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Christine Galbraith Davik
University of Maine School of Law, christine.davik@maine.edu

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DYING TO KNOW: A DEMAND FOR GENUINE PUBLIC ACCESS TO CLINICAL TRIAL RESULTS DATA

Christine D. Galbraith*

"I'm sorry, but you have cancer . . ."

Nothing can quite prepare you for hearing these words from your doctor. Especially learning of such a diagnosis in your mid-thirties, when the thought of battling a life-threatening disease hasn’t even remotely crossed your mind. Advancing in one’s career, building a family, buying a home—these are the typical sorts of things people my age are supposed to be doing. Confronting a possibly fatal illness like breast cancer certainly was not on any potential list of things to do I had ever imagined for myself. Nonetheless, several years ago I had no choice but to abruptly change course and begin planning a strategy to fight cancer, just like hundreds of thousands of other individuals in this country.

In fact, there are more than a quarter million women living in the United States today who were age forty or under when they were first diagnosed with breast cancer. Additionally, this

* Associate Professor of Law, University of Maine School of Law; B.S. University of Illinois, 1992; J.D. University of Illinois, 1995. Many thanks to Professor Thomas Ward and Professor Marty Rogoff for their insightful comments on earlier drafts. Much appreciation to Dr. Davina Ghersi, Director of the World Health Organization’s International Clinical Trials Registry Platform, as well as many of the participants at the 2008 Stanford University Law School’s Intellectual Property Scholars Conference and the 2008 Tulane Law School Works in Progress Intellectual Property Colloquium for

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year almost 1.5 million Americans will learn they have some form of cancer, and more than half a million will die this year from their disease.\(^2\) Once the initial shock of receiving a diagnosis of cancer or some other life-threatening illness wears off, the next step for most individuals is to work with their doctors to develop an appropriate treatment plan. For many, including myself, this involved contemplating whether or not to enroll in some form of a clinical trial. Quite unexpectedly, however, my position as an intellectual property professor whose scholarship focuses primarily on information control, my role as a member of my university’s Institutional Review Board that oversees studies involving human subjects, and my newly acquired status of “cancer patient” converged. While researching various clinical trial options for confronting my own disease, I soon became aware of an unacceptable and unnecessary risk directly shouldered by study participants, but also indirectly borne by patients generally.

I. INTRODUCTION

Each year approximately 10,000 clinical trials are conducted in the United States,\(^3\) with more than two million individuals enrolling in these studies on an annual basis.\(^4\) Such extremely valuable conversations. I am also grateful to Julie Welch and Kevin Haskins for their exceptional research assistance. Additionally, I’d like to thank Dean Peter Pitegoff and the University of Maine School of Law for financial support in the form of summer research grants to complete this project. This article is dedicated to the many wonderful friends I have made on my breast cancer journey, as well as to the memories of those who have been lost to the disease.

\(^1\) Figure based on the 2000 U.S. Census data and reported by the Young Survival Coalition. Young Survival Coalition, Statistics, http://www.youngsurvival.org/young-women-and-bc/statistics/ (last visited Feb. 11, 2009). Additional statistical information on breast cancer in young women has been collected and is also available. Id.


\(^3\) COMM. FOR ECON. DEV., HARNESSING OPENNESS TO TRANSFORM AMERICAN HEALTH CARE 14 (2008); FOOD & DRUG ADMIN., INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS 13 (2004).

\(^4\) See Wendy K. Mariner, Human Subjects, NAT’L L.J., May 13, 2002, at A25 (calling for the establishment of a single, independent federal entity to protect human subjects). One estimate of the number of patients needed to fill solely industry-sponsored trials
trials are an integral component of the development process for pharmaceuticals, as the data generated supplies information necessary to obtain FDA approval of a new drug. This approval is essential in allowing the investigative treatments to move from the research bench to the relevant patient population, potentially providing more effective medical care and protocols with more tolerable side effects. Moreover, to the extent approval is acquired, further clinical trials are often conducted to potentially identify other indications for which the medication might be useful or additional patient populations that could benefit from the drug in question.

Individuals register to take part in these studies for a multiplicity of reasons. Often this includes the hope that they will potentially benefit from the offered treatment if they happen to be in the arm of the trial that receives the therapy under investigation. An additional rationale for most participants is the belief that the information obtained from the study will contribute to the body of scientific knowledge, ultimately assisting future patients.

Participating in a clinical trial is not, however, without risk.


Clinical trials are also an important part of the process for obtaining FDA approval of medical devices and biologics, although the method of acquiring approval is slightly different. Furthermore, while the concerns raised in this article are also largely applicable to medical devices and biologics as well, for simplicity's sake I will limit my discussion of the issues to pharmaceuticals.

See infra Part II discussing the measures required to obtain FDA approval of a new drug.

For example, a pharmaceutical initially approved for treating breast cancer, may be tested to ascertain whether it also could effectively be utilized in connection with prostate cancer.

This might include a drug that has initially received FDA approval for use in breast cancer patients that have a very advanced form of the disease, which might then be tested to determine whether it also would be beneficial for those individuals diagnosed at a much earlier stage.

Clinical trials are frequently structured in such a way that one group of patients receives the investigational treatment, while the comparison group receives the standard therapy for the condition at issue or, in some situations, only a placebo.
As such, federal law requires researchers to provide prospective enrollees with information necessary to ideally make an educated decision regarding whether or not to take part in the study.\(^{10}\) It is only after fully considering all of the relevant advantages and drawbacks to enrolling in a clinical trial can a patient truly provide the mandatory informed consent to treatment.\(^{11}\) In most cases, potential study participants will be advised that taking part in the study by no means guarantees improvement in one’s condition.\(^{12}\) Furthermore, study investigators must supply prospective enrollees with information regarding the complete range of potential side effects, including in appropriate circumstances, disclosing that serious complications are a genuine possibility.\(^{13}\) While it is impossible to completely eliminate all of the conceivable safety threats associated with participation in a clinical trial, patients are routinely exposed to a significant hazard of which they are not only unaware, but even more disturbing, one that is for the most part avoidable.

Historically, results from previous clinical studies have not been required to be made public, and drug companies have generally been exceptionally resistant to such disclosure. The pharmaceutical industry now substantially overshadows the federal government as the single greatest source of financial support for conducting clinical trials.\(^{14}\) As such, these companies have taken the position that if they are funding the research, the data produced should consequently be deemed their property, protectable through patent, trade secret, and contract law.\(^{15}\) Additionally, the FDA has generally supported this view, and the courts by and large have similarly agreed.\(^{16}\)

\(^{10}\) 21 C.F.R. § 50.20 (2007).
\(^{11}\) Id.
\(^{12}\) Id.
\(^{13}\) Id.

\(^{14}\) The vast majority of clinical trials are now funded by for-profit companies. See Shankar Vedantam, Drugmakers Prefer Silence on Test Data, WASH. POST, July 6, 2004, at A1.

\(^{15}\) See infra Part VI discussing these legal arguments.

\(^{16}\) See infra Part II discussing FDA regulations which prohibit the disclosure of proprietary information.
Accordingly, only a small fraction of trial outcomes are eventually published in medical journals or in some other peer-reviewed format.\textsuperscript{17} Moreover, research has shown that most of the pieces ultimately published tend to be about trials that demonstrate the treatment under investigation was in fact superior as compared to the traditional therapy or placebo.\textsuperscript{18} This propensity for journals including articles on clinical studies with positive results is frequently referred to as “publication bias.”\textsuperscript{19}

From a practical standpoint, this means that future studies are generally not informed by previous research. This is particularly true of clinical trials that have negative outcomes. As a result, additional studies involving identical or similar treatment regimes may be repeated without the knowledge of patients, doctors, or other researchers. Such a possibility is not merely theoretical as, for example, competitors often develop and test molecular entities in the same class with comparable mechanisms of action or, as often the case may be, inaction.

Consequently, when clinical investigators replicate trials that have previously been shown to be ineffective or even harmful, human subjects are placed at considerable risk. By failing to release pertinent information regarding the results of earlier trials, study participants are often left to shoulder the significant danger posed by the investigational treatment without the potential for any benefit, in contradiction to commonly recognized ethical standards. Furthermore, to the extent results from clinical trials never enter the public domain, the compelling contribution of these patients becomes essentially meaningless. This has prompted many in the worldwide medical community to characterize this failure to publish the results as a form of scientific misconduct and a

\textsuperscript{17} The peer-review process is often extolled by the medical and scientific community as the ideal method of publishing and is the one used most by the leading journals. This model generally allows for review of the research data and the article itself by other experts in the field prior to publication. Nonetheless, while there are reasons to believe this may be the preferred approach, the peer-review process does not completely guarantee the accuracy of the information contained within the published piece.

\textsuperscript{18} See infra Part VII reviewing the wide body of research devoted to this topic.

\textsuperscript{19} See infra Part VII examining publication bias and its various implications.
violation of ethical principles. As an editorial in the *New England Journal of Medicine* so aptly stated, "When patients put themselves at risk to participate in clinical trials, they do so with the tacit understanding that their risk is part of the public record, not merely the secret record of the sponsor."

Additionally, the failure to disclose study results not only impacts clinical trial participants, but the health of the general public may be put in jeopardy as well. For drugs that have received FDA approval, post-market clinical trials investigating new uses of the medication often reveal important information concerning side effects and related adverse complications with the treatment. To the extent that prescribing physicians do not have this essential data, they could inadvertently be putting their patients at serious risk by continuing to recommend the medication.

Over the past few years, numerous scandals in the drug industry illustrate that concealing unfavorable research results is far from an isolated practice. Cases have implicated many of the leading pharmaceutical companies and involved such blockbuster drugs as Paxil and Vioxx, to name just a few. In a quest to boost sales and increase corporate profits, the temptation to hide or selectively disclose clinical trial data has proven to be too much.

Amid mounting claims of misconduct by drug manufacturers and increasing concern regarding the FDA's role in the various controversies, both the Senate and House held a number of hearings on the issue. Congress responded to the

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22 See infra Part III providing representative examples of several well-documented cases of such intentional deception.

23 See infra Part III reviewing these cases.

intensifying pressure by the medical community, patient rights advocates, and the general public\textsuperscript{25} by enacting federal legislation in late 2007 that purportedly provided extensive transparency regarding clinical trials by creating a clinical trial results database.\textsuperscript{26} One of the bill's sponsors, in extolling the virtues of the measure on the Senate floor, asserted that as a result of the new legislation "the public will [now] know about each trial underway, and will be able to review its results."\textsuperscript{27} Unfortunately, this characterization is far from accurate.

In actuality, the results of only a very small minority of the trials conducted involving human subjects will require disclosure under the Act as currently configured. This is due to the fact that with some minor exceptions, only data on later stage\textsuperscript{28} clinical trials must be released, and this is only if the treatment under investigation actually receives FDA approval.\textsuperscript{29} As even the FDA itself has acknowledged, "[T]he vast majority of investigational products that enter clinical trials fail."\textsuperscript{30} This scarcity of success is frequently attributable to a finding that the

\textsuperscript{25} See Fiona Godlee, An International Standard for Disclosure of Clinical Trial Information, 330 BRITISH MED. J. 7502 (2005) (discussing a recent survey that found only a quarter of Americans were of the opinion that the pharmaceutical industry was doing a good job; interestingly, such a low approval rating is in line with the public's perception of the tobacco industry.).


\textsuperscript{27} 153 CONG. REC. S11,831 (Sept. 20, 2007) (statement of Sen. Kennedy).

\textsuperscript{28} Results from Phase I studies do not have to be reported. See Section II \textit{infra} reviewing the various phases of clinical trials and Section VII \textit{infra} discussing why the disclosure of Phase I trial data should be mandatory.


compound at issue is either ineffective or has significant safety problems, such as severe side effects. As a result, a new drug entering the initial phase of trials involving human subjects is estimated to have only an eight-percent chance of ever obtaining federal approval and ultimately reaching the market.

This legislation therefore allows a tremendous amount of information to remain hidden away, falling far short of providing meaningful statutory reform. Studies which are unsuccessful may continue to go unreported with unfavorable results concealed. Ironically, most of the scandals which precipitated the push for reforms regarding data disclosure in the first place could still easily occur, as the supposed safeguards mandating release still would not require the information at issue in those situations to be made publicly available.

The only thing the statute truly appears to accomplish is to supply a means to potentially placate the public without displeasing the pharmaceutical industry. The drug companies continue to cite a wide variety of rather unconvincing arguments as to why any further disclosure would be completely unfeasible. Nonetheless, even assuming the possible merit of these contentions, it is not at all clear why the pharmaceutical industry's claims should take precedence.

Incomplete release of study results not only impedes scientific research, but of even greater concern, needlessly places human lives in jeopardy. Such a state of affairs is wholly unacceptable. Therefore, this article calls for comprehensive disclosure of meaningful clinical trial results data from all studies, including the underlying raw data, regardless of whether FDA approval is ever obtained or even sought. This would offer true transformation of the current system, as well as

31 Id. at 7.
32 Id.
33 See infra Part V discussing the numerous shortfalls of the Act and how it fails to adequately protect the public from future problems similar to those which have surfaced over the past few years in the pharmaceutical industry.
34 See infra Part VI reviewing the various arguments put forth by the pharmaceutical industry and examining their claimed merit.
ensure the risk endured by the courageous men and women that volunteer for clinical trials is not worthless.

This article begins in Part II by examining the important role clinical trials play in the FDA approval process. This section also reviews the regulations and policies that prohibit the FDA from disclosing the vast majority of relevant data included in the pharmaceutical company's application due to the fact that much of the material is classified as proprietary information. Part III discusses a number of well-documented controversies in the pharmaceutical industry involving the concealment or misrepresentation of clinical trial results data, including the FDA's actions in connection with these cases. Part IV briefly reviews the legislative precursors to the Food and Drug Administration Modernization Act ("FDAMA") which required the creation of a clinical trials database that eventually became law on September 27, 2007. Part V presents a comprehensive analysis of the FDAMA, discussing the numerous ways in which the statute is deficient. Part VI evaluates the many claims advanced by drug companies to support their position against expanded disclosure of results information. Included in this section is an analysis of the various legal constructs that drug makers have argued grant them an ability to control information regarding clinical trial results data, namely trade secret, contract, and patent law. Lastly, Part VII examines the compelling arguments that lend significant support to a demand for further release of clinical trial data.

II. THE SIGNIFICANT ROLE CLINICAL TRIALS PLAY IN THE FDA APPROVAL PROCESS

The federal government did not play an active part in the regulation of pharmaceuticals until 1906 when Congress passed the Pure Food and Drug Act.\(^{35}\) This statute prohibited the sale of misbranded and adulterated drugs.\(^{36}\) In 1938, the Federal


\(^{36}\) Id.
Food, Drug and Cosmetic Act ("FDCA") repealed the Pure Food and Drug Act.\textsuperscript{37} The FDCA required the FDA for the first time to evaluate studies conducted by manufacturers to determine if the drug was safe for its intended use prior to commercial distribution of the medication.\textsuperscript{38} In 1962, the FDCA was amended, mandating that a drug's sponsor not only prove a medication's safety as previously required, but also now validate its efficacy.\textsuperscript{39} This was to be demonstrated with evidence from adequate and well-controlled clinical trials.\textsuperscript{40}

Such a prerequisite continues today, as a pharmaceutical company must substantiate its claims that a drug is safe and effective to the FDA through studies involving human subjects before the treatment is approved for marketing.\textsuperscript{41} However, the FDA drug approval process doesn't allow for immediate testing on human beings. Instead, preclinical evidence must first be gathered. Typically, this commences with scientific researchers attempting to search for and identify chemical entities that show potential for treating or even curing a particular disease.\textsuperscript{42} Once such a compound has been ascertained, customarily the next step is to proceed with either extensive laboratory testing, or as more often the case, studies involving animals.\textsuperscript{43} If this research appears promising, a pharmaceutical maker will often continue on with the approval process by filing an investigational new drug application ("IND").\textsuperscript{44}

\textsuperscript{38} Id.
\textsuperscript{40} Id.
\textsuperscript{41} 21 U.S.C. § 355(d)(5) (2008). Pharmaceutical manufacturers must demonstrate "substantial evidence" of efficacy. See discussion infra Part II.A further discussing the FDCA's definition of this requirement and the FDA's interpretation thereof.
\textsuperscript{42} U.S. GOV. ACCOUNTABILITY OFFICE, NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS 6 (2006).
\textsuperscript{43} Id.
\textsuperscript{44} The pharmaceutical industry estimates that on average only five in every 10,000 compounds successfully complete this preclinical testing. See id.
A. Investigational New Drug Application (IND)

A pharmaceutical company may not begin clinical trials involving the administration of an investigational drug to human subjects until an IND is submitted.45 The primary purpose of an IND is to supply the FDA with sufficient information from earlier studies involving laboratory animals or in vitro laboratory testing to make a determination as to whether or not it is reasonably safe to proceed with trials involving human beings.46 Additionally, the applicant must provide assurances that all proposed studies involving human subjects will first be approved and then continually reviewed by an appropriately constituted Institutional Review Board ("IRB").47 While the FDA does not provide an official approval of the application, the planned studies may be subject to a clinical hold by the agency, namely an order to delay the anticipated clinical investigation until any problems are resolved regarding the intended protocol.48 More often than not, the proposed investigational plan does not raise concerns. Accordingly, the IND will go into effect thirty days after the FDA receives the application, at which point the drug company may proceed with clinical trials involving human subjects.49

Clinical investigations of pharmaceuticals that have not previously undergone human testing are typically divided into three principal stages.50 While these three phases usually are conducted sequentially, in some cases they may in fact overlap.51 The earliest introduction of an investigational new drug in human subjects occurs in Phase I studies.52 Such trials are

45 21 C.F.R. § 312.20(b) (2008).
47 21 C.F.R. § 312.66 (2008). The requirements for the composition, operation, and responsibilities of an IRB that reviews clinical trials regulated by the FDA is found in 21 C.F.R. § 56 (2008). Failure to obtain IRB approval of research protocols may result in an inability to submit the findings from such trials to the FDA. See 21 C.F.R. § 56.103(b) (2008).
51 Id.
generally comprised of twenty to eighty healthy volunteers.\textsuperscript{53} However, in studies examining treatments that are expected to have significant toxicities, such as chemotherapy agents, only patients suffering from cancer will be allowed to participate in the clinical trial. The primary objective of Phase I studies is to determine appropriate dosing levels for the drug in question, as well as identify possible side effects.\textsuperscript{54}

Phase II studies usually include no more than several hundred subjects.\textsuperscript{55} Individuals involved in this phase, ordinarily consist solely of persons with the disease or condition under investigation.\textsuperscript{56} These clinical trials are conducted primarily to evaluate the effectiveness of the pharmaceutical at issue, although side effects and risks associated with the drug continue to be monitored.\textsuperscript{57}

In Phase III trials, the medication is normally tested on several hundred to several thousand patients.\textsuperscript{58} Similar to Phase II trials, the subjects in this stage also have been diagnosed with the disorder at issue in the study. Such trials are performed to collect further information about efficacy and safety which will then be used to determine the critical overall risk-benefit ratio of the investigative treatment.\textsuperscript{59} Additionally, the studies provide the data that will form the basis for physician labeling of the medication.\textsuperscript{60} Phase III trials are typically the principal studies upon which the FDA relies in determining whether or not approval of the pharmaceutical is appropriate.\textsuperscript{61}

\begin{itemize}
\item \textsuperscript{53} Id.
\item \textsuperscript{54} 21 C.F.R. § 312.21(a) (2008).
\item \textsuperscript{55} 21 C.F.R. § 312.21(b) (2008).
\item \textsuperscript{56} Id.
\item \textsuperscript{57} Id.
\item \textsuperscript{58} 21 C.F.R. § 312.21(c) (2008).
\item \textsuperscript{59} Id.
\item \textsuperscript{60} Id.
\item \textsuperscript{61} The FDA can utilizes its authority to make approval of an NDA conditional on the applicant's agreement to conduct post-marketing clinical trials, often referred to as Phase IV studies. Such studies are often employed to investigate issues concerning the drug's risks, benefits, and optimal use. 21 C.F.R. § 312.85 (2008).
\end{itemize}
If the pharmaceutical company believes the evidence obtained from completed clinical trials demonstrates that the investigational drug shows potential for approval, the next step is to file a New Drug Application (“NDA”) with the FDA. The NDA is designed to provide detailed information regarding the data obtained while the IND was in effect. Accordingly, the application must contain reports of every clinical trial sponsored by the applicant involving the medication, regardless of outcome. Additionally, all relevant information about the drug that has been acquired by the applicant from any source also needs to be provided to the FDA.

The FDA will analyze the information provided to determine whether or not there is adequate evidence to establish that the pharmaceutical is safe and effective for the conditions of use advanced by the applicant. In doing so, the FDA conducts a risk-benefit analysis in order to ascertain whether the advantages of the medication outweigh the potential for harm. With regard to determining efficacy, the standard utilized by the FDA is that of “substantial effectiveness.” This term was defined by the 1962 amendments to the FDCA as follows:

Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or

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64 21 C.F.R. § 314.50 (2008).
65 Id.
suggested in the labeling or proposed labeling thereof.69

This definition has generated considerable debate, especially concerning the amount of data necessary to establish effectiveness.70 Traditionally, the FDA took the position that Congress intended this to require results from at least two clinical trials that demonstrate the investigative drug is superior to a placebo or the conventional treatment.71 However, in 1997, as part of the FDA Modernization Act, the FDCA was amended to clarify that positive results from a single trial may be adequate.72

Conversely, there is no established number of negative trials that will be grounds for rejecting the application. In fact, there may be extensive evidence from numerous clinical studies of a drug ultimately approved by the FDA that shows the medication not only performed similarly to the control treatment, but actually was inferior.73 For example, an analysis of clinical studies of antidepressants found that the makers of Prozac had to conduct five trials to obtain two that were positive, while the manufacturers of Paxil and Zoloft needed to sponsor even more.74 Such trial results historically have not been disclosed by the FDA.75 Similarly, when studies reveal significant toxicity, this evidence also has not generally been

71 Id.
72 Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 103 (codified as 21 U.S.C. § 355(d) (2008)). The amended provision now states as follows: "If the Secretary [of Health and Human Services] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence. . . ." § 355.
73 See infra Part III reviewing the negative clinical trial evidence associated with the many of the drugs involved in recent scandals.
75 See infra Part V examining how this disclosure policy was altered by the FDAAA, as well as discussing why these changes are not sufficient.
publicly released by the agency.\textsuperscript{76}

C. Confidentiality of Information Submitted to FDA

Traditionally, FDA disclosure of materials submitted to the agency has been exceptionally limited. Data that is classifiable as trade secrets\textsuperscript{77} or confidential commercial information\textsuperscript{78} typically cannot be revealed to the general public, unless the applicant grants permission to such dissemination.\textsuperscript{79} In fact, even the mere existence of an IND or NDA filing may not generally be disclosed, unless this has been previously divulged or acknowledged by the applicant.\textsuperscript{80} Furthermore, under the Trade Secrets Act, disclosure of this type of data by an FDA employee constitutes a criminal offense.\textsuperscript{81}

\textsuperscript{76} Id.

\textsuperscript{77} 21 C.F.R. § 20.61(a) (2008) defines a trade secret as consisting of "any commercially valuable plan, formula, process, or device that is used for the marking, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort." See also infra Part VI evaluating the strength of claims by pharmaceutical companies that clinical trials results data constitutes a trade secret.

\textsuperscript{78} 21 C.F.R. § 20.61(b) (2008) defines confidential commercial information as "valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs." See also infra Part VI examining the validity of drug industry arguments that clinical trials results data should be classified as proprietary information.

\textsuperscript{79} 21 C.F.R. § 20.61(c) (2008).

\textsuperscript{80} 21 C.F.R. § 312.130(a) (2008) (non-disclosure of IND filing); 21 C.F.R. § 314.430(b) (2008) (NDA filing will not be revealed before an approvable letter has been sent to the applicant).

\textsuperscript{81} 18 U.S.C. § 1905 (2008) provides:

Whoever, being an officer or employee of the United States or of any department or agency thereof, . . . publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association; . . . shall be fined under this title, or imprisoned not more than one year, or both; and shall be removed from office or employment.

See also infra Part VI examining the strength of arguments by the drug industry and the
These policies have been the source of immense frustration, as illustrated by testimony provided by a patient advocate in connection with a Senate hearing on the FDA approval process who stated as follows: "The FDA is probably one of the most secretive government agencies that any consumer will ever have to deal with. Virtually everything about a drug is considered proprietary. Agency officials will not talk with anyone about the drug unless the manufacturer gives them permission to do so."82

Although certainly subject to debate,83 clinical trial results have historically been categorized as trade secrets or confidential commercial information by the FDA. Consequently, such study data may not be disclosed without the consent of the pharmaceutical company that originally provided the information to the agency.84 Additionally, adverse events85 reports required to be submitted by the drug manufacturer

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83 See infra Part VI discussing why the FDA's conclusions regarding the classification of clinical trial data as trade secrets or confidential commercial information is arguably improper.

84 See infra Part V discussing the FDAAA and its arguably slight impact on the FDA's general policies regarding the reporting of clinical trials results data.

85 An "adverse event" is defined by FDA regulations as "[a]ny adverse experience associated with the use of the drug that is both serious and unexpected," as well as, "[a]ny finding from tests in laboratory animals that suggests a significant risk for human subjects." 21 C.F.R. § 312.32(c) (2008). An adverse experience is "serious" if it "results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect." 21 C.F.R. § 312.32(a) (2008). Additionally, an adverse experience is "unexpected" to the extent that the incident is such that:

The specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

21 C.F.R. § 312.32(a) (2008). Furthermore, the regulation provides that "unexpected" refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product. 21 C.F.R. § 312.32(a) (2008).
concerning harms experienced by clinical trial participants associated with the use of the medication are treated similarly.\(^{86}\)

As a result, the FDA has traditionally refused to release this critical information for public scrutiny on the grounds it is proprietary.\(^{87}\)

III. ALLEGATIONS OF SUPPRESSION AND MISREPRESENTATION OF CLINICAL TRIAL DATA IN THE DRUG INDUSTRY

Virtually all of the major pharmaceutical companies have come under scrutiny in the past few years over claims they concealed unfavorable clinical trial findings or distorted the results of study information that they voluntarily chose to publicly release. The FDA’s conduct has also been called into question in connection with many of these controversies, as evidence began to emerge that the agency had intentionally blocked or delayed warnings regarding use of the medications at issue from reaching the public. Additionally, these cases serve to highlight the numerous deficiencies in the law regarding the reporting of clinical trial data which allows drug manufacturers and the FDA to largely control all disclosure. As such, two of the most publicized controversies are reviewed below in more detail to provide context for the argument that increased access to study results is crucial.

A. Anti-Depressants and Pediatric Patients

1. GlaxoSmithKline’s Paxil

GlaxoSmithKline ("GSK"), one of the world’s largest drug manufacturers, produces and sells the drug paroxetine. This medication is marketed in the United States as Paxil\(^{88}\) and has

\(^{86}\) See infra Parts VI-VII examining the various arguments in favor and against further public disclosure of such information, as well as a related discussion concerning the definitional and organizational problems associated with the reporting system itself.

\(^{87}\) See infra Part VII discussing the problems associated with such a policy. See also infra Part V examining the negligible changes to these rules by the FDAAA.

\(^{88}\) This drug is also sold under the trade name Seroxat in many countries outside the United States, including Britain.
been approved by the FDA for treating a variety of indications, including depression, anxiety, and obsessive compulsive disorder in adults.\(^9\)

This pharmaceutical has not, however, received approval for use in children or adolescents.\(^9\)

Nonetheless, approximately 2.1 million prescriptions were written for use of the medication in this pediatric population of patients in a single year alone.\(^9\)

Such conduct by physicians is permitted through a common practice referred to as "off-label" prescribing.\(^9\)

While the FDA approves a drug for particular conditions and a specific type of patient population, doctors are allowed to prescribe FDA-approved medications for other indications if a physician determines it is appropriate.\(^9\)

In order to reach such a conclusion, a doctor usually must rely on his or her assessment of information received from other sources in order to perform a risk-benefit analysis of the potential treatment.\(^9\)

On June 2, 2004, then New York Attorney General Eliot Spitzer filed suit against GSK alleging that the company misrepresented safety and efficacy data by publicizing positive information about the use of Paxil in children and adolescents while withholding or misrepresenting other negative clinical trial findings.\(^9\)

GSK had conducted at least five studies examining the use of Paxil for pediatric patients.\(^9\)

The results of these studies not only failed to demonstrate efficacy, but also suggested the medication potentially increased the risk of suicidal thinking and acts.\(^9\)

Nonetheless, GSK implemented an aggressive marketing campaign to promote the questionable


\(^{90}\) Id. at ¶ 2.

\(^{91}\) Id. at ¶ 3.

\(^{92}\) Id. at ¶ 2.

\(^{93}\) Id. at ¶ 2.

\(^{94}\) Id. at ¶¶ 12, 13.

\(^{95}\) Id. at ¶¶ 4, 30.

\(^{96}\) Id. at ¶¶ 15-18.

\(^{97}\) Id. at ¶¶ 19-30.
benefits of the drug in children and adolescents.98

A confidential, internal GSK memorandum provided employees guidance on how “[t]o effectively manage the dissemination of these data in order to minimise [sic] any potential negative commercial impact.”99 This was necessary, since according to the document, the clinical trial results were “insufficiently robust” and would fail to support approval of an application for expanded use of Paxil to treat pediatric depression.100 Additionally, the memo recommended publication of a full medical journal article only on the single study which contained some favorable conclusions.101 However, it further cautioned that “[i]t would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.”102 GSK also allegedly repeatedly misrepresented the safety and efficacy outcomes from the studies to its sales representatives who consequently promoted the medication to physicians, as well as to doctors directly through the “Medical Information Letters” the company distributed.103

Furthermore, after the United Kingdom’s Medicines and Healthcare Products Regulatory Agency (MHRA)”104 advised that paroxetine should not be used by children and adolescents to treat depression,105 GSK issued a press release in Britain in which the company admitted that clinical studies revealed “a difference between [paroxetine] and placebo in terms of suicidal

98 Id. at ¶ 30.
99 Id. at ¶ 31.
100 Wayne Kondro & Barbara Sibbald, Drug Company Experts Advised Staff to Withhold Data about SSRI Use in Children, 170 CAN. MED. ASSN. J. 783, 783 (2004) (discussing the contents of the GSK internal document, which was obtained and consequently published by the journal).
101 GSK Complaint, supra note 89, at ¶ 32.
102 Kondro & Sibbald, supra note 100, at 783.
103 GSK Complaint, supra note 89, at ¶¶ 37-39, 41-45.
104 The MHRA is the British equivalent of the FDA in the United States.
105 MED. AND HEALTHCARE PRODUCTS REGULATORY AGENCY, SAFETY REVIEW OF ANTIDEPRESSANTS USED BY CHILDREN COMPLETED (2003), available at http://www.mhra.gov.uk/newscentre/pressreleases/CON002045 [hereinafter MHRA]. Following the MHRA’s decision, the Irish Medicines Board also issued a similar directive. GSK Complaint, supra note 89, at ¶ 49.
thinking or attempts, particularly in adolescents."\textsuperscript{106} However, a few days later GSK issued a very different statement in the United States in which it merely noted that "there is no evidence that Paxil is associated with an increased risk of suicidal thinking or acts in adults" and that "not a single person [who participated in the pediatric paroxetine trials] committed suicide."\textsuperscript{107}

The New York Attorney General's complaint charged that by selectively disclosing information about the clinical trials, GSK misled and deceived physicians.\textsuperscript{108} By creating the false impression that the safety and efficacy evidence in GSK's control was incontrovertible, the company deprived those in the medical community of the materials necessary to properly evaluate the risks and benefits of prescribing Paxil to children and adolescents.\textsuperscript{109} GSK publicly responded to these contentions by issuing a statement declaring it had "acted responsibly in conducting clinical studies in pediatric patients and disseminating data from those studies."\textsuperscript{110} Furthermore, the company stated that all trial data had "been made available to the FDA... and regulatory agencies worldwide."\textsuperscript{111}

Nonetheless, less than three months after the lawsuit was originally filed, GSK settled the case.\textsuperscript{112} As part of the Agreement, GSK was required to establish an online "Clinical Trials Register" to distribute summary information from company sponsored studies of FDA-approved drugs.\textsuperscript{113} Additionally, GSK promised to make certain that all

\textsuperscript{106} GSK Complaint, supra note 89, at ¶¶ 49-51.
\textsuperscript{107} Id. at ¶ 61.
\textsuperscript{108} Id. at ¶ 63.
\textsuperscript{109} Id. at ¶¶ 62, 63.
\textsuperscript{110} Owen Dyer, GlaxoSmithKline Faces US Lawsuit Over Concealment of Trial Results, 328 BRITISH MED. J. 1395, 1395 (2004) (article contains a reprint of the complete statement).
\textsuperscript{111} Id.
\textsuperscript{113} Id. See supra Section IV examining the many deficiencies of such company sponsored databases.
communications it provided to the medical community regarding off-label uses of drugs would "fairly and accurately reflect the safety and efficacy data from clinical studies."\textsuperscript{114} Lastly, the company agreed to pay $2.5 million representing "disgorgement and costs" to the State of New York.\textsuperscript{115} While the New York State Attorney General's case against GSK may have been resolved, the controversy associated with the use of antidepressants in the pediatric population for psychiatric disorders had by no means come to a conclusion.

2. Further Scrutiny of Other Manufacturers of Psychiatric Medications

Less than a month after the settlement with GSK, the New York State Attorney General's office announced in early September of 2004 that it had reached a separate agreement with Forest Laboratories, Inc. ("Forest Labs").\textsuperscript{116} Forest Labs manufactures and distributes anti-depressants under the brand names Lexapro and Celexa.\textsuperscript{117} As with GSK's Paxil, the medications are only FDA approved for treating psychiatric conditions in adults, but were nonetheless regularly prescribed off-label for children and adolescents. The Attorney General had questioned whether the company had concealed information regarding the safety and efficacy of its drug.\textsuperscript{118} Forest Labs responded to the inquiry by agreeing to publicly disclose clinical studies concerning the use of Lexapro and Celexa in pediatric populations, as well as posting online the results from all future company-sponsored studies of approved medications.\textsuperscript{119}

Additionally, the New York State Attorney General's Office also revealed in the same statement that leading

\textsuperscript{114} N.Y. State Att'y Gen., supra note 112.
\textsuperscript{115} Id.
\textsuperscript{117} Id.
\textsuperscript{118} Id.
\textsuperscript{119} Id.
pharmaceutical companies Eli Lilly and Merck had agreed to publicly disclose certain clinical trial information. Eli Lilly markets its antidepressants under the brand names Prozac and Cymbalta, while Merck sells its medication as Vivactil. Both of these companies were allegedly under scrutiny as well in connection with their selective disclosure of clinical trial data.

3. Questionable Conduct by the FDA

The FDA did not publicly acknowledge that antidepressant use by pediatric patients posed an increased risk of suicidal thoughts and actions until mid-September of 2004. The following month, the agency issued a public health advisory regarding the possible dangers associated with the use of the drugs. Additionally, the FDA directed that all manufacturers of antidepressant medications place a "black box" warning on their products, although the agency did not expressly forbid doctors from continuing to prescribe these drugs for their younger patients. Despite taking such actions, the FDA came under intense scrutiny concerning its handling of the antidepressant controversy.

120 Id.
121 While it seems fairly clear the inquiry into Eli Lilly was with regard to its conduct in relation to the promotion of Prozac and possibly Cymbalta, it is not completely evident that Merck was under scrutiny concerning Vivactil. It is possible that the New York State Attorney General's Office may have been focusing their investigation on Merck's lack of disclosure surrounding its distribution of its Vioxx-brand pain reliever, although at the time of the Office's press release, the company had not yet received the preliminary results from a clinical trial which eventually compelled Merck to withdraw Vioxx from the market.
124 Id. A "black box" warning is the most serious warning placed on the label of a prescription drug. Several years later, the FDA would expand the black box warnings to also include young adults ages 18 to 24 during initial treatment with the antidepressants. See FOOD & DRUG ADMIN., FDA PROPOSES NEW WARNINGS ABOUT SUICIDAL THINKING, BEHAVIOR IN YOUNG ADULTS WHO TAKE ANTIDEPRESSANT MEDICATIONS (2007), available at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html.
This was due to the fact that questions continued to arise over the adequacy of the agency’s response, particularly whether it came quickly enough to prevent public harm. For example, almost a year earlier British regulators had not only informed the public about the perceptible risks associated with the antidepressant medications evidenced through clinical trial data, but also generally prohibited further pediatric use of the drugs.\textsuperscript{125} In response, a scathing editorial in the medical journal \textit{The Lancet} declared that the FDA appears to have “failed to act appropriately on information provided to them that these drugs were both ineffective and harmful in children.”\textsuperscript{126} This characterization would seem even more apropos as additional evidence concerning the agency’s conduct came to light.

In early 2004, one of the FDA’s own drug safety analysts, Dr. Andrew Mosholder, completed his review of data from numerous clinical trials and concluded that antidepressant medications were clearly associated with an increased risk of suicidal behavior.\textsuperscript{127} Mosholder found that pediatric patients were almost twice as likely to suffer a serious suicide-related event.\textsuperscript{128} However, agency officials expressed skepticism over the reliability of his findings due to concerns regarding whether the sponsoring companies of the studies had classified suicidal cases properly.\textsuperscript{129} Thereupon, they ordered a second examination of the trial data by another FDA scientist.\textsuperscript{130}

Dr. Mosholder responded in a memo to this proposal by cautioning that an additional analysis was unwarranted since “it is unlikely that the new information will alter the basic finding of an association of... serious suicide-related events

\textsuperscript{125} MHRA, supra note 105. One of the few exceptions was Fluoxetine, marketed under the brand name Prozac, which according to the agency “appears to have a positive balance of risks and benefits in the treatment of depressive illness in the under 18s.” \textit{Id.}

\textsuperscript{126} Depressing Research, 363 LANCET 1335, 1335 (2004).


\textsuperscript{128} Vedantam, \textit{supra} note 127, at A6.

\textsuperscript{129} \textit{Id.}

\textsuperscript{130} \textit{Id.} \textit{See} Susan Okie, What Ails the FDA?, 352 NEW ENG. J. MED. 1063, 1063 (2005).
with active treatment." Moreover, he urged the FDA in the meantime to officially discourage the use of antidepressants in children; however, the agency refused to do so.

Instead, the FDA concealed his findings and prevented him from sharing his analysis with an FDA advisory committee convened in February of 2004 to investigate continuing public concerns surrounding the safety of the drugs. Approximately six months later, however, the additional staff analysis requested by agency officials confirmed Mosholder's original conclusions.

The continuing reluctance of the FDA to provide information to the public regarding the use of antidepressants in children and adolescents prompted a congressional hearing by the House Committee on Energy and Commerce in September of 2004. Testimony revealed that the FDA had repeatedly restrained pharmaceutical companies from publicly disclosing to physicians that clinical trials had demonstrated the drugs had performed no better than the placebos, as well as additional negative findings. The vice-president of pharmaceutical giant Pfizer recounted how the company had planned to include on the label for its medication, Zoloft, that two studies had found the drug no better than sugar pills; however, the FDA insisted that


132 Vedantam, supra note 127, at A6. Almost two months later, however, the FDA did issue a "talk paper" to medical professionals concerning antidepressant use in the pediatric population, but it continued to maintain that it was "not yet clear whether antidepressants contributed to the emergence of suicidal thinking and behavior." FOOD & DRUG ADMIN., TALK PAPER, FDA ISSUES PUBLIC HEALTH ADVISORY ON CAUTIONS FOR USE OF ANTIDEPRESSANTS IN ADULTS AND CHILDREN (2004), available at http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html. Additionally, a public health advisory published on the same date asserted that the "FDA has not concluded that these drugs cause worsening depression or suicidality." FOOD & DRUG ADMIN., PUBLIC HEALTH ADVISORY, WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT (2004), available at http://www.fda.gov/cder/drug/antidepressants/AntidepressantPHA.htm.

133 Okie, supra note 130, at 1063; Vedantam, supra note 127, at A6; Harris, supra note 122, at A1.

134 Harris, supra note 122, at A1.


136 Vedantam, supra note 135, at A2.
existing language suggesting that efficacy had not been established for depressed children was sufficient.\footnote{Antidepressants Hearing, supra note 24; Vedantam, supra note 135, at A2.}

FDA officials apparently adopted this approach due to concerns that divulging such information might scare physicians and their patients' families away from the drugs.\footnote{Vedantam, supra note 135, at A2.} Congressional committee members were incredulous with such reasoning, questioning why the FDA would not instead want to encourage such disclosures.\footnote{Id.} The agency's hesitancy to disseminate information would, however, continue to be the subject of congressional investigation and the source of public controversy.

\section*{B. Pain Relievers and Cardiovascular Risk}

\subsection*{1. Merck's Vioxx}

On September 30, 2004, Merck withdrew its pain medication Vioxx\footnote{While Merck generally marketed the medication using the trade name Vioxx, the medication is also known as rofecoxib.} from the market due to clinical trial data that demonstrated a significant risk of cardiovascular incidents such as heart attacks and strokes.\footnote{News Release, MERCK, MERCK ANNOUNCES VOLUNTARY WORLDWIDE WITHDRAWAL OF VIOXX (Sept. 30, 2004), available at http://www.merck.com/newsroom/vioxx_withdrawal/pdf/vioxx_press_release_final.pdf (last visited Feb. 4, 2009).} This represented the largest prescription-drug recall in history, as more than eighty million patients had formerly utilized this medication with annual sales for Merck estimated at more than $2.5 billion dollars.\footnote{Eric J. Topol, Failing the Public Health—Rofecoxib, Merck, and the FDA, 351 NEW ENG. J. MED. 1707, 1707 (2004).} In announcing this decision, Merck maintained that it had only recently learned of complications associated with the drug, but deemed such swift action appropriate as the company was committed to placing patient safety first.\footnote{MERCK, supra note 141; Anna Wilde Mathews and Barbara Martinez, E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, WALL ST. J., Nov. 1, 2004, at A1.} However,
internal company documents and interviews with outside scientists later revealed that Merck had in fact engaged in a deliberate campaign for years to conceal study results which demonstrated significant risks associated with the drug in order to prevent any negative impact on the sales of Vioxx.\footnote{Mathews & Martinez, supra note 143, at A1. See Alex Berenson et al., DANGEROUS DATA – Retracing a Medical Trail: Despite Warnings, Drug Giant Took Long Path to Vioxx Recall, N.Y. TIMES, Nov. 14, 2004, § 1 at 1. Both the Wall Street Journal and the N.Y. Times were able to obtain access to copies of the confidential internal Merck documents.}

As early as the mid-1990’s company officials became concerned that studies comparing less expensive pain relievers with Vioxx would reveal that its drug had much greater cardiovascular risks.\footnote{Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.} Therefore, executives at Merck discussed how to design a clinical trial that would potentially minimize the unfavorable comparison.\footnote{Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.} At the same time, however, they recognized that such concealment would be difficult.\footnote{Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.} In fact, one company e-mail warned that a proposed study may provide evidence that patients taking Vioxx had more blood clots than those clinical trial participants receiving standard treatment which could “kill [the] drug.”\footnote{Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.} Eventually, however, Merck chose not to conduct a trial to exclusively research potential cardiovascular risks.\footnote{Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.} Instead, company officials decided to simply monitor trials that had been previously planned to test Vioxx for other possible uses to determine if any additional evidence of heart attacks, strokes, or related problems emerged.\footnote{Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.}

In May of 1999, Merck received FDA approval to distribute
Vioxx for the treatment of arthritis, as well as to provide relief from other types of pain. In March of 2000, the results from a study entitled VIGOR\textsuperscript{151} of more than 8,000 rheumatoid arthritis patients that compared Vioxx to the conventional pain reliever naproxen indicated a significant difference in the number of cardiovascular problems. The clinical trial participants that received Vioxx were five times as likely to have a heart attack as those in the naproxen group. Upon review of the data, the chief of research at Merck acknowledged in an internal company e-mail that cardiovascular risks "are clearly there" and the differences were so dramatic that it could not solely be explained by any sort of protective effect offered by naproxen.\textsuperscript{152} Nonetheless, in a press release issued a month later, Merck downplayed the problems associated with Vioxx, stating that the VIGOR trial results were "consistent with" naproxen's clot-preventing properties.\textsuperscript{153} The following month, the company announced in another press release that it had "confirm[ed the] favorable cardiovascular safety profile of Vioxx."\textsuperscript{154} Although it referred to the results of the VIGOR study, it proclaimed that other trials had shown "NO DIFFERENCE in the incidence of cardiovascular events" between Vioxx and other pain relievers or placebos.\textsuperscript{155}

In November of 2000, an article on the VIGOR trial results appeared in the \textit{New England Journal of Medicine}.\textsuperscript{156} The piece was written by Merck employees, as well as academics who had financial ties to the company.\textsuperscript{157} It described the gastrointestinal benefits associated with Vioxx and the rates of heart attacks in the study. However, it implied that the

\textsuperscript{151} The name VIGOR was an acronym for Vioxx Gastrointestinal Outcomes Research.

\textsuperscript{152} Mathews & Martinez, \textit{supra} note 143, at A1; Berenson et al., \textit{supra} note 144, § 1 at 1.

\textsuperscript{153} Mathews & Martinez, \textit{supra} note 143, at A1; Berenson et al., \textit{supra} note 144, § 1 at 1.

\textsuperscript{154} Mathews & Martinez, \textit{supra} note 143, at A10.

\textsuperscript{155} \textit{Id.}

\textsuperscript{156} Mathews & Martinez, \textit{supra} note 143, at A1; Berenson et al., \textit{supra} note 144, § 1 at 1.

\textsuperscript{157} Mathews & Martinez, \textit{supra} note 143, at A1; Berenson et al., \textit{supra} note 144, § 1 at 1.
increase in cardiovascular incidents only occurred in connection with patients already at high risk for heart attacks. Furthermore, the article failed to provide information concerning other cardiovascular complications, such as strokes or blood clots.\textsuperscript{158}

In 2001, the first significant article critical of Vioxx was published in the Journal of the American Medical Association, raising public concern over the risks associated with the medication.\textsuperscript{159} Nonetheless, Merck continued to publicly maintain that clinical trial data suggested naproxen’s cardiovascular benefits were responsible for the differences in the rate of heart complications, not problems associated with the company’s drug.\textsuperscript{160} At approximately the same time, however, Merck prepared a marketing document directed to “all field personnel with responsibility for Vioxx” that provided an “obstacle handling guide.”\textsuperscript{161} If a sales representative encountered a doctor that was worried Vioxx could potentially raise the risk of a heart attack, the Merck employee was to respond by stating the drug “would not be expected to demonstrate reductions” in cardiovascular incidents and that it was “not a substitute for aspirin.”\textsuperscript{162} This evasiveness training also included a document aptly entitled “Dodge Ball Vioxx” which contained a listing of concerns doctors might be expected to bring up regarding the safety of the medication and then offered standard responses intended to neutralize the issue.\textsuperscript{163}

In September 2004, preliminary data from another Merck

\textsuperscript{158} Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.

\textsuperscript{159} D.M. Mukherjee et al., \textit{Risk of cardiovascular events associated with selective COX-2 inhibitors}, 286 JAMA 954 (2001). One of the authors of the article stated in an interview that Merck scientists visited him in an effort to convince him not to publish the piece. Merck officials have denied this allegation. See Berenson et al., supra note 144, § 1 at 1.

\textsuperscript{160} Mathews & Martinez, supra note 143, at A10

\textsuperscript{161} \textit{Id.}

\textsuperscript{162} \textit{Id.}

\textsuperscript{163} \textit{Id.} at A1. Additionally, the final four pages of the document each contained a single word in capital letters: “DODGE!” Merck officials maintain that they instructed their employees to be honest and ethical. \textit{Id.}
clinical trial labeled APPROVe,\textsuperscript{164} which was designed to study whether Vioxx might be useful in preventing colon polyps, generated significant alarm.\textsuperscript{165} Despite the fact that patients were not eligible to enroll in the trial if they had any evidence of cardiovascular disease, those participants that were treated with Vioxx had approximately twice as many heart attacks or strokes as compared to those receiving only a placebo.\textsuperscript{166} Additionally, company officials were informed that a safety monitoring board wanted to immediately terminate the study because of the potential for harm to the research subjects.\textsuperscript{167} As a result, Merck could no longer defend against the mounting public concern surrounding Vioxx and therefore had virtually no choice but to voluntarily remove the drug from the marketplace.\textsuperscript{168}

2. An Inquiry into the FDA's Actions Concerning Vioxx

Not only was Merck under investigation for its handling of Vioxx, but the FDA's role in the controversy was also being carefully examined. Commentators increasingly claimed that the agency failed to observe the many warning signs that emerged, or even worse, intentionally suppressed critical information pertaining to the drug.\textsuperscript{169} In November of 2004, a Senate committee held a hearing to explore whether the agency disregarded its responsibilities to protect the public from dangerous medications.\textsuperscript{170} Evidence began to surface that questions concerning the cardiovascular safety had been raised

\textsuperscript{164} The name APPROVe was an acronym for Adenomatous Polyp Prevention of Vioxx.
\textsuperscript{165} Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.
\textsuperscript{166} Topol, supra note 142, at 1708. See Mathews & Martinez, supra note 143, at A1; Berenson et al., supra note 144, § 1 at 1.
\textsuperscript{167} Mathews & Martinez, supra note 143, at A1.
\textsuperscript{168} Id.
\textsuperscript{169} See, e.g., Topol, supra note 142, at 1707; Daniel H. Solomon et al., Relationship Between Selective Cyclooxygenase-2 Inhibitors and Acute Myocardial Infarction in Older Adults, 109 CIRCULATION 2068 (2004). See also Berenson et al., supra note 144, § 1 at 1 (discussing additional non-Merck sponsored studies that raised concerns about Vioxx).
by drug reviewers at the FDA even before Vioxx was approved.\textsuperscript{171}

However, when Merck submitted the initial results from the VIGOR study to the agency in March of 2000, the FDA was quite alarmed by the findings.\textsuperscript{172} While the company argued the significantly greater risk of cardiovascular events suffered by participants treated with Vioxx was due to the fact that they did not receive the cardioprotective properties of naproxen, the agency was quite skeptical.\textsuperscript{173} Even top officials at the FDA testified that they found Merck’s explanation unconvincing.\textsuperscript{174} Nonetheless, nearly two years passed before the FDA required Merck to alter its drug label on Vioxx to include information regarding the cardiovascular risks. However, following negotiations with the company, the agency allowed such changes to be placed in the “Precautions” section following claims touting the gastrointestinal benefits of the drug, rather than prominently displaying it as a “Warning.”\textsuperscript{175}

In the meantime, Dr. David J. Graham, an epidemiologist who monitors drug safety for the agency, conducted an exceptionally large review of patients who had been treated with Vioxx to determine the incidence of cardiovascular problems potentially associated with its use.\textsuperscript{176} The project took nearly three years to complete and confirmed that the drug was responsible for a substantial rise in cases of heart disease. Dr. Graham would eventually conclude, in his peer-reviewed article appearing in the prestigious medical journal \textit{The Lancet}, the

\begin{footnotesize}
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\item \textsuperscript{171} \textit{Id.; Berenson et al., supra note 144, § 1 at 1.}
\item \textsuperscript{172} \textit{Vioxx Hearing, supra note 170; Berenson et al., supra note 144, § 1 at 1.}
\item \textsuperscript{173} \textit{Vioxx Hearing, supra note 170; Berenson et al., supra note 144, § 1 at 1.}
\item \textsuperscript{174} \textit{Vioxx Hearing, supra note 170. The deputy director of the FDA’s Office of New Drugs stated with regard to Merck’s explanation, “We just didn’t buy that.” Id.}
\item \textsuperscript{175} \textit{Vioxx Hearing, supra note 170; Anna Wilde Matthews, \textit{Did FDA Staff Minimize Vioxx’s Red Flags?}, WALL ST. J., Nov. 10, 2004, at 11. Interestingly, at the congressional hearing, Dr. David J. Graham testified the drug’s label change was wholly inadequate as it “had absolutely no effect on how often high-dose Vioxx was prescribed.” Vioxx Hearing, supra note 170. At this point in time, Graham believed the appropriate course of action based on the available evidence was to place the cardiovascular risk information in the “Warnings” section, as well as implement a complete ban on a high-dose formulation of the drug. Id.}
\item \textsuperscript{176} \textit{Vioxx Hearing, supra note 170.}
\end{itemize}
\end{footnotesize}
increased risk attributable to Vioxx was 3.7 times. This translated into approximately 100,000 excess cases of heart disease, with almost half of these being fatal.

However, these findings almost never became public. After Dr. Graham first approached his superiors in early August of 2004 with the results of the study, he was subsequently pressured to change his conclusions by senior officials at the FDA. He was told that as the agency was not contemplating a warning against the use of high-dose Vioxx, his contradictory recommendations were not acceptable. Additionally, Dr. Graham was informed that if he failed to make the necessary modifications, he would not be permitted to present the data at an upcoming conference at which he was scheduled to speak. Moreover, Dr. Graham was notified by a manager in the Office of Drug Safety that he would need to provide his original study results to Merck.

Eventually, Dr. Graham reluctantly conceded to his supervisors' demands by altering the results quite considerably in advance of the conference. Dr. Graham testified at the Senate hearing that he did so "because [he] thought if [he] did not, there would be no way on earth that [the] data would see the light of day." The FDA's apparent disregard for safety concerns and resistance to disclosure would further strengthen the growing public sentiment that greater transparency was urgently needed in connection with clinical trials.

177 D. Graham et al., Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients treated with Cyclo-oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs, 365 LANCET 475, 479 (2005).
178 Id. at 480. See also Vioxx Hearing, supra note 170.
179 Vioxx Hearing, supra note 170.
180 Id.
181 Id.
182 Id.
183 Id.
184 Id.
IV. INCREMENTAL MOVEMENT TOWARD GREATER ACCESS TO CLINICAL TRIAL INFORMATION

Scientists and patient advocates have long reported substantial difficulties associated with obtaining data concerning clinical trials. For more than thirty years, the creation of a clinical trial registry which could provide basic information regarding ongoing trials had been proposed as a partial solution to the problem.\(^{185}\) While the National Institutes of Health ("NIH") registered all of the studies it sponsored from 1975 to 1979, the agency discontinued this policy until the Food and Drug Act was amended almost two decades later.

The Food and Drug Administration Modernization Act of 1997 ("FDAMA") mandated the creation of a registry that would provide data on clinical trials for serious or life-threatening diseases.\(^{186}\) The statute required the information to be "in a form readily understood by members of the public" and include a description of the study's purpose, eligibility criteria for participation, trial phase, location of study sites, and the drug or therapy under investigation.\(^{187}\) Additionally, registration was mandatory regardless of whether the trial was publicly or privately funded.\(^{188}\)

In fulfillment of the statutory obligations under the FDAMA, the FDA and NIH created the ClinicalTrials.gov website. This register, maintained by the United States National Library of Medicine, became operational in early 2000.\(^{189}\) Nonetheless, the pharmaceutical industry was

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\(^{185}\) Kay Dickersin & Drummond Rennie, Registering Clinical Trials, 290 JAMA 516, 516 (2003).

\(^{186}\) Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997). The Act limited the registration requirement to clinical trials testing the effectiveness of experimental drugs or biological products, as opposed to trials merely studying toxicity. Id. Essentially, this would include all Phase 2, Phase 3, and Phase 4 trials that contain efficacy endpoints as part of their study protocol. Id.

\(^{187}\) Id.

\(^{188}\) Id.

exceptionally resistant to providing the required disclosures. In clear contravention of the FDAMA’s provisions, the pharmaceutical industry stated that it would not pledge to register its clinical trials. In a document entitled “Public Disclosure of Clinical Trial Results,” the drug companies’ trade group declared that “[s]ponsors do not commit . . . to make the designs of clinical trial protocols available publicly at inception, as in a clinical trials registry.”

Accordingly, the pharmaceutical industry repeatedly failed to comply with the law. For example, a study by FDA staff found that less than half of all cancer trials sponsored by drug companies required to be registered were actually submitted to clinicaltrials.gov, in comparison to more than ninety percent of government-funded trials. Another review of ongoing prostate and colon cancer clinical trials demonstrated similar deficiencies, as only seventeen of the thirty-two trials sponsored by industry were registered. For other serious diseases the study inclusion rate was even more abysmal, with some in the mere single digits. Furthermore, when drug companies actually did tender information to the clinicaltrials.gov registry, the information provided was often inadequate. Including meaningless information, such as “investigational drug” in place of the actual name of the medication as required by the statute or omitting the sponsor’s name, was commonplace.

Such a state of affairs was due in large part to the fact that there were no negative consequences associated with a trial

190 Dickersin & Rennie, supra note 185, at 516.
191 PHARM. RESEARCH & MFRS. OF AM., PRINCIPLES ON CONDUCT OF CLINICAL TRIALS AND COMMUNICATION OF CLINICAL TRIAL RESULTS (2002).
193 Dickersin & Rennie, supra note 185, at 519.
195 Catherine DeAngelis et al., Is This Clinical Trial Fully Registered?—A Statement from the International Committee of Medical Journal Editors, 352 NEW ENG. J. MED. 2436, 2436-38 (2005); Deborah Zarin et al., Issues in the Registration of Clinical Trials, 297 JAMA 2112, 2115-18 (2007).
196 Zarin et al., supra note 195, at 2115.
sponsor's violation of the FDAMA. The FDA did not require companies to register their clinical studies in order to utilize the data from the investigations for regulatory approval. Furthermore, refusal to submit information to the publicly accessible ClinicalTrials.gov registry did not lead to any sort of a monetary penalty.

With the anti-depressant and Vioxx controversies as a backdrop, there were increasing demands placed on Congress to considerably improve the level of transparency in the drug approval process and provide greater public access to clinical trial information. Consequently, in October of 2004, members in both houses of Congress introduced their own versions of the Fair Access to Clinical Trials (FACT) Act, which attempted to ameliorate many of the inadequacies associated with the FDAMA's clinical trial registry provisions. Although the bills were not identical, they were quite similar, including requiring registration of a study as a prerequisite to FDA authorization for testing an investigational medication. Additionally, the Department of Health and Human Services would have the authority to impose civil penalties of $10,000 per day for noncompliance. Even more significant, both of the bills would expand the type of information a drug company would need to disclose, most notably through the creation of a new clinical trial results database that would contain a modest amount of factual material from completed studies.

Not surprisingly, the pharmaceutical industry's trade group

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197 This was in stark contrast to an investigator's failure to obtain prior IRB approval of research protocols, which could result in an inability to submit the findings from such trials to the FDA. See 21 C.F.R. §54.1(b) (2008) and the discussion of the IND process in Section III supra.


199 Fair Access to Clinical Trials Act, H.R. 5252; Fair Access to Clinical Trials Act, S. 2933. See Robert Steinbrook, Registration of Clinical Trials—Voluntary or Mandatory?, 351 NEW ENG. J. MED. 1820 (2004) (providing a detailed analysis of the type of information to be included under the Fair Access to Clinical Trials Act).

200 Fair Access to Clinical Trials Act, H.R. 5252; Fair Access to Clinical Trials Act, S. 2933.

201 Fair Access to Clinical Trials Act, H.R. 5252; Fair Access to Clinical Trials Act, S. 2933.
did not support the FACT Act. Originally, the Pharmaceutical Research and Manufacturers of America (PhRMA) asserted that a results reporting requirement was unnecessary.\footnote{See, e.g., Barry Meier, \textit{Contracts Keep Drug Research Out of Reach}, \textit{N.Y. Times}, Nov. 29, 2004, at A1 (reporting on the pharmaceutical industry's response to the proposed legislation).} However, in January of 2005, faced with pressure from lawmakers, the medical community, and the public, the four largest pharmaceutical trade groups in the world, including PhRMA, released a joint statement on the disclosure of clinical trial information.\footnote{\textit{Int'l Fed'n of Pharm. Mfr. & Ass'n, Global Industry Position on Disclosure of Information About Clinical Trials} (2005), \url{available at http://clinicaltrials.ifpma.org/fileadmin/files/pdfs/EN/CTP_Release_Joint_Position_EN.pdf}. The statement included trade groups from the United States, Japan, as well as Europe. \textit{Id}.} While the group members pledged to release a nominal amount of information regarding ongoing trials, they did not commit to submitting the data to a comprehensive, government-sponsored registry.\footnote{\textit{Id}.} Instead, the provisions left open the possibility of publishing the information on individual, company-sponsored websites that could contain internal rules that might not be publicly disclosed and consequently may differ from one site to the next. A 2006 study confirmed that the potential for abuse of such a system was far from theoretical, finding that "when conclusions were listed in these [corporate] databases, they tended to be more favorable for the company's product than those found in published articles or FDA reviews of the same trials."\footnote{Zarin et al., \textit{supra} note 195, at 2118.} Furthermore, with regard to completed trials, the pharmaceutical manufacturers agreed only to make public "summary results" of the studies and, additionally, asserted such disclosure "must maintain protections for ... intellectual property and contract rights."\footnote{\textit{Int'l Fed'n of Pharm. Mfr. & Ass'n, Joint Position on the Disclosure of Clinical Trial Information Via Clinical Trial Registries and Databases} (2005), \url{available at http://en.sanofi-aventis.com/binaries/050106_release_en_tcm28-21769.pdf}.} Most problematic, however, was the fact that adherence to the proposed guidelines was completely voluntary.

Ultimately, neither version of the FACT Act of 2004 was
enacted as both bills did not succeed in making it out of committee. Over the next few years, a number of comparable bills were introduced in the House and Senate,\textsuperscript{207} as well as a few alternative proposals;\textsuperscript{208} nevertheless they all met a similar fate. However, in 2007, with a substantial FDA funding program\textsuperscript{209} set to expire that had dramatically reduced the review time of drug applications to the major benefit of the pharmaceutical companies, consumer groups and the medical community began to advocate for other provisions to be added to the reauthorization bill in order to improve drug safety. As a result, the push for the creation of a clinical trial results database increasingly gained momentum, and it soon became clear that the pharmaceutical industry would likely need to concedo at least some level of disclosure.

On May 9, 2007, the Senate passed the Food and Drug Administration Revitalization Act,\textsuperscript{210} containing clinical trial results database provisions adopted from a bill introduced earlier in the year, the Enhancing Drug Safety and Innovation Act of 2007.\textsuperscript{211} On June 28, 2007, the House of Representatives passed its own reauthorization bill, the Food and Drug Administration Amendments Act of 2007.\textsuperscript{212} The portion of the legislation pertaining to study results, although far from ideal, did contain some significant improvements over the Senate's version that certainly strengthened the bill. Unfortunately, under pressure from the pharmaceutical lobby, the final compromise legislation approved by both houses of Congress and eventually enacted into law removed most of these enhancements. Ultimately, the clinical trial results database provisions failed to impart the critical transparency necessary to


\textsuperscript{209} See infra Part VIII discussing the arguably problematic conflict of interest created by this program.

\textsuperscript{210} Food and Drug Administration Revitalization Act, S. 1082, 111th Cong. (2007).

\textsuperscript{211} Enhancing Drug Safety and Innovation Act, S. 484, 111th Cong. (2007).

\textsuperscript{212} Food and Drug Administration Amendments Act, H.R. 2900, 111th Cong. (2007).
provide meaningful reform to the clinical trial process and thus adequately protect the public.

V. DEFICIENCIES OF THE FEDERAL CLINICAL TRIALS RESULTS DATABASE REQUIREMENTS

On September 27, 2007, the Food and Drug Administration Amendments Act (FDAAA) became law.213 With regard to the clinical trials registry portion of the Act, the statute did achieve some limited success. A number of the major shortcomings associated with the Food and Drug Administration Modernization Act's ("FDAMA") clinical trial registry were remedied. Of particular significance was the fact that monetary penalties could now be assessed for the failure to register an applicable clinical trial.214 Additionally, the provisions were changed so that clinical trials related to all conditions, not merely those studies pertaining to serious or life-threatening diseases, now had to be registered.215 Nonetheless, several anticipated modifications were not instituted.216

The FDAAA also required the Secretary of Health and


214 See Section IV supra discussing the inadequacies of the FDAMA's clinical trial registry provisions. The statute now provides for monetary penalties in the amount of $10,000 for all violations adjudicated in a single proceed. 21 U.S.C. §333 (2006 & Supp. 2008). However, to the extent a violation is not corrected within the thirty-day period following notification of non-compliance, an additional fine of $10,000 per day may be assessed until such problem is corrected. Id.


216 One important change not made was an amendment to require that all submissions of registration information conform to the International Clinical Trials Registry Platform trial registration data set of the World Health Organization developed in 2004. This worldwide uniform standard contains a twenty-item minimum data set. See WORLD HEALTH ORG., INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM, available at http://www.who.int/ictrp/en/. Ironically, compliance with the standard was originally included in both of the bills passed in the House and Senate, but was removed as part of the compromise legislation eventually enacted into law, omitting several of the mandatory categories of information. Additionally, another modification that would have appreciably strengthened the clinical trials registry would be to require Phase I trials to be listed. See infra Part VII further examining the importance of incorporating these early trials.
Human Services ("Secretary") to expand the clinicaltrials.gov registry to include results of clinical trials for the first time.\textsuperscript{217} While this portion of the Act was generally heralded by Congress as a major triumph for public safety,\textsuperscript{218} in reality it appears to be more of a victory for the pharmaceutical industry. A closer look at the statutory language demonstrates the legislation as currently configured requires minimal disclosure and continues to allow drug companies to maintain a shroud of secrecy surrounding the vast majority of clinical trial result information.

\textbf{A. The First Stage of Controlled Disclosure}

The statute is essentially configured to disclose particular categories of information in successive stages. The initial stage requires that not later than ninety days after the enactment of the FDAAA, the Secretary must ensure links have been created from the ClinicalTrials.gov registry to a very narrow grouping of result information.\textsuperscript{219} This includes any public health advisories issued by the FDA regarding the drug that is the subject of the clinical trial and any previously published FDA summary documents resulting from an advisory committee meeting that considered the research study.\textsuperscript{220} Additionally, this requirement generally only pertains to Phase III or the typically voluntary post-approval studies conducted by drug manufacturers in consultation with the FDA, also known as Phase IV clinical trials.\textsuperscript{221} Furthermore, such links need not be established any earlier than thirty days after the date the drug is approved or prior to thirty days after the specified data has become publicly available by other means.\textsuperscript{222} The ultimate effect of these exceptionally restrictive provisions is to merely provide an additional website location to access this extraordinarily limited

\begin{footnotes}
\item[218] See Section I supra discussing the inaccurate portrayal of the Act by its sponsors.
\item[219] § 282(j)(3).
\item[220] § 282(j)(3)(A)(ii).
\item[221] § 282(j)(3)(A)(iii) ("those clinical trials that form the primary basis of an efficacy claim or are conducted after the drug involved is approved").
\item[222] § 282(j)(3)(A)(i).
\end{footnotes}
amount of previously obtainable information.\textsuperscript{223} While this might theoretically allow individuals to retrieve the relevant material more easily, it certainly does not obligate the drug industry to divulge any unattainable results information.

**B. The Second Stage of Controlled Disclosure**

The second stage of data disclosure is set to occur no later than one year after the enactment of the statute.\textsuperscript{224} By this time frame, the Secretary must further expand the clinical trial results database to contain additional information. Material to be incorporated includes rudimentary demographic baseline characteristics of the patients participating in the study.\textsuperscript{225} This must also include the number of individuals who dropped out of the clinical trial.\textsuperscript{226} Disappointingly, no information need be provided as to the reason for withdrawing, which could furnish potentially valuable insight as to possible problems associated with the intervention.

Further, very basic data concerning the primary and secondary outcome measures must also be submitted.\textsuperscript{227} Moreover, the existence of an agreement which restricts the ability of the principal investigator ("PI") to publicly discuss the results of the trial after its completion needs to be divulged.\textsuperscript{228} Unfortunately, this obligation is narrowed significantly by its failure to include persons other than the PI. Drug companies frequently utilize medical schools with their academic scientists and teaching hospital personnel to run clinical trials\textsuperscript{229} which would not be included in this disclosure. Moreover, this requirement is inapplicable if the PI is also an employee of the

\textsuperscript{223} Virtually all of this information would have previously been made available on the FDA or National Institutes of Health's own publicly accessible Internet website.

\textsuperscript{224} § 282(j)(3)(C).

\textsuperscript{225} § 282(j)(3)(C)(i).

\textsuperscript{226} Id.

\textsuperscript{227} § 282(j)(3)(C)(ii). Outcome measures in a clinical trial involving a new drug for the treatment of early-stage breast cancer might for example include the number of participants who were diagnosed with a recurrence of their breast cancer as a primary outcome and then the number of patients who ultimately died as a secondary outcome.

\textsuperscript{228} § 282(j)(3)(C)(iv)(2008).

\textsuperscript{229} Meier, supra note 202, at A1.
sponsor. As it is not unusual for industry-sponsored trials to designate one of their in-house scientific researchers to be the PI, this requirement is far from adequate.230

Even more problematic, however, is the fact these already limited disclosures do not pertain to those later studies involving drugs that ultimately fail to receive FDA approval.231 This is exceptionally troubling as failure to integrate clinical trial results data from studies on a drug that is ultimately not approved will severely impact the quantity of information made available to the general public. Even by the pharmaceutical industry's own estimates, only twenty percent of investigational medications successfully complete all three phases of the clinical testing process and consequently become the subject of a New Drug Application.232 Moreover, not all of these pharmaceuticals will actually obtain FDA approval.233 As a result, the overall number of trials potentially subject to this second round of possible disclosures is exceedingly small.

Additionally, the statutory provisions further narrow this already extremely limited group of clinical trials by also providing that results from Phase I trials need not be submitted.234 This is quite disconcerting as releasing such details is essential to ensuring future patient safety. This is well illustrated by the case involving TGN1412, a monoclonal antibody developed by drug manufacturer TeGenero that was

230 It should also be pointed out that this provision would not provide any sort of assistance to individuals such as Dr. Mosholder and Dr. Graham as they are employees of the FDA. Furthermore, this disclosure requirement is only with regard to "applicable clinical trials," which as defined by the Act applies solely to prospective clinical trials, not the sort of retroactive review studies conducted by Dr. Mosholder and Dr. Graham of anti-depressants and Vioxx respectively. Interestingly, the FDAAA also contained a section concerning policies on the review and clearance of scientific articles by FDA employees, which continues to allow for the agency to potentially exercise significant control. See 21 U.S.C § 379 (2006 & Supp. 2008).


233 Id. (explaining that the percentage of applications that are ultimately denied approval is approximately twenty-five percent)

thought could potentially benefit individuals suffering from multiple sclerosis or rheumatoid arthritis. Six healthy volunteers enrolled in the study were to be the first humans to receive the treatment. However, within a few hours after administration of the drug, all of the participants began experiencing multiple-organ failure and were quickly transferred to an intensive care unit. Although every individual survived the incident, some of the study volunteers remained hospitalized for up to three months. By failing to include results data from all trial phases, it is quite possible another pharmaceutical company might unknowingly repeat previous mistakes in studies of the same or similar medication, thereby needlessly placing patients at significant risk for substantial harm.

The overall impact of these restrictions is the number of clinical trials subject to these disclosure requirements is exceedingly small. Consequently, this has a dramatic impact on the amount of information that pharmaceutical companies need make publicly accessible. As such, this statutory section does not lead to anything approaching meaningful change in terms of the depth or breadth of significant clinical trial results data that must be revealed

C. The Third Stage of Controlled Disclosure

The third and final stage of expansion of the results database is exceptionally unsettled. The only information that must definitively be revealed are the elements included in the prior stage. This is due to the fact that instead of specifying any additional disclosure obligations, the Act directs the Secretary to expand the results database through regulation not later than three years from the enactment date of the Act. In connection therewith, the statute requires that a public meeting

236 42 U.S.C. § 282(j)(3)(D)(iii) (2006 & Supp. 2008) ("The regulations under this subparagraph shall require, in addition to the elements described in subparagraph (C) . . .")
be held no later than eighteen months after the date of enactment "to provide an opportunity for input from interested parties." As such, this would undoubtedly seem to allow for significant input from drug companies in shaping the clinical trial results information to be divulged under this provision of the FDAAA. In fact, an earlier Senate version of the Act made participation in further negotiated rule making explicit, requiring the formation of a committee that mandated the inclusion of members representing the pharmaceutical industry.

The Act stipulates that the final regulations promulgated must include a summary of the clinical trial and its results written in non-technical language that is understandable to the general public, as well as an additional scientific summary appropriate for researchers and medical professionals. Nevertheless, such disclosures are only necessary if the Secretary determines these summaries can be communicated in a manner that is not misleading or promotional in nature. Concerns have been raised that such narratives might provide an opportunity for those entities with vested interests in the manner in which the results are depicted to provide a biased spin on the way the data is portrayed. Consequently, the Act provides that, if the Secretary ultimately concludes this is not possible, the disclosures will not be required. However, an argument can be made that these lay summaries are essential to ensuring patients have access to understandable information regarding clinical trials, as well as provide a form of acknowledgement to the risks study volunteers take by participating in the research studies. As a result, the solution

241 Id.
242 See e.g. Zarin et al., supra note 195, at 2115-18.
is not to prohibit the summaries altogether, but ensure the ability to access the raw data to audit the information contained within the narrative, as well as provide a mechanism to make any necessary changes.

Similarly, an additional provision initially appears to compel the creation of a regulation calling for the submission of the entire clinical trial protocol for public review. However, this obligation is further weakened since an option exists to limit this solely to such protocol information necessary “to help to evaluate the results of the trial.” As a result, it is quite possible that very little information will actually be disseminated.

To the extent the regulations introduced by the Secretary provide for further disclosure of clinical trial results, such new rules only pertain to specific studies. Similar to previous sections, Phase I studies are not included. Moreover, although the Act requires that results information from all investigations involving an FDA-approved medication be listed on the expanded ClinicalTrials.gov website, data from studies concerning pharmaceuticals that do not ultimately receive FDA-approval, regardless of whether authorization was sought, may not necessarily need to be publicly divulged. This is due to the fact that instead of requiring these trials to be included at the outset, the Act instead provides the Secretary with the discretion to later determine whether or not to incorporate such studies into the publicly accessible database. Again, as discussed above, since the vast majority of drugs fail to obtain FDA-approval, excluding all clinical trials of unapproved medications will provide pharmaceutical companies with the ability to continue concealing enormous amounts of information from the public.

Furthermore, the timeline for the actual dissemination of these trial results to the public is potentially quite lengthy.

246 Id.
Although the Act initially provides that submission of clinical trial data must occur no later than one year after the earlier of the estimated or actual completion date of the trial, there are some significant exceptions. The statute allows data submissions to be delayed for a trial involving a previously approved drug that is undergoing testing for new, additional uses not currently part of the medication's labeling. This would include, for example, the various clinical studies investigating the use of the antidepressant Paxil in pediatric populations or Merck's APPROVe trial examining whether Vioxx was effective in preventing colon polyps. As long as the pharmaceutical manufacturer intends to file an application seeking approval for the new use within one year and tenders the requisite certification attesting to such plans, the information need not be submitted until thirty days following the earlier of FDA approval of the new use, agency denial of the application, or the withdrawal of the application if not resubmitted within 210 days. However, if one of these three actions has not occurred prior to two years from the date the extension was requested, the data must immediately be submitted. The ultimate effect of the interaction between these various subsections of the Act is that data required to be disclosed regarding these clinical trials investigating off-label uses most likely will not become publicly available for approximately three years after the study is completed. Clearly, the past controversies have illustrated that allowing clinical trial results data on off-label uses to be suppressed for

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250 § 282(j)(3)(E)(i). It should be noted that this stipulated time frame could potentially be extended slightly as the Secretary has the power under the Act to increase the period for submission to eighteen months by regulation. See § 282(j)(3)(D)(iv)(I).


252 Id.


254 This figure is calculated by adding the one-year time frame for the typical submission time, plus the approximate length of time it would take to obtain drug approval, denial of an application, or the two-year limitation period from when the certification is filed. So long as said certification is filed less than a year from the completion date of the study in question (or the expected completion date), the applicant would not appear to be out of compliance.
such a protracted period of time is completely unacceptable, as it continues to facilitate a system that does not adequately protect public safety.

Delays in submission of study results are also allowed for another category of trials, namely clinical investigations completed before the drug is initially approved.\textsuperscript{255} With regard to such pre-approval studies, the statute allows the deadline to be extended until thirty days following the drug's approval date.\textsuperscript{256} In light of the fact that all three phases of the clinical trial process generally take seven years to complete and the agency's application review process can typically be expected to last almost two years,\textsuperscript{257} the duration of postponement permitted for release of the data, particularly from some of the earlier applicable trials, is nothing short of astonishing.

\textit{D. Further Weaknesses of the Act}

Aside from the numerous special exceptions already articulated, the FDAAA also allows the Director of the National Institutes of Health to grant extensions to the second and third stage data submission requirements.\textsuperscript{258} The only restriction on the Director's ability to provide relief from these disclosure obligations is that a request must demonstrate "good cause;" however, this term is not defined.\textsuperscript{259} Additionally, the provision does not contain any sort of limitation on the permissible length of such an extension. Moreover, the Director is allowed to grant more than one extension for a particular clinical trial.\textsuperscript{260} While some flexibility may be desirable, such an unnecessarily broad provision leaves open the potential for abuse.

Another serious shortcoming of the Act is its failure to specify at the outset the adverse event reporting requirements. Instead, this subject is left to be addressed through future

\begin{footnotes}
\item[255] § 282(j)(3)(E)(iv).
\item[256] Id.
\item[258] § 282(j)(3)(E)(vi).
\item[259] Id.
\item[260] Id.
\end{footnotes}
regulation by the Secretary.\textsuperscript{261} In the event the Secretary fails to issue such regulations within twenty-four months of the FDAAA's enactment, the statute does provide a series of default provisions, which will then go into effect.\textsuperscript{262} However, considering the import of this type of information to other investigators who may be conducting clinical trials utilizing identical or similar interventions, physicians responsible for appropriately advising their patients, and the safety of the general public, these provisions should not have been left for future elaboration.

Similarly, the Act fails to stipulate a method for verifying the accuracy of the information that is submitted by study sponsors in accordance with the statute's various disclosure provisions.\textsuperscript{263} As this is left to future regulation by the Secretary,\textsuperscript{264} it is unclear how rigorous a process this ultimately may be in the end. However, procedures allowing for careful analysis of data provided in accordance with the Act are critical to ensuring necessary transparency.

Additionally, while not necessarily constituting a shortcoming of the FDAAA per se, it is worth noting that the Act also preempted all state provisions relating to the registration of clinical trials or the disclosure of study results in a database.\textsuperscript{265} While over the last several years many states have introduced legislation concerning clinical trials, only Maine has succeeded in passing such a law.\textsuperscript{266} The Maine state statute required that pharmaceutical companies make publicly accessible "[i]nformation concerning the results of the clinical trial, including potential or actual adverse effects of the drug" for all studies involving medications distributed in Maine.\textsuperscript{267} While the exact contours of this provision would seem to have necessitated further rulemaking by the Maine Department of Health and

\textsuperscript{261} § 282(j)(3)(I).
\textsuperscript{262} Id.
\textsuperscript{263} § 282(j)(3)(D)(v)(III).
\textsuperscript{264} Id.
\textsuperscript{265} § 282(j).
\textsuperscript{267} § 2700-A(3).
Human Services as afforded under the statute, it is quite possible that the Maine state law could have potentially required significantly greater disclosure than the federal statute. However, as a result of the preemption provision, the possibility of correcting the deficiencies of the federal law indirectly through state legislation is foreclosed. Consequently, further strengthening of the FDAAA disclosure requirements must therefore now come in the form of regulations issued by the Secretary or amendments to the statute by Congress. Nevertheless, any attempt to expand the type or amount of results information to be publicly revealed will unquestionably meet strong resistance from the pharmaceutical industry.

VI. OPPOSITION TO DISCLOSURE

Pharmaceutical companies have been exceptionally resistant to mandatory requirements to publicly reveal clinical trial materials, particularly results data. The drug industry has typically taken the position that if they are paying for an investigational study, the data generated unquestionably belongs to them. Moreover, as the purported owners of the information, they should be entitled to control its disclosure. This stance is further reflected in PhRMA's position paper entitled Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results, which succinctly provides: "As owners of the study database, sponsors have discretion to determine who will have access."

The pharmaceutical industry has asserted a wide range of proprietary-based rationales for such viewpoints. Often this includes arguments sounding in trade secret, contract, and patent law. Additionally, drug manufacturers maintain that the

268 § 2700-A(7).
269 See e.g., Meier, supra note 202, at A1.
270 PHARM. RESEARCH & MFRS. OF AM., PRINCIPLES ON CONDUCT OF CLINICAL TRIALS AND COMMUNICATION OF CLINICAL TRIAL RESULTS 21 (2004) [hereinafter PHRMA PRINCIPLES]. The document also declares that "[e]ven the fact that an exploratory study is being conducted may be highly proprietary because it reflects a company's choices to pursue certain research strategies, to test various methods of clinical trial design, and/or to utilize certain endpoint measures." Id.
ability to control clinical trial data is a competitive necessity, without which innovation would likely decrease to society's detriment. Furthermore, as much of the information is technical in nature, drug companies contend that releasing trial results to the general public is not only unlikely to be helpful, but could in fact lead to significant patient confusion or unwarranted concern. However, a closer look at these positions demonstrates their many weaknesses.

A. Trade Secrets

When the public began demanding further details concerning clinical trials involving the use of antidepressants in the pediatric population, the pharmaceutical makers refused. Instead, they claimed the study results could not be released because they constituted trade secrets. The FDA has also generally supported this line of reasoning. The agency's longstanding policy is to treat information generated in connection with clinical trials as trade secrets. Nonetheless, the FDA has indicated its hesitation about doing so.

The agency has testified on numerous occasions before Congress that federal law as currently drafted prohibits the dissemination of "useful information contained in the agency's files, and particularly, data relating to the safety and effectiveness of drugs." Furthermore, the FDA has asserted that "[e]ven if such disclosure would be in the public interest, in order to protect the public health, and even if the Commissioner wishes as a matter of discretion to release such material, such disclosure cannot lawfully be undertaken." Consequently, the agency is "bound by the present provisions until Congress acts."

272 Id.
274 Id.
276 Id.
277 Id.
However, it is not entirely clear that the statutory language invoked in support of this position actually provides for the claimed interpretation.278 Trade secrecy proponents have generally relied on § 301(j) of the FDCA which prohibits the use of any information acquired in connection with the FDA approval process “concerning any method or process which as a trade secret is entitled to protection.”279 But a compelling argument can be made that clinical trial data does not actually constitute a “method or process.”280 Nonetheless, it may be unfeasible to adopt a more narrow interpretation of the statutory language at this stage in light of the FDA’s established practice.281

Yet characterizing clinical trial data as a trade secret may be analytically difficult for still another reason. A fundamental tenet of trade secret law is that protection exists only as long as the information is kept confidential. The very nature of a clinical trial is quite public in many respects, making maintenance of complete secrecy fairly difficult.282 Large numbers of human subjects are often involved and generally not restricted in their ability to communicate about their experiences, including adverse events. As a result, information that might be initially characterized as potentially sensitive is often readily obtainable. For example “detailed pipeline information on interventions and research from the preclinical phase to the market phase is already available through various subscription websites.”283 Furthermore, data on most late-phase drug trials is effectively in the public domain at the present time through academic presentations at scientific meetings.284

Disclosure of clinical trial data often also occurs in rather

280 Id.
281 Id.
283 Karmela et al, supra note 20, at 956; see also Ida Sim et al., Clinical Trial Registration: Transparency is the Watchword, 367 LANCET 1631, 1631 (2006).
284 Gerd Antes and Iain Chalmers, Under-reporting of Clinical Trials is Unethical, 361 LANCET 978 (2003)
unexpected ways. For example, numerous reports have surfaced that preferred customers of Wall Street brokerage houses and hedge funds are frequently given access to clinical trial data, which is then used to make investment decisions. While such practices were investigated by the Securities and Exchange Commission as potentially violating insider trading laws, the actions would also potentially extinguish any purported trade secret protection. The conclusion that ultimately can be drawn is the drug industry's supposedly fail-safe argument regarding clinical trial data constituting trade secrets, is overall quite specious.

B. Contracts

Drug companies frequently rely on contracts in order to assert rights to the information collected in a clinical trial, as well as exercise virtually complete control over any communications related to the study data. It is not unusual for pharmaceutical makers to include in agreements with research scientists, and medical school personnel conducting the investigations on their behalf, a requirement that all data be maintained confidentially. Furthermore, these restrictions also usually include prohibitions on a researcher's ability to discuss the results of the trial publicly or even privately, as well as publish articles related to the study results.

While some academic institutions have opposed such constraints, for example Yale University will not accept any restrictions on publication with the exception of a short postponement to allow for a patent application or license, these entities are clearly in the minority. In fact, the authors of a survey examining agreements between medical schools and industry sponsors found that "academic institutions rarely

286 Id.
ensure that their investigators have full participation in the
design of the trials, unimpeded access to trial data, and the right
to publish their findings." 288 Furthermore, a study of
approximately 100 academic institutions found that only twelve
percent of the universities specified limits on permissible delays
in publication. 289 Drug companies often claim the contracts are
not intended to suppress possibly negative trial findings, but to
ensure data is properly analyzed before it is released. 290

Nonetheless, this has not proven to always be the
pharmaceutical industry's practice. For example, in connection
with the pediatric antidepressant controversy, the only
published article regarding a placebo controlled trial had
concluded that the antidepressant under study was found to be
safe and effective in treating adolescent depression. 291 However,
there were four other similar trials with negative results that
were never published. 292 Researchers who did have access to the
data from these industry-sponsored trials were prohibited from
publishing or speaking about the information because of the
nondisclosure provisions contained in their contracts. 293
Although they may have wanted to alert the public regarding
the potential for harm from these drugs, the researchers were
not allowed to issue such warnings.

In another case involving the experimental HIV drug
Remune, the manufacturer filed an arbitration proceeding
attempting to prevent the publication of an article by two
academic researchers involved in clinical trials of the medication
and sought millions of dollars in damages. 294 The company,

288 Kevin A. Schulman et al., A National Survey of Provisions in Clinical-Trial
Agreements Between Medical Schools and Industry Sponsors, 374 NEW ENG. J. OF MED.
1335, 1339 (2002).
289 Mildred K. Cho et al., Policies on Faculty Conflicts of Interest at U.S. Universities,
284 JAMA 2203, 2203 (2000).
290 Meier, supra note 202, at A1.
291 E. Jane Garland, Facing the Evidence: Antidepressant Treatment in Children and
292 Id.
293 Id.
class action lawsuit brought by shareholders of the Immune Response Company
Immune Response, claimed the manuscript contained confidential clinical trial data owned by the drug maker, as well as failed to include positive information and comments from the research sponsor, in violation of the parties' contract. Nonetheless, The Journal of the American Medical Association went ahead with its scheduled publication of the piece, in which the authors concluded that clinical trials demonstrated Remune was ineffective.\textsuperscript{295} The company publicly labeled the findings inaccurate, characterizing the JAMA article as "tabloid journalism," and promising that "the truth in the long run will come out."\textsuperscript{296} However, in the end the results of the private arbitration proceedings were kept quiet, although it was reported that Immune Response was not awarded any damages in its action against the researchers.\textsuperscript{297}

It is impossible to determine how often disputes over control of clinical trial data occur between the companies that fund the studies and the researchers that conduct the trials. While anecdotal evidence suggests such controversies over publication may be quite common\textsuperscript{298}, researchers "so seldom stand up to their sponsors."\textsuperscript{299} As a result, "there is no way to know how many negative studies have been suppressed—or worse, how many negative studies were converted to positives."\textsuperscript{300}

While agreements delaying or preventing publication in all

discussing the arbitration proceedings); see also Barry Meier, Medicine's Data Gap: The Academic Connection, N.Y. TIMES, Nov. 29, 2004, at A1.

\textsuperscript{295} James O. Kahn, et al., Evaluation of HIV-1 Immunogen, an Immunologic Modifier, Administered to Patients Infected With HIV Having 300 to 549 x 10^6/L CD4 Cell Counts 284 JAMA 2193, 2193 (2000).

\textsuperscript{296} In re Immune Response Sec. Litig., 375 F. Supp. 2d 983, 994 (S.D. Cal. 2005).


\textsuperscript{299} Katherine S. Mangan, Company Seeks $10 Million from Scientist and University, CHRON. HIGHER ED. Nov. 17, 2000, at A48, A50 (quoting Marcia Angell, Editor-in-Chief of the New England Journal of Medicine).

\textsuperscript{300} Id.
likelihood are enforceable from a contractual formation standpoint, a strong argument can be made that they should not be enforceable on public policy grounds. These agreements essentially create a contractual gag order on information that may be vital to society's health and safety. Accordingly, an earlier version of the federal clinical trial results database bill that eventually became law prohibited a drug manufacturer from entering into a contract that prohibited or limited the ability of an individual to either discuss the findings of a clinical trial or publish the results.\footnote{Fair Access to Clinical Trials Act, S. 470, 109th Cong. (2005).} Unfortunately, this provision was removed and replaced with a very weakly worded requirement to disclose merely the existence of such an agreement in a very narrow range of cases.\footnote{See 42 U.S.C. § 282(j)(3)(C) (Supp. 2008).} Despite the fact that Congress has failed to significantly restrain the use of these types of agreements, it still may be possible for the courts to provide some much needed constraints and send a strong signal to entities that insist on the inclusion and adherence to such data control provisions by clinical researchers.

C. Patents

With regard to patent protection, the pharmaceutical companies' arguments against disclosure of clinical trial results data are of a slightly different type. While drug companies' overriding concerns with trade secrets and contracts have been that the dissemination of study data would be a violation of such already established rights, pharmaceutical companies have maintained that the publication of trial information could have a negative effect on their ability to actually obtain patent protection in the first place. Pharmaceutical manufacturers claim that if a competitor were to gain access to this material, the rival could then utilize the data for its own patent applications, thus hindering their chances of even acquiring this form of intellectual property protection.\footnote{COMM. FOR ECON. DEV., supra note 3, at 14.} The drug industry contends that such "free riding" would ultimately impact efforts...
to commercialize the medications being tested, thereby reducing their incentives for undertaking original scientific research. Consequently, they say this would lead to a decline in innovation to the detriment of society. However, in light of the exceptionally aggressive patenting practices of the drug industry, as well as statutory changes to the law, these concerns are not especially convincing.

1. A Pharmaceutical Patent Portfolio

A patent typically provides its owner with the right to exclude others from making, using, or selling an invention for twenty years from the date of filing an application for such protection. Despite the drug industry's claims that public access to clinical trial results data could jeopardize their capacity to acquire patent protection, the fact of the matter is that most pharmaceutical manufacturers have submitted their patent applications well before any clinical trial data involving human subjects would have actually been generated. More often than not, drug companies file for patent protection while the investigational drug compound is still in its earliest, preclinical testing stage.

Such strategies do, however, create a different problem for the pharmaceutical companies. By filing so early in the drug development process, the patent could potentially expire even before the drug at issue could be commercially distributed. This is due to the fact that the intervals between patent issuance, clinical trial investigations, and finally FDA approval can be quite lengthy. However, in 1984 Congress passed the Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act"), which attempted to provide a partial solution to the pharmaceutical industry's concerns. In order to account for the delay, the statute afforded patent holders the right to extend

304 Id.
305 Id.
307 See generally, U.S. GOV. ACCOUNTABILITY OFFICE, supra note 42; Eisenberg, supra note 278.
their patents for up to five years, so long as the total time outstanding on the restored patent following FDA approval did not exceed fourteen years. This change significantly reduced the likelihood that a pharmaceutical manufacturer would finally obtain FDA approval to market a drug and subsequently find that no sizeable period of time remained on the patent.

It is also worth noting that the drug industry is generally quite proficient at utilizing the patent system to obtain protection. It is not unusual for a single medication to be under multiple patents for various aspects of the underlying invention including its composition, a method of using the drug, and the process for manufacturing the pharmaceutical. Furthermore, pharmaceutical companies have recently employed a wide variety of “evergreening” strategies to artificially extend the date a medication officially goes off-patent. The combination of these tactics often allows a drug company to attain a dominant position in the marketplace, despite concerns to the contrary.

2. ANDAs: Opening the Door to Generics

Prior to the passage of the Hatch-Waxman Act, generic pharmaceutical companies faced significant obstacles in entering the marketplace. In order to receive FDA approval, the generic firms were required to conduct their own clinical trials to support a new drug application. This was due to the fact that the FDA considered these generic versions of previously approved drugs “new drugs” themselves, thus necessitating evidence demonstrating the product’s safety and efficacy. However, the costs associated with testing were exceptionally high, and the opportunity to recover such expenses was limited.

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310 Eisenberg, supra note 278, at 348-49.
311 Kane, supra note 309, at 309.
An additional complication was the invariable delay between the time the original pharmaceutical company's patents on the drug expired and the generic firm could begin commercial distribution of their product. As conducting the requisite clinical trials would typically constitute patent infringement, generic firms could not begin carrying out these tests during the term of the brand-name pharmaceutical company's patents. Moreover, the inevitable wait associated with the FDA-review process created further time lag between the end of a brand-name pharmaceutical maker's patent term and the generic equivalent's entry to the market. However, the manufacturers of pioneer drugs were less than sympathetic to the plight of the generic firms, arguing the inadvertent marketplace exclusivity produced by the circumstances was not inequitable in light of the fact the FDA approval process often consumed many years of patent life.313

Nonetheless, in addition to extending the brand-name pharmaceutical makers patent term for up to five years as discussed above, the Hatch-Waxman Act made further changes to allow for easier entry into the marketplace by generic pharmaceutical makers. Instead of requiring such companies to complete their own clinical trials to demonstrate safety and efficacy, they would now be allowed to rely on the prior research from the brand-name manufacturer to market their essentially duplicate drug.314 As a result, the only new studies the generic manufacturers would need to conduct were clinical tests to prove the proposed drug was "bioequivalent" to the previously approved drug.315

Moreover, as carrying out such experiments would typically constitute patent infringement, the Hatch-Waxman Act also added a statutorily based research exemption to supplement the common law experimental use privilege.316 This provision offers broad exemption from traditional infringement liability by allowing the making or using of a patented invention, so long as

313 See Eisenberg, supra note 278, at 356-57.
315 Id.
such investigations are for purposes related to the development and submission of information under federal law which regulates the use of drugs. Consequently, a generic manufacturer can now complete the required studies during the term of the brand-name pharmaceutical maker's patents. Additionally, the company can submit a streamlined application called an Abbreviated New Drug Application ("ANDA") even before the patents associated with the pioneer drug have expired. This allows a generic drug maker to also effectively avoid the delay normally associated with the FDA approval process. Nonetheless, the generic manufacturer will not be able to enter the marketplace until all applicable patents and related extensions of the brand-name pharmaceutical maker have actually expired.

It should be noted that although an ANDA applicant is essentially permitted to make use of a brand-name pharmaceutical maker's prior clinical trial results, the generic drug company normally does not actually have access to this data. Instead, the generic drug manufacturer is able to take advantage of the earlier research more or less indirectly. However, for an FDA applicant that plans to make a modification to the brand-name manufacturer's formulation thus disqualifying it from the ANDA process, the Hatch-Waxman Act also included an additional section which permits such a drug maker to explicitly rely in whole or in part on another company's data.

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317 Id. Recently, this safe harbor language was interpreted quite broadly by the U.S. Supreme Court to cover a full range of pre-clinical activities, including experimentation on drugs not ultimately the subject of an FDA application. Furthermore, the Court held that the statutory exemption is not limited to only studies relating to the safety of the drug in human subjects. Merck KGaA v. Integra Lifesciences, 545 U.S. 193 (2005).


320 Id. at 312 (illustrating such a scenario by means of the example of an approved drug utilizing an active ingredient with a particular salt formation and a generic firm that wants to market a generic version of the approved drug with the same active ingredient but using a different salt formulation; in such a case the generic firm may be unable to file an ANDA because the proposed active ingredient will not be identical to that of the originally approved medication.)
3. Section 505(b)(2): Borrowing Data

Section 505(b)(2) of the Hatch-Waxman Act allows for applications in which one or more of the investigations utilized in order to acquire FDA approval “were not conducted by or for the applicant.” 321 Section 505(b)(2) differs from a traditional NDA because the applicant does not have a “right of reference,” defined as “the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application.” 322 Typically, a Section 505(b)(2) applicant is drawing upon clinical trial results appearing in published scientific literature. 323

Not surprisingly, the availability of Section 505(b)(2) generally leads to significant costs savings. The law essentially allows the applicant to “free ride” at the expense of other drug companies who had previously incurred the costs and risks associated with conducting their own trials. Nonetheless, despite objections by the pharmaceutical trade to the contrary, the FDA has somewhat surprisingly stated in drug industry guidance documents that such use of previous research “was intended to encourage innovation without creating duplicate work.” 324 Further, the FDA has maintained that both Section 505(b)(2) and the ANDA process reflect the same principles, namely that “it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug.” 325 However, also similar to ANDA applicants, Section 505(b)(2) applicants must observe the term of any applicable patents covering their pharmaceutical, consequently requiring the expiration of such intellectual property protection before they

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322 21 C.F.R. § 314.3(b) (2008).

323 FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(b)(2) 2 (1999). It should be pointed out that this is usually without the benefit of the full underlying raw data from the studies. Id. This is due to the fact that pharmaceutical companies generally view this information as confidential material and fiercely resist attempts at complete disclosure.

324 Id. at 3.

325 Id.
may begin commercially distributing their product.

4. Evaluating the Arguments

The pharmaceutical industry's concerns that the public disclosure of clinical trial results, particularly the underlying raw data, will negatively impact their ability to obtain patents appear to be quite exaggerated. Most drug companies obtain patents very early on in the drug development process prior to beginning clinical trials. This protection will prevent any attempts by a competitor to enter the marketplace until the expiration of the term of an applicable patent or market exclusivity, regardless of whether they have access to the results of another company's clinical trial data. While it is possible such data could be valuable to a competitor to assist in structuring their research strategy, as discussed above most pharmaceutical companies are already quite aware of the development activities of their fellow members in the drug industry.

Furthermore, the company that originally sponsored a study would not lose all of its benefits if the trial results are subsequently revealed, as it would have had a multi-year head start in analyzing the data, as well as formulating plans to act upon said information. As one commentator explained, "By permitting substantial free-riding even without access to the underlying data, the Hatch-Waxman Act has thus taken the wind out of the sails of an argument against data disclosure that rests upon protection from free riders." Lastly, in attempting to prevent potential commercial loss, it is also important not to lose sight of the significant societal benefits that could be gained

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326 Market exclusivities prevent the FDA from approving, or in some cases even accepting, an application for a competing drug compound for a stated period of time. These exclusivities relate to new chemical entities (five years), new clinical studies (three years), generic drugs (180-day exclusivity for first ANDA on previously approved brand-name drug), orphan drugs (seven years), and pediatric studies (extending exclusivity or patent protection on the innovator drug for six months). See THOMAS, supra note 319, at 348-73.

327 COMM. FOR ECON. DEV., supra note 3, at 15.

328 Eisenberg, supra note 278, at 382.
as a consequence of providing access to clinical trial results.

D. Competitive Necessity

The pharmaceutical industry has consistently asserted that preserving the confidentiality of clinical trial results is absolutely essential to ensuring their capacity to profit from the research they themselves conduct or financially sponsor.\(^{329}\) Without the ability to potentially generate revenue as a result of these clinical studies, drug companies argue that there would be little incentive to engage in medical research in the first place.\(^{330}\) Moreover, the resulting reduction in necessary information production “could be extremely dangerous and have a detrimental effect on health care for years to come.”\(^{331}\)

Despite the pharmaceutical industry's broad claims to the contrary, there is no credible support for the position that maintaining the secrecy of clinical trial data is necessary to promote clinical research or foster innovation.\(^{332}\) As the WHO's International Clinical Trials Registry Platform group concluded following formal consultations with representatives from the drug industry, medical community, and scientific field, “there is no convincing evidence that disclosure threatens competition and hence innovation. Indeed, openness might promote rather than stifle innovation.”\(^{333}\)


\(^{330}\) See e.g., Boyce, supra note 329; Dorfman & Reig, supra note 329; Lassman, supra note 329.


\(^{333}\) Sim et al., supra note 283, at 1631.
Greater dissemination of clinical trial results would likely reduce unnecessary duplication of research and thus improve its overall efficiency.\textsuperscript{334} Future studies could be informed by prior research which would decrease the probability of failure. Improvements in the drug development process would likely produce a considerable reduction in the cost of pharmaceutical research.\textsuperscript{335} A fairly recent study estimated that increasing the success rate from the current 21.5\% to 33.3\% would yield a reduction of $221$ million in capitalized cost per new drug candidate.\textsuperscript{336}

Additionally, disclosure of research results could also enhance a drug company's financial outlook in yet another possibly unexpected way. Industry experts identify the inability to recruit study participants as the single greatest concern in the drug development process.\textsuperscript{337} This is due to the fact that such problems can slow the approval process which can ultimately cause substantial financial losses.\textsuperscript{338} One estimate places the average cost to a drug manufacturer for each day's delay in obtaining FDA approval at an astounding $1.3$ million dollars.\textsuperscript{339}

The current public perception of the pharmaceutical industry could easily jeopardize clinical trial enrollments. However, the increased transparency associated with releasing study data may very well improve the public's perception of the benefits associated with participation in clinical trials. Consequently, this may positively affect patient accruals to the pharmaceutical industry's advantage.

Accordingly, not only would drug companies recognize considerable financial savings, but also society would likely benefit from an acceleration in the discovery of new

\textsuperscript{334} Id.
\textsuperscript{336} Id.
\textsuperscript{337} Trudo Lemmens, Commercialized Medical Research and the Need for Regulatory Reform (Univ. of Toronto Legal Studies Series, Research Paper No. 967393, 2007).
\textsuperscript{338} Id.
\textsuperscript{339} See Bodenheimer, supra note 298.
treatments.\textsuperscript{340} In fact, the FDA has even expressly stated that there is "an urgent need to ... enhance collaboration among the government, industry, and academia."\textsuperscript{341} The agency reported that pharmaceutical companies have predominantly been submitting NDAs for variations on existing drugs instead of innovative drugs.\textsuperscript{342} The FDA maintains further cooperation and sharing is essential to the development of pioneering treatments.\textsuperscript{343} This is due in large part to the fact that scientific breakthroughs rarely occur in complete isolation, but are usually the result of advancements made on the pioneering discoveries of earlier researchers.\textsuperscript{344} The ability to access and utilize information is critically important to societal progress.\textsuperscript{345}

\textbf{E. Patient Confusion}

Ironically, pharmaceutical companies also claim their reluctance to release clinical trial results is actually due to their concern for patient welfare. The drug industry argues the dissemination of results from a single study could mistakenly depict safety or efficacy hazards which multiple trials afterward would reveal were a mere aberration and clearly not present. In the interim, however, patients may suffer unnecessary distress potentially leading to the discontinuation of critically important medication. Additionally, the disclosure of such negative clinical trial findings risks the creation of an unmerited strain on the doctor-patient relationship due to decreases in confidence over health provider competency.\textsuperscript{346} Moreover, drug companies

\textsuperscript{340} See Križa-Jerić et al., \textit{supra} note 20.
\textsuperscript{341} U.S. GOV. ACCOUNTABILITY OFFICE, \textit{supra} note 42, at 2; FOOD & DRUG ADMIN., \textit{supra} note 3.
\textsuperscript{342} U.S. GOV. ACCOUNTABILITY OFFICE, \textit{supra} note 42, at 2; FOOD & DRUG ADMIN., \textit{supra} note 3.
\textsuperscript{343} U.S. GOV. ACCOUNTABILITY OFFICE, \textit{supra} note 42, at 2; FOOD & DRUG ADMIN., \textit{supra} note 3.
\textsuperscript{345} \textit{Id.}
contend the administrative resources that would inexorably be required to fulfill reporting obligations may raise the costs of pharmaceuticals.\footnote{Id.} The drug industry asserts this type of highly technical information is simply not the sort of material that can be properly evaluated by an untrained individual.

However, it seems as if the pharmaceutical companies may have improperly discounted the intellectual abilities of patients today. The testimony of a doctor at a congressional hearing on the FDA approval process provided the following contrary characterization: “You would be amazed how sophisticated a lot of patients are, and again, others on the panel can speak to this, who come to physicians [having] really done a tremendous amount of research and do know a lot.”\footnote{FDA’s Drug Approval Process: Up to the Challenge?: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions, 109th Cong. (2005) (testimony of Dr. David Fassler).} The Internet has already provided the public with access to vast amounts of medical information. Moreover, healthcare has become far more of a collaborative process between doctor and patient, rendering the rather paternalistic practice of viewing a physician as the unquestioned authority on medical issues virtually obsolete. To the extent that patients need to be alerted to the possibility that results from a single study may not necessarily provide a comprehensive estimation of the true value of a particular treatment, an appropriately worded disclaimer would seem a suitable approach to adequately advising the public. In the end, the purported disadvantages associated with disseminating results information are not compelling enough to justify preventing patients from accessing information that could allow them to make better educated decisions concerning their own health and welfare.

\textbf{VII. ADDITIONAL ARGUMENTS IN SUPPORT OF DISCLOSURE}

Leaving aside the many shortcomings associated with the arguments advanced for limiting any sort of further disclosure of clinical trial results, there are compelling independent...
justifications for further release of such data. Changes to the FDA's funding structure, in addition to the dramatic increase in private sponsorship of research studies, collectively contribute to a state of affairs that is in desperate need of enhanced transparency. Moreover, the revelation that clinical trials with negative outcomes are far less likely to be published makes improved access to the results of all clinical trials even more critical. Lastly, in order to allow for informed decision making by patients and their doctors, as well as comply with ethical norms, full disclosure of clinical trial results must occur.

A. PDUFA & FDA Transparency Issues

In response to drug industry's complaints that the FDA was taking far too long to review and approve new drug applications, Congress passed the Prescription Drug User Fee Act (PDUFA) in 1992.\(^{349}\) The legislation established a program through which additional staff would be hired with the objective of reducing approval times.\(^{350}\) This would be funded by fees paid by the pharmaceutical companies in connection with the submission of their applications for evaluation.\(^{351}\) The Act also provided for the establishment of performance goals for the agency, including completing review of a specified percentage of applications within particular time frames.\(^{352}\) Additionally, the statute provided that the funds generated by the user fee program


\(^{350}\) Id.


\(^{352}\) Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491; U.S. Gov. Accountability Office, supra note 42, at 10 (explaining that current goals state that the FDA should complete its initial review and act on ninety percent of all priority NDAs within six months and ninety percent of all standard NDAs within ten months).
would not be used for any other administrative purposes.\footnote{Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491.}

PDUFA in some respects could be considered a success. For drugs receiving priority review,\footnote{Drugs receive priority review only if they are deemed to offer a therapeutic advantage over existing medications. See, e.g., Okie, supra note 130, at 1063.} the median length for approval decreased from 14.9 months in 1997 to 6.7 months in 2003. Similarly, standard review times were also reduced from 27.2 months to 23.1 during the same time period. Nonetheless, the Act also appears to have created some very problematic conflicts of interest.

In connection with a congressional hearing examining the Vioxx controversy, a director in the FDA’s drug safety division described the existence of a culture in which the FDA “views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.”\footnote{FDA, Merck and Vioxx: Putting Patient Safety First: Hearing Before the S. Comm. on Finance, 108th Cong. (2004).} A study prepared by the General Accounting Office (GAO) at the request of the Senate’s Committee on Health, Education, Labor and Pensions, found that as a result of PDUFA, the “FDA reduced staffing levels for non-PDUFA activities each year, leaving the agency fewer resources to perform its other responsibilities” including safety-related activities. The GAO report also concluded that the legislation had “contributed to increased workload, high turnover rates, [as well as] reduced training time for scientists and medical officers on review teams.”\footnote{Okie, supra note 130, at 1063 (discussing the Office of Inspector Gen., FDA’s Review Process for New Drug Applications: A Management Review 12 (2003)).}

Moreover, a survey conducted regarding the PDUFA further echoes such concerns. According to a report prepared by the Office of the Inspector General, which was based upon responses from almost 400 FDA scientists, new drug reviewers in the FDA’s Center for Drug Evaluation and Research (CDER) have been pressured to recommend approval of a drug even if they have reservations.\footnote{Ensuring Drug Safety: Where Do We Go From Here?: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions, 109th Cong. (2005) (statement of the
almost one-fifth claimed to have been pushed to approve a new drug despite the existence of safety, efficacy, or quality questions. Additionally, with respect to drugs that were granted priority review, more than half of the respondents stated they were not given enough time to conduct an in-depth, scientific review.

These findings raise serious issues regarding the quality of FDA review and its corresponding impact on public safety. Moreover, this lends further substantiation to the need for disclosure of full clinical trial results to allow for additional scrutiny of the FDA’s approval decisions. Such transparency would help ensure that public interest is always the first priority.

B. Impact of Industry Influence on Clinical Trials

It is estimated that more than eighty percent of all clinical trials are now funded by for-profit companies. The consequences of this tidal shift away from government support of research studies is still not yet entirely clear, however, evidence is beginning to mount regarding the myriad of ways in which pharmaceutical industry sponsorship affects the outcome and reporting of clinical trials. The results of such influence can appear even in the earliest stages of a research study in connection with the way in which a company structures the drug trial. For example, one reported instance of this type of activity occurred in connection with an investigational pain medication. Initial data indicated that the sponsor’s drug had an increased risk for heart attacks when evaluated against an


359 Id. at 10.
360 See Lexchin, supra note 332, at 417.
363 Id.
existing pain reliever. Consequently, the pharmaceutical company altered the structure of the trial, replacing the original comparison drug with a different medication in its class that was considered much more risky, maximizing the potential for a favorable outcome. As one commentator notes, by utilizing these sorts of tactics, "You can usually figure out a trial that gets to 'yes.'"

Additional reports provide further evidence that commercial sponsorship of trials can result in reduced objectivity and a potentially biased presentation of evidence concerning the benefit to risk profile of the product. For example, a review of clinical trials funded by pharmaceutical companies comparing psychiatric medications showed that in ninety percent of the clinical investigations, the outcome favored the sponsor's drug. However, if a medication did well against a competitor in one particular trial, it invariably came in second when the clinical investigation was instead funded by the competitor. Similarly, an analysis of seventy articles on clinical trials evaluating the safety of drugs utilized to treat cardiovascular disorders demonstrated a comparable effect. Ninety-six percent of the authors of articles that were

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364 Id.
365 Id.
366 Id. (statement of Dr. Deborah Zarin, Director of the ClinicalTrials.gov registry). For other examples of such conduct related to trial structure see Paula A. Rochon et al., A Study of Manufacturer-Supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Arthritis, 154 ARCHIVES INTERNAL MED. 185 (2006) (dosing of the pharmaceutical manufacturer's drug was higher than that of the comparison drug) and Helle Krogh Johansen et al., Problems in the Design and Reporting of Trials of Antifungal Agents Encountered During Meta-Analysis, 282 JAMA 1752 (1999) (vast majority of company sponsored trials designed so that drugs under study were all taken orally; however, the comparison medication was known to poorly absorb and as such was traditionally only given intravenously).
368 Stephen Heres, et al., Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second Generation Antipsychotics, 163 AM. J. PSYCHIATRY 185, 185 (2006); see also AAAS, supra note 362 (statement of Shannon Brownlee).
369 AAAS, supra note 362.
supportive of the use of the drug under investigation had financial relationships with the manufacturer of the pharmaceutical, while only thirty-seven percent of those critical of the medication had industry sponsorship. Furthermore, a large survey of more than a thousand original research studies found a “statistically significant association between industry sponsorship and pro-industry conclusions.”

Issues also frequently arise in connection with the publication of articles related to industry-sponsored clinical trials. This is due in large part to the fact that industry sponsors often assert ownership over the data collected in connection with the studies they fund and consequently impose restrictions on publishing and the sharing of research results. As such, “[i]f a test suggests that a drug is effective in treating a certain condition, the company will push to get its results published in a prestigious journal. If the results reflect poorly on the drug, they often never appear in public.”

Likewise, to the extent the study results are a mixture of positive and negative outcomes, industry-funded investigators may downplay any unfavorable data or selectively report the findings. For example, in one study researchers reported that “most adverse events were not serious” when in actuality seven children were hospitalized as a result of side-effects attributable to the medication under examination. In another case involving the pain reliever Celebrex, the Journal of the American Medical Association (“JAMA”) published an article highlighting the medication’s beneficial safety profile.

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372 See infra Part VI discussing the frequent use of contracts in an attempt to delineate data ownership.
373 Bekelman, supra note 371, at 454.
374 Gardiner Harris, Spitzer sues a Drug Maker, Saying It Hid Negative Data, N.Y. TIMES, June 3, 2004, at A1.
375 AAAS, supra note 362 (statement of Shannon Brownlee).
376 Fred E. Silverstein et al., Gastrointestinal Toxicity with Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS
authors of the report claimed that the clinical trial data demonstrated that the drug was associated with significantly lower rates of gastrointestinal ulcers when compared with two older medications. However, it was only after the piece appeared in print that JAMA's editors learned that the authors of the study had utilized only the data from the first six months of the trial and failed to disclose the actual length of the clinical investigation was in fact twelve months. It turned out that the data from the year-long study showed no statistical advantage between Celebrex and the comparison drugs.

Furthermore, as part of a pharmaceutical company's publication strategy, articles on trial results are increasingly prepared by medical information companies. This practice known as "ghost writing" entails providing nearly finished manuscripts to prestigious academics to put their names on the pieces prior to publication, individuals who often have not had any involvement whatsoever in the clinical research itself. For example, in connection with marketing the drug Vioxx, a study in the Journal of the American Medical Association identified dozens of articles actually drafted by employees of the drug manufacturer Merck, but which attributed authorship to prestigious doctors who did not disclose industry financial support.

Not surprisingly, numerous studies have shown that articles appearing in published literature have a disproportionately high quantity of positive outcomes. This

Study: A Randomized Controlled Trial., 284 JAMA 1247, 1247 (2000).


379 Lemmens, supra note 337.

380 Id.; see also Stephanie Saul, Ghostwriters Used in Vioxx Studies, Article Says, N.Y. TIMES, April 15, 2008, at A1.


propensity on the part of investigators to submit manuscripts for publication based upon the positive results of the study findings is often referred to as "publication bias." Numerous studies have documented this "clear correlation between non-publication and lack of significant findings." While journal editors may have some responsibility for this situation, the unwillingness of investigators to submit inconclusive or negative research results for publication appears to be the main factor. Furthermore, trials with positive results are also generally published more quickly, on average two to three years earlier than those with inconclusive or negative results. Consequently, the cumulative impact of these issues associated with industry sponsorship of clinical trials is a quite unbalanced picture of the safety profile associated with a particular drug. Knowledge of the full range of risks and benefits is essential for physicians and patients to make truly informed decisions regarding proper medical care. Access to both negative and positive trial results is crucial to ensuring the most appropriate treatment is selected for any given individual. Additionally, if detailed information on all studies were available, it could be utilized by scientists to perform meta-analyses of all the existing studies that have been conducted involving a particular medication. The aggregation of raw data would allow for earlier detection of significant adverse effects. As such, it is absolutely essential that full trial protocols and their attendant results be made publicly accessible to ensure that this distortion of available data does not harm patients.

C. Clinical Trials and Ethical Norms

Clinical research involving human subjects can only be

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384 Jennifer L. Gold and David M. Studdert, Clinical Trial Registries: A Reform that is Past Due, 33 J. L. MED. & ETHICS 811 (2007).
385 Id.
386 S. Hopewell et al., Time to Publication for Results of Clinical Trials, COCHRANE DATABASE OF SYSTEMATIC REVIEWS, Issue 2 (2007).
387 Zarin et al. supra note 195, at 2113.
justified if the experiments conducted produce generalizable knowledge.\textsuperscript{388} Many in the medical community have interpreted this ethical principle to require the public disclosure of all research results.\textsuperscript{389} This is due to the fact that individuals voluntarily participating in clinical trials expect information obtained from the study will be available to future patients and ultimately improve medical care.\textsuperscript{390} Nonetheless, this is not possible to the extent trial results are concealed or remain hidden.

Moreover, if research results never become public, study participants may have risked the harm of the treatment with no recognizable benefit. This is in complete conflict with ethical codes that prohibit human subjects from being unnecessarily exposed to research harms.\textsuperscript{391} The sponsor of a clinical trial therefore has an obligation to acknowledge the contribution of the participants by ensuring that study results are in the public domain.\textsuperscript{392} Additionally, to the extent that studies are not published, there exists a very real possibility the same mistakes may be repeated by other companies who are also developing drugs with the same or similar properties. Particularly when there are adverse effects related to the investigative medications, it seems immoral not to report such findings to prevent future trial participants from needlessly being subjected to harm.\textsuperscript{393}


\textsuperscript{389} See e.g., David Korn & Susan Ehringhaus, Principles for Strengthening the Integrity of Clinical Research, 1 PLOS CLINICAL TRIALS e1 (2006); Drazen & Wood, supra note 21, at 2809.

\textsuperscript{390} See Korn & Ehringhaus, supra note 389, at 2-3; Drazen & Wood, supra note 21, at 2809.


\textsuperscript{392} Jeffrey M. Drazen et al., Open Clinical Trials, 357 NEW ENG. J. MED. 1756, 1756 (2007).

Individuals who agree to participate in clinical trials typically assent to treatment in the belief that they are actually contributing to medical knowledge. If, however, the insight obtained from the study is never reported, ethical issues also arise over whether the patient was truly able to provide the obligatory informed consent. This is particularly concerning where drug companies are "gaining financially from public involvement in trials, but refusing to reciprocate by making information from industry-sponsored trials generally available." Ethical guidelines clearly require that the rights of clinical trial participants must take precedence over commercial interests. Furthermore, failure to do so is simply not defensible, since as between study participants and drug industry sponsors, it is very obvious who is taking the greater risk.

VIII. CONCLUSION

It is imperative that the pharmaceutical industry recognize that without clinical trial participants they would not be able to generate the findings necessary to potentially obtain FDA approval on their products. Even more importantly, however, patients enrolled in such studies place their trust in these companies to ensure their safety, as well as advance medical knowledge. This cannot happen when drug companies and the FDA fail to disclosure meaningful clinical trial results. As such, genuine statutory reform to make the clinical trials process more transparent must occur so that proper protection is provided for all patients requiring medical care.

394 Dickersin & Rennie, supra note 185, at 517.
395 Id.
396 Id.
398 Drazen et al., supra note 392, at 1756.