

Reinvigorating the Concept of Benefit: The Failure of Drug Company-Sponsored Research on Human Subjects

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I. INTRODUCTION

In the early 1970s, Congress directed the Secretary of Health, Education and Welfare to create a commission for the purpose of ascertaining the important principles that should guide biomedical research that uses human research subjects. The report of this commission was to be published by the Secretary in the Federal Register and, unless the Secretary made any other proposals, it was to become law, a statement of what the United States government required. This report became known as the Belmont Report, and its contents are widely known,¹ though its legal status is not as well-known or appreciated.

The world of research and science has changed dramatically since the Belmont Report was written. This Article is not making a new claim when it says that pharmaceutical companies manipulate and suppress data that is generated on human research subjects in order to protect and expand on the industry's profitability. However, the interplay between this use of data and the requirements of the Belmont Report have, until now, gone unexamined.

Last year literally millions of Americans were participants in medical research, with estimates ranging from 2.3 million to upwards

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¹ See generally TOM L. BEAUCHAMP & JAMES F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS (5th ed. 2001).

of 10 million persons enrolled as subjects in roughly 80,000 separate studies.² The pharmaceutical and medical device industry is the largest consumer of human research subjects in the world³ because these companies must prove a minimal level of safety and efficacy of their products in order to receive governmental permission to market them, and this regulatory approval requires conducting drug trials on people.⁴ Pharmaceuticals and medical devices make up an industry whose annual sales are measured in the hundreds of billions of dollars.⁵ This large industry has recently been the subject of much criticism focused on the problem of undisclosed risks of harm for those taking its products.⁶ The medical and professional commentary on this issue has focused on the ethical implications of undisclosed risks to the consumer and prescribing physician. A deeper problem lies beneath this. We have, perhaps, a unique regulatory structure that governs the use of human research subjects. The regulations in effect in the United States were written as a direct response to a moral problem of exploitation of and harm to human subjects.⁷ The foundation of these regulations rests upon the Belmont Report, written in

² See MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES* 29 (2004); see also Adil E. Shamoo, *Medical Research Subjects Must Be Better Protected*, DAILY YOMIURI ONLINE, June 1, 2006, <http://www.yomiuri.co.jp/dy/columns/syndicate/2006061dy0d.htm>. The ten million subjects only includes those enrolled in drug trials; worldwide, Shamoo estimates that as many as fifty million persons are currently subjects enrolled in research. *Id.* These numbers are almost impossible to calculate accurately, as there is no requirement that participation be reported to anyone and the definitions of research can vary. For purposes of this Article, it is assumed that the number in the United States falls somewhere between those two estimates, and that the international number is also quite large.

³ See Richard A. Rettig, *The Industrialization of Clinical Research*, 19 HEALTH AFF. 129, 129–146 (2000).

⁴ Drug companies are dependent on early clinical information to ensure that they progress rapidly. This dependency makes them exquisitely sensitive to legal and regulatory actions that facilitate or constrain human experimentation. Barry Bloom, *The Role of Human Experimentation in Drug Research*, in HUMAN EXPERIMENTATION 42 (Robert L. Bogomolny ed., 1976) (describing in detail drug company dependency on human subjects throughout the process of developing and marketing drugs, a dependency that has not changed in the thirty years since this article was written).

⁵ PhRMA, the lobbying group for the U.S. pharmaceutical industry, calculated that the 2005 worldwide sales by its members amounted to more than \$250 billion. See PHARMACEUTICAL RESEARCH & MANUFACTURERS OF AMERICA, PHARMACEUTICAL INDUSTRY PROFILE 49 (2006), [http://www.pharma.org/files/2006 percent20Industry percent20Profile.pdf](http://www.pharma.org/files/2006%20percent20Industry%20Profile.pdf) [hereinafter PHARMA PROFILE].

⁶ The medical devices industry is subject to similar criticism. See, e.g., Richard A. Friedman, *What You Do Know Can't Hurt You*, N.Y. TIMES, Aug. 12, 2003, at A17.

⁷ See *Quality of Health Care-Human Experimentation: Hearing on S. 974, S. 878, and S.J. Res. 71 Before the Subcomm. on Health of the S. Comm. on Labor and Public Welfare*, 93d Cong. 3–5 (1973) [hereinafter *Senate Hearings*] (statement of Sen. Jacob K. Javits, Ranking Minority Member, S. Comm. on Labor and Welfare).

response to a congressional mandate to establish the ethical principles that must be complied with in order for research to be appropriately conducted on human beings.⁸ Through a series of legislative and regulatory actions,⁹ the ethical principles explained in the Belmont Report bear the weight of law. This foundation consists of three ethical principles: (1) beneficence, (2) autonomy, and (3) justice, as well as the specific implications of these principles as explained in the Belmont Report.¹⁰ This Article is concerned with the principle of beneficence, which, as described herein, maintains that it is of primary and fundamental importance that people who volunteer as subjects of dangerous research be assured of a reasonable likelihood of societal benefit resulting from that research.

Current controversies about data disclosure and suppression reveal that this foundational principle is no longer garnering consistent compliance.¹¹ If the data generated through the use of human research subjects is not properly utilized for the benefit of society, the research is failing to satisfy this requirement of its legality. Moreover, other forms of legal regulation pertaining to the pharmaceutical industry, which enable it to control financially valuable information, diminish the likelihood of the information being made broadly available,¹² further undermining the chance that a research project will generate a societal benefit that can pass muster. This controversy is fundamental and deep, and is not cashed out in a discussion of undisclosed risk of harm to the public.

Commentators have noted that suppression and manipulation of data concerning prescription drugs presents a critical problem for patients and for the overall goals of the scientific community,¹³ yet the connection between this problem and the regulation of human research subjects has not been adequately addressed. Professor Norman Dorsen, as the chair of a panel convened by the Food and Drug Administration (FDA) in the 1970s to examine the FDA's drug ap-

⁸ See Protection of Human Subjects: Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg. 23,192 (Dep't of Health, Educ. & Welfare Apr. 18, 1979) (codified at 45 C.F.R. § 46) [hereinafter Belmont Report]; see also National Research Act, Pub. L. No. 93-348, § 202, 88 Stat. 342, 353 (1974) (repealed 1990).

⁹ See National Research Act (setting forth Congress's statement of intent).

¹⁰ Belmont Report, *supra* note 8.

¹¹ See *infra* Part IV.

¹² See *infra* Part III.

¹³ See Thomas O. McGarity & Sidney A. Shapiro, *The Trade Secret Status of Health and Safety Testing Information: Reforming Agency Disclosure Policies*, 93 HARV. L. REV. 837 (1980).

proval process, recognized some ethical problems regarding data suppression and the use of research subjects but did not see the full range of legal implications.¹⁴ The negative impact of data suppression on the scientific community was also noted in the early 1980s during a robust debate concerning whether drug safety and efficacy information submitted by companies to the FDA as part of the drug approval process should be subject to Freedom of Information Act (FOIA) disclosure by the FDA.¹⁵ This Article contends that many of the problems that have arisen since the 1970s regarding accurate information about drug safety and efficacy could have been averted by a proper application of the requirement of benefit from the Belmont Report, which would have, in turn, assuaged the ethical concerns expressed by Professor Dorsen and others.

Part II of this Article establishes the concept of benefit to society as a foundational element within the context of the laws governing research on human beings in the United States.¹⁶ In context, this means that research, in order to be morally proper, must create a societal benefit. The merit of the normative value is not particularly relevant for purposes of the thesis presented here. Rather, its importance lies within the fact that the normative value underlies and is explicitly part of the regulatory structure governing human research subjects in this country.¹⁷ This Part explains what the law requires, analyzing the legal framework developed in the 1970s within which the current regulations reside. Benefit to society emerges as far from an empty requirement.¹⁸

¹⁴ See REVIEW PANEL ON NEW DRUG REGULATION, DEP'T OF HEALTH, EDUC., & WELFARE, FINAL REPORT (1977) [hereinafter FINAL DORSEN REPORT]; REVIEW PANEL ON NEW DRUG REGULATION, DEP'T OF HEALTH, EDUC., & WELFARE, INTERIM REPORT (1977) [hereinafter INTERIM DORSEN REPORT].

¹⁵ See generally McGarity & Shapiro, *supra* note 13; see also Freedom of Information Act, 5 U.S.C. § 552 (2000). *But see* Toxic Substances Control Act, 5 U.S.C. § 2602(6) (2000).

¹⁶ Belmont Report, *supra* note 8.

¹⁷ For example, during the process of IRB review, an IRB must decide that certain substantive regulatory requirements will be prospectively met based on the study's design. One such requirement is that the potential benefits of the trial be substantial enough to balance the risk of actual harm to the subjects. The benefit side of this equation is not a benefit that inures directly to the research subject. It means the trial has to be reasonably calculated to contribute a benefit to society. No direct benefit to the trial participants is usually possible or anticipated. See 45 C.F.R. § 46.111 (2007). Data suppression and manipulation are contrary to this requirement.

¹⁸ This analysis is done with the caveat that not all trials on human subjects conducted in this country must submit to regulation by the federal government, an outrage to many ethicists who write in this area. The reach of the regulations is limited to trials where the results will be submitted to the FDA or where the study is funded

Part III describes the regulatory and market culture that has helped to prematurely bury the benefit requirement. The legal and institutional culture under which research is conducted has undergone changes in the last forty years, which has resulted in a fracturing of this foundational element, such that research often fails to properly satisfy it and that no additional safeguards in the approval process have been created to ensure its satisfaction. This Part describes the shift from a culture where data dissemination was the norm to one where its suppression and manipulation is common. There are multiple reasons for this important change. During that time, the federal government had been pursuing a policy of protecting market incentives that, in theory, encouraged pharmaceutical companies to innovate.¹⁹ For example, as alluded to above, these protections include the FDA giving trade secret protection to safety and efficacy data filed with the FDA by those seeking FDA approval for their drugs and devices, which in turn protects this data from disclosure in response to FOIA requests.²⁰ Further, many research results that once belonged to the federal government by virtue its status as research sponsor are now given to private companies who keep the results secret in order to enhance their profitability.²¹ The policy goals behind these schemes are internally coherent for the most part. In effect, the goal is to take data derived from volunteer human research subjects and maximize the profitability that it offers to those who control it. This Part shows how these policy goals conflict with the straightforward requirements of the human-research-subject regulations, in that one must take the same valuable information and maximize the broad societal benefit that can be derived from it in a way that the current practices of the pharmaceutical industry cannot satisfy.

In the last three years, antidepressant use in a pediatric population was revealed to be far more dangerous than previously known,

in any part by the federal government. From a purely ethical perspective, this raises substantial questions. If one asserts that the federal regulations are ethically required to be followed, having research conducted that is not compelled to submit to these regulations is an ethically suspect endeavor. Discussion of this is outside the scope of this Article, which, again, is not focused on explicating normative claims regarding the proper ethical requirements of research conducted on human beings. Rather, the legal framework that exists is analyzed in the ethical context in which it was developed.

¹⁹ See, e.g., Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.); see also Bayh-Dole University and Small Business Patent Procedures Act, 35 U.S.C. §§ 200–212 (2000).

²⁰ 5 U.S.C. § 552(a).

²¹ See 35 U.S.C. § 202.

presenting a valuable case study of the full scope of this problem of data suppression and manipulation.²² As a case study, Part IV examines the recent scandal concerning the pharmaceutical industry's suppression of both the raw data²³ and subsequent analysis that showed risks of suicidality and of limited or no efficacy for pediatric populations using selective serotonin reuptake inhibitors (SSRIs). The data was generated using human research subjects in at least fifteen drug trials that took place over the course of at least as many years. All of these studies were subject to federal regulations,²⁴ which illustrates two important points: first, it shows the persistent failure of pharmaceutical manufacturers to comply with the requirement of conducting a study that creates a benefit for humankind; second, and perhaps more importantly, it shows some of the myriad ways that this possible benefit is not achieved—more specifically, it shows that the potential societal value of the information is lessened through data manipulation and suppression.

The conclusion and recommendations at the end of this Article suggest the need to rethink what a commitment to the principle of benefit to society means in the context of this Article's criticisms of the current research culture and to examine how the scientific community and pharmaceutical industry have degraded the benefit that is derived.

At a certain point in medical progress, we use human beings as research subjects because their bodies can generate data that we cannot yet ascertain in any other way.²⁵ In theory, we use these research subjects to benefit society and many times there is no possibility of direct benefit for the subjects themselves. When we do this, we enter a highly regulated area with an unusually ethically driven regulatory structure. The implications for the drug industry have failed to be properly examined with respect to the requirement that research must strive to generate a benefit for humankind.

²² Alex Berenson, *Medical Journal Criticizes Merck Over Vioxx Data*, N.Y. TIMES, Dec. 9, 2005, at A1. Paxil and other antidepressants are used as a case study in this Article primarily because Congressional hearings, a lawsuit by the State of New York, and other similar events have brought to light an unusual wealth of information about what occurred with that class of pharmaceuticals. See *infra* Part IV.

²³ For purposes of clarity, the use of the terms "data" and "datum" in this Article refer to information that was collected or derived in some manner from the use of human research subjects unless it is stated otherwise in the specific context.

²⁴ These studies were all submitted to the FDA, bringing them within the scope of the US regulations. See 5 U.S.C. § 2606(6) (2000).

²⁵ CARL H. COLEMAN ET AL., *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* 6 (2005).

II. THE MEANING OF BENEFIT

This Part explains the role of benefit in analyzing the propriety of any particular research proposal and further examines from where this concept is derived and why it is legally relevant. We use human beings as research subjects because we, as a society, need information gleaned from their bodies to improve our lives. Research has often been defined by contrasting it with the treatment of patients because pure research, unlike medical care, is designed to test a hypothesis, whereas medical care is performed to treat and heal individual patients.²⁶ In research, the human subject is being used as a means by society to achieve a more general benefit.²⁷

A. Background

Legal, historical, philosophical, and normative concerns arise when we contemplate using humans as research subjects. To address these concerns, we have developed a complex regulatory and ethical structure.²⁸ Our concern about human research subjects in the modern age is often traced back to World War II and the Nazis' use of concentration camp victims as involuntary subjects of medical research.²⁹ The Nuremberg Code, drafted in preparation for the war crimes trials of the Nazi officers at those concentration camps, is at the root of most subsequent regulatory work.³⁰ The World Medical Association adopted the Helsinki Accord in 1964, with subsequent amendments, to provide basic guidelines for conducting biomedical research.³¹ Both of these documents are relevant to this Article's analysis, as they are precursors to the Belmont Report and are frequently cited in the supporting reports in its appendix.

The regulatory structure was developed to ascertain how the use of humans could be condoned and conducted in an appropriate

²⁶ See Robert J. Levine, *The Boundaries Between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine*, in THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH app. 1, at 1-1 (1978) [hereinafter BELMONT REPORT APPENDIX I].

²⁷ The benefit that accrues to the subject as part of society is merely the same as accrues to all other members, now and in the future.

²⁸ COLEMAN ET AL., *supra* note 25, at 3-54 (discussing the history of this development).

²⁹ See Rosamond Rhodes, *Rethinking Research Ethics*, 5 AM. J. BIOETHICS 7 (2005); see also COLEMAN ET AL., *supra* note 25, at 16-31.

³⁰ COLEMAN ET AL., *supra* note 25.

³¹ World Med. Ass'n, Declaration of Helsinki (June 1964) (last amended 2000), available at <http://www.wma.net/e/policy/b3.htm> [hereinafter Declaration of Helsinki].

manner.³² It is important when examining this structure to understand that it is considered inherently problematic to use people in the way that research does.³³ The overlapping and widely accepted principles of respect for persons and the autonomy of individuals, for example, discourage the idea of a human body used as a machine by and for the benefit of others.³⁴

Once it is conceded that research on humans is problematic, the ethical task becomes shaping the research in a manner that will resolve the problem or, if this is not possible, that will justify continuing with research in its problematic position. In this context, how do we respect a person, protect their autonomy, and somehow not use them solely as a means to a greater societal gain, while at the same time pursuing our research objectives? To keep this challenge in perspective, it is critical to recognize that research does not have to occur. While we as a society stand to benefit greatly from this type of research, there is no clear moral obligation upon society to perform it.³⁵ As Hans Jonas said, “[o]ur descendants have a right to be left an unplundered planet, [but] they do not have a right to a new miracle cure. . . . [W]e have not sinned against them if by the time they come around arthritis has not yet been conquered (unless by sheer neglect).”³⁶ Medical progress is an optional social goal. If no person volunteers to be a research subject, we have no mechanism in place to compel participation. In such a circumstance, if no volunteers were forthcoming, research on volunteers would simply stop.³⁷ Given that the pursuit of research is not legally or morally required, it

³² COLEMAN ET AL., *supra* note 25, at 16–31.

³³ Much of the literature on human research subjects tangles with this issue. See Maurice Natanson, *A Philosophical Perspective on the Assessment of Risk-Benefit Criteria in Connection with Research Involving Human Subjects*, in THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH app. 2, at 21-17 (1978) [hereinafter BELMONT REPORT APPENDIX II].

³⁴ For further discussion, see David DeGrazia & Tom L. Beauchamp, *Philosophy, in METHODS IN MEDICAL ETHICS* 31 (Jeremy Sugarman & Daniel P. Sulmasy eds., 2001).

³⁵ See Natanson, *supra* note 33, at 21-17 (quoting Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 DAEDALUS 228–29 (1969)).

³⁶ See *id.*; see also NATIONAL BIOETHICS ADVISORY COMMISSION, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS, at i (2001), http://www.bioethics.gov/reports/past_commissions/nbac_human_part.pdf [hereinafter BIOETHICS COMMISSION] (quoting Jonas, *supra* note 35, and reaffirming that progress is an optional goal).

³⁷ We do have mechanisms in place for conducting research on those who cannot give consent, such as infants and emergency department patients, and this presents a more problematic scenario regarding a blanket statement about compelled participation. See 45 C.F.R. § 46.116(d) (2006). While permissible under these specific conditions, there is no legal mandate that this research occur. See *id.*

should then follow that if research cannot be conducted appropriately, it is not to be conducted at all. To be explicit, the appropriate default position is that no research occurs if it cannot occur properly. This default position is important because this Article asserts that much of current research sponsored by drug companies is not being properly conducted and so should no longer be conducted unless these problems are fixed.

The ethical framework for using human research subjects has a peculiarly powerful legal relevance in the United States due to the Belmont Report.³⁸ The Belmont Report holds a unique place in American legal history. The Department of Health, Education and Welfare (HEW), now known as the Department of Health and Human Services (HHS), adopted the very short, philosophical paper to form a foundation for its policies for research on human subjects.³⁹ The Belmont Report explains the “ethical principles and guidelines for research involving human subjects.”⁴⁰ This philosophical paper was published in the Federal Register, was commented upon, and then became a binding regulation of the federal government.⁴¹ It is still in effect.⁴²

By adopting this paper as a statement of policy, HHS made its ethical, normative analysis of the use of human research subjects part of the law. The regulations that were adopted to govern the use of human subjects shortly after completion of the Belmont Report were primarily drafted by those responsible for writing the Belmont Report, making the connection between them even clearer.⁴³

³⁸ Belmont Report, *supra* note 8.

³⁹ See National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974) (repealed 1990).

⁴⁰ Belmont Report, *supra* note 8.

⁴¹ *Id.*

⁴² *Id.*

⁴³ The recommendations of the Commission are “embodied in a living way in the regulations” that govern human subject research. Interview by The National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research with F. William Dommel, Jr., J.D., NIH Liaison to the National Commission, NIH, in Bethesda, Md. (Sept. 16, 2004) (Dommel was a staff person for the Commission and assisted in drafting the regulations); see also Interview by Bernard A. Schwetz, D.V.M., Ph.D., Director, Office for Human Research Protections, HHS, with LeRoy B. Walters, Joseph P. Kennedy, Sr. Professor of Christian Ethics, Georgetown University, in Washington, D.C. (Sept. 24, 2004) *available at* <http://www.hhs.gov/ohrp/BelmontReportArchive.html#histArchive2> [hereinafter Walters Interview] (explaining that the Secretary had 180 days to either adopt or respond to the recommendations of the Commission.); Interview by Bernard A. Schwetz, D.V.M., Ph.D., Director, Office of Human Research Protections, HHS, with Tom Lamar Beauchamp, Ph.D., Senior Research Scholar, Kennedy Institute of Ethics in Washington, D.C. (Sept. 22, 2004), *available at* <http://www.hhs.gov/ohrp/BelmontReportArchive.html#histArchive2>

In the early 1970s, a series of news stories appeared about biomedical research and medical treatment that provoked the Senate to hold hearings about how research on human subjects was being conducted. The Tuskegee syphilis study had recently been exposed,⁴⁴ along with reports of involuntary sterilization of African-American women and unapproved experimentation on newly aborted fetuses.⁴⁵ These hearings, in turn, led to the passage of the National Research Act,⁴⁶ which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the “Commission”).⁴⁷

The Commission was given specific charges in its enabling act. It had recommendations and reports on certain topics which it was to prepare and then file with the Secretary of HEW.⁴⁸ The Secretary then had 180 days to act on each recommendation either by formulating regulations to implement it or by explaining why the proposal was not an appropriate action.⁴⁹ An observer of current presidential bioethics councils will be struck by how the design of the Commission differs from those we have seen since.⁵⁰ By giving it clear topics, assignments, and dates by which it was to complete its work, and by ordering the Secretary to respond within six months to its recommen-

[hereinafter Beauchamp Interview] (“Interviewer: ‘The [Belmont Report] is pretty clearly the basis for the regulations[?]’ Beauchamp: ‘Yeah.’”); Interview by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research with Bonnie M. Lee, B.A., Associate Director for Human Subject Protection Policy, FDA, in Rockville, Md. (Aug. 13, 2004) (explaining that the 1981 HHS and FDA IRB regulations were based on the Commission’s recommendations and that the 1991 Common Rule is very similar); Interview by Patricia C. El-Hinnawy, Office for Human Research Protections, HHS, with Norman Fost, M.D., Professor of Pediatrics, University of Wisconsin Medical School, in Madison, Wis. (May 13, 2004), available at <http://www.hhs.gov/ohrp/BelmontReportArchive.html#histArchive2> [hereinafter Fost Interview] (The “Commission [was] unlike any other in the history of this country . . . in that it had this statutory authority to write rules, which would become law . . . unless changed by the Secretary of [HHS.]”).

⁴⁴ COLEMAN ET AL., *supra* note 25, at 39–45.

⁴⁵ *Senate Hearings*, *supra* note 7.

⁴⁶ See National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974) (repealed 1990).

⁴⁷ *See id.*

⁴⁸ *See id.*

⁴⁹ *Id.* According to language in the Act, the recommendation from the Commission would then become law if the Secretary failed to act within the proper time frame. *Id.*

⁵⁰ For a discussion of these commissions, see *The President's Council on Bioethics and Approaches to Public Deliberation Taken by National Bioethics Commissions*, 15 KENNEDY INST. ETHICS J. 221–322 (2005).

dations or the recommendation would be binding, the Commission was designed to effectively make and implement policy in this area.

The Belmont Report was written by the Commission in response to its charge to “identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with these principles.”⁵¹

Due to the legislative background of the Commission’s work, the normative values that are described in the Belmont Report and other writings by it have an important role in analyzing whether any one particular type of research on human subjects is legal. This role is fundamentally different from other normative studies related to the development of laws, because the work of the Commission is not merely useful as evidence of intent of the type found in legislative history. Rather, in the case of the Belmont Report, it is part of the actual regulatory framework that governs this type of research.⁵²

As we examine what the guiding principles are for research on humans, it will become clear that certain ethical requirements must be met in each separate incident of research. One such requirement is that the study must be designed to generate certain benefits to society⁵³—benefits that must, under the rules, be anticipated in the design of the study and accrue from that study alone.⁵⁴ However, these benefits are primarily measured by assessing the possible advancement of scientific knowledge derived from analyzing any data generated by the study, not contributions to some larger economic or social scheme.⁵⁵

To reiterate, research on human subjects is an inherently selfish undertaking by society. Society hopes to benefit from the use of a human’s body in circumstances where the human does not stand to benefit directly on his or her own from this same use.⁵⁶ The most basic requirement of research, as demanded by the Belmont Report, is

⁵¹ Levine, *supra* note 26.

⁵² Belmont Report, *supra* note 8.

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ The subject is not, individually, conceived as a beneficiary by the researcher. There is a problem with informed consent called the therapeutic misconception, whereby a subject believes he or she is likely to benefit from participation in a study, even when this is impossible or unlikely. When this arises, it is a problem with informed consent and is not part of the benefit analysis. BEAUCHAMP & CHILDRESS, *supra* note 1, at 9.

that we must not undertake this research unless the possible benefit to society is substantial enough to justify this use of humans.⁵⁷ This requirement alone is certainly not enough to satisfy all ethical requirements for proper use of human research subjects; it is a necessary but not sufficient condition.⁵⁸

Two separate claims are made here about the regulatory structure governing research on human subjects. The first is that a potential benefit to society, or to phrase it differently, to humankind, is a fundamental requirement of the design of all research conducted on human beings subject to federal regulations. It is the first quality of a proposed research project that must be assessed, and if it is absent the research project cannot go forward.⁵⁹

The second claim is that the benefit, for purposes of this type of analysis, must be assessed as to the probability of it being generated within the boundaries of the individual proposed research project.⁶⁰ It cannot be enhanced through the addition of possible externalities that could benefit humanity, such as the profitability of drug companies.

B. Foundational Status of the Concept of Benefit

1. Early Foundations and the Belmont Report

This Article claims foundational status for the requirement that a study on human subjects must be designed to benefit society. This requirement is embodied in United States law,⁶¹ and is also explicitly present in the Nuremberg Code⁶² and the Helsinki Accord.⁶³ This goal of research appears to be assumed as a primary motivator for research by participants writing in this field.⁶⁴ Due to changes in the culture in which research is now conducted, those who sponsor and conduct studies have changed their motivation.⁶⁵ Because of this cultural change, it is necessary to carefully examine the immutable responsibilities that this foundational requirement of benefit actually

⁵⁷ Belmont Report, *supra* note 8.

⁵⁸ *Id.*

⁵⁹ *Id.* The other requirements are autonomy and justice. *Id.*

⁶⁰ *Id.*

⁶¹ See 45 C.F.R. § 46 (2006).

⁶² See 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, 181–83 (1949) [hereinafter NUREMBERG].

⁶³ Declaration of Helsinki, *supra* note 31.

⁶⁴ See *infra* notes 74–80 and accompanying text.

⁶⁵ See *infra* Part III.

imposes on those who would conduct research on humans, as this requirement can no longer simply be assumed to be satisfied.

Paragraph two of the Nuremberg Code states that an “experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature.”⁶⁶ The primary legal and scholarly focus since World War II has been on ensuring the voluntary, informed consent of research subjects. The Nazis used concentration camp prisoners as objects of their experiments. Many of the research scandals in the United States involved subjects who were not given adequate opportunity to decide for themselves if they wished to be a part of a specific research project.⁶⁷ In light of these events, issues concerning consent and exploitation of subjects have dominated the discussion, for example, as to whether consent is truly voluntarily given (such as with prisoners or hospitalized patients) and how to ensure sufficient information has been disclosed concerning risks to make a subsequent consent truly informed.⁶⁸

The concept of benefit derived from research has had a poor history in terms of scholarly focus—it is depended upon, but a bit taken for granted. Scientific research has historically been conducted for the dual purposes of acquiring respect from one’s peers and the betterment of humankind.⁶⁹ Publication of research in peer-reviewed journals accomplished both of these goals, which gave the more prestigious journals tremendous power in the scientific community.⁷⁰ The history of biomedical research is filled with people who took risks on themselves, their children, and innumerable vulnerable subjects to prove a hypothesis that would later save lives.⁷¹ It is also filled with those whose hypotheses failed, even after also putting subjects at a high level of risk.⁷²

The early framework for biomedical research in this country, dating back to the foundation of Johns Hopkins Medical School and

⁶⁶ NUREMBERG, *supra* note 62.

⁶⁷ See, e.g., M. P. KING, *The Dangers of Difference*, 22 HASTINGS CENTER REP. 35 (1992).

⁶⁸ See generally RUTH R. FADEN & TOM L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT* (1986).

⁶⁹ See *infra* Part IV; see also Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177, 182 n.17 (1987).

⁷⁰ See Frank Davidoff et al., *Sponsorship, Authorship and Accountability*, 135 ANNALS OF INTERNAL MED. 463, 463–66 (2001).

⁷¹ M.H. PAPPWORTH, *HUMAN GUINEA PIGS: EXPERIMENTATION ON MAN* 31–174 (1967).

⁷² *Id.*

the Rockefeller University in the early 1900s, was of researchers working without any expectation of profiting financially from their work.⁷³ It is difficult in the current environment to imagine this, but many researchers and academic research centers expressly eschewed financial motivations, worried that it could corrupt the research enterprise.⁷⁴ This continued into the 1970s. Dr. Albert Jonsen, a member of the Commission, stated in an interview conducted in 2004 that “at the time the Commission was working, researchers rarely even thought of profiting from anything they might produce. That’s what they did, and it became a public good.”⁷⁵

Biomedical researchers were focused on variable degrees of social good, public benefit, and their own acclaim upon publication.⁷⁶ The concern was that the researchers were liable to not sufficiently respect the individual persons upon whom their experiments were being conducted.⁷⁷ This logically led to the scholarly focus on the voluntary nature of the subject’s undertaking and the question of informed consent. With researchers fueled by a sense of pursuing a greater social good, the risk was of exploitation and damage to an individual’s autonomy. In the early years of successful biomedical research in the United States, the language of the more prominent figures was of fighting a battle on disease, and their losses of research subjects have been justified as necessary losses.⁷⁸ A crude utilitarian argument held sway, fueled by a paternalistic relationship between doctors and patients that already failed to give adequate voice to a patient’s autonomy.⁷⁹

In light of this culture there are two sets of concerns reflected in the Belmont Report, and which still hold sway in the field. The first is with the prevention of gross crimes such as those that occurred

⁷³ See JOHN M. BARRY, *THE GREAT INFLUENZA: THE EPIC STORY OF THE DEADLIEST PLAGUE IN HISTORY* 11–87 (2004), for a history of the culture of research at these institutions in the early 1900s.

⁷⁴ Eisenberg, *supra* note 69, at 181 nn.8–9.

⁷⁵ Interview by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research with Albert R. Jonsen, Ph.D., Professor of Medical Ethics, University of California at San Francisco Medical School, in San Francisco, Cal. (May 14, 2004).

⁷⁶ Sheldon Krimsky, *Publication Bias, Data Ownership, and the Funding Effect in Science: Threats to the Integrity of Biomedical Research*, in *RESCUING SCIENCE FROM POLITICS: REGULATION AND THE DISTORTION OF SCIENTIFIC RESEARCH* 61 (Wendy Wagner & Rena Steinzor eds., 2006).

⁷⁷ See *infra* notes 170–77 and accompanying text.

⁷⁸ See generally JAY KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* (1972).

⁷⁹ BARRY, *supra* note 73; COLEMAN ET AL., *supra* note 25, at 14–16; see generally JAY KATZ, *THE SILENT WORLD OF DOCTOR AND PATIENT* (2002).

with the Nazis and, on a smaller scale, in the Tuskegee syphilis studies.⁸⁰ The second is with how to impose a balance upon the profession, with the desire to achieve a benefit on one hand and the rights of the research subjects on the other.⁸¹

The Belmont Report is divided into three parts. Part A defines the boundaries between practice and research.⁸² This section serves the purpose of showing that when research occurs, it must be subject to review by an institutional review board (IRB).⁸³ The goal is to define research broadly in order that the protections provided by an IRB review will be broadly available to those subjects who will need it.⁸⁴ Part B delineates the basic ethical principles that are relevant to the ethics of research involving human subjects.⁸⁵ These principles are respect for persons, beneficence, and justice.⁸⁶ Part C describes where it is anticipated these general principles delineated in Part B will be applied.⁸⁷

Principle One,⁸⁸ respect for persons, is similar to Paragraph One of the Nuremberg Code, which states that the voluntary consent of the human subject is absolutely essential.⁸⁹ Respect for persons is a principle that engages ideas of autonomy, and, for those who cannot exercise autonomy, a requirement that they be adequately protected.⁹⁰

Principle Three, justice, may be implicated in the problem identified here, though the requirements of justice as delineated in the Belmont Report do not make as clear-cut a case for requiring disclosure of research data.⁹¹ "Who ought to receive the benefits of research and bear its burdens?"⁹² This is a question that brings issues of

⁸⁰ Belmont Report, *supra* note 8, at 23,192.

⁸¹ *Id.* at 23,192–93.

⁸² *Id.* at 23,193.

⁸³ *Id.*

⁸⁴ Levine, *supra* note 26.

⁸⁵ Belmont Report, *supra* note 8, at 23,193–94.

⁸⁶ *Id.* The primary author of the Belmont Report, Thomas Beauchamp, working with Jim Childress, a philosopher who had also been involved in the project of preparing the Belmont Report, wrote *The Principles of Biomedical Ethics* soon after publication of the Report, explaining these principles in greater detail. BEAUCHAMP & CHILDRESS, *supra* note 1.

⁸⁷ Belmont Report, *supra* note 8, at 23,193–94.

⁸⁸ Belmont Report, *supra* note 8.

⁸⁹ NUREMBERG, *supra* note 62.

⁹⁰ Belmont Report, *supra* note 8.

⁹¹ Interestingly, a claim could be made that justice arguments support a pharmaceutical industry that generates a net societal gain.

⁹² See Belmont Report, *supra* note 8, at 23,194.

societal benefits to the forefront, in the context of who the proper subjects of research are. For example, if the poor are subjects of research, yet only the wealthy receive subsequent medical care as a result of that research, have we created an affront to notions of justice? Arguably, it is entirely exploitative to have a class of research subjects who do not stand to be recipients of the benefit that may be derived from the results of the trial, even as members in the broader societal group.

Principle Two, beneficence, is the relevant portion of Part B of the Belmont Report for purposes of this Article's analysis. The concept of beneficence is complicated in the Belmont Report; there is an economy used in stating principles in this Report⁹³ and each one is expected to move the project of the Commission quite far.

The principle of beneficence is used to describe both the mandate to do no harm and the mandate to maximize benefits and minimize possible harms from the research project as a whole.⁹⁴ The concept "do no harm" comes from the Hippocratic Oath, as stated directly in the Belmont Report.⁹⁵ This concept is included at the beginning of the discussion, rather than an end point.⁹⁶ The challenge for the drafters of the Belmont Report, and the challenge generally in this area, is how to ethically justify an undertaking that exposes an individual to a risk of harm with no expectation of an immediate, physical, or direct benefit to the subject. The Belmont Report asserts that learning both what will benefit patients and what will cause them risk is an integral part of the process of protecting each individual patient, and thus makes the biomedical research agenda acceptable notwithstanding the requirement that the treating physician "do no harm."⁹⁷ In effect, by learning how to treat patients more effectively in general, one is acting within the requirement to do no harm.⁹⁸

The Belmont Report asserts that since learning these facts may require exposing subjects to risk, the next challenge under beneficence is to assess "when it is justified to seek certain benefits despite

⁹³ See *id.* at 23,193–94; see also generally BEAUCHAMP & CHILDRESS, *supra* note 1.

⁹⁴ Belmont Report, *supra* note 8, at 23,194.

⁹⁵ *Id.* Interestingly, the use of the Hippocratic Oath reflects the role of physicians in defining the ethics of research on humans, though scientists without medical degrees conduct much of modern research.

⁹⁶ Belmont Report, *supra* note 8, at 23,194.

⁹⁷ *Id.*

⁹⁸ This argument seems to stem from a desire to pursue research on human subjects even while recognizing that it is ethically problematic for physicians to do so in light of the Hippocratic Oath, with its stated duty to the well-being of the individual patient.

the risks involved.”⁹⁹ Beneficence is the concept that normatively justifies the research endeavor—the same motivation for the betterment of humankind that historically led physicians and scientists to conduct biomedical research on human beings.¹⁰⁰ It introduces the concept of benefit and the challenge of finding an appropriate balance between the benefit and acceptable levels of risk to the subject.

2. Explication of the Principles of the Belmont Report

In preparing the Belmont Report, the Commission requested specific people to prepare a number of reports on issues relevant to identifying and defining the principles to be respected in conducting research—these reports were published in a two-volume appendix.¹⁰¹ In searching for the meaning of benefit as used both in the Belmont Report and in the literature on this issue generally, it is helpful to see how that concept is treated by the authors of the different reports in the appendix.

Dr. Robert Levine prepared a series of reports for this project of the Commission.¹⁰² His first report, and the first in the appendix, seeks to delineate the boundaries between research on human subjects and medical practice on patients.¹⁰³ This report was prepared primarily because, in distinguishing between these two kinds of subjects, a definition of research had been developed. Levine states that “[w]hile the health care professional might be assumed to see the well-being of the patient as the most important end, the investigator is assumed to see development of new knowledge as a major, if not ultimate, end.”¹⁰⁴ What we see here is the role played by this assumption of the investigator’s motive, the development of new knowledge.

In Dr. Levine’s second report, concerning the role of risk-benefit criteria, he analyzes in some detail what an IRB should properly consider when analyzing risk and benefit for purposes of approval of a

⁹⁹ Belmont Report, *supra* note 8, at 23,194.

¹⁰⁰ See PAPPWORTH, *supra* note 71, at 8–12 (criticizing human experimentation that forgets beneficence and looks only to the value of knowledge).

¹⁰¹ See BELMONT REPORT APPENDIX I, *supra* note 26; BELMONT REPORT APPENDIX II, *supra* note 33.

¹⁰² See BELMONT REPORT APPENDIX I, *supra* note 26, at 1-1 to 4-103.

¹⁰³ See generally Levine, *supra* note 26.

¹⁰⁴ *Id.* at 1-4. The Common Rule is the popular name for the assortment of rules governing research on human subjects that have been agreed upon by the majority of federal agencies.

research proposal.¹⁰⁵ The two concepts of risk and benefit are closely related and do not necessarily occupy entirely separate columns. For example, if the goal of research is to benefit society, one possible risk of not doing research is a loss of this societal benefit.¹⁰⁶

One important requirement of the Belmont Report¹⁰⁷ and the Common Rule¹⁰⁸ is that research be designed to enhance the probability of something relevant being discovered. This requirement is tied to the concept of benefit in this report, where Dr. Levine states:

There is no way to separate the issue of quality of scientific design of research from the ethical considerations as to whether it should be done. If research is badly designed, it is not likely to benefit anyone[.] [I]t seems inappropriate to put human beings at risk to develop information (or misinformation) that cannot conceivably benefit either the individual or society.¹⁰⁹

Dr. Levine also references the Nuremberg Code as giving support to this concept; it states “[t]he experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature.”¹¹⁰ Dr. Levine cements his adoption of this concept from the Nuremberg Code by then stating that “[i]t is inappropriate to put humans at risk to gain information that can be secured without putting humans at risk.”¹¹¹

This principle is important here because it tells us how a research proposal is to be measured: first, by what it hopes to accomplish for society, and, second, how well it is designed to accomplish that task.¹¹² Some minimum must be met in the quality of design for accomplishing this task (the good of society) for the research to be an ethical and appropriate undertaking.

Dr. Levine contemplates benefits to society and benefits to the individuals who are the research subjects (as does the Belmont Report).¹¹³ In analyzing benefits to society, Dr. Levine divides research

¹⁰⁵ See Robert J. Levine, *The Role of Assessment of Risk Benefit Criteria in the Determination of the Appropriateness of Research Involving Human Subjects*, in BELMONT REPORT APPENDIX I, *supra* note 26, at 2-3.

¹⁰⁶ *Id.*

¹⁰⁷ See Belmont Report, *supra* note 8, at 23,194.

¹⁰⁸ 45 C.F.R. § 46.101 (2006).

¹⁰⁹ Levine, *supra* note 104, at 2-30.

¹¹⁰ *Id.* at 2-32 (citing NUREMBERG, *supra* note 62).

¹¹¹ *Id.* at 2-32.

¹¹² Belmont Report, *supra* note 8, at 23,195-96.

¹¹³ See Levine, *supra* note 105, at 2-32 to 2-33; see also Belmont Report, *supra* note 8.

into four categories, only the first of which is relevant here.¹¹⁴ This category of research is applied biomedical and behavioral research, which he defines as research for developing and perfecting diagnostic, prophylactic, and therapeutic modalities.¹¹⁵

For this type of research, Dr. Levine makes it clear that the benefits to society that should be relevant in the IRB analysis are those that are potentially generated by that specific project.¹¹⁶ This supports the assertion made earlier in this Article that one cannot satisfy the requirement of a benefit by claiming a net societal good from our pharmaceutical industry as currently constructed.¹¹⁷ As Dr. Levine explains, it is far easier to demonstrate the benefit of research in general than of any particular proposed research project.¹¹⁸ For example, the benefits to society of antibiotics, or of a particular antibiotic, are quite large. This does not result in any study of antibiotics presumptively satisfying the requirement that it be likely to produce a benefit merely because the focus is on this generally beneficial substance. At the same time, “some well-conceived research projects have yielded no valuable drugs”; nevertheless, pursuing them was not unethical.¹¹⁹ “When speaking of a particular research proposal one can only discuss potential or hoped for benefit.”¹²⁰ This is a complex undertaking that requires an examination of the details of the study being proposed, divorced from the generalized notion of societal benefit of the pharmaceutical industry generally.¹²¹ Dr. Levine also includes possible negative findings, those that show a failure of efficacy, as potentially counting towards the assessment of the benefit of a proposed study.¹²² It seems accurate to interpret this language as asserting that a reference to a broad, historical, achieved benefit is not appropriate in a risk-benefit analysis performed by an IRB.

Dr. Levine’s report gives detailed consideration to what an IRB is meant to consider when assessing benefit in the risk-benefit analy-

¹¹⁴ The other three are basic research using human subjects, basic research not using human subjects, and social research. Levine, *Assessment*, *supra* note 105.

¹¹⁵ *Id.*, at 2-32. Dr. Levine considers how economic benefit can be considered and uses it in a benefit equation as those economic benefits that come from a reduction of cost in the treatment of the specific illness whose treatment is being tested. *Id.*

¹¹⁶ *Id.* at 2-32 to 2-33.

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ *Id.*

¹²⁰ Levine, *supra* note 105, at 2-33.

¹²¹ *Id.* at 2-36 to 2-44.

¹²² *Id.* “[R]esearch that proves with certainty that a specific . . . maneuver is not valuable . . . safe . . . [or] effective [] also benefits society.” *Id.* at 2-33.

sis.¹²³ The IRB must identify the benefit that is hoped for at that specific time, from that specific project.¹²⁴ This “hoped-for” benefit needs to be described to an IRB in the context of the expected benefit to the subject and to society.¹²⁵ It is meant to be described with some detailed analysis of probability and magnitude, and the analysis should consider expected duration of all aspects of the benefit.¹²⁶ Duration of a benefit is often connected to the plans of the study sponsor and can have an important impact on the calculus of both individual and societal benefits.¹²⁷ An example of a duration issue given in the report is where a drug is proven to have a beneficial modality in a small number of subjects, yet the sponsor decides to discontinue producing it.¹²⁸ In this hypothetical, the sponsor’s decision is driven by the fact that the study has failed to show the drug is beneficial to a sufficient number of individuals to make its further development worth the sponsor’s continued investment.¹²⁹

Dr. Levine’s report appears to call for a complex and nuanced assessment of the benefit of a particular study. The report also explicitly states that the possible benefit from that study is potentially reduced based on what the study sponsor may do in the future with the fruits of the study.¹³⁰ This analysis has critical implications for the effect of current behaviors of the drug industry on IRB considerations.

In another report prepared for the Commission in anticipation of the Belmont Report, H. Tristram Engelhardt outlines what he believes are the basic ethical principles that are implicated concerning human experimentation.¹³¹ He arrives at three principles.¹³² The first is respect for persons as free moral agents.¹³³ The second is a concern to support the best interests of human subjects in research.¹³⁴ The

¹²³ *Id.* at 2-44 to 2-54.

¹²⁴ *Id.*

¹²⁵ *Id.*

¹²⁶ Levine, *supra* note 105, at 2-50.

¹²⁷ *Id.*

¹²⁸ *Id.* at 2-51.

¹²⁹ *Id.*

¹³⁰ *See id.*

¹³¹ See H. Tristram Engelhardt, Jr., *Basic Ethical Principles in the Conduct of Biomedical and Behavioral Research Involving Human Subjects*, in BELMONT REPORT APPENDIX I, *supra* note 26, at 8-1 to 8-2.

¹³² *Id.* at 8-8.

¹³³ *Id.* This is not surprising. The backdrop of historical events where this particular principle was violated has consistently made this the most prominent issue discussed in this area.

¹³⁴ *Id.*

third, and most relevant here, is an interest in assuring that the use of human subjects in experimentation will, in sum, redound to the benefit of society.¹³⁵ He expands on this third moral principle by stating that one should have concern to maximize the benefits accruable to society from research involving human subjects.¹³⁶

The conflict Engelhardt perceives with these three principles is to some degree insoluble. We are putting individuals at risk for society's general benefit, and so we are using them. How do we justify this? Importantly, we make sure their choices are voluntary and informed, as protected by his first principle.¹³⁷ Equally important, as reflected in his three principles, is to make sure their sacrifice is not for a frivolous purpose. The identified beneficiary is society, and part of the job in policing research is to ensure that society's interest is not squandered.

Philosopher Maurice Natanson's paper for the Commission, *A Philosophical Perspective on the Assessment of Risk-Benefit Criteria in Connection with Research Involving Human Subjects*,¹³⁸ like Engelhardt's report, shows who the contemplated beneficiaries are in this risk-benefit calculation. "Ultimately, society itself is said to benefit from the advance of medical knowledge . . . [one cannot] reduce the meaning of benefit to patient-benefit alone."¹³⁹ The issue in Natanson's paper is balancing the needs of society and the rights of individuals.¹⁴⁰ In assessing what individuals are being asked to undergo, he recognizes that even minimal or acceptable risk may mean severe suffering or death to some.¹⁴¹ He then worries, as "it is not easy to reconcile medical intervention done with a bare minimum of ethicality with serving the good of society. It would seem that such intervention has only a limited connection with the welfare of the patient-subject but a powerful relationship to the abstract development of medical knowledge."¹⁴²

¹³⁵ *Id.*

¹³⁶ *Id.* at 8-5.

¹³⁷ Natanson, *supra* note 33, at 8-9.

¹³⁸ *Id.* at 21-1.

¹³⁹ *Id.* at 21-12.

¹⁴⁰ *Id.* at 21-15.

¹⁴¹ *Id.* at 21-12. There was a recent reminder of the meaning of an acceptable degree of risk in the Phase I trial conducted in England in the spring of 2006, where six healthy young men were given a drug known as TGN1412 and quickly went into multiple organ failure. Ganesh Suntharalingam et al., *Cytokine Storm in a Phase I Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 NEW ENG. J. MED. 1018, 1018-19 (2006). At the time this Article was printed, their prognosis was unknown, though it appeared grim; signs of rapidly developing cancers were detected in two of the trial subjects since the study took place. *Id.* at 1022.

¹⁴² Natanson, *supra* note 33, at 21-18.

Clearly, from his perspective, there are two actors in this analysis—society in general and the individual research subject.

In an essay prepared by Dr. Lawrence Raisz, we also see this presumed limitation on the beneficiaries to be considered.¹⁴³ As he discusses the proper components of informed consent, he details what information should be made clear to a possible research subject who is not going to experience any physical benefit from participation in the study.¹⁴⁴ “It does seem appropriate to tell the volunteers in a study what the expected benefits to the other members of society might be . . . [, as] any volunteer should have the privilege of knowing why they are being asked to take a risk.”¹⁴⁵ Note that this implies, in the inverse, that the only possible reason for being asked to take a risk, such as one contemplated here, is a potential benefit to society, and it is the delineation of this benefit that proper informed consent requires. The choice presumably faced by the individual is whether or not the potential benefit is enough, in his or her own mind, for him or her to undergo the risk.

3. Interviews with Contributors to the Belmont Report

In 2004, the Office for Human Research Protections (OHRP) conducted a series of interviews with the participants in the original Commission of the 1970s.¹⁴⁶ In the interviews, some of the participants alluded to the concept of benefit, or beneficence, and to society as the proper beneficiary.¹⁴⁷ The interview with Tom Beauchamp, who worked for the Commission as a staff philosopher and was the principal author of the Belmont Report, is an example.¹⁴⁸ He stated that, in his opinion, the biggest failure in the IRB system is that people do not adequately understand the implications of the rules and guidelines. “Being a research subject is a burden The whole point of research is to protect people against injury and disease and the like . . . so it becomes a balancing consideration.”¹⁴⁹ To refer to the whole point of research as protecting people, as he does here, is

¹⁴³ Lawrence C. Raisz, *Essay on Some Problems of Risk-Benefit Analysis in Clinical Pharmacology*, in BELMONT REPORT APPENDIX II, *supra* note 33, at 22-1.

¹⁴⁴ *Id.*

¹⁴⁵ *Id.*

¹⁴⁶ HHS Office for Human Research Protections, Oral History Archive, http://www.hhs.gov/ohrp/Belmont_ReportArchive.html#histArchive2 (last visited Jan. 25, 2008).

¹⁴⁷ See Beauchamp Interview, *supra* note 43.

¹⁴⁸ *Id.*

¹⁴⁹ *Id.*

to make it clear that the only acceptable end point of research is that protection.

Michael Yesley's interview brought up two relevant issues.¹⁵⁰ The first was his concern that human subject protections have become both over- and under-regulated, as the regulations have tended to focus on the "minutiae of regulatory compliance" and missed the broad goal they were meant to achieve.¹⁵¹ One of his primary concerns was with the international research currently being conducted.¹⁵² This concern has bearing on the concept of society as the beneficiary of research and relates to outsourcing the risk of research.¹⁵³ Along with other challenges to international research, such concerns often focus on the community where the research is occurring, and how, in many cases, that population is not likely to ever benefit from the medicines or devices that are being tested.¹⁵⁴ This is particularly true of a population that does not suffer from a problem or one that has a limited or no medical infrastructure with which to provide any required care of the type being tested.

The concern among those studying the ethics of international research from this perspective is that there may be a requirement under the justice principle of the Belmont Report and other bioethical structures that use a principle-based analysis that "society" be read to include the more immediate community where research is being conducted as a likely beneficiary.¹⁵⁵ It is potentially too exploitative to have the human subjects on one side undertaking the inherent risks, and then to have a community far removed from them as the probable recipient of the hoped-for benefit.¹⁵⁶ This adds a nuance to the concept of "benefit to society" discussed here. In effect, the society that stands as the beneficiary should be drawn narrowly enough to satisfy the requirements of justice as described in the Belmont Report and as embodied in the Common Rule. Analyzing this from a justice perspective reinforces what a benefit is in this context: something concrete a society can hope to actually have.

¹⁵⁰ Interview by Patricia C. El-Hinnawy, Office for Human Research Protections, HHS, with Michael Yesley, J.D., Manager, Ethic, Legal and Social Implications, Human Genome Project, in Santa Fe, N.M. (Aug. 19, 2004), *available at* http://www.hhs.gov/ohrp/Belmont_ReportArchive.html#histArchive2 [hereinafter Yesley Interview].

¹⁵¹ *Id.*

¹⁵² *Id.*

¹⁵³ *Id.*

¹⁵⁴ *Id.*

¹⁵⁵ *Id.*

¹⁵⁶ Yesley Interview, *supra* note 150.

Norman Fost, interviewed in May 2004, spoke of science and the advancement of knowledge, using the concepts apparently interchangeably in discussing the conflict between the subject and the goal of research.¹⁵⁷ When you are doing research,

[y]ou're not doing it for the interest of the subject, you're asking him or her to sacrifice their interests in the name of science. . . . [I]n the research setting, the interest of the subject is never the primary interest. The primary interest is always to advance knowledge. And the question is how to do that in a way that's ethically acceptable.¹⁵⁸

Albert Jonsen felt that beneficence is defined "quite narrowly" in the Belmont Report.¹⁵⁹ "We talk about 'beneficence' in a relatively general way as bringing some benefit to the subject . . . and [a] benefit to society, but then we immediately make the practical application of risk-benefit assessment."¹⁶⁰ In his opinion, beneficence as used in the Belmont Report could be "susceptible of broader interpretation."¹⁶¹

Jonsen felt that in this current decade conflicts of interest are emerging as a critical problem related to beneficence:

[N]ow the question, I think, has to do with researcher's affiliation with commercial enterprises and with the opportunity of the clinician to get patents—or the researcher to get patents to profit by the work that he or she is doing. And at the time the Commission was working, researchers rarely even thought of profiting from anything that they might produce. That's what they did, and it became a public good.¹⁶²

He then went on to say this problem is "a matter of beneficence, because one of the problems in conflict of interest is what benefit is motivating this work, and who gets that benefit."¹⁶³

Robert Cooke, another interviewee, when asked which principle was most important, said:

¹⁵⁷ Fost Interview, *supra* note 43.

¹⁵⁸ *Id.*

¹⁵⁹ Interview by Bernard A. Schwetz, D.V.M., Ph.D., Director, Office for Human Research Protections, HHS, with Albert R. Jonsen, Ph.D., Professor of Medical Ethics, Univ. of Cal. at San Francisco Med. School, in San Francisco, Cal. (May 14, 2004), available at <http://www.hhs.gov/ohrp/BelmontReportArchive.html#histArchive2> [hereinafter Jonsen Interview].

¹⁶⁰ *Id.*

¹⁶¹ *Id.*

¹⁶² *See id.*; see also Walters Interview, *supra* note 43.

¹⁶³ Jonsen Interview, *supra* note 159. He also believes conflicts of interest implicate the other two principles, as well. *Id.*

Well, as a researcher, you'd like to think that beneficence would be the most important; because why do you do research unless you're trying to help somebody out? But from my standpoint the greatest protection comes from respect for persons. It really means that you value someone as a human being, and not just as a subject of research.¹⁶⁴

From this and other quotes, it becomes clear that benefit to society was already an important part of research ethics before the Belmont Report. The Belmont Report made benefit to society explicitly part of the regulatory policy for the United States government. It did this in the context of adding a requirement for a rigorous assessment of benefit in a risk-benefit analysis.¹⁶⁵ The discussion of respect for persons really added something new, especially as it was viewed as almost in competition with the desire for a benefit for society. One has to balance the two to achieve ethically conducted research, but both must be there in adequate quantities and qualities. Each is necessary but neither, alone, is sufficient. Cooke also expressed his own worry about beneficence in the modern era, stating “[t]he individual investigator, without any kind of review would be a disaster[;] they may have great financial benefit and at times, maybe benefit to humanity isn't the primary consideration.”¹⁶⁶

III. THE CHANGING CULTURE OF MEDICAL RESEARCH—THE DECLINE OF BENEFICENCE

As shown in Part II, when the Belmont Report was written, beneficence was assumed to be a primary motivator of researchers and its presence is now a necessary regulatory component of an acceptable research proposal. As this Part will demonstrate, a number of legal and financial changes to the environment in which research occurs have altered the motivations and conduct of researchers, such that the financial goals of drug companies are now the primary value being served in much of the research being conducted, and the relevant requirement of beneficence, to generate a benefit for humankind, is at risk. As discussed in Part II, the regulations now in place governing research on human beings actually have the power to make sufficient demands on research to rectify this problem in all

¹⁶⁴ Interview by Bernard A. Schwetz, D.V.M., Ph.D., Director, Office for Human Research Protections, HHS, with Robert E. Cooke, Chairman, Department of Pediatrics, Johns Hopkins School of Medicine, in Baltimore, Md. (May 15, 2004) *available at* <http://www.hhs.gov/ohrp/BelmontReportArchive.html#histArchive2>.

¹⁶⁵ *Id.*

¹⁶⁶ *Id.*

studies that are required to comply with the federal regulations drafted in connection with the Belmont Report. However, the ramifications of the cultural shift described here have not been properly recognized or responded to by the research community in the context of this regulatory power. Commentators as varied as Norman Dorsen and LeRoy Walters have noted the ethical ramifications of a failure to satisfy the beneficence requirement, yet never made the final, necessary connection to the regulations that can affect change.¹⁶⁷

We have moved from a world where the search for answers was an assumed primary motivator of research to one where a prudent person understands that the suppression and manipulation of data that occurred with SSRI safety and efficacy data can easily happen with other drugs or medical devices. If this broad cultural shift had not occurred, one could argue that cases such as those described in Part IV, below, were occasional problems of a type that is not new or particularly remarkable and which require no broad reassessment of how studies should be assessed.¹⁶⁸ Given the cultural shift described here, however, it is clear we can no longer focus primarily on acceptable risks and informed consent. The benefit requirement for acceptable studies appears to be failing. In response to this, a concerted effort to identify and judge the potential benefit of a given study, such as is called for by Dr. Levine, with particular attention paid to a sponsor's ability and motivation to distort data, needs to occur in any study that is placed before an IRB.¹⁶⁹

In past centuries, those under his power often justifiably feared the medical researcher.¹⁷⁰ The researcher characteristically had a robust ego and a sense of being in a battle against disease for the betterment of humanity.¹⁷¹ Fueled by this sense of mission, a researcher

¹⁶⁷ See Walters Interview, *supra* note 43; see also INTERIM DORSEN REPORT, *supra* note 14, at D-39.

¹⁶⁸ See *infra* Part IV. For example, drug companies have been successfully sued by consumers for withholding and falsifying safety and efficacy data as early as the 1950s. Note the cases about the drug MER/29, where side effects such as cataracts, baldness, severe skin reactions, and sexual depression were not properly disclosed by the manufacturer. See PAPPWORTH, *supra* note 71, at 175 (quoting MORTON MINTZ, *THE THERAPEUTIC NIGHTMARE* (1971)).

¹⁶⁹ Levine, *supra* note 26. How such an assessment should occur is a complex question and, in the past, would likely have been the subject of a new commission's analysis. However, given the politicizing of the Bioethics Commission enterprise in recent years, this Article hesitates to make such a recommendation. See Madison Powers, *Bioethics as Politics: The Limits of Moral Expertise*, 15 KENNEDY INST. ETHICS J. 305 (2005).

¹⁷⁰ PAPPWORTH, *supra* note 71.

¹⁷¹ See H.K. BEECHER, *CLINICAL INVESTIGATION: MEDICAL, ETHICAL, AND MORAL ASPECTS* (1963) ("Any classification of human experimentation as 'for the good of

could forgive himself for maltreatment of those who passed through his hands, and researchers often felt justified in imposing a level of risk on their subjects that would be incomprehensibly high today.¹⁷² Coupled with the desire to learn something new was a cultural focus on publication and the corresponding respect of peers in the same fields.¹⁷³ Dr. Levine, described earlier as a participant in the reports prepared for the Belmont Report, and one of the original and pre-eminent scholars on clinical research ethics, noted in 1986 that “[m]ost scientists [were, at that time,] under great pressure to conduct research and publish it. Publication [was] the sole route to professional success, to salary increases, to tenure, to promotion. Scientists, therefore, regard[ed] the terms and conditions of publication as matters of considerable importance.”¹⁷⁴

Patients were often viewed as tools or raw material by these researchers.¹⁷⁵ This problem is what the concept of a subject’s self-determination or autonomy was meant to address, as described in Part B of the Belmont Report.¹⁷⁶ The requirement of truly informed consent, including a serious attempt by the researcher to explain the risks to be faced by the subject and with the subject holding enough

society’ is to be viewed with distaste, even alarm. Undoubtedly, all sound work has this as its ultimate aim, but such high-flown expressions are not necessary, and have been used within living memory as cover for outrageous ends.” (quoted in PAPPWORTH, *supra* note 71, at 28)).

¹⁷² A highly regarded scientist, in a speech before an international audience in 1961 on what made a brilliant researcher, said that “[t]he desire to alleviate suffering is of small value in research—such a person should be advised to work for charity. Research wants egoists, damned egoists, who seek their own pleasure and satisfaction, but find it in solving the puzzles of nature.” PAPPWORTH, *supra* note 71, at 11 (quoting Dr. Albert Szent-Gyorgi).

¹⁷³ See Eisenberg, *supra* note 69, at 181.

¹⁷⁴ See ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 28 n.74 (2d ed. 1986) (quoting Y. Brackbill & A.E. Hellegers, *Ethics and Editors*, HASTINGS CTR. REPORT 174 (1980)); see also Norman W. Storer, *The Internationality of Science and the Nationality of Scientists* (stating that in 1970, scientists were centrally motivated by credit, recognition, and celebration by other scientists), in EXPERIMENTATION WITH HUMAN BEINGS 118 (Jay Katz ed., 1972) [hereinafter EXPERIMENTATION]; Derek J. de Solla Price, *Science Since Babylon*, in EXPERIMENTATION, *supra*, at 116 (researchers “seek an immortal brainchild in order to perpetuate themselves,” and they refer fondly to a time when it was possible “for men to fashion bricks of science engraved with their own names”).

¹⁷⁵ See ROBERT VEATCH, THE PATIENT AS PARTNER: A THEORY OF HUMAN-EXPERIMENTATION ETHICS 208 (1987). Consider the example of William Beaumont, whose studies on the gastric physiology of his subject, Alexis St. Martin, were made possible by forcing St. Martin to agree to a lifetime of indentured servitude to Dr. Beaumont in exchange for Dr. Beaumont agreeing to treat St. Martin’s life-threatening gunshot wound. *Id.*

¹⁷⁶ Belmont Report, *supra* note 8, at 23,193.

power in the relationship to refuse participation if so inclined, is the primary expression of this notion of autonomy.¹⁷⁷

The ideal, reflected in the language of the Belmont Report and the subsequent federal regulations, was to have a balance between these two aspects of research, the complex and driven desire for a better world held by researchers and the protection of the subjects of their research. The regulatory and ethical communities have assumed up to this point that it was this presumed societal benefit that was in need of being controlled and kept in balance by vigorously protecting the autonomy of the subjects. The struggle has been perceived as being over the conflict between the search for knowledge and the subjects' individual rights.¹⁷⁸ However, beneficence can no longer be assumed to be a motivator of researchers. In fact, it is probably safe to assume that beneficence is now the most endangered essential element of a great deal of medical research.

In 1973, the United States Senate held a series of hearings about human experimentation.¹⁷⁹ The purpose of the hearings was to investigate allegations of abuse of subjects, and the hearings led directly to the creation of the Commission that prepared the Belmont Report.¹⁸⁰ Many of the prominent figures in research at that time testified at those hearings and their testimony, in retrospect, gave strong hints as to the cultural and legal changes the field was on the cusp of experiencing. For example, Dr. Watson, a noted professor of molecular biology at Harvard University, spoke about a fiscal crisis in academic sciences due to government cuts in funding of basic science research in academic institutions.¹⁸¹ He and others holding similar positions in academia spoke of institutions beginning to look for funding from

¹⁷⁷ See FADEN & BEAUCHAMP, *supra* note 69, with a particular focus on Chapter 7, The Concept of Autonomy, and Chapter 9, Understanding for a discussion of these normative concepts.

¹⁷⁸ "In the end we have to accept the fact that some limits do exist to the search for knowledge." Paul A. Freund, *Problems in Human Experimentation*, 273 NEW ENG. J. MED. 687 (1965), *quoted in* PAPPWORTH, *supra* note 71, at 7 (1967); see BIOETHICS COMMISSION, *supra* note 36, at 3 (noting that researchers have a serious obligation to science that might conflict with their attention to the interests of participants).

¹⁷⁹ See *Senate Hearings*, *supra* note 7.

¹⁸⁰ See *supra* Part II.

¹⁸¹ Basic science refers to research that is focused on natural processes rather than on marketable products. See, e.g., Univ. of S. Cal., Norris Comprehensive Cancer Center, Glossary, <http://uscnorriscancer.usc.edu/health/uscnorris/glossary/index.html#b> (last visited March 2, 2007). It is often a necessary component of the creation of new products but occurs far earlier, often when commercial implications are unclear. *Id.*

different sources, with an accompanying shift in the focus of the research.¹⁸²

To be very clear, the cultural shift described here has been away from a research enterprise where success was measured by peer-reviewed publication in prestigious journals, by achieving tenure and the respect of peers, and, perhaps, by the ability to generate grant money for one's institution. Prior to this shift, most research occurred in an academic setting under the control of the researchers.¹⁸³ Furthermore, the accepted values of the scientific community at that time included the sharing of information so that it could be challenged, criticized and eventually further developed by subsequent research.¹⁸⁴ The current climate is different. A deep conflict exists between the regulatory structure we have in place governing the use of human research subjects and the regulatory structure we have in place governing the manufacture and sale of pharmaceuticals and medical devices.¹⁸⁵ The ultimate goal of the regulatory structure in place for drug companies is to improve the common good, and in furtherance of this goal we have created a regulatory structure that gives drug companies rights to control much or all of the data they generate using human research subjects. Even when the data is directly applicable to safety and effectiveness of a given drug and is submitted to a federal agency, the government pledges to keep it secret.¹⁸⁶

The idea underlying this secrecy and control is that making drug development profitable will encourage more and better drug development and so that we, as a society, will experience a net gain in well-

¹⁸² See *Senate Hearings*, *supra* note 7, at 511–12 (testimony of James D. Watson, Professor of Molecular Biology, Harvard University).

¹⁸³ See, e.g., BARRY, *supra* note 73 (giving a detailed account of the medical establishment in the early 1900s).

¹⁸⁴ See, e.g., Norman W. Storer, *The Internationality of Science and the Nationality of Scientists* (asserting that scientific knowledge requires an opportunity for competent response and that availability to other scientists is an “intrinsic value” of scientific research), in EXPERIMENTATION, *supra* note 174, at 118; see also Karl W. Deutsch, *Scientific and Humanistic Knowledge in the Growth of Civilization* (“Science itself depends for its life on the acceptance of certain fundamental values, such as the value of curiosity and learning, the value of truth, the value of sharing knowledge with others [and] the value of respect for facts . . .”), in EXPERIMENTATION, *supra* note 174, at 121.

¹⁸⁵ See Einer R. Elhauge, *Can Health Law Become a Coherent Field of Law?*, 41 WAKE FOREST L. REV. 365 (2006) (discussing theoretical conflicts within the regulations that govern health law).

¹⁸⁶ Under the scheme that regulates drug companies, the FDA has been highly protective of pharmaceutical company control of this data. See generally *Pub. Citizen Health Research Group v. FDA*, 997 F.Supp. 56 (D.D.C. 1998); *Pub. Citizen Health Research Group v. FDA*, 539 F.Supp. 1320 (D.D.C. 1982).

being. The ability to keep information secret will, in theory, increase profitability. If profitability is the driver of progress, this furthers the goal of society that a net “good” will occur. One can, and perhaps one should, debate the soundness of this policy and its underlying assumptions. This Article does not do so. Here, the policy of utilizing profitability to encourage drug development is utilized as a legal and historical description of how we function and the choices we have made, rather than presenting it as successful or unsuccessful, coherent or deeply flawed.

The justification of a net societal gain is inapplicable within the framework of the regulations of human subject research because of the beneficence requirement. What we end up with are dueling justifications, and hence the resulting conflicting regulatory structures. When testing pharmaceuticals, we must satisfy all necessary requirements of human subject research, one of which is that the particular project must be calculated to generate knowledge for the good of mankind.¹⁸⁷ And yet our drug regulatory structure allows this very same knowledge to be kept secret, to be manipulated and to be distorted in its presentation to society, a direct affront to this first requirement of benefit.

To state it succinctly, the good of society, writ broadly as it is in the justification for our drug regulatory structure, cannot be used to justify the suppression of data generated by using human research subjects. This is because one cannot use a broad societal benefit of an entire industry to satisfy the legal requirement of a potential benefit within the human research subject analysis.

In concrete terms, consider the following example: DrugCo is a drug company. It is allowed to consider using Joe Smith as a research subject to try a new drug if what it learns from Mr. Smith is likely to help us all in the future (thus satisfying the benefit requirement). DrugCo uses him, finds out something important and yet suppresses the very knowledge the researchers have learned, the hopes of which justified using Mr. Smith in the first place, thus depriving other researchers or physicians from knowing the results that were discovered. In this scenario something violative of human research ethics and regulations has occurred. A necessary element of ethical research on human beings has been compromised, and so the research does not satisfy the relevant regulations embodied in the Belmont Report.¹⁸⁸

¹⁸⁷ Belmont Report, *supra* note 8, at 23,194.

¹⁸⁸ *Id.*

Pharmaceutical companies now exercise control over how research is conducted in academic institutions to a degree that was unheard of in the 1970s,¹⁸⁹ effectively “load[ing] the dice to make sure their drugs look good.”¹⁹⁰ Trials performed or funded by drug companies to prove the safety and efficacy of their products “can be rigged in a dozen ways, and it happens all the time” in order to make the results appear more positive than they might otherwise seem.¹⁹¹ Beginning in the 1980s, academic researchers began to see themselves as partners of the drug industry, and a measurable pro-industry bias began to appear in published medical research.¹⁹² The decision as to whether to publish data or conclusions derived from studies is often controlled by the drug companies.¹⁹³ Researchers do not necessarily have to internalize a pro-industry bias, as they are often bound by contracts that give the sponsor of the study the right to control publication and all other forms of dissemination of the data derived from the study.¹⁹⁴ As will be illustrated by the SSRI case study in Part IV, this lack of control over the findings of a study can present significant ethical problems for researchers but, even given those known problems, confidentiality or nondisclosure agreements are still commonplace between the people conducting the research and the sponsoring drug or device manufacturer whose product is being tested.¹⁹⁵ It is particularly enlightening for purposes of describing the current

¹⁸⁹ Krimsky, *supra* note 76, at 70–74.

¹⁹⁰ ANGELL, *supra* note 2, at xviii. Dr. Angell recently stepped down as editor of the *New England Journal of Medicine*, where she worked for thirty years. The *New England Journal of Medicine*, along with the *Lancet* and the *Journal of the American Medical Association*, is one of the most prestigious medical journals in the world today. For an example of a study design that serves to accomplish this type of goal, consider events related to the Pfizer drug trials conducted in Nigeria, where Pfizer was alleged to have used purposefully low doses of the accepted treatment for meningitis in children to enhance the comparative performance of their own drug, which was the subject of the trial. See AURORA PLOMER, *THE LAW AND ETHICS OF MEDICAL RESEARCH: INTERNATIONAL BIOETHICS AND HUMAN RIGHTS* 6 (2005).

¹⁹¹ ANGELL, *supra* note 2, at 95.

¹⁹² See Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 *JAMA* 454, 454–63 (2003) (presenting a statistical analysis of the impact of drug company sponsorship of studies and showing a persistent and large increase in the number of pro-industry outcomes when the studies are financed by drug companies); see also ANGELL, *supra* note 2, at 8.

¹⁹³ Bekelman, *supra* note 192, at 463.

¹⁹⁴ *Id.*

¹⁹⁵ Guidelines promulgated by the International Committee of Medical Journal Editors (ICMJE) forbid these agreements, but a study published in the *New England Journal of Medicine* in October 2002 concluded that these guidelines were not being followed, and articles that fail to follow them were still being published. See K.A. Schulman et al., *A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors*, 347 *N. ENG. J. MED.* 1335, 1339 (2002).

culture that researchers have reported feeling powerless in negotiations with corporate sponsors regarding confidentiality and publication rights even though the contracts may be in direct defiance of journal publication guidelines.¹⁹⁶ The academic institutions where many of these researchers work have ceded levels of control over their studies to the sponsors to a degree that has prompted much criticism.¹⁹⁷ Many of the studies now conducted are done merely to satisfy regulatory requirements, rather than for the purpose of generating information deemed relevant by the researcher, making the desirable outcome easy to determine in advance and its success financially critical to the study sponsor.¹⁹⁸

A series of legislative and regulatory actions have helped create the incentives for the problematic changes described above. The primary piece of legislation responsible for cementing attitudes regarding control of data is FOIA,¹⁹⁹ as interpreted by the FDA to protect safety and efficacy data of drug companies from disclosure to the public.²⁰⁰ The Hatch-Waxman Act of 1984,²⁰¹ the Bayh-Dole Act,²⁰² and the various legislative schemes designed to increase and encourage drug testing on children²⁰³ have also been important.

A. *Freedom of Information Act*

Starting in 1962, the FDA's mandate from Congress required applicants who sought FDA approval for marketing of pharmaceuticals to show both safety and effectiveness of those drugs, which in turn required the use of drug trials on human subjects to generate

¹⁹⁶ *Id.*

¹⁹⁷ ANGELL, *supra* note 2, at 103; *see also* Krinsky, *supra* note 76, at 61.

¹⁹⁸ This raises the question as to whether it is ever appropriate to use human research subjects for purposes of regulatory approval. It may very well turn out to be appropriate, but the work of determining this has not yet been done. This is one of numerous analytical problems that need to be examined in light of a newly invigorated concept of beneficence.

¹⁹⁹ *See* 5 U.S.C. § 552 (2000).

²⁰⁰ The author would like to thank Dr. Ruth Faden for her helpful insights regarding the FOIA that she gave when this article was presented in an earlier form in Baltimore in 2005.

²⁰¹ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.).

²⁰² Bayh-Dole University and Small Business Patent Procedures Act, 35 U.S.C. §§ 200-212 (2000).

²⁰³ *See, e.g.*, Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C.).

the data.²⁰⁴ To support drug applications, drug companies submit large amounts of data to the FDA consisting of “thousands of pages of proprietary data, including both trade secrets and confidential business statistical data.”²⁰⁵ Some contend that the FDA “possesses among its routinely collected files some of the most sensitive nonmilitary data in the whole universe of federal records.”²⁰⁶ The drug industry has gone to great lengths to prove the financial competitive value of its safety and efficacy data contained in these files, including sponsoring a number of studies by economists on this topic.²⁰⁷ The financial value of the secrecy of this data has not been seriously questioned by any commentators.

The FDA has consistently committed to keeping this data secret. When FOIA was written in the 1970s, the goal was to increase citizen access to government process.²⁰⁸ There are a series of exceptions to what the government is required to release in response to a FOIA request.²⁰⁹ The exception relevant here is for non-governmental, private sector trade secrets.²¹⁰ The FDA has determined that safety and efficacy data submitted by drug companies in support of applications before the FDA will be protected from disclosure in response to FOIA requests under the trade secret exemption.²¹¹ This decision was the subject of debate when it was made in the early 1970s and is still subject to criticism.²¹² Congress did not specifically include safety and efficacy data in the trade secret exemption, but it has also not acted to change the FDA’s interpretation since it was published in the Federal Register, despite its clear power to do so.

The FDA has received tens of thousands of FOIA requests from corporations for other corporations’ filings.²¹³ “Perhaps 85 percent

²⁰⁴ Toxic Substances Control Act, 15 U.S.C. § 2602(6) (2000); ANGELL, *supra* note 2, at 34.

²⁰⁵ 1 JAMES T. O’REILLY, FEDERAL INFORMATION DISCLOSURE § 14:92 (3d ed. 2000).

²⁰⁶ *Id.*

²⁰⁷ *Id.* For example, *Study to Assess Impacts of Releasing Safety and Effectiveness Data on the Pharmaceutical Industry’s Incentives to Invest in and Conduct Research and Development Programs*, was conducted by Pracon, Inc. and submitted to the FDA in 1978. *Id.* § 14:92 n.6.

²⁰⁸ Freedom of Information Act, 5 U.S.C. § 552(a) (2000).

²⁰⁹ *Id.* § 552(b).

²¹⁰ *Id.* § 552(b)(4).

²¹¹ Public Information, 39 Fed. Reg. 44,602, 44,603 (Dec. 24, 1974) (codified at 21 C.F.R. pts. 1, 2, 4, 8, 10, 90, 121, 135, 146, 312, 314, 431, 601, 720, and 730).

²¹² See, e.g., FINAL DORSEN REPORT, *supra* note 14; Letter from Donald Kennedy, Commissioner, FDA, to Sen. Edward M. Kennedy, U.S. Senate (May 5, 1978) (on file with author) [hereinafter Kennedy Letter].

²¹³ O’REILLY, *supra* note 205, § 14:92.

of the FDA's 30,000 annual FOIA requests at the height of its pre-[I]nternet FOIA period had come from businesses seeking other firms' reports."²¹⁴ The corporate identity of the information seekers strongly supports a conclusion that there is a commercial motivation to these requests. This, coupled with the expressed concerns of the drug manufacturers whose data is at risk, appears to have influenced agency response, taking the position that it needs to protect the financial interests of the industry it regulates from those who would unfairly benefit from others' work product.²¹⁵

It is quite simple to show that FOIA releases of safety and efficacy data can create a commercial harm for drug companies, as has been done in a number of studies. To quote from one of the early studies conducted to assess this potential harm:

[S]afety and efficacy data that is submitted to the FDA as part of a drug approval process serves to confirm or refute scientific hypotheses about class[es] of drugs—a process of information that is extremely valuable for the second or subsequent research firms, which would not need to look at those particular drug entities [to establish the information already proven]. If the data from FDA files were disclosed, there would be a change in the research pattern of [the drug industry,] arguably worsening the burdens on United States pharmaceutical innovation.²¹⁶

In a world committed to creating financial incentives for drug companies, the cost of releasing the data is clear.²¹⁷ It will serve to diminish the financial incentives for drug companies by reducing their profitability.

There are other costs to a drug company from releasing safety and efficacy data. Data is vulnerable to manipulation in how it is presented and in the results it claims to prove. If other scientists are given access to this same data, they can analyze and criticize the tri-

²¹⁴ *Id.* § 10:1.

²¹⁵ See WILLIAM L. CASEY, JR. ET AL., *ENTREPRENEURSHIP, PRODUCTIVITY, AND THE FREEDOM OF INFORMATION ACT* 169 (1983) (giving an in-depth discussion of these concerns from a drug company perspective).

²¹⁶ O'REILLY, *supra* note 205. This analysis is derived from a study referred to as the most comprehensive analysis of the impacts of FOIA on the pharmaceutical industry in the 1980s, when the issue was still being hotly debated. CASEY, JR. ET AL., *supra* note 215.

²¹⁷ For an example of federal court acceptance of the validity of this economic analysis, see *Tri-Bio Laboratories, Inc., v. U.S.*, 836 F.2d 135, 138–41 (3d Cir. 1987) (noting that the economics of drug research tend to discourage full test data dissemination). See also *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1003–04 (1984) (finding that the submitter of test data to the FDA continues to have a reasonable expectation that the law and regulations will continue to protect commercial value of the test data).

als.²¹⁸ Drug companies risk being challenged on the design of the study, the interpretations of study results, and the way negative trial events are recorded. These are the types of costly events that occurred with the FDA's analysis of SSRIs in a pediatric population, as discussed in Part IV. It is not difficult to surmise that the risk to drug company interests increases if other scientists outside of government employment are given access to the same quality of information available to the FDA. Claims of safety or efficacy are vulnerable to being refuted with very little financial or time investment on the part of those who would challenge them. A further risk is that with access to preliminary data, it becomes easier to design studies that compare the effectiveness of one treatment with another, or with a series of others. Drug companies under the current regulatory system do not have to prove that a new product performs better than current products; it merely must be proven to outperform a placebo.²¹⁹ Thus, a new drug that either performs significantly worse than those currently on the market or that can offer only a minor improvement with a significant cost increase can be approved and marketed. Any heightened exposure to comparative cost-benefit data that could influence patients, doctors, and, perhaps more importantly, third-party payers, is a significant financial risk for drug companies.

The analysis of the impact of FDA protection of FOIA disclosures of safety and efficacy data is strikingly different when analyzed from the perspective of human-research-subject regulation. The fundamental requirement of a benefit to be derived from research on human subjects brings with it a need to view structures that materially lessen these benefits with some concern. One clear goal of the human-research-subject regulations in the United States should be to reduce the number of persons who will be subjects of research to the smallest number possible to accomplish the identified benefit, thus reducing the overall risk of any given project and ensuring that no one person is sacrificing himself unnecessarily. A second goal should be to have the benefit be as robust as possible and to have the accomplishments of any given study resonate as broadly as possible in terms of what they add to the knowledge base of humankind. Here, in the FOIA exception debate, we have a series of studies and assertions that proving the FDA's protection of the safety and efficacy data of drug companies will result in repetitive studies being conducted, because one company will not be able to build on what another com-

²¹⁸ Krimsky, *supra* note 76, at 63.

²¹⁹ 21 C.F.R. § 314.126 (2006).

pany has already proven.²²⁰ Thus, this secrecy makes it highly likely that more people will be used as research subjects in situations where their participation is difficult, if not impossible, to justify within the scheme envisioned by the current human research subject regulations. We also know from this same debate that the scientific community as a whole will not move forward as quickly as it could if it were given full access to this information, thus minimizing the potential benefit of the knowledge gained from any given study.

Viewed from the perspective of human research subject ethics and regulations, the drug industry arguments presented in defense of FOIA exemptions show an industry that early on lost sight of its obligations as a participant in, and beneficiary of, research on human subjects. It also shows a deep and persistent conflict between protecting competitive advantage and maximizing societal benefit.²²¹

The FDA, responding to the concerns of the drug companies and recognizing the financial value of the information it received from them, agreed to extend trade secret protection to safety and efficacy data.²²² However, that agreement did not come from a unified FDA. While the regulatory ramifications of a reduction in benefit derived from a study were not perceived by any of the commentators in terms of human research subject regulations, the actual reduction of societal benefit itself was a cause of tremendous concern.²²³ A letter written by Dr. Donald Kennedy while he was the Commissioner of the FDA in 1978 shows his concerns regarding the impact of secrecy in this area.²²⁴ The letter, written to United States Senator Edward Kennedy, argues for the release of safety and effectiveness data submitted to it by drug companies.²²⁵ He takes the position that government decisions should, whenever possible, be based on publicly available

²²⁰ O'REILLY, *supra* note 205, § 14:92 n.6.

²²¹ The argument that data suppression minimizes societal benefit is fairly straightforward as regards the benefit that can accrue from an individual research project, but the arguments presented in this Article about the impact of suppression on the scientific community as a whole tend to support the argument that benefit, across the society, is being negatively impacted by this phenomenon.

²²² See O'REILLY, *supra* note 205.

²²³ This is evidenced by several documents. See FINAL DORSEN REPORT, *supra* note 151; McGarity & Shapiro, *supra* note 13; Kennedy Letter, *supra* note 212.

²²⁴ Kennedy Letter, *supra* note 212. Donald Kennedy has a Ph.D. in biology. In light of this Article's assertion that a change in culture has led to a reduction of data dissemination, it is interesting to read the perspective of Dr. Kennedy, a scientist who was trained at Harvard in the earlier culture, on the risks he perceived from this FDA policy.

²²⁵ *Id.*

information.²²⁶ More relevant to this point, he refers to peer review and the publication of scientific information as the system “at the heart of the scientific process . . . a fundamental requirement of science that hypotheses and conclusions of one scientist be subjected to public examination, criticism, and debate by other scientists before their validity is accepted.”²²⁷ Furthermore, he wrote, “secrecy is antithetical to good science, . . . [and] release of safety and efficacy data would promote the spread and growth of scientific knowledge.”²²⁸

Dr. Kennedy quotes from a presidential Scientific Advisory Committee Report from 1973, written by a committee appointed by the Nixon administration, stating that “[n]ot allowing the academic research community access to the retained results of safety testing is believed to have adversely affected progress in the understanding of the presence or absence of unfortunate effects of chemicals on people.”²²⁹ He then writes, “[i]n assessing the impact of release of the data on drug innovation, it is important to consider that release of data would increase general knowledge, reduce error and waste, and thereby reduce the cost and increase the efficiency of drug research.”²³⁰ Given that the

FDA is one of the largest repositories of drug information in the world . . . on matters such as pharmacokinetics, estimation of human risks from animal studies, potential new uses for older drugs, and techniques to reduce human risk and increase the scientific validity of drug testing, information of immense value to humanity may be locked away in the agency’s files Release of safety and effectiveness data would also encourage the improved design and more careful execution of studies.²³¹

Furthermore, Dr. Kennedy remarked that “[t]he opportunity for review by scientists outside the agency will provide a valuable additional incentive for drug sponsors to produce the best and most reliable data.”²³²

In 1977, Norman Dorsen headed a government-appointed panel on drug regulations²³³ that commented on the possible impact of this type of secrecy. Dr. Kennedy refers to that panel’s conclusions in his letter, stating that he has ethical concerns about “routinely treating as

²²⁶ *Id.*

²²⁷ *Id.*

²²⁸ *Id.*; see also Krimsky, *supra* note 76.

²²⁹ Kennedy Letter, *supra* note 212.

²³⁰ *Id.*

²³¹ *Id.*

²³² *Id.*

²³³ See FINAL DORSEN REPORT, *supra* note 14.

'proprietary' research involving human subjects," at least partially due to concerns that this secrecy may diminish the subjects' contributions to humanity.²³⁴

Both Dr. Kennedy and Mr. Dorsen recognized an ethical problem in keeping safety and efficacy data secret, but neither of them saw the direct relationship between this problem and the regulatory requirements of research on human subjects.²³⁵ Under the Belmont Report, there is a legal mandate that this "contribution to humanity" be respected and not unduly minimized.²³⁶ In effect, it is possible for the suppression or manipulation of data derived from these studies to undermine the benefits of the study initially presented to the IRB for approval under the guise of prospectively contributing to humankind. The drug companies lost sight of the underlying ethical balance between benefit and respect for persons that led to the U.S. regulations, instead focusing entirely on the impact of any data disclosure on their financial incentives to conduct business. An example of this drug industry stance is also in Dr. Kennedy's letter.²³⁷ Prior to the creation of the relatively recent regulatory structure that governs generic drugs,²³⁸ drug companies holding the original patents to substances were faced with the fact that generic drug manufacturers could profit from their own work on these substances once the original patent expired. Before Dr. Kennedy wrote his letter, drug company representatives testified before Congress on this issue. Robert Clark, a drug company industry representative, testified that he wanted to require generic drug manufacturers to repeat all of the safety and efficacy studies of the original patent holder, with the goal of repetitive testing creating a barrier to the generic drug companies' respective entries into the marketplace.²³⁹ Dr. Kennedy challenged this notion of repetitive testing for purposes of creating a barrier to entry in his letter to Senator Kennedy as ethically unacceptable, but he did not go into detail as to why this is so.²⁴⁰ This would be ethically

²³⁴ Kennedy Letter, *supra* note 212.

²³⁵ This may be based on the timing of the FOIA debate, which occurred soon after the drafting of the Belmont Report and early in the development of the regulations. The ethical concerns were recognized, but it was perhaps not yet clear as to their legal status.

²³⁶ See Belmont Report, *supra* note 8; see also *supra* Part II.

²³⁷ Kennedy letter, *supra* note 212.

²³⁸ See, e.g., Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.).

²³⁹ See *Senate Hearings*, *supra* note 7.

²⁴⁰ See Kennedy Letter, *supra* note 212.

questionable on numerous levels. The human beings who volunteered for the first tests would suffer a diminishment of the benefit for which they sacrificed. As for new subjects, it exposes them to the risks of being a test subject with no hope for the possibility of gain for humankind; a subject of a test with no scientific rationale to justify it at all. The entire justification of using the second round of human subjects is to protect economic incentives for drug companies. This is unacceptable under the federal regulations for human research subjects detailed above.²⁴¹ What is interesting is how this statement of the drug company executive is made with no apparent awareness of the implications for human research subjects, a blindness that continues to this day.

The Dorsen Panel was created on February 21, 1975 to assess drug regulations and the functioning of the FDA.²⁴² It was created by Caspar Weinberger, then the Secretary of HEW, in response to Senate subcommittee hearings which had raised questions about the FDA's process of reviewing new drugs.²⁴³

The Dorsen Panel reported to the Secretary of HEW and had no powers or responsibilities other than preparing its reports.²⁴⁴ Among other issues, it examined whether FOIA should protect safety and efficacy data submitted to the FDA as trade secrets and discussed this in both an interim report issued in November 1976 and the final panel report issued in May 1977.²⁴⁵ The panel's reports were quite critical of suppression of data, but also failed to connect the two relevant regulatory schemes—that of the FDA's drug approval process and the other used for the regulation of research on human subjects. The interim report states that “[c]urrent trade secrets policy conflicts with fundamental moral principles that human beings not be subjected to wasteful new drug testing and that scientific knowledge collected at public risk be publicly disclosed.”²⁴⁶ Furthermore:

²⁴¹ See *supra* Part II.

²⁴² This panel is quite similar to the more recent Institute of Medicine Panel that issued its report on the FDA in September of 2006. See COMMITTEE ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYSTEM, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC (Alina Baciu et al. eds., 2007), available at http://www.nap.edu/catalog.php?record_id=11750.

²⁴³ FINAL DORSEN REPORT, *supra* note 14.

²⁴⁴ *Id.* Contrasting this with the power of the Commission provides further evidence of the unusual scope of the Commission's brief.

²⁴⁵ Together, the different interim reports and the final report are referred to as the Dorsen Report and were cited to in many of the discussions in the late 1970s and 1980s about the role of the FDA in general. See generally INTERIM DORSEN REPORT, *supra* note 14; FINAL DORSEN REPORT, *supra* note 14.

²⁴⁶ INTERIM DORSEN REPORT, *supra* note 14, at D1.

[F]ailure to release . . . [safety and effectiveness] data tends to encourage wasteful and unjustifiable duplicative testing in humans. The failure also interferes with the free exchange of scientific knowledge The sole justification for this trade secrets policy is that it may protect the market position, and thus the incentive to innovate, of companies that invest in research and development of new drugs.²⁴⁷

The Dorsen Panel examined the policy debate that took place in Congress prior to the passage of FOIA.²⁴⁸ The debate in Congress over trade secret protection apparently included problems regarding safety and efficacy information. As the panel stated, “[p]erhaps the most controversial question in formulating this policy concerned the status of safety and efficacy test data.”²⁴⁹

The report noted that in recent years (that is, recent relative to 1976) the FDA had interpreted the trade secret exemption to extend protection to animal and human test data.²⁵⁰ The Dorsen Final Report examined the FDA process as of 1977 and criticized it for its lack of openness in reviewing drug applications.²⁵¹ One criticism was that the system was essentially closed to public review and participation.²⁵² The lack of openness stemmed primarily from the FDA’s trade secret protections that prohibited the FDA from disclosing most scientific data held by it and thus this trade secret protection prevented the FDA from releasing to the public information underlying its decisions.²⁵³ The committee was concerned about “suppression of important scientific information about new drugs” and wanted Congress to see how to encourage research and development without the sup-

²⁴⁷ *Id.*

²⁴⁸ *See id.*

²⁴⁹ *Id.* For the language of the regulations discussed in the Dorsen Report, see Freedom of Information Act, 5 U.S.C. § 552 (2000).

²⁵⁰ *See* Safety and Effectiveness Data for New Drugs and New Animal Drugs, 39 Fed. Reg. 44,601 (Dec. 24, 1974); Food and Drug Administration, 37 Fed. Reg. 9, 128–29 (May 5, 1972). For purposes of the debate, the FDA defined safety and effectiveness data as “all studies and tests of a drug on animals and humans and all studies and tests on the drug for identity, stability, purity, potency and bioavailability.” *See* 21 C.F.R. §§ 314.14(i), 514.11(h), 4.111(e) (1976). This definition treats data that are very different from one another in terms of the moral and regulatory requirements imposed on them as though they were the same. Data derived from human subjects, versus animal studies or studies on the substance itself will have different regulatory schemes governing those being studied. This Article argues that the fact that the data is derived from human beings imposes a beneficence requirement upon it that must be supported by the treatment of that data subsequent to its development. Data not derived from humans has a different legal status.

²⁵¹ *See* FINAL DORSEN REPORT, *supra* note 14.

²⁵² *Id.* at 2.

²⁵³ *Id.* at 33.

pression.²⁵⁴ The committee called for “closer review of drug testing to ensure that studies are not misdirected, that human test subjects are not exposed to undue safety risks, that important drug applications are not neglected, and that data submitted by drug sponsors are neither fraudulent nor misleading.”²⁵⁵ The Dorsen Panel observed that “clinical testing of new drugs is defensible only if it offers the possibility of social benefits, [and that] incomplete or inaccurate reporting of clinical data raises serious questions about the ethics of such testing.”²⁵⁶

The FDA’s stated justification for protecting the confidentiality of this data was based entirely on a financial incentive theory of drug development.²⁵⁷

The public is dependant upon private pharmaceutical manufacturers for development of drugs. In some instances [the drug or substance being tested] may not be patented. If a manufacturer’s safety and effectiveness data are to be released upon request, thus permitting “me-too” drugs to be marketed immediately, it is entirely possible that the incentive for private pharmaceutical research will be adversely affected.²⁵⁸

The drug industry consistently expressed its concerns that the FDA needed to make a firm commitment to protecting data disclosed to it in order to prevent a competitive harm from occurring due to a broad societal increase in knowledge, which was clearly perceived as a negative outcome. Once the information became broadly available, it would lose proprietary value to the drug company.²⁵⁹

The Dorsen Panel saw this trade secret protection as doing harm to scientific progress, undermining FDA credibility in decision-making and greatly reducing the benefit that could be achieved from the studies that had been conducted.²⁶⁰ In light of its commitment to keeping information confidential, the FDA must publicly justify its decisions regarding drug applications without being able to explicitly refer to the data upon which the decisions are based. This approach presents a problem of both credibility and accountability that has not yet been resolved; furthermore, the FDA is consistently deprived of

²⁵⁴ *Id.* at 2.

²⁵⁵ *Id.* at 6.

²⁵⁶ *Id.* at 8.

²⁵⁷ FINAL DORSEN REPORT, *supra* note 14.

²⁵⁸ *Id.* at 34 (quoting 39 Fed. Reg. 44,634 (1974)).

²⁵⁹ See CASEY, JR. ET AL., *supra* note 215, at 169.

²⁶⁰ FINAL DORSEN REPORT, *supra* note 14.

valuable opinions and challenges from other scientists and the public, increasing the risk of arbitrary or irrational decisions.²⁶¹

The Dorsen Panel specifically addressed implications of this policy for human research subjects: “[W]ithout access to supporting data, informed public debate on controversial decisions and on broad questions such as the ethics of human testing becomes impossible.”²⁶² The Dorsen Panel condemned keeping scientific research hidden from the public view because it

often forces pharmaceutical companies to engage in testing which duplicates work already performed by other companies. Because duplicative testing has little social value, the ethics of such testing are always questionable. In fact, duplicative testing might lead to deaths or illnesses which could have been avoided had the investigator been familiar with another firm’s findings.²⁶³

The Dorsen Panel further added that the trade secrets policy of the FDA interfered with the free exchange of scientific knowledge.²⁶⁴ Arguably, this free exchange of information is an intimate part of what makes research on human subjects proper, as it adds so much to the value of what is learned. Scientists will not be given access to suppressed data, thus hampering their work by not giving them access to “scientific advances which have a bearing on their own work.”²⁶⁵ “One of the most troublesome aspects of [the system] is that the FDA must rely almost exclusively on the accuracy and objectivity of industry-generated data” without it being subject to the challenges that other scientists might raise.²⁶⁶

The submission of inaccurate or misleading data also poses a problem relating to the ethics of human testing. Although the testing of new drugs on human volunteers subjects them to unknown risks for unknown benefits, those experiments ordinarily are justified on the ground that they may produce larger social gains. When test results do not accurately reflect the outcome of clinical trials, human test subjects will have been exposed to the risks of an experimental drug without countervailing benefit.²⁶⁷

The Dorsen Report, in the end, disagreed with the FDA’s conclusion that trade secret law mandated the position the FDA took re-

²⁶¹ The case study presented in Part IV is a good example of these concerns bearing fruit.

²⁶² FINAL DORSEN REPORT, *supra* note 14, at 35.

²⁶³ *Id.*

²⁶⁴ *Id.* at 35.

²⁶⁵ *Id.* at 36.

²⁶⁶ *Id.* at 83.

²⁶⁷ *Id.*

garding safety and efficacy data and believed that the FDA could legally release this type of data in response to FOIA requests.²⁶⁸ It stated that it would also be beneficial for the FDA to do so.²⁶⁹ The Dorsen Report also called for Congress to address the problem directly since the FDA had reached a contrary decision in its stated policies.²⁷⁰ That change has not yet occurred, and therefore FDA regulations still protect drug companies from disclosure of data under FOIA. The Dorsen Panel concluded that the present safeguards in the system (those present in 1977 and still roughly the same today) were not enough to prevent bias in how data was presented to the FDA, based on a desire by drug companies for a commercially successful product.²⁷¹

The FDA failed to properly take into account the impact of its regulatory decision concerning FOIA release of drug company data on the regulations governing human subject research. This does not mean that the duty to comply with the human research subject regulations is an onus upon the FDA. It still rests quite firmly with those who are proposing to conduct a study. The FDA stance is relevant because it permits the drug companies to use the data they generate on human subjects to gain government approval of a product and yet still fail to satisfy the benefit requirement of the human research regulations. A countervailing pressure to be forthcoming and open that could have been generated by the need to satisfy FDA regulations is not present. The debate regarding the FDA's policy decision is also relevant because those who have addressed it, including Dr. Kennedy and the Dorsen Panel, have done an excellent job of detailing many of the wrongs that are caused by this FOIA policy.²⁷² The failure of the analysis in both the letter from Dr. Kennedy and the Dorsen Panel reports²⁷³ was a lack of understanding of the implications of the beneficence requirement of the human subject regulations. Thirty years later, this Article seeks to rectify that omission.

²⁶⁸ FINAL DORSEN REPORT, *supra* note 14.

²⁶⁹ *Id.*

²⁷⁰ *Id.*

²⁷¹ *Id.* at 85.

²⁷² See FINAL DORSEN REPORT, *supra* note 14; Kennedy Letter, *supra* note 212.

²⁷³ This analysis was echoed in a subsequent article in the Harvard Law Review, co-authored by a lead author of the Dorsen Report. See McGarity & Shapiro, *supra* note 13.

B. *The Bayh-Dole and Hatch-Waxman Acts*

The Bayh-Dole Act²⁷⁴ reflected changes in the culture of research while also radically accelerating the speed and depth of the changes that occurred. This Act made it possible for research that was conducted with federal funds to be used for the profit of those conducting it, either by exploiting the technology themselves or by licensing it to another firm.²⁷⁵ The Act allows companies to gain a proprietary interest in drugs and technologies that in the past were controlled by the federal government.²⁷⁶ The Bayh-Dole Act specifically changed prior federal laws that explicitly called for this information to be made public.²⁷⁷ The stated rationale for this change was that for-profit business would serve to bring the fruit of technological advances to the public more quickly and efficiently than occurred when information was freely available to all who might seek to utilize it.²⁷⁸ The legislation seeks to “promote the commercialization and public availability of [these] inventions.”²⁷⁹ The government maintains rights in what is covered under the Act, but primarily for purposes of ensuring that the full market potential is actually pursued.²⁸⁰ Congress also enacted a confidentiality provision in the Act that allows the relevant federal agency to choose to keep any information related to specific inventions confidential so that the interested private parties have time to pursue a patent.²⁸¹

Consider the impact this could have on an academic research institution, and, furthermore, on the large drug companies. First, the researcher is given the option of pursuing research under federal grants, with the added possibility of becoming wealthy due to exclu-

²⁷⁴ Bayh-Dole University and Small Business Patent Procedures Act, 35 U.S.C. §§ 200–212 (2000).

²⁷⁵ *See id.*

²⁷⁶ *Id.*

²⁷⁷ For example, the explicitly changes the laws governing the Department of Agriculture, specifically, 7 U.S.C. § 1624(a) (2000), which governed research grants and contracts to conduct research and concluded, prior to Bayh-Dole, that “[a]ny contract made pursuant to this section shall contain requirements making the result of such research and investigations available to the public by such means as the Secretary of Agriculture shall determine.” This type of language was consistent across federal agencies prior to the Bayh-Dole Act. *See* Rebecca S. Eisenberg, *Public Research and Private Development*, 82 VA. L. REV. 1663, 1663 n.2 (1996).

²⁷⁸ *See* 35 U.S.C. § 200 (2000).

²⁷⁹ *Id.*

²⁸⁰ *Id.* § 203. This section of the Act discusses what are known as “March-In Rights.”

²⁸¹ *See id.* § 205.

sive rights in whatever marketable advances might be discovered.²⁸² This introduces a new set of motivations into the researcher's decision-making that was entirely absent when the federal government maintained the rights to these results. Failure to prove that a drug or device works well presents a possibility of financial loss to the researcher. Given the amount of money that is usually involved in bringing a drug or device to market, most researchers license these products to large drug companies.²⁸³ Thus, the goals of the researchers and the drug companies can easily become aligned due to consistent financial pressures on both of them. Furthermore, the drug companies no longer have the same motivation to invest in new technologies, given that under Bayh-Dole, it is far less risky to allow the federal government to finance the development of new technologies and drugs that the drug companies will then take through the approval process and market.

Bayh-Dole then has served to remove much data that was derived through the use of human research subjects from the public domain, resulting in what presumably is a predictable subsequent reduction in scientific benefit from secrecy of data, which has already been described in some detail in this Article. Furthermore, the Act creates financial incentives for researchers to distort and manipulate data such that they and their institutions can profit from the resulting product's profitability. Finally, Bayh-Doyle continues the research institutions' cultural shift away from pursuing a social benefit, as originally conceived, and satisfaction from scientific results of research that increase the knowledge of human kind toward a different policy concept of benefit. This benefit is measured by the success of the drug companies, as drug company profitability and social good are conflated into one measurement.

The Hatch-Waxman Act of 1984 was created primarily for the purpose of making it possible for generic drugs to be approved by the FDA without requiring the same level of testing to show proof of

²⁸² See *id.* § 203. Under the March-In Rights retained by the federal government, if the researcher decides to forgo pursuing profit, the rights of that researcher can simply be taken away and passed to someone the government believes will pursue it more vigorously. See *id.*

²⁸³ PhRMA estimates that it costs about \$800 million to bring a drug to market. PHARMA PROFILE, *supra* note 5, at 10 (citing U.S. DEP'T OF HEALTH & HUM. SERVS., NIH, SUMMARY OF THE FY2007 PRESIDENT'S BUDGET (2006), <http://www.nih.gov/news/budget/FY2006presbudget.pdf>).

safety and efficacy that the non-generic drug required.²⁸⁴ A generic in this instance is substantially the same as a substance that has already been approved by the FDA, and by creating a scheme that primarily required proof that the generic substance did not differ substantially from the older, already approved substance, the generic could be brought to market more efficiently.²⁸⁵ The Act also gave increased exclusivity rights to the manufacturers of the original drugs as a trade-off.²⁸⁶ The generics cannot be brought to market for a substantial period of time, allowing the original marketer time to profit from its monopoly.²⁸⁷

One would think that this law could have served to make it possible for drug companies to be open about the data they controlled, since their rights were both more completely protected with the extension of exclusivity and were more concretely limited, given the explicit approval of bringing generic drugs to market that piggy-back on drug-company approvals already conducted by the FDA. This has not occurred. What did happen is that, during the debate about generics (which is still ongoing), the drug companies have maintained that the data is theirs, developed for their own profit, and that generics should have to conduct the research again themselves.²⁸⁸ This is particularly interesting in light of the fact that the source of much of the original inventions being debated is government-funded research, later licensed to the drug companies for exploitation under Bayh-Dole.²⁸⁹

The reasons public disclosure of this information tends to be financially costly to the drug companies are remarkably similar to the reasons this Article argues they need to be made public. The motivation for the call for disclosure is to reassert the original, and still binding, ethical legal structure that was built around the complex issue of how to use human beings as research subjects. The incentive structure that has developed since the 1970s for drug companies was misinformed and poorly planned in light of drug company dependency on human research subjects. It cannot coexist with human research subject regulations as they now stand. The parties involved,

²⁸⁴ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.).

²⁸⁵ 35 U.S.C. § 156 (2000).

²⁸⁶ *See id.*

²⁸⁷ *See id.*

²⁸⁸ *See Kennedy Letter, supra note 212.*

²⁸⁹ *See ANGELL, supra note 2, at 8* (discussing the amount of new technology being generated by drug companies themselves).

from government agencies to the drug companies themselves, should have recognized this flaw. With disclosure of study results, innovation would move more quickly, basic research would not need to be repeated, and people could “free ride” on the work done by others, a term used in a pejorative way in the economic studies prepared by the drug industry²⁹⁰ though this is exactly what a free exchange of scientific information is meant to accomplish. The current treatment of safety and efficacy data appears to slow the rate of learning and development at a society-wide level in order to, in theory, encourage it on an individual company’s part. If we could, indeed, free-ride on one company’s development of information from the test data it controls and thus move more quickly toward an improved drug or away from a faulty one, this would seem to be an ideal achievement from the perspective of a risk-benefit analysis of a study, adding significantly to the possible benefits that could be derived. Clearly, that is not the goal of current research culture.

IV. CASE STUDY OF SSRIS IN A PEDIATRIC POPULATION

Current events have presented case studies that show the risk of corporate suppression of important data derived from volunteer research subjects is more than a theoretical concern.²⁹¹ The primary case examined here is the suppression of data concerning the danger and lack of efficacy associated with children’s antidepressants. This information started to become public knowledge in the summer of 2003 when GlaxoSmithKline (Glaxo) applied for British approval for the use of Paxil, an SSRI, in a pediatric population.²⁹² The SSRI class also includes Prozac and other commonly prescribed antidepressants.²⁹³ Within two weeks of receiving the application, Medicines and Healthcare Products Regulatory Agency (MHRA), the British regulatory agency charged with reviewing these applications, contraindicated the use of Paxil in patients under the age of eighteen.²⁹⁴

²⁹⁰ See, e.g., O’REILLY, *supra* note 205, § 14:93. This book, written for FOIA practitioners, is solely concerned with the financial costs to enterprise from inappropriate FOIA disclosures and offers a valuable perspective on the industry concerns.

²⁹¹ Berenson, *supra* note 22.

²⁹² See *FDA’s Role in Protecting Public Health: Examining FDA’s Review of Safety & Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. on Energy and Commerce*, 108th Cong. 4–5 (2004) [hereinafter *House Hearings*] (statement of Rep. Joe Barton, Chairman of House Comm. on Energy and Commerce).

²⁹³ More than ten million children a year are prescribed antidepressants, as of 2004. *Id.* at 6.

²⁹⁴ This was first reported in the press in June 2003. See, e.g., Sarah Boseley, *Mood Drug Seroxat Banned for Under 18s*, THE GUARDIAN, Jun. 11, 2003, available at <http://>

In December 2003, MHRA contraindicated all antidepressants, except for Prozac, for children, due to an increase in suicidal behaviors combined with failure to show efficacy.²⁹⁵ This, in turn, prompted a number of articles in the popular press about the possible dangers of these drugs.²⁹⁶ In the United States, Congress convened hearings on this subject in the fall of 2004 calling for the FDA to explain how these drugs were on the market and freely available to the pediatric population in the U.S., given the dangers that the studies had disclosed.²⁹⁷

It is important to note here that these studies on children were conducted primarily as a result of widespread concern over the lack of available data about how drugs work in children.²⁹⁸ For decades, children have been perceived as a vulnerable population that needs to be protected from exploitation, and so have been prevented from participating in most drug trials as subjects.²⁹⁹ This led to limited scientific understanding of how drugs are metabolized by children's bodies, which in turn led to a series of policy decisions meant to encourage an ethical and appropriate increase in the use of children as research subjects.³⁰⁰ The goal was to begin to fill in what science knows little about: how drugs work in children.³⁰¹

We have learned much about the drug industry's behavior since MHRA made its initial finding against Glaxo's application in 2003. This Part describes how there have been numerous studies that support a finding of increased suicidal thoughts among children, and probably adults, when using these antidepressants, and that these studies began to generate this information at least as long ago as 1996.³⁰² The drug companies that controlled this data did not make

www.guardian.co.uk/uk_news/story/0,3604,974901,00.html. The use of the word "contraindicated" has a slightly different meaning in England than it does in the United States. In England it is not a ban on prescribing the substance but is, instead, a harsh warning as to the risks of doing so. In the United States it is highly unusual for a physician to prescribe a substance that has been "contraindicated" by the FDA as a treatment, and thus the impact of such a communication is effectively a ban. *Id.*

²⁹⁵ *Id.*

²⁹⁶ See, e.g., Erica Goode, *British Ignite a Debate on Drugs and Suicide*, N.Y. TIMES, Dec. 16, 2003, at F1.

²⁹⁷ See *House Hearings*, *supra* note 292, at 490.

²⁹⁸ See, e.g., Connie Lenz, *Prescribing a Legislative Response: Educators, Physicians, and Psychotropic Medication for Children*, 22 J. CONTEMP. HEALTH L. & POL'Y 72 (2005).

²⁹⁹ COLEMAN ET AL., *supra* note 25, at 527-32.

³⁰⁰ *Id.*

³⁰¹ See, e.g., Jerome Groopman, *The Pediatric Gap: Why Have Most Medications Never Been Properly Tested on Kids?*, NEW YORKER, Jan. 10, 2005, at 32.

³⁰² See *House Hearings*, *supra* note 292, at 490 (citing Letter from James F. Knudsen, FDA, to Martha A. Brumfield, Senior Associate Director, Pfizer, Inc.) ("We note that

it public, and these same companies went to great efforts to make sure no one else who also had access to the information went public with it.³⁰³ This failure to be forthcoming about these studies caused at least two distinct problems. First, it prevented physicians and parents from making the best possible individualized risk-benefit decisions for depressed children. The efficacy issue goes to the possible benefit of a treatment, which in this case has never been proven to occur at a rate higher than placebo.³⁰⁴ The increase in suicidal thoughts goes to the risk to be considered, and so both sides of the equation as presented to the public were inaccurate. The second problem is that without disclosure of the risks, even if a decision would have been made to go forward with the treatment, children would not be monitored for occurrences of the side effects that the research had revealed, making it more likely that occurrences of side effects would be under-reported and under-treated.

This case study is particularly important here because the data about these drugs was derived through the use of volunteers, specifically, depressed children who became research subjects rather than simply receiving the care their personal physicians thought best. All of the participants were suffering to a sufficient degree to be considered clinically depressed.³⁰⁵ These trials were primarily placebo-

there appears to be an increase [sic] frequency of reports of suicidally [sic] in the pediatric/adolescent patients exposed to sertraline compared to either placebo or sertraline-treated adult OCD [obsessive-compulsive disorder] patients.”); see also *id.* at 58 (statement of Greg Walden, Vice Chairman, H. Subcomm. on Oversight and Investigations, citing Memorandum from Dr. Andrew Mosholder, Medical Officer, FDA, to Sulvay Pharmaceuticals (Dec. 13, 1996)) (regarding Luvoxamine maleate (Luvox), an SSRI, which stated that the incidence of agitation among the pediatric population taking this drug in the test was four times greater than that of the placebo group, and that “there is emerging literature pointing to behavioral reactions to SSRI drugs in children”).

³⁰³ See, e.g., Complaint at 1, *People v. Glaxosmithkline* (N.Y. Sup. Ct. June 2, 2004), available at http://www.oag.state.ny.us/press/2004/jun/jun2b_04_attach1.pdf.

³⁰⁴ E. Jane Garland, *Facing the Evidence: Antidepressant Treatment in Children and Adolescents*, 17 CAN. MED. ASS’N. J. 489 (2004).

³⁰⁵ Careful subject selection can be important because it increases the coherency of a study, making the results more reliable. However, it can also limit the usefulness of the information for the general population because the group in the trial is narrowly defined. In the case of antidepressants, the inclusion/exclusion criterion is very limiting, and results in the selection of a very small percentage of people who would actually present at their physician’s office complaining of depression. See Mark Zimmerman et al., *Are Subjects in Pharmacological Treatment Trials of Depression Representative of Patients in Routine Clinical Practice?*, 159 AM. J. PSYCHIATRY 469, 469 (2002).

controlled, meaning that a significant percentage of the subjects received sugar pills.³⁰⁶

These studies involved at least two kinds of predictable risks for the children, both common in placebo trials. The first was being placed in the placebo “arm” of the trial and not receiving the most effective treatment at the earliest possible time if the placebo arm of the trial proved to be less effective than the arm given the SSRI. The second risk was the negative effects of the drugs themselves, a risk that in these trials materialized as a substantially increased incidence of suicidal ideations, meaning an increase in thoughts about suicide and an increase in actions taken to harm oneself.

A number of studies conducted over the past fifteen years show SSRIs are no more effective in children and adolescents than a placebo, and present a substantial risk of suicidality.³⁰⁷ These studies were conducted on human subjects under the age of eighteen who were symptomatic with depression.³⁰⁸ Glaxo paid for many of these studies and other pharmaceutical companies funded the others.³⁰⁹ The physicians who conducted these studies were bound by confidentiality agreements with the manufacturers who sponsored them.³¹⁰ These agreements forbid the physicians to independently disclose any results of these studies.³¹¹

Dr. Andrew Mosholder, a child psychiatrist at the FDA, reviewed the clinical data about Paxil drug trials in pediatric populations and observed that some trial events reported under the column of clinical trial adverse events as “emotional liability” were actually severe enough to qualify as suicidal behavior or ideation.³¹² He then had the FDA request clarification from Glaxo as to these events, asking it to search its records using search terms the FDA generated that were more likely to reveal the more severe events.³¹³ In March 2003, Glaxo gave Dr. Mosholder the data he requested and it showed an increase

³⁰⁶ See, e.g., Garland, *supra* note 304.

³⁰⁷ *Id.* at 489; see Gardiner Harris, *Debate Resumes on the Safety of Depression's Wonder Drugs*, N.Y. TIMES, Aug. 7, 2003, at A1.

³⁰⁸ Garland, *supra* note 304, at 489.

³⁰⁹ See *House Hearings*, *supra* note 292, at 22 (statement of Dr. Andrew Mosholder, Medical Officer, FDA).

³¹⁰ *Id.* at 22.

³¹¹ See *id.* at 22; see also Harris, *supra* note 307.

³¹² *House Hearings*, *supra* note 292, at 22. Adverse events in a clinical trial can mean a multitude of things and may or may not be connected to the drug or procedure being tested. It is not a simple task to deduce if an event is related to the trial or will prove to be statistically relevant. Manipulating adverse event reporting can hide much that could prove relevant.

³¹³ *Id.*

in suicidal thoughts and behaviors in those children taking Paxil compared with those taking the placebo.³¹⁴ In July 2003, the FDA asked the other manufacturers of SSRIs to analyze their data the same way Glaxo had, using FDA-derived search terms to check for adverse events that needed to be reported separately from the “emotional liability” category.³¹⁵ Dr. Mosholder analyzed all of the data in the fall of 2003, and subsequently prepared a report showing that these severe adverse events were 1.9 times more likely to occur with the drugs than with placebos.³¹⁶

Glaxo prepared the analysis that Dr. Mosholder requested in the spring of 2003 and sent it to the British agency, MHRA, in the summer of 2003 along with its application for a license.³¹⁷ In effect, it was Dr. Mosholder’s analysis of Glaxo’s data that caused Glaxo to designate adverse events in a way that then prompted MHRA to issue its contraindication of SSRI use in pediatric populations.³¹⁸ The FDA did nothing public with this analysis or data until it was leaked to the press in the United States in February of 2004 that Dr. Mosholder had assessed the increased risk of suicidality and the FDA was not doing anything to address it.³¹⁹ The FDA responded by starting a criminal investigation into who had leaked this confidential information about the drugs to the press.³²⁰

³¹⁴ *Id.*

³¹⁵ *Id.*

³¹⁶ It has been shown that adverse events are poorly reported in most mental health trials. This problem is multi-determined, in that economic incentives for not disclosing the problems are combined with the difficulty of accurately describing events that can be difficult to objectively assess. See Panagiotis N. Papanikolaou et al., *Safety Reporting in Randomized Trials of Mental Health Interventions*, 161 AM. J. PSYCHIATRY 1692, 1693–97 (2004) (giving statistics that support this assertion and calling for standardized reporting of these events). The problem is not limited to mental health trials; the economic incentives to underreport problems are present in all areas of drug and device testing. See, e.g., John P.A. Ioannidis & Joseph Lau, *Completeness of Safety Reporting in Randomized Trials: An Evaluation of 7 Medical Areas*, 285 JAMA 437 (2001).

³¹⁷ See *House Hearings*, *supra* note 292, at 23–26 (statement of Dr. Andrew Mosholder, Medical Officer, FDA).

³¹⁸ There was a suspicion among some at the FDA that the drug companies had hidden the adverse events by “various inappropriate coding maneuvers.” *House Hearings*, *supra* note 292, at 135 (citing E-mail from Russell G. Katz to Dr. Andrew Mosholder, Medical Officer, FDA (June 3, 2003)).

³¹⁹ See Goode, *supra* note 296.

³²⁰ The FDA’s focus was on protecting drug company safety and efficacy data from inadvertent disclosure, even when it was the FDA’s own analysis of that data that had been disclosed. The investigation was ordered by Dr. Seligman of the FDA, who has justified his actions by stating that even though the information being leaked was not proprietary or a trade secret, it was “confidential” and should not have been released by the FDA. See *House Hearings*, *supra* note 292, at 118 (statement of Dr. Paul Selig-

One issue here was the statistical validity of the increased risk that the SSRI data presented. Dr. Mosholder stated that the conclusion he reached about the danger was much more convincing when he put the data from all of the different studies from the drug companies together, giving him a larger data pool to analyze.³²¹ When looking at the data from an individual study, “it is harder to have the same level of confidence that you have when you combine all the studies.”³²²

Dr. Mosholder was scheduled to present his research to an FDA advisory panel of experts concerning treatment for pediatric depression.³²³ This advisory panel would then make recommendations to the FDA. The administration at the FDA did not let him present his conclusions, and this decision apparently led to the leak and to accusations in the press of an attempt by the FDA to suppress his analysis.³²⁴ The FDA claimed it was worried that presenting Mosholder’s analysis would be misleading to the public, and it would not let him present until further analysis of the issue occurred.³²⁵ The fear, oft repeated in hearings before Congress on this issue, was that people would stop prescribing the SSRIs for pediatric depression if faced with the data, and the administration wasn’t sure that was the best response.³²⁶ The FDA has received a tremendous amount of criticism for its handling of the matter of children’s use of antidepressants.³²⁷

man, FDA). This does not create a clear justification for a criminal charge, but as will be discussed in more detail, it reveals the culture at the FDA regarding information it has that could impact the profitability of drug companies.

³²¹ *Id.*

³²² *Id.* at 29. The FDA had access to much of the data on SSRIs from the different companies that manufacture them, allowing Dr. Mosholder to perform this analysis on the large pool. There are many drugs that share common properties or chemical structures and pooling of the data may reveal important statistical information.

³²³ *House Hearings, supra* note 292, at 29 (statement of Dr. Andrew Mosholder, Medical Officer, FDA).

³²⁴ For more on Dr. Mosholder’s role in the SSRI problem with the FDA, see Greg Koski, *FDA and the Life Sciences Industry: Business as Usual?*, 34 HASTINGS CENTER REP. 24–27 (2004) (analyzing the relationship between the FDA and drug companies).

³²⁵ *House Hearings, supra* note 292, at 29.

³²⁶ This fear is exactly the opposite of the ideal of informed consent. The FDA appears to be functioning under a presumption that an incorrect and unsophisticated risk-benefit analysis would be done by the advisory panel, and by physicians and parents, if given access to information it has not carefully edited. The doctrine of informed consent encourages disclosure of the maximum amount of information possible in a comprehensible format, and places great faith in the appropriateness of the patient as the best decision maker.

³²⁷ See Laurel K. Leslie et al., *The Food and Drug Administration’s Deliberations on Antidepressant Use in Pediatric Patients*, 116 PEDIATRICS 195 (2005) (collected references much of this criticism).

Many feel that given its access to the bulk of this data over the last two decades, it should have been far more aggressive in issuing warnings and informing the medical and patient populations of the known risks.³²⁸ Recent congressional hearings and law review articles have examined this issue in detail,³²⁹ and a thorough examination of the propriety of the FDA's role in the SSRI debacle is outside the scope of this Article. What is clear is that the FDA is extremely cautious in how it responds to negative trial results. To quote Dr. Robert Temple, director of the Office of Medical Policy at the FDA, "overall, 15 studies in pediatric [depression] do not support the effectiveness of these drugs in pediatric populations."³³⁰ However, he then says that to conclude based on these studies that the drugs do not work is premature.³³¹

While it has not chosen to draw substantive conclusions from this failure to show efficacy, the FDA has been critical of drug company claims of efficacy in these studies.³³² An internal FDA email written by Dr. Mosholder about a study published in JAMA concerning the efficacy of Zoloft in a pediatric population, where the trial results

³²⁸ *Id.*

³²⁹ See, e.g., Sarah D. Gordon, Note, *Antidepressants and Teen Suicide: An Analysis of the FDA's Regulation of Pharmaceuticals for Use in Pediatric Patients*, 57 ADMIN. L. REV. 927 (2005) (writing from the perspective of pediatric medicine, Gordon is highly critical of the FDA process as well as the handling of pediatric SSRI testing generally).

³³⁰ *House Hearings*, *supra* note 292, at 79 (statement of Robert Temple, FDA). This number would include studies concerning Paxil and Zoloft that were published in medical journals as positive studies, i.e., studies that stated they had proven efficacy, but which failed to show efficacy under the FDA's own analysis. *Id.*

³³¹ The FDA asked the drug companies to perform these tests on a pediatric population under a system wherein the FDA can send a Written Request for a pediatric trial, which then triggers an additional six-month exclusivity of the drug being tested. Dr. Temple testified that because there was no requirement of a positive trial result to trigger the six-month exclusivity extension, he believed the drug companies were not properly motivated to design trials that would result in a positive finding. *Id.*; see also Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C.). The Best Pharmaceuticals for Children Act reauthorized and expanded pediatric testing as initially presented in the Food and Drug Administration Modernization Act of 1997. See, e.g., Gregory Hazard, *Please Sir, I Want Some More: Congress' Carrot-and-Stick Approach to Pediatric Testing Leaves Therapeutic Orphans Needing More Protection*, 20 J. CONTEMP. HEALTH L. & POL'Y 467 (discussing these acts and pediatric drug testing regulation in general). Most strikingly, Dr. Temple's testimony seems to imply that the drug companies could design a study to generate a positive result if it was necessary for their exclusivity. Given that a positive finding is supposed to be an objective measure of effectiveness, this is an extraordinary notion, one that exposes how open to manipulation these trials might actually be and how acclimated to that manipulation the FDA has become.

³³² See *House Hearings*, *supra* note 292, at 166 (statement of Dr. Andrew Mosholder, Medical Officer, FDA).

had been previously submitted to the FDA and rejected as failing to prove efficacy, shows this:

[W]e turned down this supplement[al application for drug approval] because each trial by itself failed. This article combines the two trials to show a statistically significant effect. I don't see where they say the individual trials failed and they had to pool them to have a result. Instead, the authors tout the combined analysis for having a large sample size . . . talk about spin!³³³

While the lack of public access to SSRI data was widespread, the criticism of Zoloft described above involved a published study, one that, however flawed, was presented to the public by being published in a medical journal.³³⁴ Glaxo submitted at least nine studies of SSRIs in a pediatric population to the FDA, and little of that data has ever been published.³³⁵ Dr. Graham Emslie was a researcher in four of these nine studies and stated that he believed the results were not published at least in part due to their negative results. Dr. Emslie knew of at least six other trials for drugs similar to Paxil in a pediatric population that had also been completed but not published; in an interview with the *New York Times* on this subject, Dr. Emslie would not disclose the names of the companies or drugs due to his being a party to confidentiality agreements regarding these studies.³³⁶

Nondisclosure contracts between investigators and sponsors are common, as are other clauses that can prevent investigators from independently examining the data they have helped collect or submitting a manuscript for publication without sponsor approval.³³⁷ These contracts are not limited to the SSRI example. The International Committee of Medical Journal Editors (ICMJE) recognized that these limitations could severely impair the objectivity of the articles received by member journals and so in 2001 it began to require that au-

³³³ *Id.* This is further evidence of the problem being described here: the risk that when one entity has control of data it can exert control over how it is perceived, and is thus protected from challenges supported by other interpretations of the same information. Another example of this is Celebrex, a Cox-2 inhibitor. Data published in the JAMA showed that it caused fewer side effects than two older arthritis drugs. The results submitted turned out to be for the first six months of a twelve-month trial. The twelve-month trial data showed no advantage of Celebrex over the other drugs and the drug company had the full twelve months of data when it submitted the six month results to the journal. ANGELL, *supra* note 2, at 109.

³³⁴ Karen D. Wagner et al., *Efficacy of Sertraline in the Treatment of Children and Adolescents with Major Depressive Disorder: Two Randomized Controlled Trials*, 290 JAMA 1033 (2003).

³³⁵ See *House Hearings*, *supra* note 292.

³³⁶ Harris, *supra* note 307.

³³⁷ Robert Steinbrook, *Gag Clauses in Clinical-Trial Agreements*, 352 N. ENG. J. MED. 216, 216 (2005).

thors not be parties to these contracts, and not have the power to review data, make publication decisions, or write their own articles.³³⁸ These ICMJE requirements have simply not been complied with, as a detailed study of these journals has revealed.³³⁹ The professional and financial risks for researchers of failing to comply with the contracts with drug companies are grave, and few universities have the resources to forego drug company funding. Drug companies have been known to sue researchers for failing to comply with confidentiality agreements, even with regard to safety concerns.³⁴⁰ A well-known example of this involved Dr. Nancy Olivieri at the University of Toronto. Dr. Olivieri published an article expressing her concerns about the safety of a drug she had tested for the drug company Apotex. Subsequently, she was sued by Apotex, lost her position at the university, and ended up embroiled in a multi-year legal battle with both of those institutions.³⁴¹ The university eventually adopted one of the stricter codes for limiting sponsor control of researchers.

Dr. Jane Garland was another researcher involved in many of the studies of SSRIs for a pediatric population. She has written that she too saw negative results of industry SSRI trials over the course of years but was also prohibited from disclosing them due to nondisclosure contracts she had with the sponsors. In her article on this subject she describes in detail the numerous studies of these drugs that have

³³⁸ *Id.*

³³⁹ See Schulman et al., *supra* note 195.

³⁴⁰ There are examples of problems that motivated drug companies in the 1990s to insist on these highly controlling contracts. See *Hoffmann-La Roche, Inc. v. Yoder*, 950 F. Supp. 1348 (S.D. Ohio 1997). In *Yoder*, Dr. Yoder, a primary investigator for drug trials concerning Accutane, an acne drug that has been shown to cause suicidality in children, was unsuccessfully sued by Hoffman-La Roche for selling his research documents concerning Accutane under a theory that he had violated trade secret protections of the drug company. *Id.* The failure of a theory of trade secret protection to protect company interests probably contributed to the development of strongly-worded contract provisions protecting the sponsor's interest in the data. *Id.* In another incident, Immune Response, a drug company, sponsored a trial in a number of academic centers. ANGELL, *supra* note 2, at 109–11. In 1996, the lead investigators said the results were negative, meaning the trial had failed to prove what it set out to prove. *Id.* The drug company fought with the investigators over publishing the results, filing suit in an attempt to stop them, but the suit failed. *Id.* at 110. Immune Response apparently wanted to alter the wording of the publication to show a result in a small subset of the subjects in order to have a positive result to publish. *Id.* The researchers said the result would not be scientifically valid. *Id.* The CEO of Immune Response justified its attempt to alter the results for publication by saying, "Just put yourself in my position. I spent over \$30 million. I would think I have certain rights." *Id.* at 111.

³⁴¹ See Laura Bonetta, *Olivieri to Testify Against Apotex in Europe*, 7 NATURE MED. 644, 644 (2001).

failed to show efficacy and have shown an increase in suicidality risk.³⁴² Dr. Garland also discusses some statistics that illuminate another problem with SSRIs. According to recent statistics, twenty percent of children will suffer from an episode of major depressive disorder before turning eighteen.³⁴³ Modern medicine has no readily available treatment that has been widely accepted and proven effective for this illness. The placebo effect of SSRI therapy is very high, meaning that forty to sixty percent of those given sugar pills show a statistically significant improvement.³⁴⁴ The SSRIs tend to have the same percentages of effectiveness as placebos, though with the two-fold increased risk of suicidality over the placebo incidence.³⁴⁵ The obvious answer to this would be for doctors to simply prescribe the placebo, generating the statistical level of effectiveness with limited risks of side effects. However, American physicians may not ethically prescribe placebos.³⁴⁶ The finding that SSRIs do nothing better than placebos, when you have a high placebo response rate, means that the SSRIs still perform better than doing nothing at all. Physicians are left with two choices: (1) use the SSRI with serious risks of side effects in order to generate the effectiveness of the placebo; or (2) give the patient nothing and forego the 40 to 60 percent chance of the child finding relief.³⁴⁷ Given this quite real conundrum, the FDA may have felt itself to be in a far more complex problem than was readily apparent from the news coverage.

In 1991, Eli Lilly (“Lilly”), the manufacturer of Prozac, was confronted with concerns about the safety and efficacy of Prozac that were very similar to the ones more recently raised about Paxil and SSRIs in general. Lilly defended Prozac to an FDA panel and convinced this panel that Prozac did not cause an increased risk of sui-

³⁴² See Garland, *supra* note 304, at 489–91; see also David Healy, *Lines of Evidence on the Risks of Suicide with Selective Serotonin Reuptake Inhibitors*, 72 PSYCHOTHERAPY & PSYCHOSOMATICS 71, 77 (2003) (analyzing the studies of adult populations and drawing similar conclusions).

³⁴³ Garland, *supra* note 304, at 489.

³⁴⁴ *Id.*

³⁴⁵ *Id.*

³⁴⁶ For discussions of this complex question, see I. Klienman et al., *Placebo Pain Medication: Ethical & Practical Considerations*, 3 ARCH. FAM. MED. 453 (1994), and M.B. Kapp, *Placebo Therapy and the Law: Prescribe with Care*, 8 AM. J. LAW MED 371 (1982).

³⁴⁷ A letter to the editor of the American Journal of Psychiatry illustrates this dilemma, describing a shift from the “biopsychosocial” model to the “medical model of disease and intervention,” leaving physicians less inclined to offer any treatment that is not pharmaceutical. Thus, the letter concludes that if the pharmaceutical intervention is not efficacious, the psychiatrists are left saying, “Don’t take away the only thing we have to offer these kids.” See Lawrence Diller, Letter, *Antidepressants and Children’s Depression*, 162 AM. J. PSYCHIATRY 1226 (2005).

cidality or suicidal ideation in children and adolescents, which has now clearly been proven to occur.³⁴⁸ Participants of that panel have since stated that were they given access to the data recently made public, and at least some of which appears to have been known by Lilly at the time of the panel's deliberations, it is likely that they would have voted against Prozac's approval for use by children.³⁴⁹

Glaxo was sued by the State of New York in June of 2004 for failing to release accurate data about children's reactions to antidepressants.³⁵⁰ The complaint stated that Glaxo "engaged in repeated and persistent fraud by misrepresenting, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication . . . in treating children and adolescents with Major Depressive Disorder."³⁵¹ The complaint further alleged that Glaxo allowed positive information about pediatric use of SSRIs to be disclosed but withheld and concealed related negative information.³⁵² The complaint went into great detail about documents used by Glaxo as part of a deceptive marketing campaign and about internal emails regarding negative studies.³⁵³ The disclosed documents do much to illuminate a culture where data is merely one element among many of a business to be managed, rather than something with independent scientific merit that is judged solely by its accuracy. Glaxo quickly settled this lawsuit,³⁵⁴ but not before these internal documents were made public.

³⁴⁸ See Harris, *supra* note 307.

³⁴⁹ See *id.* It appears that Lilly suppressed data from the 1980s that showed a substantial risk of self-harm and violence to others in adults taking Prozac, failed to provide the data to the FDA, and did not provide it in response to discovery requests in a subsequent lawsuit from 1989. See Jeanne Lenzer, *FDA to Review "Missing" Drug Company Documents*, 330 BRIT. J. MED 7, 7 (2005). Furthermore, Lilly had been given substantial post-marketing data from physicians reporting adverse events, but the drug company edited the data before presenting it to the FDA, excluding seventy-six of ninety-seven cases of reported suicidality among patients who had been prescribed Prozac, according to an FDA memorandum dated September 11, 1990. *Id.*

³⁵⁰ See, e.g., Complaint at 1, *People v. Glaxosmithkline* (N.Y. Sup. Ct. June 2, 2004), available at http://www.oag.state.ny.us/press/2004/jun/jun2b_04_attach1.pdf.

³⁵¹ *Id.*

³⁵² *Id.* at 2.

³⁵³ *Id.* passim.

³⁵⁴ Settlement was reached on August 26, 2004. See Press Release, Office of the New York State Attorney General Andrew M. Cuomo, *Leading Pharmaceutical Company Settles Suit Alleging Pricing Scheme for Cancer Patient Medications and other Drugs: Settlements Will Yield Millions for Government Health Plans and Consumers* (Aug. 10, 2006), available at http://www.oag.state.ny.us/press/2006/aug/aug10a_06.html; see also Brooke A. Masters, *Paxil Maker Will Post Its Unfavorable Test Results*, WASH. POST, Aug. 27, 2004, at E1.

The crux of the internal documents showed that as early as 1998 Glaxo, recognizing that its sponsored studies on Paxil were generating problematic data about Paxil's safety and efficacy in a pediatric population, hoped to "manage the dissemination of data in order to minimize any potential negative commercial impact."³⁵⁵ According to an internal document from Glaxo written for the purpose of managing the data from these trials, "[i]t would be commercially unacceptable to include a statement that efficacy had not been demonstrated" even though efficacy had, in fact, not been established.³⁵⁶ According to the State of New York's complaint, the management of these data for this purpose appears to have extended to the content of practitioner letters and the promotional materials used by drug company sales staff.³⁵⁷

In response to the leaks to the press, the heightened concerns of the public, congressional hearings and, likely, a multitude of other reasons, the FDA eventually mandated that a black box warning be placed on all SSRIs prescribed in this country.³⁵⁸ A black box warning is the strongest type of warning that can be put on a label.³⁵⁹ It consists of bold letters surrounded by a thick black border.³⁶⁰ The SSRI warning says, in relevant part:

³⁵⁵ See Masters, *supra* note 354.

³⁵⁶ See Wayne Kondro & Barbara Sibbald, *Drug Company Experts Advised Staff to Withhold Data About SSRI Use in Children*, 170 CAN. MED. ASS'N. J. 783, 783 (2004).

³⁵⁷ Practitioner letters are letters sent by drug companies to physicians that inform them of information about the drugs they are prescribing. The promotional materials are ones handed to the doctors by the direct sales representatives of the drug companies. A surprising amount of physician education about new treatments occurs through non-medical sales representatives of the drug companies. For a detailed discussion about the difficulty in separating pharmaceutical education from promotion, see Carl Elliot, *Pharma Goes to the Laundry: Public Relations and the Business of Medical Education*, 34 HASTINGS CENTER REP. 18, 18-23 (2004).

³⁵⁸ See FDA PROPOSED MEDICATION GUIDE: ABOUT USING ANTIDEPRESSANTS IN CHILDREN OR TEENAGERS, <http://www.fda.gov/cder/drug/antidepressants/SSRIMedicationGuide.htm> (last visited Mar. 2, 2007) [hereinafter FDA PROPOSED MEDICATION GUIDE], for information regarding antidepressants in children and teenagers in October 2004. Interestingly, this guide, meant for parents and children, states that "[t]here are Benefits and Risks When Using Antidepressants," a statement about the benefit of the drugs which is highly disputed. *Id.*

³⁵⁹ FDA Labeling Change Request Letter, <http://www.fda.gov/cder/drug/antidepressants/SSRILabelChange.htm> (last visited Mar. 2, 2007) [hereinafter FDA Labeling Change Letter]. In real numbers, if ten million children a year are prescribed these drugs in this country, that means two hundred thousand of them will predictably suffer from suicidality with no counter-balancing proven usefulness of the drug the children are taking. In addition, the studies have all been short-term, which means that risks of long-term use, both physical side effects on children's developing bodies and future psychiatric problems, have not been studied.

³⁶⁰ See FDA PROPOSED MEDICATION GUIDE, *supra* note 358.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4 percent, twice the placebo risk of 2 percent. No suicides occurred in these trials.³⁶¹

What happened with children's antidepressants has become a quick way of referring to a complex set of problems. The main point for purposes of this Article's thesis is that drug companies do, in fact, suppress and manipulate data that is derived from the use of human research subjects. That which is learned, but not shared, from the subject's sacrifices can easily be used to mislead scientists, physicians and the public, clouding rather than clarifying, which entirely confounds the purpose behind the sacrifice being made by the subject.

V. CONCLUSION AND RECOMMENDATIONS

A disservice has been done to millions of people: the positive effects of their very real and measurable sacrifices as research subjects have been unconscionably minimized. Congress's initial legislative goal leading to the development of the Belmont Report has been substantially thwarted. Those who regulate these undertakings have failed to instill the discipline necessary to ensure that their own regulatory requirements are fulfilled. Much of the research sponsored by pharmaceutical companies that is conducted on human beings is deeply flawed because it fails to satisfy a foundational element of properly conducted research on human beings: it must be calculated to generate a benefit for society. The failure to recognize the necessary legal implications of benefit to society in research has led to the creation of regulatory inconsistencies and incoherencies on multiple levels between the structure that regulates research on human subjects³⁶² and that which regulates the pharmaceutical industry as an industry.

The pharmaceutical industry recognizes the financial value of the information it collects from the use of human research subjects. The desire to create financial incentives for the development of new treatments and cures makes perfect sense, springing from our fear of

³⁶¹ FDA Labeling Change Letter, *supra* note 359.

³⁶² This structure is meant to include the Belmont Report and the Common Rule. See Belmont Report, *supra* note 8.

illness, our desire to save loved ones from pain and suffering, and a belief that by offering an industry large profits it will be encouraged.

As stated in Part II, as much as we desperately fear illness, and just as desperately as we need human subjects to experiment on in our search for cures, we have no legal or normative right to use people in this manner. This use requires a difficult philosophical analysis and justification. The normative challenge inherent in the project of conducting research on human subjects is not susceptible to simple or easy answers. The possibility of conflict with other societal desires is unavoidable because of the very nature of the undertaking. In an attempt to create a system for the use of human subjects that is normatively defensible, Congress directed the Commission to prepare the Belmont Report, and this report has become law. If the principles in the Belmont Report have any meaning, the societal benefit derived from the use of human research subjects has to be protected far more vigorously than has been done in recent years. The fact that this may have negative financial implications for the industry is not a legal or philosophically valid ground for continuing to maintain the status quo.

Pharmaceutical companies have routinely claimed that there may be significant negative health implications for our population if we fail to protect the financial incentives for drug companies that are created by giving them full control over this type of data, due to a reduction in drug company research and development. Even if this is entirely correct, it does not function as an excuse for failure to behave properly in this context. If possible, a rethinking of the incentive structure should be contemplated in order to protect the positive effect of incentives while ending the negative implications for human research subjects, but that is not a necessary corollary to the reform that is called for here.

As was shown in Part II, the requirement of a benefit to society, to humankind, from a specific research endeavor, is not subject to balancing against a different good or benefit, including one that is produced through the machinations of the pharmaceutical industry. This type of balancing is inapplicable to the analysis that must take place in assessing the potential benefit of an experiment. To put it another way, potential research subjects reside in a room with one locked door that leads into it. In order to open that door, the researcher must comply with the principles embodied in the Belmont Report. Entering the room is a privilege, not a right, and the regulations are meant to protect the integrity of the undertaking, not to effectuate an efficient access to subjects. Viewed that way, the pharma-

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ceutical companies' suppression and manipulation of the data they control should function to prevent the industry from unlocking that door.

There are a number of specific steps that can be taken as part of reinvigorating the concept of benefit in research. HHS can propose regulations that would enable IRBs to demand specific plans from researchers as to dissemination of data and analysis likely to be generated by the study under review. The FDA can publicly reexamine its stance as regards protection of safety and efficacy data from FOIA requests, given the unintended consequence this has had of further isolating data that could, if released, promote a greater beneficial outcome from a research project. With the regulations that are currently in effect, some change in enforcement is clearly necessary.

What this Article hopes to provoke with its analysis is an informed examination of our presumptions regarding the role of benefit in research on human subjects, with the different participants examining their current role and motivation in the scientific endeavors they participate in. We have a model for this in the critical examination we gave to the principle of autonomy that occurred around the time that the Belmont Report was being drafted, and which resulted in a far more vigorous approach to informed consent in research and in the private physician-patient relationship. That examination caused enormous upheaval in many of the relationships that make up the research enterprise. A similar shift is necessary for the concept of benefit to have a meaning beyond platitude.