had yet to legislatively provide enough guidance to overcome the rule of lenity.[110] Again, the government disagreed with the district court, but this time it argued that criminal liability was proper because of a newly issued regulation, 21 C.F.R. § 312.62, which explicitly imposed a duty on clinical investigators to maintain accurate records.[111]

On appeal, the Eighth Circuit agreed with Dr. Garfinkel that it was unclear whether FDA had any authority over clinical investigators.[112] However, the appellate court also noted that section 355(i) allows FDA to promulgate regulations that protect the public health and impose record-keeping requirements on clinical investigators that clearly protect the public health.[113] Additionally, if clinical investigators did not have to maintain accurate records, it would be extremely difficult for FDA to discover any fraud.[114] The court concluded that, for policy reasons, FDA is allowed to promulgate regulations prohibiting investigator fraud.[115]

106. United States v. Garfinkel, 29 F.3d 451, 453 (8th Cir. 1994).

107. "Barry D. Garfinkel, Final Debarment Order (Notice)." Federal Register 62:63 (Apr. 2, 1997) p. 15713.

108. *Garfinkel*, 29 F.3d at 453.

109. *Id.*

110. *Id.*

111. *Id.* ("Pursuant to § 355(i) of the Act, FDA regulations impose explicit recordkeeping requirements upon protocol investigators such as Garfinkel. *See* 21 C.F.R. §§ 312.62, 312.64, 312.68 (1993).").

112. *Id.* at 456.

113. *Id.* at 456; *see also* 21 U.S.C. § 355(i) ("The Secretary shall promulgate regulations . . . among other conditions relating to the protection of the public health . . . .").

114. *Garfinkel*, 29 F.3d at 456.

115. *Id.*

The court then turned its attention to the statutory interpretation of section 355(i). It found nothing in the legislative history of section 355(i) that suggested that Congress intended to limit FDA's authority to only regulating clinical data created by the sponsors and manufacturers of investigational drugs.[116] Furthermore, the court determined that FDA's interpretation of section 355(i) did not conflict with Congress's expressed intent.[117] The court then employed a *Chevron* analysis and held that, because Congress was silent on the issue, the court had to defer to FDA's interpretation of section 355(i).[118]

Finally, the Eighth Circuit turned its attention to the nondelegation doctrine.[119] Under the nondelegation doctrine, a Congressional act lays down a principle to which an agency should conform.[120] So long as the agency does not do anything that violates the principle of the Congressional act, a court will defer to the agency's interpretation.[121] With respect to section 355(i), the court in *Garfinkel* found that the statute expressly imposed restrictions on FDA's authority to regulate the reporting of clinical trial data.[122] The court held that regulations promulgated under section 355(i) must relate to the protection of public health and to the investigation of drugs.[123] Additionally, the statue explicitly stated that FDA cannot require clinical investigators to submit reports directly to the Agency.[124] Here, FDA's regulation imposing a duty on clinical investigators to maintain accurate records did not violate the nondelegation doctrine because it did not directly conflict with Congress's expressed intent.[125] The Eighth Circuit reversed the dismissal of criminal charges under section 355(i), and remanded the

116. *Id.*
117. *Id.* at 457.
118. *Id.* at 456–57.
119. *Id.*
120. *Id.*
121. *Id.*
122. *Id.* at 458.
123. *Id.*
124. *Id.*
125. *Id.* at 456–57.

case back to district court.[126] Subsequently, Dr. Garfinkel was sentenced to a prison term of six months.[127]

D. Palazzo and the FDA's Authority to Impose Criminal Sanctions

The most recent attempt to convict a clinical investigator under section 355(i) was resolved in 2009. Dr. Maria Carmen Palazzo was hired by SmithKline Beecham Corporation to conduct a clinical investigation on Paxil (paroxetine), which is used to treat major depression and other mental disorders.[128] The sponsor hired Dr. Palazzo to oversee a clinical investigation testing the efficacy of Paxil in children and adolescents with major depressive disorders.[129] As part of her responsibilities overseeing the clinical trial, Dr. Palazzo was responsible for strictly complying with the study protocol and for personally reviewing all documentation generated during the study.[130] Unfortunately, Dr. Palazzo failed on both counts—she did not comply with the trial protocol or review trial documentation.[131] Additionally, Dr. Palazzo submitted false reports saying that she personally examined all of the study subjects even though she did not and other reports saying that certain patients suffered from disorders that they did not actually have.[132] SmithKline Beecham fired Dr. Palazzo after the sponsor discovered her fraud.[133] Dr. Palazzo was subsequently indicted under section 355(i).[134]

The district court dismissed the charges against Dr. Palazzo under section 355(i), citing the *Smith* decision.[135] On appeal, the Fifth Circuit specifically reviewed only the issue of whether section 331(e) imposes *criminal* sanctions on clinical investigators who violate section 355(i).[136] The court relied solely on statutory interpretation.[137]

126. *Id.* at 459.

127. John Henkel, *Psychiatrist Sentenced for Research Fraud—University of Minnesota Child Psychiatrist Barry Garfinkel* FDA CONSUMER (Apr. 1994), http://findarticles.com/p/articles/mi_m1370/is_n3_v28/ai_15330335/.

128. United States v. Palazzo, 558 F.3d 400, 402 (5th Cir. 2009).

129. *Id.*

130. *Id.*

131. *Id.*

132. *Id.*

133. *Id.*

134. *Id.*

135. *Id.*

136. *Id.* at 405. Dr. Palazzo conceded that FDA has the authority to promulgate regulations that impose record-keeping requirements on clinical investigators under 21 C.F.R. § 312.62. *Id.*

The court found that the plain language of section 331(e) prohibits violations of section 355(i), and violations of section 331(e) carry criminal penalties under section 333(a).[138] The court then held that the FDA properly established reporting requirements that required clinical investigators to maintain accurate records.[139] The court reasoned that these regulations fell within section 355(i).[140] Specifically, section 355(i) allows FDA to promulgate regulations which "protect the public health."[141] The Fifth Circuit held it was reasonable to impose duties on clinical investigators to protect the public health.[142]

Dr. Palazzo did not disagree with the court's decision affirming the validity of 21 C.F.R. § 312.62(b), the FDA regulation that imposed a duty on clinical investigators to maintain accurate records.[143] Instead, Dr. Palazzo asserted that the criminal sanctions imposed by section 333(a) only applied to reports submitted *directly* to FDA.[144] Since section 355(i) explicitly disallows forcing clinical investigators to make direct reports to the FDA, Dr. Palazzo argued that criminal sanction could not be imposed on her.[145] However, the Fifth Circuit found no language in section 333(a), section 331(a), or section 355(i) which limited criminal sanctions to direct reports to FDA.[146] Consequently, criminal liability for violating these regulations, which were promulgated under section 355(i), was proper based on the prohibitions of section 331(e) and the criminal penalties imposed by section 333(a). The court held that criminal sanctions under section 333(a) were not limited to reports made directly to FDA, as Dr. Palazzo contended.[147]

The penalties for violating section 331(e) are specifically stated under section 333(a), and include imprisonment for no more than one year.[148] The Fifth Circuit held that since Dr. Palazzo had conceded

137. *Id.*
138. *Id.*
139. *Id.*
140. *Id.* at 407.
141. *Id.*
142. *Id.*
143. *Id.* (affirming the validity of 21 C.F.R. § 312.62(b)).
144. *Id.*
145. *Id.*
146. *Id.*
147. *Id.*
148. 21 U.S.C. § 333(a) (2010).

that FDA could promulgate regulations requiring accurate reporting from clinical investigators under section 355(i), the fact that a violation of section 355(i) would result in criminal penalties was explicitly anticipated under section 333(a).[149] The court reversed and remanded the district court's decision. On remand, Dr. Palazzo was sentenced to a total of thirteen months imprisonment for this and other charges.[150]

E. Circuit Split

As the discussion of the previous cases have shown, the federal circuit courts of appeal are split over whether FDA has the authority to promulgate regulations imposing criminal sanctions on clinical investigators. Both the Fifth and Eighth Circuits have agreed that clinical investigators who commit fraud in violation of FDA regulations and section 331(i) of the FDCA can be criminally punished under section 333(a). In contrast, the Ninth Circuit's *Smith* decision indicates that section 355(i) did not give FDA the authority to impose criminal sanctions on clinical investigators. However, the *Smith* decision was reached before FDA promulgated regulations that specifically imposed duties on clinical investigators. Assuming the new regulation is valid, it is likely that the Ninth Circuit would concur with the holding of the Fifth Circuit and the Eight Circuit.

The Ninth Circuit's decision also analyzed whether FDA had the requisite authority to promulgate regulations imposing duties on clinical investigators. The circuit split can be characterized as whether the Agency has the requisite authority to promulgate regulations imposing affirmative duties of record keeping on clinical investigators under section 355(i). The Eighth Circuit, after utilizing a *Chevron* analysis, held that FDA did have the authority to promulgate such regulations to protect the public health. The Fifth Circuit was silent on the issue. The Ninth Circuit disagreed, citing the rule of lenity. However, the Ninth Circuit's analysis was always aware of the criminal penalties involved. Technically, section 355(i) itself does not impose criminal penalties, and therefore should be analyzed under a *Chevron* Doctrine analysis such as the one performed by the Eighth Circuit. A rule of lenity analysis would be proper when analyzing whether section 333(a) extends to valid regulations under section

149. Palazzo, *supra* note 128, at 407.

150. David Guitierrez, *Psychiatric Researcher Pleads Guilty to Research Fraud*, NATURAL NEWS (Nov. 29, 2010, www.naturalnews.com/030557_psychiatry_fraud.html.

355(i), and both the Fifth Circuit and Eighth Circuit have held that it does.[151]

If the Ninth Circuit were to decide *Smith* today, it would likely be decided differently. Post *Smith*, FDA promulgated 21 C.F.R. § 312.62, which explicitly created an affirmative duty on clinical investigators to keep accurate records. Clinical investigators now had ample notice that they could be subject to criminal sanctions. This new regulation therefore satisfied the due process concerns of the rule of lenity raised by the Ninth Circuit in *Smith*. The new regulation was also explicitly allowed by the statute. Congress contemplated and expected FDA to promulgate regulations to "protect the public health." Congress also explicitly enacted sections 331(e) and 333(a)(1) of the FDCA, which make violators of section 355(i) subject to criminal sanctions. Congress was not at all "silent" on the issue of criminal penalties against clinical investigators. This therefore satisfies the separation of powers concerns of the rule of lenity.

At the time of the Ninth Circuit's decision, there was no formal notice to clinical investigators that their actions could result in criminal sanctions. Consequently, the Ninth Circuit was correct in dismissing the charges against Dr. Smith based on the rule of lenity—at the time, clinical investigators lacked notice that they had a duty under section 355(i) to maintain accurate clinical records. However, after the *Smith* decision, the FDA used its rule-making authority to promulgate a regulation that imposed record-keeping requirements directly on clinical investigators. A regulation carries the force of law, and therefore this regulation was sufficient to provide notice and alleviate the Ninth Circuit's due process concerns.

However, even under a rule of lenity analysis, FDA's investigator record-keeping regulations should be upheld. At the time of the Ninth Circuit's *Smith* decision, the record-keeping regulation did not exist. FDA tried to impose criminal penalties on a clinical investigator by using a regulation that required *sponsors* to obtain a document from investigators that stated that they would keep accurate records.[152] The Ninth Circuit held that the document with this statement, in and of itself, was not enough to overcome the rule of lenity. Merely signing a form was not enough to give clinical

151. For a contrary analysis discussing how section 355(i) does not impose criminal liability, see Megan S. Peterson, Casenote, *Clinical Book-Cooking: United States v. Palazzo and the Dilemma of Attaching Criminal Liability to Experimental Drug Investigators for Faulty Record-Keeping*, 56 LOY. L. REV. 311 (2010).

152. Smith, 740 F.2d at 737; *see also* 21 C.F.R. § 312.1(a)(1), (a)(13).

investigators notice that they could be subject to criminal penalties. The *Smith* prosecution was therefore a violation of due process concerns.

It was for this reason the Eighth Circuit did not analyze due process concerns relating to notice. The Eighth Circuit instead turned to the *Chevron* Doctrine in an attempt to analyze whether the new regulation was a permissible use of the FDA's authority.

Prior to the Fifth Circuit hearing the case, Dr. Palazzo conceded that 21 C.F.R. § 312.62(b) was valid. Therefore, the Fifth Circuit's decision did not consider whether the FDA had the authority to promulgate such a regulation. But, despite the Ninth Circuit's due process concerns, it is likely that the Supreme Court would uphold the regulation as valid because of the *Chevron* Doctrine. Imposing requirements on clinical investigators does not violate any principles set forth by Congress, and the Court will therefore accede to the FDA's interpretation. Consequently, because the Ninth Circuit decided *Smith* before 21 C.F.R. § 312.62(b) was created, it is likely that it would now concur with the Fifth and Eighth Circuits that the government can rely on the FDCA to bring criminal charges against fraudulent clinical investigators.

IV. The Park Doctrine: Fraud by Corporate Officers

The FDA may also be able to rely on the *Park* Doctrine to pursue criminal charges against fraudulent clinical investigators. Under the *Park* Doctrine, also known as the Responsible Corporate Officer Doctrine, the government can bring misdemeanor charges against company officials for violating the FDCA—even if the corporate official was unaware of the violation—so long as the company official was in a position of authority to prevent or correct the violation and failed to do so.[153] The *Park* Doctrine has been used to impose a high standard of care on corporate officers in positions of power.[154] The *Park* Doctrine has been used in the past to prosecute sponsors for fraud. However, the *Park* Doctrine has never been used to prosecute clinical investigators for fraud and it is not clear whether the doctrine is applicable in these situations. Parts 3.1 through 3.3, *infra*, explain how FDA has previously applied the *Park* Doctrine and

153. United States v. Park, 421 U.S. 658, 676 (1975).

154. *See* Anne E. Walsh, *FDA Finally Releases "Non-binding" Park Doctrine Criteria*, FDA LAW BLOG, Feb. 6, 2011, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2011/02/fda-finally-releases-non-binding-park-doctrine-criteria.html.

analyze whether the doctrine can be used against clinical investigators who commit fraud.

A. United States v. Park

The *Park* Doctrine originated in the early 1970s when FDA held John Park strictly liable for FDCA violations caused by his company even though Mr. Park had no personal knowledge of the violations.[155] Mr. Park was the chief executive officer of Acme Markets, a national retail food chain that had over 800 retail outlets at the time.[156] In 1970, FDA informed Acme that one of its food storage warehouses in Philadelphia had a rat infestation.[157] Acme fixed the rat infestation in Philadelphia, but the next year FDA discovered another rat infestation at Acme's warehouse in Baltimore.[158] Because Acme continued to sell food contaminated by rodents, the government indicted both Acme and Mr. Park for shipping adulterated food into interstate commerce in violation of section 331(k) of the FDCA.[159] Section 331(k) states that the following is prohibited:

> (k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale . . . after shipment in interstate commerce and results in such article being adulterated or misbranded.

Acme pleaded guilty to the charges while Mr. Park pleaded not guilty. In his defense, Mr. Park argued that he was unaware that the warehouse in Baltimore had a rat infestation.[160] FDA conceded that Mr. Park had no knowledge of the Baltimore rat infestation, but argued that he knew that there *could* be a rat infestation at the Acme warehouses and had the requisite control to investigate and fix any infestation.[161] The district court agreed with FDA and convicted John Park, sentencing him to pay fines.[162]

155. Kurt R. Karst, *FDA May Increase Misdemeanor Prosecutions Against Responsible Corporate Officials*, FDA LAW BLOG, Mar. 4, 2010, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/03/fda-may-increase-misdemeanor-prosecutions-against-responsible-corporate.html; *Park*, 421 U.S. at 678.

156. *Park*, 421 U.S. at 660.

157. *Id.* at 661.

158. *Id.* at 660, 661.

159. *Id.* at 660.

160. *Id.* at 663.

161. *Id* at 662–63.

162. *Id.* at 666.

The Court of Appeals for the Fourth Circuit reversed Park's conviction.[163] However, the Supreme Court reversed the decision of the intermediate court and reinstated the trial court's judgment.[164] The Supreme Court noted that previous cases reflected the view that knowledge or intent is not required for criminal convictions under section 331(k) and that "responsible corporate agents" could be subject to criminal sanctions for violations of the FDCA.[165] The Court explained that corporate agents are vested with responsibility and have the power to devise any measures necessary to ensure compliance with federal statutes.[166] Corporate agents therefore bear a "responsible relationship" to the violations.[167] The Court held that the FDCA imposes a positive duty to seek out and remedy violations when they occur and "a duty to implement measures that will insure the violations will not occur."[168] Mr. Park was convicted under section 331(k), but was not sentenced to any jail time or probation and was only fined $250.[169]

B. The Park Doctrine

The theory of criminal liability under the FDCA created by *United States v. Park* is now referred to as the *Park* Doctrine or the "Responsible Corporate Officer" Doctrine.[170] Under the *Park* Doctrine, the government can charge a corporate officer with a criminal misdemeanor violation of the FDCA under 21 U.S.C. § 333(a)(1).[171]

The *Park* Doctrine does not call for the absolute imposition of liability. The Supreme Court recognized that the FDCA "does not require that which is objectively impossible."[172] Lower courts have held that a defendant can avoid a conviction if he "took

163. *Id.* While the court agreed that John Park did not require any "awareness of wrongdoing" to be convicted under section 331(k), the court held that Park had to commit "some act of commission or omission" as an element of the crime. *Id.* at 666–67.

164. *Id.* at 667.

165. *Id.* at 670.

166. *Id.* at 672.

167. *Id.*

168. *Id.*

169. John R. Fleder et al., *FDA and the Park Doctrine*, HYMAN, PHELPS & MCNAMARA P.C., 44 (Oct. 8, 2010), http://www.fdalawblog.net/files/fda-and-the-park-doctrine.pdf.

170. *Id.*

171. 21 U.S.C §333(a)(1).

172. *Park*, 421 U.S at 673.

'extraordinary care' to comply with the FDCA."[173] However, this does not mean that a corporate officer can avoid liability by simply asserting that he was unaware of the violation.[174] So long as an official was in a position to correct or prevent the violation, he can be subject to criminal penalties even if he was unaware of the violation.[175] The prohibited acts that can warrant a *Park* Doctrine prosecution are enumerated in 21 U.S.C. § 331, and include the introduction of adulterated and misbranded drugs into interstate commerce.[176]

The FDA tends to bring cases through "bottom up" prosecutions.[177] FDA would find a violation and report it to the relevant FDA center.[178] The FDA District Office would then decide if the situation warranted criminal prosecution.[179] FDA's Chief Counsel would then present the matter to the Department of Justice's Office of Consumer Litigation.[180] Once the requisite approval was obtained, the Office of Consumer Litigation would then submit the charges to the U.S. Attorney to file the case.[181] In general, FDA chooses to file charges against high-ranking employees, although occasionally FDA has chosen to file charges against lower-level employees instead.[182]

In recent decades, FDA has rarely used the *Park* Doctrine against violators of the FDCA and instead pursued felony cases based on conspiracy, mail fraud, wire fraud, and other theories of criminal liability.[183] However, in 2009 FDA resumed pursuing cases relying on the *Park* Doctrine. And the next year FDA published a letter from Commissioner Margaret Hamburg outlining the Agency's plan to "increase the appropriate use of misdemeanor prosecutions [i.e., *Park* Doctrine prosecutions], a valuable enforcement tool, to hold

173. Fleder et al., *supra* note 169, at 17.

174. *Id*. at 5.

175. *Id.*

176. *Id.* at 7.

177. *Id.* at 19.

178. *Id.* at 21.

179. *Id.*

180. *Id.*

181. *Id.*

182. *See* United States v. Gen. Nutrition, Inc., 638 F. Supp. 556, 563 (W.D.N.Y. 1986).

183. Fleder et al., *supra* note 169, at 31. By the late 1980s, the FDA's use of the *Park* Doctrine was in decline. Prosecutors had alternative means to charge violations of FDCA, and it was easier for judges to understand Title 18 violations, such as mail fraud, false statements, criminal conspiracy, and obstruction of justice, as opposed to provisions in the FDCA statutes. *Id.* at 32. Title 18 violations were also easier for jurors to understand, and jurors felt like they were convicted people for actual criminal charges as opposed to technical regulatory violations. *Id.*

responsible corporate officials accountable."[184] In early 2011, the FDA released an updated version of its internal procedural manual containing an overview of how the Agency will pursue *Park* Doctrine prosecutions.[185] The manual lists how to analyze whether a *Park* Doctrine prosecution is necessary, depending on the corporate official's relationship to the violations and the factors surrounding the violation. Among the factors to be considered are whether the official actually had the scope of authority to correct the violation.[186] The manual also indicates that FDA will consider certain aggravating factors related to an alleged violation before pursuing a *Park* Doctrine prosecution, such as the risk of harm to the public, the seriousness of the violation, and whether the violation reflects a pattern of illegal behavior.[187]

C. The Park Doctrine and Clinical Investigator Fraud

The *Park* Doctrine only applies to "corporate officials" or "responsible corporate officers" of a company regulated by the FDA. Typically, the responsible corporate officers prosecuted in *Park* Doctrine cases are high-level managers and executives within a violating company. However, it is not clear whether the *Park* Doctrine applies to clinical investigators because they are not typically employees of the pharmaceutical company sponsoring the clinical trial. Instead, clinical investigators are usually contractors who function independently of the sponsor. It is arguable that clinical investigators can be subjected to liability under the *Park* Doctrine because they are in charge of the study site. They therefore bear a "responsible relationship" to the clinical site, and could be charged using the *Park* Doctrine, even if they did not have an awareness of wrongdoing.

The *Park* Doctrine itself is mainly used to impose liability without a showing of knowledge or intent. By definition, clinical investigators engaging in fraudulent activities are aware of the wrongdoing, so proof of intent is not generally an issue when pursuing criminal charges against them. However, if an investigator were to

184. Letter from Margaret Hamburg, FDA Comm'r, to Sen. Chuck Grassley (Mar. 4, 2010), *available at* http://grassley.senate.gov/about/upload/FDA-3-4-10-Hamburg-letter-to-Grassley-re-GAO-report-on-OCI.pdf.

185. FDA, REGULATORY PROCEDURES MANUAL ch. 6, at 6–49 (2011), *available at* http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074317.pdf.

186. *Id.*

187. *Id.*

accidentally fail to keep adequate records, he would be subject to liability under the *Park* Doctrine, even absent fraudulent intent. Furthermore, the *Park* Doctrine would also be useful in targeting clinical investigators for fraud that occurs by other employees. Clinical investigators are not the only people who engage in fraud during clinical trials. Other employees who work on the clinical study can and have also engaged in fraudulent behavior.[188] If the clinical investigator were aware the he would be prosecuted for the fraud of other site employees, he would have an incentive to seek out and prevent fraud. Thus, the *Park* Doctrine can be used to strengthen the clinical investigator's loyalty to an above-board study.

V. Suggestions for Addressing Investigator Fraud

FDA has been struggling under the current regulatory regime to effectively prosecute fraudulent clinical investigators. The circuit split over FDA's authority under section 355(i) of the FDCA means that the Agency cannot currently rely on that route to punish clinical investigators who commit fraud. It is necessary for either the Supreme Court to step in and resolve the circuit split, or for Congress to amend section 355(i) of the FDCA to include requirements on clinical investigators. Furthermore, the *Park* Doctrine is untested in this area—as this writing, FDA has only pursued Park Doctrine prosecutions against sponsors and not clinical investigators. Consequently, FDA's ambiguous authority is insufficient to address the problem of clinical investigator fraud. To solve this problem, we propose the following suggestions.

A. Strengthen FDA's Usage of Section 355(i) and the Park Doctrine

FDA has already indicated a willingness to use the *Park* Doctrine to ensure clinical investigations are run according to FDA regulations.[189] However, to date FDA has only used the *Park* Doctrine against sponsors and direct employees of the sponsor. Due to the circuit split, it is ambiguous whether the regulations promulgated have the full force of law even if FDA tried to use the *Park* Doctrine against a clinical investigator. A simple way to clear this up would be for Congress to explicitly add requirements on clinical investigators as an amendment to section 355(i) of the FDCA.

188. *See* United States v. General Nutrition, Inc., 638 F. Supp. 556, 563 (W.D.N.Y. 1986).

189. Fleder et al., *supra* note 169, at 38.

Alternatively, the Supreme Court should grant certiorari on the next case which involves clinical investigator fraud and violations of section 355(i). The Court should affirm the FDA's position that the regulations promulgated under section 355(i) allow them to bring criminal sanctions against fraudulent criminal investigators, based on the non-delegation doctrine and *Chevron* analysis.

FDA should also make more of an effort to utilize the *Park* Doctrine against clinical investigators. While pharmaceutical companies are responsible for overseeing the clinical trials they are sponsoring, maintaining clear oversight can often times be practically impossible, especially for larger companies that may have hundreds of clinical trials running simultaneously testing multiple drug candidates. Additionally, even if a sponsor does determine that a clinical investigator engaged in fraud, the sponsor may itself commit fraud by hiding or destroying the investigator's findings as opposed to informing FDA. Any divergent findings will cause FDA to extend the amount of time required to approve the new drug. However, by making clinical investigators aware that they will be subject to criminal penalties, the investigators will then have an additional reason to report such fraud. Additionally, the investigators will not be as willing to perpetrate fraud on behalf of sponsors.

There is yet another advantage to strengthening the scope of section 355(i). Under the Patient Protection and Affordable Care Act (PPACA) of 2010, the penalties for health care fraud have been expanded. Specifically, the PPACA amended the section of the federal criminal code that defines a "federal health care offense" to include violations of 21 U.S.C. § 331(a).[190] The only limitation is that the violation must be "related" to a health care benefit program.[191] The drug approval process arguably has a direct effect on a patient's health-care costs and well-being and could be considered reasonably related to a health-care benefit program. It is likely that stiffer penalties can be utilized if an investigator is prosecuted under section 355(i) rather than generic mail fraud statutes.. Given the direct effect the drug industry has on health care costs, the stiffer penalties should be utilized for section 355(i) prosecutions.

190. 18 U.S.C. § 24 (2010).

191. *Id*.

B. Sponsor Reporting of Clinical Investigator Fraud

The FDCA contains an adverse-event reporting provision that requires a sponsor to inform FDA of an adverse event caused by its drug within fifteen days of learning about the event.[192] If a company fails to report the adverse event, it can be criminally prosecuted.[193]

Similarly, Congress should make it mandatory for sponsors to report clinical investigator fraud. If a sponsor does not report fraudulent conduct by a clinical investigator, then the sponsor should be subject to criminal sanctions. Fraud in drug trials is a very real problem, and FDA should incentivize transparency and reporting wherever possible. Unfortunately, it is difficult for FDA to discover fraud on its own. As stated earlier, FDA only has the resources to audit a tiny fraction of clinical trial sites.[194] The drug sponsors are in a much better position to detect fraud than FDA investigators.

Currently, drug sponsors arguably have little incentive to report clinical investigator fraud. Suppose, for example, a drug company is running a multi-site Phase III clinical trial. One site reports back amazing results, while all the other sites report a more normal range of effectiveness. The drug company investigates, and discovers the clinical investigator padded the results. If the drug company reports the investigator, and the site data, it will likely delay FDA approval. The drug company knows the data from the site is useless and irrelevant and already has enough data without this site. Considering the enormous investment, the drug company may be tempted not to report any data or activity from the fraudulent site.

The argument against this scenario is that drug companies have to register their clinical trials; if a drug company drops a site, FDA will know. However, only certain types of drugs are required to report their clinical sites to FDA.[195] Many other types of drugs are encouraged to register their clinical trials, but are not explicitly required to do so.[196] And even when sponsors are supposed to report on clinical trials, they often fail to do so. For example, FDA reported in 2005 that approximately one-third of clinical trials were not

192. 21 C.F.R. § 312.32(c) (2010).

193. United States v. Eli Lilly & Co., No. IP85-53CR (S.D. Ind. Aug. 1985) (Eli Lilly eventually paid a $25,000 fine.).

194. *See* note 78 and accompanying text.

195. ERIN D. WILLIAMS, CONG. RESEARCH SERV., RL 32832, CLINICAL TRIALS REPORTING AND PUBLICATION 6 (2007).

196. *Id.*

registered with the Agency.[197] Effectively, there is no requirement that the results of clinical trials be made publically available, except those included in order to obtain approval. However, by creating an affirmative duty, FDA can incentivize clinical investigator fraud reporting.

C. Implementing a Criminal Statute for Investigator Fraud

Congress should also pass a criminal statute that explicitly subjects anyone to criminal penalties who falsifies data that is submitted to FDA. This statute should be similar to the Federal False Statements statute, under which a person who submits false statements under oath to a government official will be subject to criminal penalties.[198] Similarly, we propose that Congress should enact a statute that makes anyone who knowingly submits false data to a government agency pursuant to a Federal law regulating the manufacture, sale or use of drugs or biological products subject to criminal penalties.[199]

Effectively, this proposed statute would act as an expansion of section 355(i). Currently, clinical trial sites are required to maintain proper documentation. If a site does not have proper documentation for all data and clinical test subjects, the sponsor can be indicted even if the lack of documentation occurred without the sponsor's knowledge under the *Park* Doctrine. A new criminal statute could instead require an intent to defraud. Therefore, if a clinical investigator is falsifying data and the sponsoring drug company is unaware, the investigator can be indicted under this statute and face harsher penalties than exist under the current framework.

VI. Conclusion

Clinical investigator fraud is a very real problem, and falls squarely within FDA's mandate to protect the public health. As part of this mandate, the Eighth Circuit held in *Garfinkel* that FDA has the authority to impose affirmative duties to protect the public health by promulgating relevant regulations.[200] FDA did promulgate such regulations, and the Eighth Circuit held that a failure to follow these regulations is a violation of section 355(i) of the FDCA. A violation

197. *Id.* at 8.

198. 18 U.S.C. §1001 (2010).

199. This language mirrors that of the safe harbor provision of section 271(e)(1) of the Patent Act.

200. United States v. Garfinkel, 29 F.3d 451, 458 (8th Cir. 1994).

of section 355(i) is considered a violation of section 331(e), and a violation of 331(e) can result in criminal sanctions under section 333(a). Thus, this tenuous chain of statutes allows the government to bring criminal charges against fraudulent criminal investigators.

It is also important to understand the effect clinical investigator fraud has on the public health. With so many new drugs undergoing clinical trials every year, it is unlikely that FDA can detect fraud unless it is especially egregious, or revealed to the Agency by a person working on the clinical trial. While sponsors have a duty to oversee their clinical trials, the reality is that clinical trials are often run relatively autonomously by clinical investigators at multiple test centers with thousands of participants. It is likely that a sponsor will miss instances of fraud, and a drug could be approved and enter the marketplace without accurately testing its safety and efficacy.

Clinical investigators are paid by the sponsors of drug trials. If an instance of fraud is discovered, the sponsor will be subject to criminal sanctions, not the investigator. By imposing criminal sanctions on clinical investigators, the government can modify the behavior of investigators who allow or conduct fraud. Clinical investigators need to know that they will be subject to criminal penalties if any fraud is discovered. To protect the public health, the clinical investigators need to be held accountable.

For similar reasons, the *Park* Doctrine itself should also be utilized against clinical investigators. Even if investigators are unaware of wrongdoing, they have the "responsible relationship" with the documents. Also, currently clinical investigators are beholden to the sponsors, who ultimately sign their paychecks. If they are aware they will be liable, and subject to criminal penalties under the *Park* Doctrine, even when they are unaware of any problems, they will be more likely to seek out problems and report any wrongdoing they discover.