

5-1-2013

Playing Doctor: How the FDA's Regulation of Access to Developmental Drugs Limits Patient Autonomy

Benjamin Joel Smith

Follow this and additional works at: https://scholarship.shu.edu/student_scholarship

Recommended Citation

Smith, Benjamin Joel, "Playing Doctor: How the FDA's Regulation of Access to Developmental Drugs Limits Patient Autonomy" (2013). *Law School Student Scholarship*. 304.
https://scholarship.shu.edu/student_scholarship/304

INTRODUCTION

By the time more than 1,000 members of the AIDS Coalition to Unleash Power (“ACT UP”) surrounded the FDA’s headquarters on the morning of October 11, 1988, more than 62,000 Americans had already died of HIV/AIDS.¹ The epidemic, though only a few years old, was claiming thousands of lives a month and new diagnoses were increasing exponentially.² The members of ACT UP had gathered outside of the FDA’s suburban Maryland headquarters to demand several immediate steps to stem the flood of AIDS-related illness and death.³

The conceptual thread connecting the demands made of the FDA that day was expanding access to experimental drug therapy and treatment for the seriously or terminally ill.⁴ Although the FDA had—just over a year before the mass demonstration—implemented a new avenue for access,⁵ those actually suffering from terminal illness had not experienced any significant relief.⁶ The demonstrators demanded that the FDA shorten the drug approval process for the seriously or terminally-ill by allowing access to experimental drugs as early as the beginning of Phase 2 trials.⁷ Further, ACT UP called for the end of double-blind placebo trials—in which some subjects will necessarily receive a placebo and not the new treatment—due to ethical concerns.⁸ While these demands were not immediately met by the FDA⁹, they did raise the profile of terminally-ill patients and the groups that advocate for them.¹⁰

¹ Cathy Olufs, *The AIDS Timeline*, available at <http://www.thebody.com/content/art390.html#1988>.

² Craig A. Rimmerman, *ACT UP*, available at <http://www.thebody.com/content/art14001.html>.

³ Douglas Crimp, *Before Occupy: How AIDS Activists Seized Control of the FDA in 1988*, available at <http://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302/>.

⁴ *Id.*

⁵ Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19,466 (May 22, 1987). Commonly known as the Treatment IND application (discussed in detail below), this was the FDA’s somewhat belated attempt at responding to rising criticism of its drug approval process (also discussed in detail below).

⁶ Olufs, Rimmerman, and Crimp all attest to the inadequacy of the currently available remedies in 1987-88.

⁷ Crimp. The FDA’s multi-phase drug approval process will be described below, but for immediate explanatory purposes, access in the beginning of Phase 2 trials would have been unprecedentedly early access.

⁸ Crimp, *Before Occupy*.

⁹ Rimmerman, *ACT UP*.

¹⁰ Philip J. Hilts, *How the AIDS Crisis Made Drug Regulators Speed Up*, N.Y. Times, Sept. 24, 1989, at D5.

The ACT UP demonstration—and the FDA’s response to the horrible crisis that motivated it—illustrates a critical shortcoming in modern American healthcare. The desperation of the protestors that morning, driving them to forcibly occupy the headquarters of an entity created to protect them, was a result of the FDA’s utter failure to adapt to the needs of terminally-ill patients.¹¹ Today, nearly thirty years after the ACT UP demonstrations, individuals with serious or terminal illnesses face similar challenges. Ironically, while ACT UP was protesting FDA inaction, the primary obstacle now to accessing developmental treatment is a recent FDA action.¹²

Individual autonomy, the freedom of a man or woman to make fundamental life-decisions for themselves, is not only a deeply held and jealously guarded concept in the U.S., it is one of the founding principles of the nation.¹³ Yet in some realms of the healthcare industry, especially in the regulation of clinical access to developmental drugs for the critically ill, individual autonomy is severely restrained.¹⁴ Entities empowered to limit individual freedom and autonomy are, in almost every instance, given that authority in order to act in the best interest of the individual.¹⁵ In essence, government agencies like the FDA really only exist—as their statutory mandates make plain—to protect the life and health of citizens. When an agency regulates individual behavior which does not endanger the lives of others—especially when Congress has not given the agency explicit power to prohibit that behavior—or when it restricts conduct and behavior that may very well save an individual’s life, that agency has overstepped its mandate.¹⁶

¹¹ Crimp, *Before Occupy*.

¹² 21 C.F.R. §312.34 (the 1987 Treatment IND) and its replacement (the 2009 regulations, to be codified at §312 and §316). Section 312.305 of the 2009 regulations functions as the most significant obstacle.

¹³ Jerry Menikoff, *Law and Bioethics*, p. 356 (2001). Menikoff is one of many excellent sources on the centrality of individual autonomy in American life and culture; for the purposes of this paper, he very effectively ties this concept to bioethics and medical decision-making.

¹⁴ Abigail Alliance, <http://abigail-alliance.org/> (last accessed 10/30/2012).

¹⁵ Stephen G. Breyer, et al., *Administrative Law and Regulatory Policy*, p. 1-3 (2006).

¹⁶ This point is best illustrated by the development of the “Chevron Doctrine” by the Supreme Court. Outlined in the majority’s opinion in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the Court held that when a legislative delegation to an agency on a particular question is implicit rather than explicit, a court may not substitute its own construction of the statutory provision for a *reasonable* interpretation made by the administrator of the agency. If the statute is silent or ambiguous with respect to the specific issue, the Court said, the

In the context of regulating access to experimental drugs, the FDA is tasked with assessing both the safety and effectiveness of the proposed new drug.¹⁷ The FDA has attempted to satisfy this mandate by creating a multi-phase clinical trial process, and strictly limiting access to the drug while it is being assessed.¹⁸ Patients who satisfy the rigorous requirements for entrance into a trial may access a drug in Phase 2 testing.¹⁹ However, those who are seriously or terminally-ill typically cannot meet these requirements.²⁰ For over 25 years, they simply had to wait until testing was completed, a process that averages 12 years.²¹ Since 1987, the FDA has made multiple attempts to expand access to experimental drugs for the seriously or terminally-ill, with little success.²² The most recent incarnation of this parade of half-measures came in 2009, when the FDA promulgated a new set of regulations to replace the 1987 rules.²³ The new rules attempted to expand access to those disqualified from clinical trials by allowing access when the patient's treating physician has determined that several treatment criteria have been met.²⁴ The fundamental flaw in the new

question for the court is whether the agency's answer is based on a permissible construction of the statute. In the context of the FDA, this doctrine was recently applied in *Food and Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000). The Court held that the FDA's regulations were invalid because Congress had already created a clear and explicit stance on regulation of tobacco products.

¹⁷ Pub. L. No. 87-781, 76 Stat. 780 (1962).

¹⁸ 21 C.F.R. §355(b)(5).

¹⁹ *Id.* at § 312.305. One enormous caveat to this early access—to be discussed in detail below—is the fact that controlled trial participants (most clinical trials overseen by the FDA have control groups) stand a good chance of receiving a placebo. Therefore, at least some controlled trial participants will unknowingly receive a placebo and thus not receive the experimental treatment.

²⁰ Most studies self-select for subjects afflicted only with the specific disease targeted by the drug, with any other conditions seen as potentially complicating or obscuring any data gathered. Unfortunately, those who are seriously or terminally-ill rarely have only one significant medical condition (serious illness usually including multiple co-morbidities), and would thus be disqualified from most clinical trials. Two excellent resources on co-morbidity and its impact on healthcare decisions—up to and including trial participation—are M. van den Akker, et al, *Multimorbidity in General Practice: Prevalence, Incidence, and Determinants of Co-occurring Chronic and Recurrent Diseases*, *J Clin Epidemiol*, 51:367–375 (1998), and M. Fortin, et al, *Prevalence of Multimorbidity Among Adults Seen In Family Practice*, *Ann Fam Med*, 3:223–8 (2005).

²¹ Elizabeth M. Rutherford, *The FDA and "Privatization"—The Drug Approval Process*, 50 *Food & Drug L.J.* 213 (1995).

²² 21 C.F.R. §312. Codified in 1987 but substantially amended by the 2009 regulations.

²³ *Id.* at §312.305(a)(2).

²⁴ *Id.* at §312.305(b)(2). Section 312.305 generally establishes a new multi-step program (to be discussed in detail below) for access for those excluded from participating in a clinical trial, but this is the key provision that inserts the FDA into the physician-patient relationship.

regulations—specifically section 312.305—is that they require the FDA to do a “risk-benefit” analysis of the physician’s decision before releasing the drug.²⁵

This paper argues that, while the FDA’s attempts to expand access to experimental drug treatment for the seriously and terminally-ill is laudable, it not only falls short of achieving its objective, it oversteps its statutory authority. The FDA is tasked with assessing the safety and efficacy of proposed drugs before they are released to the public, not with assessing the private, intimate discussions and decisions made between a patient and her physician. Individual autonomy is a central and deeply-held concept in this country, and it is an especially central concern in the context of healthcare decision-making.

This paper will address this fundamental point in five parts. Part I will discuss the history of the FDA’s statutory mandate to assess the safety and effectiveness of drugs. Part II will discuss and analyze the FDA’s effort to satisfy this mandate through the clinical trial process. Part III will discuss and analyze the FDA’s recent attempts to expand access to experimental drugs for the seriously and terminally-ill. Part IV will discuss the various legal and ethical concerns raised by expanding access. Part V will offer critiques of the FDA’s efforts, as well as recommending possible improvements that could both expand access and address the concerns discussed in Part IV.

I. BACKGROUND

A. FDA’s Mandate and the Statutory Basis for Regulation of Access

Since its inception in 1938, the FDA has been tasked with ensuring that all drugs offered for general use have been subjected to rigorous pre-market testing.²⁶ The Food Drug and Cosmetic Act

²⁵ Id.

²⁶ David G. Adams, *Food and Drug Law and Regulation*, p. 3 (2nd ed. 2011). Prior to the creation of the FDA, Congress had authorized the USDA’s Bureau of Chemistry to monitor drugs for any adulteration or misbranding. The Bureau could recommend that a violator be prosecuted by the Department of Justice, but the law did not authorize any pre-market review or intervention before distribution. Essentially, from the Federal government’s entrance into the arena of drug regulation in 1906 until the creation of the FDA in 1938, the regulatory scheme was entirely reactive and only addressed issues of adulteration or misbranding as they arose. With the passage of the FDCA, many of these early deficiencies were remedied. The new law authorized pre-market review of drugs, and established standards for the safety, identification, quality, and manufacture of those drugs. For the first time, the

of 1938 (“FDCA”) established two separate but complimentary schemes for the FDA’s new role as pre-market drug regulator.²⁷ In the first, the FDA relied on the adulteration and misbranding provisions of the FDCA to address claims about the integrity and quality of drugs.²⁸ This scheme closely tracked the early, pre-FDA attempts at intervention based on allegations from consumers, and was rarely invoked in the drug context. In the second and more expansive scheme, the FDA functioned as a pro-active gatekeeper assessing drug safety *before* marketing.²⁹ Utilizing the new drug application (“NDA”) provisions established by the FDCA³⁰, the FDA required any manufacturer of a new drug to submit a full report outlining the proposed drug’s safety, as well as several other quality control elements.³¹ In essence, the FDA could restrict—and even prohibit—the introduction of any new drug it found unsafe. This new authority effectively closed the enforcement gap inherent in the 1906 Act and allowed the FDA to play an integral role not only in the marketing and manufacture of new drugs, but in their very inception.³²

This new, more proactive role for the FDA was intensified with the passage of the Kefauver-Harris Amendments of 1962 (the “Drug Amendments”).³³ Throughout the late 1950’s, the drug Thalidomide was widely used in Europe as a morning sickness treatment for pregnant women. In an

Federal government was not just responding, ad hoc, to allegations of adulteration or misbranding, but was actually intervening before drugs were introduced onto the market.

²⁷ Daniel Kracov, *Food and Drug Law and Regulation*, p. 317 (2nd ed. 2011).

²⁸ FDCA of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1932) (codified as amended at 21 U.S.C. § 321(p) (2000)). Section 505(a) specifically refers to “adulteration” and “misbranding”.

²⁹ *Id.* at (b)

³⁰ *Id.* A “new drug” under the 1938 FDCA was defined as:

“Any drug ... the composition of which is such that such drug is not generally recognized, among experts ... as safe and effective for use under the conditions prescribed, recommended, or suggested ... [or] any drug ... the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions”.

³¹ FDCA of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1932) (codified as amended at 21 U.S.C. § 355(a)(1)(2000)). The FDCA of 1938 required that a full report of the investigations on a drug’s safety be submitted including a full list of the components of the drug, a full description of the method used in manufacturing and packing the drug, and samples of the drug and the proposed labeling.

³² Under the idea that industry would now have to actively anticipate an FDA pre-market response rather than just mitigate a post-marketing consumer complaint based on misbranding, etc.

³³ Pub. L. No. 87-781, 76 Stat. 780 (1962).

effort to introduce the drug in the U.S., the manufacturer applied to the FDA for a new drug approval.³⁴ Just before widespread distribution commenced, the FDA's commissioner put a hold on the drug due to emerging adverse reactions reports.³⁵ Ultimately, the U.S. was only minimally affected by the risks posed by Thalidomide, due in large part to the efforts of the FDA to keep the drug off the market.³⁶ This brush with pharmacological disaster led both the American people, and Congress, to demand more of FDA; and this charge came with commensurate authority. The Drug Amendments were almost as earth-shaking for the FDA and drug industry regulation as the FDCA itself because they charged the agency with assessing not only the safety of a proposed drug, but its efficacy for treating the targeted disease or condition as well.³⁷

II. THE FDA'S REGULATION OF ACCESS THROUGH THE CLINICAL TRIAL PROCESS

Under the Drug Amendments, the FDA must engage in a rigorous analysis of both safety and efficacy in every NDA it receives.³⁸ This pre-market, pre-approval analysis must conclude that the new drug's claims of safety and efficacy are supported by "substantial evidence".³⁹ The FDA has interpreted "substantial evidence" to mean evidence from adequate and well-controlled clinical studies.⁴⁰ And the FDA has historically required at least two independent studies to demonstrate minimal efficacy.⁴¹ Manufacturers of a new drug must obtain pre-market FDA approval by submitting an application containing data which confirms some baseline level of safety and

³⁴ Sam Peltzman, An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments. *The Journal of Political Economy*, Vol. 81, No. 5., pp.1051 (Sep.- Oct., 1973).

³⁵ Id.

³⁶ Much of Europe was not so fortunate, Thalidomide has been estimated to have caused serious birth defects in at least 10,000 children; this compared to only seventeen in the U.S. Linda Bren, Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History, *FDA Consumer Magazine*, Mar.-Apr. 2001, at 24.

³⁷ James N. Czaban & Geoffrey M. Levitt, *Food and Drug Law and Regulation*, p. 377 (2nd ed. 2011).

³⁸ FDCA § 505(d), 21 U.S.C. § 355(d).

³⁹ 21 C.F.R. § 314.105(c).

⁴⁰ FDCA § 505(d), 21 U.S.C. § 355(d).

⁴¹ Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices, Notice, 60 Fed. Reg. 39,180, 39,181 (1995).

efficacy.⁴² Integral to this drug approval process are clinical trials, especially those involving humans, and the FDA has aggressively regulated the process since 1962.⁴³

A. The Pre-Trial Approval Process

Following the passage of the Drug Amendments, the FDA established a multi-phase process for pre-market testing and approval of new drugs.⁴⁴ To accomplish the goal of rigorously assessing both safety and efficacy, the FDA required all prospective marketers and manufacturers of new drugs to file an Investigational New Drug application (“IND”) before commencing trials on human subjects.⁴⁵ The purpose of an IND application is to both alert the FDA that a drug sponsor is hoping to initiate clinical testing, and to offer data showing that this testing would at least not pose an unacceptable risk of harm to human subjects.⁴⁶ To further protect potential human subjects, the IND must contain a commitment from the sponsor to conduct the proposed clinical trials under the supervision of an Institutional Review Board (“IRB”).⁴⁷ The fundamental purpose of an IRB is to ensure that the rights and welfare of the human subjects are protected.⁴⁸ To facilitate this protective purpose, IRBs—and the INDs creating them—must operate under a vigorous Informed Consent (“IC”) rubric.⁴⁹ The principal thrust of the IC regulations are to ensure that the human subject’s participation in the trials is voluntary and knowing.⁵⁰ Potential candidates must be adequately

⁴² 21 U.S.C. § 355(b)(1) (2000).

⁴³ Id. § 355(b)(5).

⁴⁴ Czaban, at 364.

⁴⁵ 21 U.S.C. § 355(b)(5).

⁴⁶ Specific IND contents vary by drug, but all INDs must include the following basic elements: 1) an introductory statement and general investigative plan, 2) a set of comprehensive investigative protocols, 3) information on the proposed drug’s chemistry, manufacturing and controls, 4) pharmacology and toxicology information from pre-clinical studies, 5) a summary of previous human experience with the drug, etc. For the full list see 21 C.F.R. § 312.23.

⁴⁷ IRBs play a central role both in the IND and in the subsequent running of the trial. The IRB’s role in the Informed Consent context is more relevant to this paper, but the board must also take a sufficiently active role in the conduct of the study to ensure that pertinent medical and scientific standards are maintained, as well as maintaining general compliance with FDA standards and regulations. In essence, the IRB is the trial’s functional and logistical manager, as well as its moral compass. 21 C.F.R. § 312.56 and Czaban, at 362-63.

⁴⁸ 21 C.F.R. § 312.56.

⁴⁹ 21 C.F.R. § 312.50

⁵⁰ Id. Further, subjects cannot be forced to waive any potential future claims for negligence against the study’s sponsor, and may withdraw consent at anytime without penalty or loss of benefit. In an attempt to balance the

informed about risks, possible benefits, alternative courses of treatment and other relevant information before consenting.⁵¹

B. The Clinical Trial Process

Once the drug sponsor has gathered sufficient data evidencing safety for introduction into a human subject pool and compiled a satisfactory IRB protocol and the FDA has approved these efforts, the actual clinical trial may begin.⁵² The FDA has created a multi-phase trial process that consists of three principal phases followed by one possible, though not always mandatory, post-approval phase.⁵³ Phase 1 involves the initial administration of the experimental drug to human subjects.⁵⁴ The stated purpose of this initial data gathering is “to determine the metabolism and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness”.⁵⁵ Although any early evidence on effectiveness is recorded and reported to the FDA, the central goal of Phase 1 testing is to determine the metabolism and toxicity properties of the new drug in relation to use in healthy test subjects.⁵⁶ Phase 1 trials really only demonstrate that a proposed experimental drug will not seriously harm a healthy subject; therefore it is important not to rely too heavily on results from this early stage for potential

autonomy of the subject with concerns over her safety, the FDA promulgated regulations providing a narrow exception to the general IC requirements. In cases where: 1) a subject is in a life-threatening situation and all other available treatments are unproven or unsatisfactory; or 2) the subject cannot provide effective consent due to his or her medical condition; or 3) treatment must be administered before consent from a legal representative is feasible, the IC requirements may be lessened or in some other way mitigated. The exception also requires that the use of the experimental drug holds the potential to benefit the patient, that the investigation could not practicably be carried out without the waiver, and that additional patient protections are provided.

⁵¹ Id. §50.25

⁵² James N. Czaban & Geoffrey M. Levitt, *Food and Drug Law and Regulation*, pp. 361-62 (2nd ed. 2011).

⁵³ Id. at 364.

⁵⁴ 21 C.F.R. §312.21(a)(1).

⁵⁵ Id.

⁵⁶ Susan Okie, *Access Before Approval—A Right to Take Experimental Drugs?*, 355 *New Eng. J. Med.* 437, 438 (2006).

disease treatment opportunities.⁵⁷ Finally, the drug’s sponsor must derive sufficient pharmacokinetic and general pharmacological data from Phase 1 trials to devise appropriate and safe Phase 2 studies.⁵⁸

Phase 2 trials mark the beginning of experimental drug testing on subjects with the targeted illness.⁵⁹ Once the drug has been shown to pose no immediate risk to healthy test subjects, it is introduced to a much larger test population, which includes individuals suffering from the disease or illness the new drug purports to treat.⁶⁰ The trial group may include as many as several hundred subjects, and the stated purpose of this phase is to “obtain evidence of the drug’s effectiveness against the targeted disease, to explore further risk and side-effect issues and to confirm preliminary data regarding optimal dosage ranges.”⁶¹ Phase 2 trials typically run for about two years⁶², and the FDA requires that they operate as adequate and well-controlled studies allowing for clear identification of the effects of the drug, as well as differentiation between the effects of the study drug and any effects emanating from other factors.⁶³ To effectively differentiate between the effects of the study drug and any effects arising out of other sources, most trials will involve randomly assigned control groups receiving either placebos or the “best current” treatment; results from these groups are then given a blind outcome assessment.⁶⁴

Because Phase 2 study participants have the potential for unknowingly receiving either the experimental study drug, the “best currently available” treatment or a placebo, sponsors must explicitly inform participants that they are involved in an experimental study and *not* experimental treatment.⁶⁵ Further, most sponsors call study participants subjects rather than patients to emphasize

⁵⁷ In essence, this early testing may produce some data on efficacy, but its relevance to the treatment of specific diseases is fundamentally limited by the nature and composition of the testing sample.

⁵⁸ James N. Czaban & Geoffrey M. Levitt, *Food and Drug Law and Regulation*, p. 364 (2nd ed. 2011).

⁵⁹ *Id.*

⁶⁰ 21 C.F.R. § 312.21(b).

⁶¹ *Id.*

⁶² *Id.*

⁶³ P.P. De Deyn & R. D’Hooge, *Placebos in Clinical Practice and Research*, 22 *J. Med. Ethics* 140-141 (1996).

⁶⁴ *Id.*

⁶⁵ Frances H. Miller, *Symposium Trust Relationships Part 1 of 2: Trusting Doctors: Tricky Business When it Comes to Clinical Research*, 81 *B.U. L. Rev.* 423-433 (2001). This explicit distinction between “experimental treatment”

this distinction.⁶⁶ To further cement this distinction, the FDA has mandated that Phase 2 studies are not meant to function as treatment but are solely intended to evaluate whether the experimental drug offers therapeutic benefits.⁶⁷ If the drug sponsor is able to gather adequate data evidencing effectiveness against the targeted disease, indications for optimal dosage, and showing minimal negative side-effects from usage, the drug may move on to the third and final stage of pre-market testing.⁶⁸

Phase 3 clinical trials commence once the drug's sponsor has gathered and presented this "preliminary evidence suggesting [that the] effectiveness of the drug" adequately balances out the risk to the patient, and the FDA accepts the data.⁶⁹ The primary goal of a Phase 3 trial is to collect the data necessary to meet the safety and efficacy standards required by the FDCA, which the FDA has interpreted to mean any and all data needed to "evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling" and prescription.⁷⁰ Once an adequate amount of data on the drug's risk-benefit profile has been gathered, the sponsor files a summary NDA with the FDA's Center for Drug Evaluation and Research for final marketing approval.⁷¹ The FDA must then decide whether to request additional safety and efficacy testing, or approve the drug for introduction into the market and use by the general public.⁷² If the FDA requests a further level of

and "experimental study" is central to the issue of patient autonomy because it clearly demonstrates that the FDA believes that, as long as a potential participant is not unduly influenced by hopes for an experimental treatment or "cure", they may make a free choice to participate.

⁶⁶ Id.

⁶⁷ 45 C.F.R. § 46.109 (2007). In the second, wider phase of testing, the IRB's task of creating and enforcing an adequate informed consent rubric would seem to be much more complicated. In Phase 1, subjects are presumably participating purely for remunerative purposes, and the potential ethical dilemmas are minimal. In Phase 2 however, participants may be motivated by much more complicated incentives (as will be discussed below), and the IRB must respond appropriately when devising an IC scheme.

⁶⁸ Id.

⁶⁹ 21 C.F.R. § 312.21(c).

⁷⁰ Id. This final pre-market phase may involve up to several thousand subjects, frequently takes place in multiple locations, and includes both controlled and uncontrolled testing.

⁷¹ FDA's Drug Review Process, Food and Drug Admin., www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (last accessed 10/18/12).

⁷² Id.

testing, there are two options at their disposal. The agency may employ either a fourth trial phase⁷³, or conduct what is called a Risk Evaluation and Mitigation Strategy (“REMS”)⁷⁴. If, however, the FDA concludes that the drug’s risk-benefit profile (as measured by safety and efficacy data) is satisfactory, it will approve the drug for introduction into the public market.

Historically, this process has taken roughly 12 years to complete⁷⁵, and pharmaceutical companies claim that the cumulative cost can average up to one billion dollars for each new drug.⁷⁶ Due to these cost and time pressures, the FDA has faced consistent pleas from the drug industry to accelerate the pace of drug approvals.⁷⁷ The FDA also, however, has been faced with several scenarios which seem to illustrate the importance of a robust and detailed pre-clearance process.⁷⁸ These often well-publicized adverse outcomes add pressure to an agency trying to balance consumer safety, industry innovation, and patient autonomy.

III. A HISTORY OF THE FDA’S ATTEMPTS TO EXPAND ACCESS

A. The Aftermath of the 1962 Amendments: *U.S. v. Rutherford* and Treatment INDs

Since the passage of the 1962 amendments and the new mandate to assess both safety and effectiveness, the FDA has been under sustained pressure to accelerate the drug approval process.⁷⁹

Pharmaceutical companies have argued that the U.S. lags far behind other nations in both drug

⁷³ Phase 4 trials may be initiated pursuant to 21 C.F.R. § 314(h)’s accelerated approval provisions, they may also be agreed to between the sponsor and FDA to further address safety issues, or they may be voluntarily conducted by the sponsor to expand labeling for the drug. Further, a fourth phase of testing may be required under the FDAAA (James N. Czaban & Geoffrey M. Levitt, *Food and Drug Law and Regulation*, p. 364 (2nd ed. 2011)).

⁷⁴ FDCA § 505-1(a)(1), 21 U.S.C. § 355-1(a)(1), added by Pub. Law No. 110-85, tit. IX. REMS is provided for under the authority of the FDAAA, and FDA may require a sponsor to include a REMS in its NDA if the agency deems it necessary to ensure that the benefits of the drug outweigh the risks.

⁷⁵ Elizabeth M. Rutherford, *The FDA and “Privatization”—The Drug Approval Process*, 50 Food & Drug L.J. 203, 213 (1995).

⁷⁶ Joseph DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ., 151 (2003).

⁷⁷ Leonard G. Shifrin, *Lessons from the Drug Lag: A Retrospective Analysis of the 1962 Drug Regulations*, 5 Harv. J.L. & Pub. Pol’y 91 (1982).

⁷⁸ Gardiner Harris, *FDA Official Admits “Lapses” on Vioxx*, www.nytimes.com/2005/03/02/politics/02fda.html (last accessed 10/18/2012). The Vioxx incident is merely the most recent and high-profile of a number of dramatic recalls of approved drugs from the market due to significant, and sometimes foreseeable, health risks.

⁷⁹ Leonard G. Shifrin, *Lessons from the Drug Lag: A Retrospective Analysis of the 1962 Drug Regulations*, 5 Harv. J.L. & Pub. Pol’y 91 (1982).

approval rates and the time it takes to get a drug to market, and patient advocacy groups maintain that these shortcomings put their members at grave risk.⁸⁰ The first major challenge to the agency's new role—created by the Drug Amendments—of assessing a drug's "safety and effectiveness" came in 1979 when a group of terminally ill cancer patients sought to enjoin the FDA from prohibiting the dissemination of a new, unapproved cancer drug.⁸¹ The cancer patients sought to establish a right to the unapproved drugs—and thus escape the reach of the FDA's safe and effective requirement—due to the end-stage or terminal nature of their illness.⁸² The Supreme Court explicitly rejected this position, holding that the FDA was well within its statutory authority when it interpreted the FDCA to encompass even those drugs aimed at benefitting the terminally ill.⁸³ Further, in discussing the importance of the new effectiveness prong of the FDA's analysis, the Court held that "there is a special sense in which the relationship between drug effectiveness and safety has meaning in the context of incurable illnesses [because] an otherwise harmless drug can be dangerous to any patient if it does not produce its purported therapeutic effect."⁸⁴ In the first major challenge to the FDA's authority to limit access to experimental drugs under the new safe and effective pre-market analysis, the Court found that the FDA not only possessed the requisite authority to limit access, it was obligated to do so. However, eight years after this setback for patient choice, the FDA introduced a new avenue of access for terminally ill patients.

⁸⁰ Id. Shifrin mentions that, by the 1980's, the U.S. had fallen behind other industrialized nations not only in drug approval times, but even in the gross number of medications that ultimately made it to market. Pharmaceutical companies concluded, logically it would seem, that the ordeal of the approval process ended up generally reducing the industry's incentive to even introduce experimental drugs.

⁸¹ *United States v. Rutherford*, 442 U.S. 542 (1979).

⁸² Id. at 546.

⁸³ Id. at 551-552. The majority went on to elaborate that the terminally ill (because of the nature of their illness and the psychological and emotional vulnerability resulting from it) are perhaps the most at-risk members of the group FDA is mandated to protect, and thus the statutory obligation to pre-authorize drug use is most critical in this scenario.

⁸⁴ Id. at 556. The Court went on to state that "[f]or this reason, even before the 1962 Amendments incorporated an efficacy standard into new drug application procedures, the FDA considered effectiveness when reviewing the safety of drugs used to treat terminal illness." Id.

In 1987, the FDA created the Treatment IND in an attempt to expand access to experimental drugs for the seriously and terminally-ill.⁸⁵ The Treatment IND was a significant breakthrough for both advocacy groups and patients because it provided access to investigational drugs *outside* of the context of controlled clinical trials.⁸⁶ This new IND option further modified the standard application process in that it allowed access—for certain patient groups—to an experimental drug if sponsors could establish that: (1) the drug is intended “to treat a serious or immediately life-threatening disease”, (2) there is “no comparable or satisfactory alternative” treatment, (3) the drug “is under investigation in a controlled clinical trial”, and (4) the sponsor is “actively pursuing market approval”.⁸⁷ The Secretary of Health and Human Services (“HHS”)⁸⁸ is empowered to decide whether there is adequate evidence of both safety and effectiveness for the proposed use of the drug.⁸⁹ Despite its initial promise, patients and advocates quickly found that the new scheme ultimately did little to expand access for the critically ill.⁹⁰

⁸⁵ Investigational New Drug, Antibiotic, and Biological Drug Product Regulations. 52 Fed. Reg. 19,466 (1987). This has been most recently codified in 21 C.F.R. §§312.305 and 312.320 (2011).

⁸⁶ 21 C.F.R. §312.34. This new option for access was so ground-breaking because it allowed patients being treated outside of controlled trials—who may have been previously disqualified or unable to participate for various reasons—to still have a chance at getting the drug. Clinical trials may, and often do, have rigorous standards for participation. Most studies self-select for subjects afflicted only with the specific disease targeted by the drug, with any other conditions seen as potentially complicating or obscuring any data gathered. Unfortunately, those who are seriously or terminally-ill rarely have only one significant medical condition (serious illness usually including multiple co-morbidities), and would thus be disqualified from most clinical trials. Two excellent resources on co-morbidity and its impact on healthcare decisions—up to and including trial participation—are M. van den Akker, et al, *Multimorbidity in General Practice: Prevalence, Incidence, and Determinants of Co-occurring Chronic and Recurrent Diseases*, J Clin Epidemiol, 51:367–375 (1998), and M. Fortin, et al, *Prevalence of Multimorbidity Among Adults Seen In Family Practice*, Ann Fam Med, 3:223–8 (2005).

⁸⁷ 21 C.F.R. §§312.305(a)(1), 312.320(a)(1)(i), 312.320(a)(2) (2011) respectively.

⁸⁸ The Secretary is a figure who, for the purposes of the FDA’s analysis in these matters, is the higher authority. In essence, although the FDA operates with great autonomy within the federal government, they ultimately answer to HHS, under whose delegatory umbrella they fall.

⁸⁹ 21 C.F.R. §312.320(a)(3)(i). There would be very little efficacy data at this point and the Treatment IND invests a significant amount of discretionary authority in the Secretary, allowing her to determine—on what is likely very little information—whether there is “substantial evidence” of “safety” and “effectiveness”.

⁹⁰ Jerome Groopman, *The Right to Trial; Should Dying Patients Have Access to Experimental Drugs?*. The New Yorker, Dec. 18, 2006, at 40-47.

As implemented by the FDA, the Treatment IND option effectively foreclosed potential candidates from gaining access until well into the third phase of ongoing trials.⁹¹ Citing concerns over both consumer and industry protection, the FDA argued that allowing access at any time before Phase 3 would endanger patients as well as potentially reduce the number of willing participants in future experimental drug trials.⁹² As a result of this concern, the Treatment IND is practically only available in Phase 3 or beyond.⁹³ The FDA did carve out one very narrow exception to this rule—in the case of an immediately life-threatening disease when all other treatment options have been exhausted—by allowing access between the post-Phase 2 period and the beginning of Phase 3.⁹⁴ However, even this patient “in extremis” cannot get access *before* the conclusion of Phase 2, and even then the Commissioner may deny access.⁹⁵ Another aspect of the Treatment IND which ultimately limited program usage was originally intended as a cost-control device to protect consumers.⁹⁶ Burdened by these issues—and widely criticized as both “inadequate and

⁹¹ 21 C.F.R. §312.34(a) and Groopman at 45-47.

⁹² Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. On Gov. Operations (Concerning the FDA’s Proposals to Ease Restrictions on the Use and Sale of Experimental Drugs), 100th Cong. 71-72 (1987). The FDA’s then-Commissioner, Frank Young, testified at the hearing that allowing patient access at any time before Phase 3 could pose a serious danger to those seeking treatment, as well as potentially reducing the number of people willing to participate in future trials. The Commissioner argued that if an individual could pursue new or experimental treatment through a Treatment IND, they would have no incentive to actually participate in a trial. In essence, opening up access to experimental drugs outside of the context of a trial effectively removes any and all incentive for participating in a trial. It went unmentioned in the 1987 hearing, but the subtext here is the fact that at least some controlled trial participants will unknowingly receive a placebo rather than the new drug, and thus be potentially worse off than if they had merely remained on whatever treatment they had previously undergone. It would follow that any rational—and seriously-ill—person would opt for the Treatment IND and be guaranteed the new drug, making it difficult for any clinical trial to get out of Phase 1 and begin efficacy testing.

⁹³ Id. §312.34(a).

⁹⁴ Id. In essence, a patient may get access after Phase 2 testing and data-gathering has concluded but before the Phase 3 process begins.

⁹⁵ Id. §312.34(b)(3)(i)(A)-(B). The Commissioner has the discretion to deny a Treatment IND application even in this extreme situation if she determines that the “available scientific evidence fails to show that the drug is effective for its intended use or provides reasonable grounds which indicate that the patient would be exposed to an unreasonable and significant additional risk of illness.” Id. This is essentially the same cost-benefit analysis done in the case of a “seriously ill” or “terminally ill” patient under the 1987 regulations.

⁹⁶ Id. §312.7(d)(3). The 1987 regulations prohibited the pharmaceutical industry from profiting on a Treatment IND and restricted recovery to the cost of research, development and manufacture. This removal of the profit-motive, along with the industry’s concern over the potential for fewer trial subjects, effectively eliminated most pharmaceutical companies from participation in Treatment INDs. Because the FDA does not mandate participation in the program, many companies simply refused to offer their developmental drugs outside of the trial context.

underutilized”⁹⁷—the Treatment IND program was eventually viewed even by the FDA as a failed attempt to expand access.⁹⁸ In an effort to remedy this shortcoming, and expand access “to investigational products intended for serious diseases”, Congress stepped in and passed the Food and Drug Administration Modernization Act of 1997 (“FDAMA”).⁹⁹

B. The Patient, the Physician and the FDA: The FDAMA and the FDA’s 2009 Regulations

In passing the FDAMA, Congress explicitly set out to establish a route to access for the individual patient excluded—for whatever reason—from the clinical trial process.¹⁰⁰ Specifically, section 360bbb states that individual patients seeking treatment outside of clinical trials and “acting through a physician...may request from a manufacturer or distributor...an investigational drug or investigational device,” subject to certain conditions.¹⁰¹ Section 360bbb of the FDAMA, like the Treatment IND before it, maintains the two-tier test for serious and terminally ill patients.¹⁰² Functionally, section 360bbb makes no mention of FDA supervision or input outside of determining whether the proposed new treatment has been shown to be at least minimally safe and effective.¹⁰³ Under the new framework, the decision to seek an experimental treatment is one for the patient and her physician alone, with the FDA merely deciding whether initial clinical trials have established some level of safety and efficacy.

⁹⁷ James N. Czaban & Geoffrey M. Levitt, *Food and Drug Law and Regulation*, p. 369 (2nd ed. 2011)

⁹⁸ FDA, *Speeding Access to Important Therapeutic Agents*, available at www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies/default.htm. In promulgating the regulations that replaced the 1987 rules, the FDA stated that the Treatment IND process had ultimately failed because it had led to dramatically “disparate access to treatment” among seriously and terminally ill patients. 71 Fed. Reg. 75,147, 75,149 (2006).

⁹⁹ Pub. L. No. 105-115, 111 Stat. 2296 (1997).

¹⁰⁰ See supra note 118.

¹⁰¹ 21 U.S.C. §360bbb(b) (2010). Subsection (b)(1) requires an individual patient's doctor to determine that: 1) the patient has exhausted treatment options, and 2) the “probable risk to the person from the investigational drug or investigational device is not greater than the probable risk from the disease or condition.” Subsections (b)(2) and (b)(3) set forth the determinations to be made by the HHS Secretary, who delegates this function to the FDA Commissioner. Repeating the mandate of the 1962 Amendments, subsection (b)(2) states that the Secretary—acting through the FDA—must determine “that there is sufficient evidence of safety and effectiveness” to support the requested use of the drug.

¹⁰² Id. §360bbb(c).

¹⁰³ Id. §360bbb(1)-(3).

In response to growing criticism over the discrepancy between the promise of expanded access under the §360bbb framework and the actual state of things,¹⁰⁴ the FDA created new rules for its developmental drugs access scheme.¹⁰⁵ The final rules, promulgated in 2009, established three population categories eligible for expanded access: 1) individual patients (including emergency requests, formerly known as “compassionate” or “emergency use” INDs), 2) intermediate-sized patient groups, and 3) general access (also known as a treatment protocol).¹⁰⁶ Further, the new regulations established a baseline criteria for expanded access, stating that the FDA must determine: 1) that “the patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;” 2) “[t]he potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated;” and 3) “[p]roviding the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.”¹⁰⁷ Under the 2009 rules, the FDA evaluates the operative criteria on a sliding scale, which in some cases could provide access to drugs based on as little as early Phase 1 safety data.¹⁰⁸ The rules also clarified that eligible patients must have a serious disease or condition, but do not need to be currently considered seriously-ill with that specific disease or condition.¹⁰⁹

In promulgating the new rules, the FDA intended to clarify existing procedure, create new categories of expanded access, and “improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and who

¹⁰⁴ See supra note 118.

¹⁰⁵ See Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40,900, 40,901 (Aug. 13, 2009). Later codified in 21 C.F.R. §§312 & 316.

¹⁰⁶ Id.

¹⁰⁷ See 71 Fed. Reg. at 75,150-51.

¹⁰⁸ Id. at 75,151.

¹⁰⁹ See supra note 117.

may benefit from such therapies.”¹¹⁰ In an attempt to balance the agency’s mandate to foster research and development while also protecting potential consumers, the FDA sought to “appropriately authoriz[e] access to promising drugs while protecting patient safety and avoiding interference with the development of investigational drugs.”¹¹¹ To further this effort at balancing the competing interests involved in the expanded access context, the FDA also promulgated new regulations to allow drug sponsors to recover the cost of expanded access to investigational drugs.¹¹² Specifically, drug sponsors can recover the direct costs of making the investigational drug available, which are typically limited to the costs of manufacturing and shipping the drugs as well as monitoring the treatment protocol.¹¹³ Finally, in yet another attempt to balance the interests of patients, physicians, and pharmaceutical manufacturers with the pressures of the FDA’s mandate to evaluate new and experimental drugs, the new rules required that doctors overseeing patients with access to investigational drugs outside of clinical trials report both positive and adverse outcomes to the FDA.¹¹⁴ Beyond ensuring that each instance of expanded access does not interfere with a sponsor’s clinical testing of the proposed new drug, this measure seems to facilitate an expanded access program actually making a contribution to the FDA’s evaluation of a drug.

Taken together, Congress’ creation of a pathway to access—by passing section 360bbb of the FDAMA—and the FDA’s subsequent promulgation of the 2009 rules are a significant development for terminally-ill patients. However, while these measures seem to offer an increased opportunity for patient autonomy and decision-making, a single provision in the FDA’s new rules stands as both an unprecedented expansion of the agency’s authority as well as a significant obstacle to expanded access. Section 312.305 of the 2009 regulations, which authorizes the FDA to assess the

¹¹⁰ See supra note 125.

¹¹¹ Id. at 40,940.

¹¹² Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. 40,872 (Aug. 13, 2009). Although, as the following sections will discuss, only allowing recovery of direct costs still functions to limit industry incentive to participate. Sections 4 and 5 will discuss the implications of this shortcoming and offer a potential solution.

¹¹³ See 21 C.F.R. §312.8(d)(1)-(2) (2011).

¹¹⁴ Id. at §312.310(c)(2) (2011).

“reasonableness” of a patient’s decision to take a developmental drug,¹¹⁵ threatens to undermine the promise of expanded access created by §360bbb. Without corrective action, this single provision could prevent seriously or terminally-ill patients from accessing the developmental treatments Congress intended to authorize in the FDAMA.

IV. THE ETHICAL AND LEGAL IMPLICATIONS OF EXPANDING ACCESS

While the FDA has attempted—through the various means described above—to expand access to developmental drugs for the terminally ill, these efforts have only served to restrict and complicate matters. Opponents of deregulation argue that the risk of expanding access outweighs any potential benefit,¹¹⁶ but while there are considerable legal and ethical concerns implicated by expanded access, individual patient autonomy should trump the FDA’s authority to regulate in this area. When analyzing the varied and competing interests involved in the regulation of developmental drugs, and the potential ethical and legal implications created by their interaction, addressing each of the key actors in the enterprise is worthwhile.

A. The Seriously-Ill Patient

The argument advanced most often by both patients and their advocates is that, when suffering from a serious or terminal illness, time is of the essence.¹¹⁷ Completion of the full clinical trial process *averages* 12 years,¹¹⁸ and many patients simply cannot wait this long. Abigail Burroughs—after whom the Abigail Alliance is named—is a striking example of a young person who lost her battle with cancer while a promising developmental drug slowly progressed through the clinical trial process.¹¹⁹ This tragic outcome illustrates the moral hazard created by withholding a potentially life-saving drug, because it might be dangerous, while the patient slowly succumbs to

¹¹⁵ 21 C.F.R. §312.305(a)(2) (2011).

¹¹⁶ Ralph W. Moss, *No Way to Save a Life: Allowing Terminally Ill Cancer Patients Access to Drugs That Have Not Completed Clinical Trials is a Dangerous Move*, *New Scientist*, June 3, 2006, at 21.

¹¹⁷ Groopman, *supra* note 108.

¹¹⁸ Joseph DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 *J. Health Econ.* 151, 181 (2003).

¹¹⁹ Robert Manor, *FDA Seeks to Ease Access to New Drugs*, *Chi. Trib.*, Dec. 12, 2006, at C1.

their illness.¹²⁰ Referring to this dilemma, a former senior FDA official said that “delaying new treatments for the sake of generating more rigorous and complete medical evidence helps patients, to a point. But in the field of cancer...the FDA’s strict posture is probably overkill...and many more patients will die waiting for the good medicines than from using the bad ones.”¹²¹ When weighing the risk of imminent death from an untreated or untreatable illness and potentially suffering an adverse reaction to a developmental drug that could be life-saving, it is the individual actually facing death who should ultimately make that decision.¹²²

A discussion of this patient-directed risk-benefit analysis is not complete without a discussion of the forces and pressures inherent in the decision. The most glaring and obvious factor would seem to be the acute physical condition of the patient herself.¹²³ Many commentators argue that not only is it impossible for an patient *in extremis* to make this decision objectively and reasonably, it is unethical for a physician—and the government tasked with protecting that patient—to accept whatever decision the individual happens to make.¹²⁴ This difficulty is compounded by the fact that many seriously-ill patients do not qualify for participation in clinical trials and thus this type of access is their only option.¹²⁵ In essence, a person with their very life at stake and no other options is at the greatest risk of making a poor decision, and thus requires an even higher level of protection.¹²⁶

¹²⁰ Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 Rutgers L. Rev. 883 (1996).

¹²¹ Scott Gottlieb, M.D., *FDA’s Caution Hurting Patients*, Oklahoman, May 30, 2005, at 19A.

¹²² *Abigail Alliance*, 495 F.3d 699 (D.C. Cir. 2007). This question was raised by the Abigail Alliance in its briefs leading up to the rehearing en banc and later discussed by the court in its opinion.

¹²³ George J. Annas, *Faith (Healing), Hope, and Charity at the FDA: The Politics of AIDS Drug Trials*, 34 Vill. L. Rev. 771 (1989).

¹²⁴ *Id.* Annas comes to the conclusion that, at least in the AIDS context, it was bad public policy to effectively facilitate the false hope for a cure in seriously ill individuals.

¹²⁵ *Supra* note 99. Further, even if they could qualify for a trial, both the time and expense of trial participation may make that option impossible. See *supra* Part III A generally.

¹²⁶ Similar to the conclusion of the majority in *Rutherford*.

While there are definable limits to individual autonomy and decision-making,¹²⁷ the patient in this context is seeking a potentially life-saving experimental treatment under the professional supervision of their physician.¹²⁸ Further, and this fact distinguishes the expanded access patient from the physician-assisted suicide patient, the ultimate goal in seeking experimental treatment is an extension of life. In the end-of-life context, many patients are either seeking to withdraw care or directly end their life; and it is exactly this decision that triggers the government's interest in protecting their life.¹²⁹ By contrast, the patient here is struggling to prolong their life by attempting to access all available treatment options. It seems counterintuitive that, when a patient seeks death with the assistance of a physician the government must immediately intervene in the interest of life, but when a terminally-ill patient struggles to extend their life through experimental treatment, the government has decided that the potential risks outweigh any benefit.¹³⁰ As the former FDA official said, more patients die waiting for good drugs than would have died from taking bad ones.¹³¹ But the patient is not the only interest to be weighed in this analysis.

B. The Pharmaceutical Manufacturer

Although it might seem at first to be in a pharmaceutical manufacturer's best interest to support deregulating access to their drugs—it would allow drug makers to sell their product at market value with minimal testing—several serious concerns arise. The first is the risk of tort liability arising

¹²⁷ A key example of this concept is the fact that nearly every state has either banned or placed significant restrictions on physician-assisted suicide. While—at the time of this writing—two states allow it (Oregon and Washington), every other state has effectively banned the practice. The Supreme Court affirmed the states' ability to limit patient autonomy by holding that there is neither a due process nor equal protection right to physician-assisted suicide. See *Washington v. Glucksberg*, 521 U.S. 702 and *Vacco v. Quill*, 521 U.S. 793 (1997). Both cases stand as a testament to the idea that the government can, in the name of protecting its citizen's well-being, significantly limit individual autonomy.

¹²⁸ Janet L. Dolgin & Lois L. Shepherd, *Bioethics and the Law* 48 (2005). And this seems to be the crux of the plaintiff's argument in both *Rutherford* and *Abigail Alliance*.

¹²⁹ See *Washington* and *Vacco*, supra note 138.

¹³⁰ This is especially relevant in relation to section 312.305 of the 2009 regulations (discussed below).

¹³¹ Supra note 132.

out of pre-approval usage.¹³² As with any drug, there would be risks inherent in the use of a developmental drug; but in this scenario—operating outside of the tight controls of a clinical trial—predicting or anticipating any adverse reactions to the drug would be extremely difficult.¹³³ The potential for widespread harm to a particularly vulnerable patient population is only increased by the fact that, without scientifically-derived protocols directing distribution and a dramatically increased subject base, any response to an adverse event would be severely hampered.¹³⁴

Despite attempts at disclaiming liability or instituting informed consent protocols, pharmaceutical manufacturers would likely face a tidal wave of litigation arising out of expanded access and the heightened likelihood of adverse events.¹³⁵ It is hard to imagine that the prospect of endless litigation and costly settlements would not discourage both pharmaceutical innovation and development, especially where the speed at which the creation and marketing of new drugs already lags so far behind other countries.¹³⁶ Beyond the immediate legal concerns, this issue poses the ethical question of whether allowing access to a relatively small number of individuals is worth potentially stifling an industry capable of helping a vast number of people.¹³⁷

C. The Regulator

As discussed above, the role of the regulator in this context is as seemingly simple and straightforward as it is enormous. The FDA must—following the passage of the 1962 Amendments

¹³² Elizabeth Weeks Leonard, *Right to Experimental Treatment: FDA New Drug Approval, Constitutional Rights, and the Public's Health*, 37 J.L. Med. & Ethics 269 (2009).

¹³³ *Id.* at 272.

¹³⁴ *Id.* Predicting patient response to any given drug would be complicated by the fact that whatever co-morbidities they might possess (which would very likely have prevented them from entering a clinical trial) could interact with the developmental drug. In essence, the complicated nature of their condition comes into play outside of the relatively safe confines of a controlled clinical study. The irony here is powerful.

¹³⁵ *Id.* at 273. This increased risk of adverse side effects raises the potential for manufacturer liability in areas as diverse as product liability, failure to warn, fraud, and negligence.

¹³⁶ *Supra* note 92.

¹³⁷ While this question does seem to implicate the Utilitarian argument (which would presumably find that—because helping a few people potentially endangers many more—expanding access to developmental drugs is *per se* unacceptable), this paper will argue in the final section that concerns over individual autonomy can be balanced with Utilitarian concerns over not harming the many to help the few (a balance achieved through thoughtful regulatory policy).

to the FDCA—assess all new drugs for both safety and efficacy.¹³⁸ To accomplish this task the FDA instituted the multi-phase clinical trial process,¹³⁹ and many argue that challenging this process constitutes a direct challenge to the FDA’s very legitimacy and purpose.¹⁴⁰ If the FDA is not authorized or endowed with the authority to effectively regulate—in order to protect the public—new drugs, then it seems to no longer serve a purpose.¹⁴¹

The FDA argues, as it did in *Abigail Alliance for Better Access to Developmental Drugs v. Eschenbach*,¹⁴² that without completion of both Phase 1 and Phase 2 trials, there will be inherent uncertainty concerning a new drug’s safety and effectiveness.¹⁴³ Phase 1 testing alone—according to many experts—is not sufficient to ascertain either safety or effectiveness for humans, and especially not those actually afflicted with the targeted disease.¹⁴⁴ Further, most drugs in Phase 1 trials are not “life-saving”, and without complete testing a large number of ineffective and potentially dangerous drugs could find their way to the patient population.¹⁴⁵ Without the full “safety and efficacy” assessment completed by the FDA in the first two phases of clinical trials, a developmental drug that ended up having a smaller than expected benefit and a larger than expected adverse effect would not be recognized until large numbers of patients had been exposed to it.¹⁴⁶ An effective dismantling of the FDA’s pre-market screening and monitoring system could ultimately permit the drug industry to push potentially dangerous products to market in a manner not seen since the Thalidomide scare.¹⁴⁷

¹³⁸ Supra note 36.

¹³⁹ See Part II B.

¹⁴⁰ Leonard, supra note 130, at 273.

¹⁴¹ Id.

¹⁴² *Abigail Alliance*, 445 F.3d 470, 473 (D.C. Circuit 2006).

¹⁴³ See Lois K. Perrin, Note, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69 S. Cal. L. Rev. 105 (1995).

¹⁴⁴ Groopman, supra note 120. As discussed above, Phase 1 testing really only assesses the metabolic response to the drug in *healthy* individuals; it provides no data on how patients with that specific disease would respond. That data-gathering does not begin until Phase 2.

¹⁴⁵ Moss, supra note 120.

¹⁴⁶ Perrin, supra note 141, at 144.

¹⁴⁷ Which led to the 1962 Amendments mandating “safety and effectiveness” assessment. See *Abigail Alliance* at 482.

The FDA also claims that drug sponsors would not be able to fill their clinical trials if there was a way for patients to circumvent the existing restrictions.¹⁴⁸ Without a reason to participate in a controlled trial—which carries the chance of receiving a placebo treatment instead of the new drug—¹⁴⁹patients afflicted with the targeted illness would have no incentive to participate.¹⁵⁰ Drugs sponsors would be unable to move out of Phase 1 and into Phase 2 “safety and effectiveness” studies without sufficient numbers of subjects suffering from the targeted disease or illness.¹⁵¹

V. WHAT THE FDA’S 2009 REGULATIONS GOT RIGHT, WHAT THEY GOT WRONG, AND WHAT CAN BE DONE ABOUT IT

Although the FDA purportedly promulgated its 2009 regulations in an effort to expand access to developmental drugs, they ultimately only served to reinforce the agency’s existing practice. Further, by interposing a distant, outside regulator¹⁵² into a decision-making process that should be both deeply personal and individualized,¹⁵³ the FDA’s regulations exceeded the agency’s statutory authority. In an attempt to both critique the agency’s action and offer potential solutions, it would be helpful to divide the analysis and look first to the statutory and practical problems created by the new rules. Part B will then offer potential solutions for an expanded access scheme which seeks to address the concerns of patients, the industry, and the FDA.

A. The FDA Exceeded Its Statutory Authority in Promulgating §312.305(a)(2) of the 2009 Regulations

In promulgating the 2009 rules—specifically §312.305(a)(2), which delegates to the FDA the risk-benefit analysis determining whether a patient should receive a developmental drug—¹⁵⁴the

¹⁴⁸ *Abigail Alliance* at 482, 483.

¹⁴⁹ See supra note 109.

¹⁵⁰ Groopman, supra note 120.

¹⁵¹ *Id.*

¹⁵² 21 C.F.R. §312.305(a)(2) (2011).

¹⁵³ As mandated by §360bbb of the FDAMA.

¹⁵⁴ See supra note 24.

FDA has exceeded the statutory mandate of the FDAMA.¹⁵⁵ In passing §360bbb of the FDAMA, Congress delegated a very limited power to the FDA in the context of allowing access outside of clinical trials, only intending it to play its traditional role of reviewing clinical data to inform physician prescription practices.¹⁵⁶ Section 360bbb does not at any point refer to individual patient cost-benefit analysis and only authorizes an inquiry into whether there is sufficient evidence of safety and efficacy.¹⁵⁷ This clearly functions as a reinforcement of the spirit of the 1962 Amendments and in no way expands the FDA’s authority beyond that point. In §312.305(a)(2), however, the FDA has created a far more invasive role for itself by stating that the Secretary of HHS has both the discretion and the authority—not to mention the scientific and medical expertise—to assess potential patient benefits and risks and ultimately decide what is “best” for that patient.¹⁵⁸ Assuming that an outside regulatory body could—without first-hand knowledge of a patient’s condition—actually have a better understanding of that patient’s immediate medical needs than her own doctor, Congress explicitly prohibited just such agency action in the FDAMA.¹⁵⁹ Section 360bbb very specifically reserved the type of risk-benefit analysis at issue here for the physician and her patient.¹⁶⁰

In promulgating §312.305(a)(2), the FDA not only interposed itself into a situation it does not have the authority to encroach upon, it dramatically rewrote the fundamental role of the FDA.¹⁶¹ The FDA—in one of its central operating manuals—defined its role in the clinical trial context as one of reviewing information submitted by drug sponsors, aggregating and interpreting this data, and offering this information as a foundation for prescribing physician’s treatment decisions.¹⁶² Section 360bbb(b)(1) of the FDAMA seems to reinforce this conclusion by giving physicians the authority to

¹⁵⁵ 21 U.S.C. §360bbb(b)(2) (2010).

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*

¹⁵⁸ §312.305(a)(2) (2011).

¹⁵⁹ §360bbb(b)(1).

¹⁶⁰ *Id.*

¹⁶¹ See Ctr. for Drug Evaluation & Research, Food & Drug Admin. & Dep’t of Health & Human Servs., *The CDER Handbook* (1998).

¹⁶² *Id.* at 7-9.

weigh and assess the relevant factors of an individual’s case in deciding treatment, while the FDA has the authority to ensure that there is a sufficient evidential foundation supporting the decision.¹⁶³ Simply ensuring that there is enough evidence to support a physician’s decision is a very different proposition than attempting to ensure that the physician has made the right decision.

This type of institutionalized second-guessing of clinical treatment decisions has never been a part of the FDA’s mandate, and Congress—in passing §360bbb and creating separate duties for physicians and the FDA—¹⁶⁴seems to have gone out of its way to reinforce this idea. Further, the Supreme Court has held that an agency, absent explicit authorization from Congress, should not assume “a responsibility that runs counter to its previously delegated powers and responsibilities.”¹⁶⁵ In promulgating §312.305(a)(2), the FDA has both violated the *Brown* doctrine—by assuming a new role that runs counter to previous duties—and overstepped the authority delegated by §360bbb of the FDAMA, which merely served to reinforce the FDA’s previous practice of assessing safety and efficacy. As long as patients are making reasoned and informed decisions in consultation with their physician, the FDA should limit itself to assessing the adequacy and veracity of the data on safety and efficacy, and not on the substance of the patient’s treatment decision.

B. Proposals for an Expanded Access Scheme that Serves the Patient, the Regulator, and the Pharmaceutical Manufacturer

Historically, the FDA has only been one of many obstacles to expanded access. Perhaps *the* principal limiting factor has been drug manufacturers’ unwillingness to shoulder the costs of

¹⁶³ See §360bbb(1)-(3). Subsections (b)(1) and (b)(2) are especially relevant in this delegation of authority.

¹⁶⁴ *Id.* Subsection (b)(1) delegates decisional authority for individual patient treatment to the physician, and (b)(2) reiterates the information-gathering and aggregating duties of the FDA. The two subsections, both in their language and clear intent, contemplate a separation of the duties incumbent upon treating physicians and the FDA.

¹⁶⁵ See *FDA v. Brown & Williamson Tob. Corp.*, 529 U.S. 120 (2000). The Court held that an agency could not simply assume that Congress had assigned it a new authority without explicit statutory language. In *Brown*, the FDA had created not only a more involved and extensive role for itself, it had embarked on a regulatory scheme which ran counter to any action it had taken in the past. In essence, the agency completely reversed its regulatory stance. The Court found that this action, because it took place in the absence of explicit statutory authorization, was an invalid exercise of agency authority.

participating in expanded access programs.¹⁶⁶ Potentially increased liability due to adverse reactions and decreased participation in clinical trials make expanded access economically unattractive.¹⁶⁷ In the past this had been compounded with FDA-mandated limitations on cost-recovery.¹⁶⁸ Although the FDA has amended the previous regulations to allow drug sponsors to recover the cost of expanded access,¹⁶⁹ this new cost recovery is limited to the direct costs of making the investigational drug available, which are usually limited to the costs of manufacturing and shipping the drug, as well as monitoring the treatment protocol.¹⁷⁰ Balancing the risks and costs of participation for pharmaceutical manufacturers is an essential aspect of a successful expanded access scheme.

The FDA's recent decision to rule out recovery for the costs of research and development will presumably decrease industry incentive to participate in expanded access programs.¹⁷¹ At the very least, allowing a drug sponsor to provide their product at or near market value would make participation in an expanded access program slightly more attractive. If industry was allowed to recoup some of the cost of research and development—especially when the drug was still in the testing phase and not bringing in any revenue—not only would incentive to participate increase, incentive to introduce new treatments for less lucrative illnesses would increase. Especially in the context of drugs targeted towards diseases that afflict a relatively small population-base, recovery at or near market value for expanded access would function as an incentive for developing new drugs for those illnesses. This does raise the specter of dubious sponsors proposing dubious drugs, but §360bbb's safety provisions provide a solid framework for vetting treatments introduced under this new cost-recovery scheme. Increased cost-recovery also raises issues of payment and insurance-coverage; increased recovery for industry will mean increased cost for insurance providers. While

¹⁶⁶ George J. Ames, *Cancer and the Constitution*, 357 New Eng. J. Med. 408-413 (2007).

¹⁶⁷ Id.

¹⁶⁸ Id.

¹⁶⁹ Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. 40,872 (Aug. 13, 2009). This new provision will be codified in 21 C.F.R. 312.

¹⁷⁰ 21 C.F.R. §312.8(d)(1)-(2) (2011).

¹⁷¹ See Benjamin R. Rossen, *FDA's Proposed Regulations to Expand Access to Investigational Drugs for Treatment Use: The Status Quo in the Guise of Reform*, 64 Food & Drug L.J. 183 (2009).

this is a significant concern, it is one that many other industrialized nations have effectively addressed.¹⁷² Even if a physician and patient have to negotiate or fight for insurance pre-certification and coverage for a developmental treatment, that is an improvement on the status quo. Without industry participation, and thus without developmental treatments, patients will not even have the opportunity to request insurance coverage.

Similarly, in an attempt to strike a balance between expanding access, providing incentives to industry, and maintaining its responsibility for monitoring the development of new drugs, the FDA's new regulations require that physicians overseeing the use of investigational drugs outside of clinical trials report all outcomes, both positive and adverse.¹⁷³ This is a clear example of the FDA's 2009 regulations getting something right. The pharmaceutical industry has—since the beginning of expanded access—voiced a concern that allowing participation outside of trials will stifle the process. They argue that any patient who can access a drug outside of clinical trials, thus avoiding potentially receiving a control group placebo, will do so. As access expands, trial participation will shrink. This new provision will ensure that each instance of expanded access not only does not interfere with clinical testing, but actually provides drug sponsors with another source of data that could be reported to the FDA. In essence, industry is receiving a supplementary source of outcome data which the FDA will accept and include in its final NDA analysis. These two measures, allowing cost recovery at or near market value and mandated outcome reporting used to bolster existing clinical trial data, should alleviate some of the pharmaceutical industry's economic concerns over an expanded access program.

¹⁷² Although it falls outside the scope of this paper, one proven solution to the problem of covering the increased costs generated by expanded access is a single-payer healthcare system. Single-payer health systems in Western Europe and Japan—because they function as a lone, somewhat monolithic entity—have far greater bargaining power with the pharmaceutical manufacturer and thus usually pay far less than comparable U.S. providers. In essence, a single-payer health system in the U.S. could presumably negotiate far lower prices for developmental drugs, while still allowing the manufacturer to recover at the new (though lower) market rate. See generally T.R. Reid, *The Healing of America: A Global Quest for Better, Cheaper, and Fairer Health Care* (2010).

¹⁷³ 21 C.F.R. §312.310(c)(2) (2011). The FDA has held that these reporting burdens should not exceed the typical reporting done by physicians, but that under previously existing Treatment IND rules, a treating physician must report all adverse reactions in the same way a trial sponsor would. See §312.310(a)(2).

With expanded access—especially access outside of the controlled environment of clinical trials—an increase in tort claims arising out of adverse reactions seems unavoidable. As more and more patients get access to drugs that have not fully completed “safety” and “effectiveness” testing, instances of negative outcomes will likely rise. Industry concern over increasing liability has not been addressed by the FDA in the past, and the 2009 regulations are no different. Although IRB regulations prohibit asking a participant to waive any future tort or negligence claims,¹⁷⁴ there are effective tools for mitigating liability. An increased focus on the importance and practical effectiveness of informed consent would be productive here. While many patients will not want to risk the chance of adverse effects from experimental treatment, many will,¹⁷⁵ and it is difficult to justify respecting the preferences of one class of patients and not the other. Although there are concerns over decision-making capacity, studies have shown that patients in the late stages of an illness still make reasoned and informed decisions.¹⁷⁶ Informed consent provides a framework in which these preference-based decisions can be made and respected while also providing the drug manufacturer with some level of liability protection.¹⁷⁷ If the expanded access patient has made an informed and reasoned decision, based on initial clinical data from the sponsor and guidance from her physician, industry liability should be minimal. As long as the manufacturer follows the guidelines set out in the IRB, IND, and NDA, responsibility for the patient’s decision should rest with the patient. Which raises a final concern created by the 2009 regulations.

¹⁷⁴ See supra note 50.

¹⁷⁵ See Teresa J. Melink et al., *The Impact of Phase 1 Clinical Trials on the Quality of Life in Patients with Cancer*, 3 *Anti-Cancer Drugs* 571 (1992).

¹⁷⁶ See generally Austin Winniford, Note, *Expanded Access to Investigational Drugs for Treatment Use: A Policy Analysis and Legislative Proposal*, 19 *Health Matrix* 205 (2009). Winniford discusses numerous studies on how seriously-ill people handle decisions of this magnitude; although there is no easily-reached consensus among the studies, a recent one has shown that even the most desperately ill patients have the capacity to effectively weigh the benefits and risks involved in seeking experimental care. See David J. Casarett et al., *Identifying Ambulatory Cancer Patients at Risk of Impaired Capacity to Consent to Research*, 26 *J. Pain & Symptom Mgmt.* 615 (2003).

¹⁷⁷ *In re Caremark Int’l Inc. Derivative Litig.*, 698 A.2d 959 (Del.Ch. 1996). A key case in which the court established a standard of care based on the relevant statutory penalties for violative behavior. In this context, §§312.60-70 could function similarly.

Section 312.60 mandates an intricate informed consent protocol that, while satisfactorily addressing many of the industry concerns discussed above, makes the prescribing physician responsible for any patient decisions made under the influence of her medical judgment.¹⁷⁸ Failure to follow these strict rules may result in loss of investigator privileges¹⁷⁹ and—because these rules could ultimately inform standards of care—open the practitioner up to medical malpractice claims.¹⁸⁰ By requiring a prescribing physician to essentially be as knowledgeable about the developmental drug and its attendant usage protocols as its sponsor,¹⁸¹ as well as potentially liable if the treatment is for any reason contraindicated for that patient, the FDA’s 2009 regulations establish a significant burden of care for the physician. And while this new standard of care makes the secondary FDA analysis required by §312.305 both redundant and cumbersome,¹⁸² it will also presumably reduce physician participation rates.

A significant liability burden is placed on the prescribing physician when they must know as much about the drug as its sponsor, and the risk of increased negligence claims resulting from expanded access will most likely drive down physician participation. However, a slight rewording of §312.60 should alleviate the concerns of prescribing physicians. While the 2009 regulations shifted the informed consent burden from the sponsor to the physician, which is entirely appropriate in the expanded access context, they failed to elucidate a clear and coherent standard of care. Rather than

¹⁷⁸ Id. §312.60. The section makes the physician responsible for many of the tasks the drug sponsor would shoulder in the clinical trials context.

¹⁷⁹ Id. §312.70. Loss of investigator status would be especially devastating for a physician practicing in a research or academic setting.

¹⁸⁰ See Supra note 180.

¹⁸¹ Id. §312.60. See supra note 171. On a comparative note, both Britain and Germany have significantly faster rates of access to developmental drugs because they place much of the decisional burden on the prescribing physician. In both countries, the treating doctor is expected to decide—typically without the input of any regulatory body—whether the new drug is appropriate for her patient. Neither country has reported significant adverse event outcomes as a result of having the physician function as an intermediary between the patient and the pharmaceutical manufacturer. See generally, Arthur A. Daemmrich, *Pharmacopolition in the United States & Germany* 6, 9 (The Univ. of N.C. Press 2004).

¹⁸² To support this secondary analysis, one also has to assume that the FDA has both the resources and the wherewithal to go through each individual patient’s medical records, history, and prognosis in enough detail to justify potentially countermanding the doctor’s orders.

let a court determine what the standard of care is by assessing the intent of the regulation's punitive measures,¹⁸³ the FDA should have created an explicit standard for a physician prescribing a developmental drug. In the medical malpractice context generally, most states use the “what would a reasonable physician in a similar situation have done” standard, which essentially looks to the common medical practice appropriate for that scenario.¹⁸⁴ Similarly, a re-drafting of §312.60 which explicitly establishes a “common practice” protocol for the expanded access physician would alleviate concerns over increased liability. The FDA should re-draft the regulation—with input from physicians who regularly prescribe and administer experimental treatments—in such a way that any potential prescriber has no doubt as to what his or her obligations are. A clear and explicit standard of care for the prescription and administration of developmental treatments would not only protect the patients who might receive the drug, it would offer a substantial liability shield for the prescribing physician.

CONCLUSION

While the risk of adverse effects for patients and economic burdens for manufacturers is very real and plays a significant role here, arguably the greatest obstacle to expanded access created by the 2009 regulations is §312.305(a)(2). Whatever improvements the new rules effected are negligible compared to the enormous setback §312.305(a)(2) constitutes. Its severe and unprecedented restriction on patient autonomy effectively eliminates choice in a scenario where choosing between treatments truly is a life or death proposition. Therefore, changing §312.305(a)(2) is essential to expanding access to developmental drugs.

Although the FDA has explicitly and repeatedly rejected calls for a re-wording of §312.305(a)(2),¹⁸⁵ this would seem to be the simplest and most direct route to rectifying the FDA's

¹⁸³ As the court in *Caremark* did. See supra note 180.

¹⁸⁴ See generally Paul Coltoff, et al., 70 C.J.S. Physicians and Surgeons § 134.

¹⁸⁵ Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40,900, 40,910 (Aug. 13, 2009).

overstep here. Congress could amend the FDCA¹⁸⁶ to directly address the issue, including language specifically separating the analysis done by physicians and the analysis done by the FDA.

Congressional action of this sort would make §312.305(a)(2) immediately invalid and subject to litigation if the FDA does not alter it. Patients or patient’s rights groups could also challenge the regulation on the grounds that it exceeds the statutory delegation of authority provided by §360bbb of the FDAMA, therefore constituting an agency overreach of the type seen in *Brown*.¹⁸⁷

While litigation could force the FDA’s hand, and Congressional action could clarify misconceptions and cement the parallel but separate functions of physicians and the FDA, both of these options are expensive and time-consuming. The simplest, most efficient, and most direct form of change in this circumstance would be remedial action by the FDA itself. In crafting the provisions outlining the physician’s responsibilities under the new framework, the FDA imported the exact language from the FDAMA.¹⁸⁸ It would be difficult to argue that simply importing the FDAMA’s language on the separate function of the FDA in this context would be untenable. In promulgating §312.305(a)(2), the FDA overstepped the authority granted it by Congress, and a simple re-wording of that subsection would radically alter the new regulations’ impact on the seriously and terminally-ill. A revised subsection—which echoed the mandate of §360bbb—would firmly place a deeply personal and life-altering decision in the hands of the individuals most qualified to make it, the patient and her physician.

¹⁸⁶ Congress has a long history of amending the FDCA. See David L. Stepp, *The History of FDA Regulation of Biotechnology in the Twentieth Century*, 46 Food & Drug L.J. 1, 6-20 (Winter 1999).

¹⁸⁷ See supra note 162. Further, patients could potentially challenge the rule under the *Chevron* doctrine, which holds that, without clear statutory language authorizing certain actions, any action falling outside of that delegation of authority that appears to be “arbitrary and capricious” may be found invalid. This is, however, a high bar and the courts tend to defer to agencies when applying this test. See *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

¹⁸⁸ See 21 C.F.R. §312.30(a) (2011).