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THE COST OF EVIDENCE: EXAMINING THE FDA'S TREATMENT OF CRITICALLY-NEEDED DRUGS FROM AN EX ANTE PERSPECTIVE

JULIE DORAIS*

INTRODUCTION

“Substantial evidence” may be the two costliest words in the Food Drug and Cosmetic Act (FDCA). Congress first introduced the term in 1962 as a part of the Kefauver amendments to the FDCA.¹ In addition to requiring premarketing approval of new drugs for the first time, it requires sponsors to provide “substantial evidence” of a new drug’s effectiveness in order to obtain the necessary approval.² As a result, the cost and length of time for drug development immediately skyrocketed in 1962 and continues to rise to this day.³

However, the cost of the “substantial evidence” requirement is not simply the estimated \$2 billion it takes to bring a drug to market.⁴ The requirement also brought about two secondary costs—delayed access to critically-needed therapies and disincentives to develop drugs with small market potential.⁵ Accordingly, it is not insurance companies, drug manufacturers, or consumers who feel the costs of the “substantial evidence” requirement most acutely, but patients with serious conditions and without

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1. Linda Katherine Leibfarth, *Giving the Terminally Ill Their Due (Process): A Case for Expanded Access to Experimental Drugs Through the Political Process*, 61 VAND. L. REV. 1281, 1287 (2008).

2. 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, 185 (2009).

3. See Barbara J. Evans, *Seven Pillars of A New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 424 (2010).

4. Cost estimates vary widely, and their accuracy and comparability are hotly debated. Evans, *supra* note 3, at 424. Estimates from other studies range from \$500 million to \$2 billion. *Id.* at 424 (citing Comm. on the Assessment of the U.S. Drug Safety Sys., Inst. of Med., THE FUTURE OF DRUG SAFETY 32 (Alina Baciú et al. eds., 2007)). According to a study conducted by the Tufts Center for the Study of Drug Development, the average cost of developing a drug in 2005 was \$1.3 billion dollars in 2000 U.S. dollars. Avik Roy, *Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials*, Project FDA Report No. 5 April 2012, at 1.

5. See Leibfarth, *supra* note 1, at 1287.

any available therapy. Patients with serious orphan diseases often fit this description.

Congress and the Food and Drug Administration (FDA) are clearly aware of this fact and have attempted to address the problems by allowing expanded access to unapproved therapies under qualified circumstances and by providing orphan drug sponsors with financial incentives through the Orphan Drug Act. However, given the limits of these two measures, the FDA also utilized a third method—flexibly interpreting the “substantial evidence” requirement to effectively reduce the evidentiary requirements for many such drugs. However, it has not consistently done so, nor has it provided any reliable indication of whether, or to what extent, a reduced standard would apply. If a sponsor cannot judge ahead of time that a reduced standard will apply to its drug, it has no incentive to develop drugs with expected low revenues. Because post-hoc flexibility does not adequately address ex ante incentives, Congress and the FDA must adjust evidentiary standards in order to encourage the development of critically-needed drugs.

Part I of this paper will address the articulated “substantial evidence” requirement, and Part II will discuss the FDA’s approach of adjusting the standard on a case-by-case basis. Part III will discuss two indirect ways that Congress and the FDA attempt to counter the secondary harms of the requirement, namely, through expanded access and the Orphan Drug Act, and the incomplete success of these reforms. Part IV will discuss the reasons for reducing evidentiary standards for critically needed drugs, and Part V will discuss why clarifying this adjustment is critical from an ex ante perspective.

PART I. THE SUBSTANTIAL EVIDENCE REQUIREMENT

1. The Gold Standard: Background

Under the FDCA, any entity that intends to market a new drug in the U.S. must first convince the FDA, with “substantial evidence” from “adequate and well-controlled investigations,” that the drug is effective under conditions of use specified in the label.⁶ This, in a nutshell, is the “substantial evidence” requirement.⁷ As Congress defined “substantial evidence” in

6. The term “substantial evidence” applies only to evidence establishing efficacy. For evidence of safety, the statute requires “adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof,” and that the “results of such tests” must show “such drug is safe for use under such conditions.” See 21 U.S.C.A. § 355(d).

7. Although this paper will use the term “drugs,” most of the discussion applies to biologics as well as drugs. The “substantial evidence” requirement in § 355(d) technically applies to drugs and not

broad terms, the FDA has borne the primary responsibility for determining exactly what this means in practice.⁸

To ultimately satisfy the “substantial evidence” requirement, the typical drug candidate must navigate a lengthy, expensive process.⁹ Before a sponsor may test a drug on humans, it must engage in extensive preclinical testing of the drug and include this information in an investigational new drug application (IND).¹⁰ Only after the FDA approves the IND may the sponsor begin clinical, or human, testing.¹¹ Typically, pre-approval clinical testing occurs in three phases.¹² In Phase I, the drug is administered to about 20-80 participants, usually healthy volunteers, with the purpose of learning how the drug pharmacologically operates in humans and to identify any adverse events.¹³ Phase II trials are typically conducted on a few hundred participants who have the disease of interest, usually over the course of several months,¹⁴ to provide preliminary evidence of efficacy and identify any short-term side effects or risks.¹⁵

However, it is the Phase III trials that usually qualify as the “adequate and well-controlled investigations” referenced in the statute,¹⁶ which in turn serve as the “the primary basis” for satisfying the substantial evidence re-

biologics. (See 42 U.S.C.A. § 262 and 21 C.F.R. §§ 600.20 - 600.90 for the treatment of biologics.) However, the FDA maintains that the same effectiveness requirement applies to pharmaceuticals and drugs composed of biological compounds. In practical application, different standards may actually be applied. Jennifer Kulynych, *Will FDA Relinquish the “Gold Standard” for New Drug Approval? Redefining “Substantial Evidence” in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 137-38 (1999).

8. Evans, *supra* note 3, at 423-425. Under the statute, “substantial evidence” is “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by [qualified] experts..., on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.” See 21 U.S.C.A. § 355(d).

9. Although many of the procedural requirements may be considered independent of the substantial evidence requirement itself, the process consists of various evidentiary hurdles that a sponsor must satisfy before ultimately convincing the FDA that a drug is safe and effective for its intended use. See 11 C.F.R. §§ 312.20-312.38.

10. Rossen, *supra* note 2, at 185. See also 21 C.F.R. § 312.23(a)(8) (2014) (requiring “adequate information about pharmacological and toxicological studies of the drug” through animal and/or in vitro studies, to allow the sponsor to “conclude[] that it is reasonably safe to conduct the proposed clinical investigations”).

11. § 312.20(b).

12. § 312.21 (stating that “[t]he clinical investigation of a previously untested drug is *generally divided into three phases*”) (italics added).

13. See § 312.21(a).

14. Michael J. Malinowski & Grant G. Gautreaux, *Drug Development-Stuck in A State of Puberty?: Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability*, 56 ST. LOUIS U. L.J. 363, 376 (2012).

15. 21 C.F.R. § 312.21(b) (2014) (defining Phase II studies as “controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug”).

16. Malinowski & Gautreaux, *supra* 14, at 378.

quirement.¹⁷ The FDA typically invokes what is now called the “gold standard” to determine whether a trial is “adequate and well-controlled.”¹⁸ It describes aspects of this standard through regulations and guidance, while reserving for itself discretion to depart from it.¹⁹ Under the gold standard, a sponsor should present statistically significant results from each of two Phase III randomized controlled trials (RCTs).²⁰ The study should utilize “clinical endpoints,” which means that the drug must have a statistically significant effect upon the clinical outcome of interest.²¹ A typical Phase III trial is conducted on thousands of participants across multiple sites and takes about 1-4 years.²²

To show statistically significant effects on clinical endpoints in two separate trials, sponsors require large sample sizes and, in turn, a large financial investment.²³ Not surprisingly, the cost of drug development immediately began to skyrocket after 1962.²⁴ According to a recent study, the average cost of developing a drug was \$1.3 billion in 2005,²⁵ and the current cost may be far higher.²⁶

17. 21 C.F.R. § 314.126(a) (2014) (“Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is ‘substantial evidence’ to support the claims of effectiveness for new drugs.”).

18. Leibfarth, *supra* note 1, at 1285.

19. See Kulynych, *supra* note 7, at 129 (noting that the FDA makes use of regulations and guidance to “describ[e] the necessary attributes of an “adequate and well-controlled” clinical trial,” that the “regulations appear to incorporate ... the agency’s ‘gold standard’ for demonstrating ‘substantial effectiveness,’” but that it permits “certain modifications” from these specifications).

20. FDA, *Guidance for Industry: Providing Evidence of Effectiveness for Human Drug and Biological Products*, May 15, 1998, at 3 [hereinafter *Guidance*]. Statistical significance with a p-value < 0.05 means that, assuming there is no association in fact, there is less than a 5% chance of erring in finding an association. Joseph W. Cormier, *Advancing FDA’s Regulatory Science Through Weight of Evidence Evaluations*, 28 J. CONTEMP. HEALTH L. & POL’Y 1, 9 (2011).

21. Russell Katz, *Biomarkers and Surrogate Markers: An FDA Perspective*, 1 NEURORX 189, 190 (2004) (noting that, “in practice,” the FDA only approve drugs if they show “manifest effects on the clinical signs and/or symptoms of the disease for which they are intended as treatments,” even though this does not necessarily follow from “a strict reading” of the statutory definition of “substantial evidence”).

22. Malinowski & Gautreaux, *supra* note 14, at 376; Evans, *supra* note 3, at 446.

23. Even if the drug has an effect, a study would not have a good chance of reporting a p-value < 0.05 unless it has adequate power, which, in practical terms, means that the sample size must be sufficiently large. Power is not only affected by the sample size but by the event rate; if a longer trial captures more events, it would have greater power, all else equal. See Kenneth Schulz & David Grimes, *Sample Size Calculations in Randomised Trials: Mandatory And Mystical*, 365 LANCET 1348, 1348-49 (2005). Accordingly, the requirement for clinical endpoints also leads to high costs and lengthy trials, since, the more infrequent the outcome of interest, the greater the required sample size and time. See *Id.* at 1349-50.

24. Evans, *supra* note 3, at 424.

25. The study was conducted by the Tufts Center for the Study of Drug Development, and the figures are in 2000 U.S. dollars. See Roy, *supra* note 5, at 1.

26. See *supra*, note 9.

2. FDA Regulations

However, it is worth noting that the law does not actually demand this high standard. The regulations do not require the use of concurrent controls, a showing of statistical significance, or even Phase III trials.²⁷ Rather, the regulations elaborate upon certain characteristics that are the “*essentials* of an adequate and well-controlled clinical investigation,” which the FDA “considers” in deciding whether a particular investigation qualifies as such.²⁸ While placebo controls or dose-comparison concurrent controls may be preferable, the FDA recognizes that a study using only historical controls may qualify as an “adequate and well-controlled trial” under certain circumstances.²⁹

The regulations assert some minimal requirements. For one, they explicitly state that “uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness,” and they will only be considered in conjunction with well-controlled studies.³⁰ However, for the most part, the regulations are carefully worded to allow significant room for flexibility.³¹

3. The Official Response to the Secondary Costs of the “Substantial Evidence” Requirement

A. The FDA’s Reforms

As the secondary costs of the “substantial evidence” became evident, the FDA soon found it necessary to exercise this flexibility. The early 1980s marked the beginning of the AIDs epidemic in the U.S.³² In the mid-1980s, Dr. David Broder discovered that the compound AZT demonstrated anti-viral activity against the poorly-understood AIDs virus; however, by that time, the typical drug approval process already took 8 years.³³ Facing significant pressure from activists, the FDA decided to substantially speed the

27. The regulations recognize five types of controls, including historical controls and “no treatment concurrent controls.” See 21 C.F.R. § 314.126(b)(2)(i-v). Also, while FDA regulations recognize that trials “generally” occur in the three phases, it does not explicitly require Phase III trials. See § 312.21.

28. § 314.126(a).

29. § 314.126(b)(2)(v).

30. § 314.126(e).

31. § 314.105(c) (stating, “While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards.”)

32. Leibfarth, *supra* note 1, at 1282.

33. Donna A. Messner, *Rulemaking under Fire: Accelerated Approval as a Case Study of Crisis-Mode Rulemaking* 8-9 (Georgia Inst. of Technology, School of Public Policy, Working Paper, April 27, 2006).

approval process for AZT.³⁴ After a Phase I trial reported a small but statistically significant effect upon a biomarker in each of the nineteen subjects, the researchers proceeded to conduct a placebo-controlled Phase II trial, which they were able to stop after 4 months based on the positive interim results. A few months afterwards, the FDA approved the drug on the condition that the sponsor conducted a post-marketing study.³⁵ Not long after, the FDA approved ddi for the treatment of AIDs based solely on “Phase I-II” trials that used historical controls and surrogate endpoints.³⁶

The FDA essentially “codified” these approval stories through the Subpart E and Subpart H regulations.³⁷ Written in permissive language, Subpart E essentially clarifies that the FDA *could* apply the same standards and procedures used in the AZT approval for new drugs intended to treat “life-threatening or severely-debilitating diseases,”³⁸ although it did not obligate it to do so.³⁹ Subpart H, or the “accelerated approval regulations,” similarly applies to drugs intended to treat “serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.”⁴⁰ Importantly, it permits the FDA to approve an NDA based on the drug’s apparent effect on a “surrogate endpoint,” an intermediate variable that points to the clinical outcome.⁴¹ This allows researchers to conduct smaller trials with the same statistical power, reducing both time and cost.⁴²

In 1997, Congress incorporated much of Subpart H into statute under the “fast track” provisions in the Food and Drug Administration Modernization

34. *Id.*

35. *Id.* at 9-10.

36. *Id.* at 14-15.

37. *Id.* at 12-13.

38. In the publication of the regulations, the FDA explicitly acknowledges that Subpart E was loosely modeled after the details in the AZT approval story. *Id.* at 12-13 (citing 53 Fed. Reg. 41516-41524 (21 Oct. 21, 1988)).

39. Even if the mechanisms of Subpart E applied, a sponsor could not know ahead of time whether Phase III trials would ultimately be required. A sponsor “may request” early meetings with the FDA, including an end-of-Phase I meeting to agree on the design of Phase II stud(ies) that may possibly qualify as “adequate and well-controlled studies.” 21 C.F.R. § 312.82 (2014). However, following conclusion of the Phase II stud(ies), the FDA will use a “medical risk-benefit judgment,” still applying the “statutory standards for marketing approval,” to decide “whether the benefits of the drug outweigh the ... risks.” § 312.83. The FDA may conclude that the Phase II data is inadequate, notwithstanding adherence to a design that resulted from an end-of-Phase I meeting. *See* § 312.84(c).

40. § 314.500.

41. § 314.510.

42. The more infrequent the outcome of interest, the greater the required sample size and time. *See* Schultz & Grimes, *supra* note 23, at 1349-50. The provision for surrogate endpoints is therefore particularly important for life-saving therapies because the clinical endpoint for such drugs is mortality. Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL’Y 295, 310-313, 323. (2000). Technically, the clinical outcome of interest is “survival,” but for statistical purposes, the endpoint is considered to be mortality. *See* Katz, *supra* note 21, at 191.

Act (FDAMA).⁴³ Sponsors may request “fast track” designation, when or after they submit the initial IND, for drugs “intended for the treatment of a serious or life-threatening condition” and that “demonstrate the potential to address unmet medical needs for such a condition.”⁴⁴ If the FDA designates the drug as a fast track product, it must “facilitate the development and expedite the review of such drug.”⁴⁵ Using language that closely resembles that of Subpart H, the Act permits the FDA to approve a fast track product based on the drug’s impact on a surrogate variable.⁴⁶ In addition to enacting the fast track provision in FDAMA, Congress amended the FDCA through FDAMA to clarify that the FDA may rely on “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to find substantial evidence of a drug’s efficacy.⁴⁷

More recently, on July 9, 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act (FDASIA), which, among other things, adds new mechanisms for fostering and speeding the development of therapies for drugs for serious or life-threatening conditions.⁴⁸ Under the “breakthrough therapy” amendment, the FDA may designate a drug or a new drug use as a “breakthrough therapy” if it is “intended...to treat a serious or life-threatening disease or condition” and if “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies.” Breakthrough and fast track designation, although similar, are distinct and may separately be pursued.⁴⁹ Once designated as a breakthrough therapy, the drug would enjoy all the benefits of fast track designation and should receive even closer guidance by the FDA.⁵⁰

43. Rossen, *supra* note 2, at 191. According to the FDA, the fast track amendment “essentially codifies...FDA’s accelerated approval regulations.” FDA, *Guidance, supra* note 2, at 27.

44. 21 U.S.C.A. § 356(b) (2012).

45. *Id.*

46. *See* § 356 (1997). As currently amended, this provision is not limited to fast track products but more generally to those intended to treat a “serious or life-threatening disease or condition, including a fast track product.” § 506(c)(1)(a) (2012).

47. *See* 21 U.S.C.A. § 355(d) (2013). This is an amendment to the section defining “substantial evidence.”

48. Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012).

49. According to the FDA, the primary difference lies in “what needs to be demonstrated” to obtain the designation. Fast track designation simply requires that the drug “demonstrate the potential to address unmet medical needs for the serious condition,” which may be shown with nonclinical data, while a breakthrough designation requires “preliminary clinical evidence” of a “substantial improvement ... over existing therapies.” FDA, *Frequently Asked Questions: Breakthrough Therapies*, (Sept. 11, 2014), *See also* 21 U.S.C. §§ 356(a)-(c) (2012). <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendmentstotheFDCAAct/FDASIA/ucm341027.htm>.

50. *Id.* (“A breakthrough therapy designation conveys all of the fast track program features... [as well as] more intensive FDA guidance on an efficient drug development program”) *See also* 21 U.S.C. § 356(a)-(b) (2012). 21 U.S.C. § 356(a)(3) (2012) (The statute requires that the FDA “take such actions

B. The “Same Statutory Standard”

Given these reforms, it may appear that the evidentiary standards now depend, in part, on the need for the drug.⁵¹ Critically, however, the “substantial evidence” requirement still legally applies in full force to all new drug candidates.⁵² Even though it amended the section defining “substantial evidence” in FDAMA, Congress never actually compromised the true meaning of “substantial evidence.”⁵³ Also, although the stated purpose of FDASIA is to “encourage the [FDA] to utilize innovative and *flexible approaches*” in evaluating the evidence for drugs intended to treat serious or life-threatening diseases,⁵⁴ Congress explicitly maintains that the “substantial evidence” requirement remains unchanged, and that the same standard continues to apply to drugs that qualify for fast track designation, breakthrough designation, or accelerated approval.⁵⁵

Even if it could be argued that the standards were altered, the reform measures at most merely *allow* the FDA to apply this reduced standard, but do not explicitly require it to do so. The FDA is simply “required to exer-

as are appropriate to expedite the development and review,” where such actions “may include” that of “holding meetings,” giving “timely advice,” or providing a “collaborative” review).

51. In particular, Subpart H and the fast track legislation allow the FDA to accept what epidemiologists call “unvalidated” surrogate endpoints, where it has not been scientifically established that the drug’s effect on the surrogate predicts its effect on the clinical endpoint. Katz, *supra* note 21, at 190 (defining an “unvalidated surrogate” as “a surrogate that is, as the regulation describes, ‘reasonably likely’ to predict the clinical benefit of interest, but for which there is insufficient evidence to establish that such an effect, does, in fact, result in the desired clinical outcome”). The FDA actually does not need to refer to Subpart H to recognize “validated” endpoints, where the predictive relationship is fairly established according to the scientific community. *Id.* See also FDA, *Guidance, supra* 20, at 11 (stating, “A pharmacologic effect that is accepted as a *validated surrogate endpoint* can support ordinary approval ... [while] a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval”) (italics added). The problem with relying on an unvalidated surrogate is that it may become evident after approval that the drug’s effect on the surrogate does not adequately predict the effect on the clinical endpoint. Greenberg, *supra* note 42, at 323-24.

52. See 21 C.F.R. § 314.105(c) (2014).

53. See Kulynych, *supra* note 7, at 146. Congress purposefully wrote the single-study provision in “permissive” language, rejecting industry proposals for a presumptive standard for qualifying drugs. The amendment rather served as a clarification that one study could satisfy the substantial evidence requirement. In the text of the Act, Congress entitled the specific amendment as “Clarification of the Number of Required Clinical Investigations for Approval.” See also FDAMA, Pub. L. No. 105-115, 111 Stat. 2313 (1997); FDA, *Guidance, supra* note 20, at 4. (The FDA also characterizes it as a mere “clarification”).

54. 21 U.S.C.A. § 356(e)(1) (2012) (italics added).

55. See 21 U.S.C. § 356(e)(2) (2012). The FDA similarly comments that the fast track and breakthrough therapy provisions do not alter the evidentiary standards, going further to state that it “has been vigilant in assuring that reducing the time necessary for drug development has not compromised the safety and effectiveness of drugs for patients with serious diseases.” FDA, *Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review: Expediting Availability of New Drugs for Patients with Serious Conditions*, (May 30, 2014), <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucml128291.htm>.

cise its scientific judgment” to determine the requirements for each “particular drug to meet the statutory standards.”⁵⁶ Rather than officially tailor the evidentiary standards to the need for the drug, Congress instead confirmed the FDA’s discretion to do so on a case-by-case basis.

That the FDA wishes to maintain this approach of flexibility, without announcing any reduced standard, is perhaps even more obvious. In the past few decades, the FDA revealed not only a belief in its authority to exercise significant case-by-case flexibility, but a marked hesitancy to give any indication of when it would likely exercise this flexibility. For instance, the FDA clearly believed that it has the authority to approve AZT prior to passing Subpart E, and it only later passed it reluctantly in response to pressure from the executive branch.⁵⁷

Also, although the FDA issued a guidance document in 1998 that was meant to clarify its standards,⁵⁸ the guidance actually reveals the FDA’s desire to maintain an approach of case-by-case flexibility and a relatively conservative image on paper.⁵⁹ It strongly emphasizes the importance of the gold standard,⁶⁰ and it narrowly describes study characteristics that “could” support a single-study approval.⁶¹ However, no single characteristic is “necessarily determinative,” and, in the end, the FDA’s decision to approve a drug based on a single trial is “inevitably a matter of judgment.”⁶²

PART II. CASE-BY-CASE FLEXIBILITY: THE UNOFFICIAL REFORM

1. *Increased Case-by-Case Flexibility*

Therefore, throughout all of these reform measures, both Congress and the FDA revealed a willingness to address the secondary harms of the “sub-

56. See 21 C.F.R. § 314.105(c) (2014).

57. Leibfarth, *supra* note 1, at 1290 (stating that the FDA promulgated Subpart E “[i]n response” to the Vice President’s request); Messner, *supra* note 33, at 11. More generally, see *id.* at 22 (claiming that the “the sliding standards for NDA approval continue to be a moving target, judged in practice on a case-by-case basis”).

58. FDA, *Guidance*, *supra* note 20, at 2. The stated purpose is more generally to “articulate [the FDA’s] current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics.”

59. See Messner, *supra* note 33, at 23 (stating that the FDAMA, in requiring the FDA to issue the guidance, “seems to have put the FDA in the uncomfortable position of discouraging single-study trials even while they advised on how to design them”).

60. See FDA, *Guidance*, *supra* note 20, at 4-5 (discussing in detail the possibility of error arising from “unanticipated, undetected, systematic biases,” chance, etc., if reliance is made on a single study alone).

61. *Id.* at 6, 13-15. Examples of such characteristics are a demonstration of “consistency across key patient subsets,” use of a factorial design, and a finding an association with a very low p-value.

62. *Id.* at 13, 15.

stantial evidence” requirement, but a reluctance to openly assert any compromise to it, even with regard to critically-needed drugs.

However, in practice, the FDA itself seems to recognize that the face-value of the reforms are not enough, and that it is necessary to truly tailor the evidentiary requirements to the need for the drug. Perhaps the most remarkable demonstration of the FDA’s flexibility comes from cases of orphan drug approvals. Although the FDA maintains that orphan drugs are subject to same standard of efficacy, possibly with an exception of allowing smaller sample sizes,⁶³ a few recent studies show that the FDA often applies highly liberal standards to orphan drug approvals. For instance, Kesselheim et al. analyzed the “pivotal trials,” or those that give the primary support for an NDA, for the 27 cancer drugs the FDA approved from 2004 to 2010, and found that 30% of the pivotal trials for the orphan drugs were randomized, as opposed to 80% of those for non-orphan drugs.⁶⁴ In another study on drugs for neurological diseases, every non-orphan drug in the sample were approved based on at least two double-blinded, placebo-controlled RCTS, while only 32% of orphan drugs were approved with two such trials, and 26% without even one.⁶⁵

However, the most striking evidence comes from a detailed report published by the National Organization for Rare Disorders (NORD) in 2011. The report discusses the evidence the FDA relied on for the 135 non-cancer orphan drugs approvals it made from 1983 to June 30, 2010.⁶⁶ NORD divided the approvals into three categories based on the “quantum of effectiveness evidence” required. 45 fell under the first category for “conventional or traditional quantum of evidence.”⁶⁷ 32 fell under the “administrative flexibility” category, where a deviation from the conventional standard

63. For instance, the FDA stated in a briefing document in 2010 that “the requirements to establish effectiveness are not different [for orphan diseases], with the exception that the overall database may be smaller,” and that the FDA “usually requires more than one trial to provide independent substantiation of efficacy.” According to Sasinowski, this is how the FDA usually responds when it is “asked about the quantity and quality of effectiveness evidence required of an orphan drug.” See also Frank J. Sasinowski, National Organization for Rare Disorders, *Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs: Cataloguing FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders*, at 4 (2011), <https://www.rarediseases.org/docs/policy/NORDstudyofFDAApprovaloforphandrugs.pdf>. (citing FDA Pulmonary-Allergy Drugs Advisory Committee Division Memorandum, Feb. 12, 2010, at 15-16).

64. *Id.* at 2325. Aaron S. Kesselheim et al., *Characteristics of Clinical Trials to Support Approval of Orphan vs. Nonorphan Drugs for Cancer*, 305 JAMA 2320, 2324 (2011). Overall, the efficacy evidence supporting approval for orphan cancer drugs is “limited.” *Id.* at 2325.

65. J. Misumoto et al., *Pivotal Studies of Orphan Drugs Approved for Neurological Diseases*, 66 ANN NEUROL. 184, 184 (2009).

66. Sasinowski, *supra* note 63, at 2.

67. *Id.* at 2-3. NORD defined this as approvals supported by “two adequate and well controlled trials when each [met] its primary endpoint by its prespecified primary analysis with a p value of less than 0.05.”

could be explained by “some formal FDA system for exercising discretion.”⁶⁸ Finally, 58 fell under what NORD called the “case-by-case flexibility” category, where the deviations from the traditional standard could not be fully explained by a “formal exception.”

Several of the approvals within this third category reveal a level of flexibility that perhaps may surprise anyone in the industry who is familiar with the rigors of the typical “gold standard” requirements. The FDA appears to have approved several drugs without the benefit of a truly controlled study.⁶⁹ Some pivotal trials failed to achieve statistical significance; some contained serious design defects; and some were based on extremely sparse or problematic data.⁷⁰ The single-study approvals are further remarkable because the FDA asserts that, if it were to rely on a single study, it “pre-sume[s]...that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal,” and that “reliance on a single study ... leaves little room for study imperfections.”⁷¹ However, not only do many of these approvals contain instances of baseline imbalance, unblinding, post-hoc changes in analysis, and other negative study characteristics, many arguably do not even have a single “adequate and well-controlled” study.⁷²

2. The FDA's Unpredictability

However, it does not follow from these select stories that orphan status or the severity of the illness necessarily predict a lowered standard, nor how reduced the standard may be if it did apply. According to a recent study, about 73% of non-orphan oncology drugs and nearly one half of orphan oncology drugs approved from 1995 to 2008 were supported by Phase III trials.⁷³ In a 2011 report to the National Institute of Health (NIH),⁷⁴ the IOM Committee stated that the evidence the FDA relied on for orphan

68. *Id.* at 3. The sources of the “formal, expressed FDA system[s] for flexibility” included 1) the 1998 FDA Guidance, 2) Subpart H, and 3) the provision in the FDAMA for approval based on “one adequate and well-controlled” study.

69. *See Id.* at 16. (noting that the FDA approved Panhematin based on 6 small open-label studies which did not have concurrent controls and did not appear to have historical controls). For other striking examples, *see* Appendix A.

70. *See* Appendix A for descriptions of select drug approvals included in the NORD report.

71. FDA, *Guidance*, *supra* note 20, at 6.

72. *See* Appendix A.

73. *See* IOM, *Regulatory Framework for Drugs for Rare Diseases*, RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT, 96. (citing Richey et al. *Accelerated Approval of Cancer Drugs: Improved Access to Therapeutic Breakthroughs or Early Release of Unsafe and Ineffective Drugs?* 27 JOURNAL OF CLINICAL ONCOLOGY 4398, 4398-4405 (2009)).

74. *See* IOM, *Summary*, RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT, at 1-2 (2011). The IOM Committee composed this report pursuant to an NIH request for a study on the “opportunities for and obstacles to the development of drugs and medical devices to treat rare diseases.”

drugs exhibited “considerable variability” and acknowledged “concerns about the consistency of judgments across review divisions of CDER.”⁷⁵ Accordingly, the Committee recommended that the FDA “promot[e] predictability, consistency, and reasoned flexibility in the regulatory process within and across its review units.”⁷⁶ Scholars and the industry are also keenly aware of the FDA’s inconsistency, calling for greater predictability to aid in the development of important therapies.⁷⁷

The complicated story about one particular drug clearly illustrates this unpredictability. The FDA approved Iplex (mecasermin rinfabate recombinant) in 2005 for the treatment of growth hormone insensitivity syndrome, based on one, non-randomized, open-label prospective study on 36 subjects.⁷⁸ The open-label study merely compared the effects of two different doses of the drug on height velocity, without the benefit of a concurrent control group and without the benefit of randomization. The study also failed to produce reliable safety data.⁷⁹

The story becomes more puzzling when it later appeared that Iplex might be effective in the treatment of the highly fatal neurodegenerative disease, amyotrophic lateral sclerosis (ALS).⁸⁰ The drug was already being used for treatment of ALS in Italy.⁸¹ However, Iplex’s sponsor took the drug off the U.S. market in 2007, pursuant to a patent settlement agreement.⁸² There-

75. IOM, *Regulatory Framework*, *supra* note 73, at 95-96.

76. *Id.* at 97.

77. See Radcliffe S. BIO (Biotechnology Industry Organization), *Statement to IOM Committee on Accelerating Rare Diseases Research and Orphan Product Development*, November 23, 2009, available at http://www.bio.org/sites/default/files/20091123_0.pdf, (calling for, among other things, “greater consistency among FDA’s review divisions,” in order that the company many better meet the unmet needs of patients with rare diseases); Kulynych, *supra* note 7, at 136-7 (recognizing the criticism that the “agency inconsistently applies the effectiveness provision of the 1962 Drug Amendments”).

78. Sasinowski, *supra* note 63, at 19.

79. James Gebert, FDA, *Statistical Review and Evaluation: Iplex*, NDA no. 21884 at 14 (July 12, 2005),

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021884_s000_Iplex_Statr.pdf (noting that he “could not perform a “statistical evaluation of safety” because of the lack of a control group, leaving it to “clinical judgment to evaluate the safety” of Iplex). The FDA’s acceptance of weak or nonexistent safety data may be surprising, not merely because growth hormone insensitivity syndrome is not life-threatening, but because of the enormous potential for off-label use.

80. See E. J. Sorenson et al., *Subcutaneous IGF-1 is Not Beneficial in 2-year ALS Trial*, 71 *NEUROLOGY* 1770, 1770-1775 (2008); See also Amy Harmon, *Fighting for a Last Chance at Life*, N.Y. Times, May 16, 2009, available at http://www.nytimes.com/2009/05/17/health/policy/17untested.html?_r=2.

81. Jamie Talan, *FDA Approves Compassionate Use of Growth Factor Therapy for ALS: Specialists Say Evidence to Support Its Use is Weak*, 9 *NEUROLOGY TODAY* 5, 5 (2009), available at http://www.aan.com/elibrary/neurologytoday/?event=home.showArticle&id=ovid.com:/bib/ovftdb/00132985-200905040-00004_.

82. *Id.* at 6.

fore, patients could not obtain the drug through off-label prescriptions but had to request the FDA for a treatment IND.⁸³

What followed was a bitter battle between the FDA and terminally ill patients for access to the treatment IND's. The FDA initially denied the requests, citing concerns about lack of data on safety and efficacy.⁸⁴ However, existing studies had not reported serious safety concerns,⁸⁵ and the initial efficacy evidence that the FDA faced was weak, but mixed.⁸⁶ Eventually, the FDA decided to deny individuals access to treatment IND's for applications postmarked after March 6, 2009, citing a few failed trials.⁸⁷ The failure of the clinical trials perhaps should not have been dispositive, as they suffered from a number of limitations and may not have been fully relevant.⁸⁸ Regardless, the drug was discontinued in 2009.⁸⁹ While the effec-

83. Daniel J. Popeo, Op-Ed., *If FDA Blocks Meds, How Will Government Health Care Work?* WASH. EXAMINER, (Nov. 20, 2009), <http://washingtonexaminer.com/opinion/op-eds/2009/11/daniel-j-popeo-if-fda-blocks-meds-how-will-government-health-care-work/33292>.

84. *Id.*; Talan, *supra* note 81, at 6.

85. The FDA admitted in a policy statement that the studies reported "no serious, immediate drug-related toxicities." Talan, *supra* note 81, at 6.

86. See *infra*, note 87.

87. See *FDA Position on Allowing Patients with ALS Access to Iplex Under an IND*, July 1, 2009 <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm118121.htm>.

88. See FDA, *FDA Summary of Controlled Clinical Data for Human IGF-1 in Treatment of Patients with Amyotrophic Lateral Sclerosis*, <http://www.fda.gov/downloads/drugs/resourcesforyou/healthprofessionals/ucm118131.pdf>. The FDA cited 5 studies to support its conclusion. First, it is worth noting that the cited trials used human insulin-like growth factor 1 (IGF-1), while Iplex employs a combination of IGF-1 and rhIGFBP-3. Nonetheless, the FDA described IGF-1 as a "very similar drug" and considered the studies relevant. Even accepting this, a close examination of cited studies reveals that the failures may not be as conclusive as they would initially appear to be. In the first cited study, a U.S. study conducted in 1997, the group of patients receiving the higher dose (0.1 mg/kg/day) actually had a statistically significant reduction in disease symptom progression; however, since this was secondary analysis and since the study failed to meet its primary, prespecified objective, it was considered by the FDA to be a failure. See FDA, *Summary on IGF-1* (citing Lai et al., *Effect of Recombinant Human Insulin-Like Growth Factor-I on Progression of ALS: A placebo-Controlled Study*, 49 *NEUROLOGY* 1621, 1621-30 (1997)). A European study conducted on 124 patients reported no statistically significant difference. However, not only did the study have low power, the sponsor noted that there was an imbalance of characteristics at baseline, with the experimental group happening to have poorer prognostic factors. See *id.* (citing G.D. Borasio, *A Placebo-Controlled Trial of Insulin-Like Growth Factor-I in Amyotrophic Lateral Sclerosis*, 51 *NEUROLOGY* 583, 583-586 (1998)). This may have biased the results to the null. The third cited study, also reporting no statistically significant effect, was a multi-center U.S. clinical trial conducted in 2008. See Sorenson et al., *supra* note 80. However, Charles Howe commented that the study may have chosen the incorrect method of delivery of the drug, stating that "the concept of peripheral delivery of tolerable levels of IGF-1 is predestined to fail therapeutically" and that "it was premature to conclude" that the drug was not effective in the treatment of ALS. Charles L. Howe et al., *Reply to: 'Subcutaneous IGF-1 is Not Beneficial in 2-year ALS Trial,'* 73 *NEUROLOGY*, (Feb. 23, 2009), <http://www.neurology.org/content/71/22/1770/reply>. The fourth study was based on an analysis of treatment IND's, rather than a randomized trial; and the final study was an unpublished foreign study, where the FDA was not even aware of the identity of the prespecified endpoint. See *FDA Summary on IGF-1*.

89. FDA, *Access to Iplex for Patients with ALS* (July 27, 2009), <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm118117.htm>

tiveness of Iplex in the treatment of ALS may be an open question, this story demonstrates that the “quantum of evidence” that the FDA requires is highly unpredictable and that the intense need for a drug certainly cannot guarantee a lowered standard.

Therefore, the approach of “case-by-case flexibility” remains unpredictable and perhaps, to a certain extent, unofficial. Although both Congress and the FDA implemented reforms that permit “accelerated approval” and acknowledge the FDA’s ability to engage in flexibility, the “substantial evidence” requirement officially remains untouched, and sponsors still cannot be sure ahead of time that they will benefit from this flexibility.

PART III: EXPANDED ACCESS AND THE ORPHAN DRUG ACT

Rather than directly addressing the “substantial evidence” requirement, Congress instead chose to address the secondary harms of the “substantial evidence” requirement in two indirect ways. One was to provide “expanded access” to unapproved therapies; the other, to offer compensatory financial incentives through the Orphan Drug Act. Each presents alternative means of addressing the two primary health-related costs of the “substantial evidence” requirement, delayed access and disincentives to development of critically-needed drugs.⁹⁰ However, for reasons discussed below, neither can be considered an equivalent to reforms that focus on evidentiary standards for approval.

1. Expanded Access

The FDA began an informal practice of selectively granting “expanded access” to unapproved drugs on an individualized, case-by-case basis soon after the 1962 amendments were passed.⁹¹ In 1987, reacting in part to the outcry from the AID’s crisis, the FDA passed regulations that formally recognized “Treatment IND’s,”⁹² by which qualifying individuals may formally obtain expanded access to unapproved drugs that meet certain criteria and that are clearly on the path to approval.⁹³ Later, Congress confirmed the FDA’s ability to grant such IND’s through a provision in FDAMA that closely mirrors the FDA’s treatment IND regulations.⁹⁴ Under current law, the FDA may grant expanded access to unapproved drugs if it concludes 1) that the patient(s) “have a serious or immediately life-threatening disease or

90. See Leibfarth, *supra* note 1, at 1287.

91. Rossen, *supra* note 2, at 193; Greenberg, *supra* note 2, at 315-6.

92. Rossen, *supra* note 2, at 193.

93. Greenberg, *supra* note 42, at 316.

94. See 21 U.S.C.A. § 360bbb(c)(1)-(4); Rossen, *supra* note 2, at 191 (stating that the relevant portion of the statute addressing treatment IND’s “parallels FDA’s treatment IND regulations”).

condition,” with no “comparable or satisfactory alternative therapy,”⁹⁵ 2) that the “potential patient benefit justifies the potential risks,”⁹⁶ and 3) that the expanded access would not interfere with any clinical trials, or “otherwise compromise the potential development of the expanded access use.”⁹⁷

By addressing the concern of delayed access, expanded access may operate as a partial solution to the problems raised by a lengthy, expensive drug approval process. However, not only does it fail to address the concern of disincentives to development, it fails to adequately address the problem of delayed access. Expanded access is unpredictable and unreliable, as it is largely falls under the discretion of the FDA,⁹⁸ and it is often only available when sponsors are in the final stages of approval.⁹⁹ Under the statute, the sponsor must be “actively pursuing marketing approval of the investigational drug ... with due diligence.”¹⁰⁰ To allow expanded access to an unapproved drug for “widespread treatment use” under a “treatment IND,”¹⁰¹ the sponsor must have either completed all necessary trials or be conducting a controlled trial at the time it provides such access.¹⁰²

Secondly, drug sponsors remain substantially disincentivized to participate in expanded access programs.¹⁰³ Although sponsors may seek limited

95. 21 C.F.R. § 312.305(a)(1) (2014). *See also* 21 U.S.C.A. § 360bbb(b), (c)(1)-(2) for comparable requirements.

96. 21 C.F.R. § 312.305(a)(2). *See also* 21 U.S.C.A. § 360bbb(b) (in the case of “individual patient” IND’s, requiring a physician finding that “the probable risk to the person from the investigational drug ... is not greater than the probable risk from the disease or condition”).

97. 21 C.F.R. § 312.305(a)(3).

98. *See* Greenberg, *supra* note 42, at 320.

99. *Id.*

100. 21 U.S.C.A. § 360bbb(c)(4). The regulations apply the same requirement with respect to treatment IND’s only. *See* 21 C.F.R. § 312.320 (2014). This requirement does not exist for intermediate-sized, or single patient IND’s. In the case of single patient IND’s, Congress simply requires that the FDA “determine[] that provision of the investigational drug ... will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.” § 360bbb (b)(3). More liberally, FDA regulations simply require that it either make this determination or otherwise find that the expanded access would not “compromise the potential development of the expanded access use.” *See* 21 C.F.R. § 312.305(a)(3) (2014). Presumably, intermediate-size IND’s fall out of the statute’s reach regarding treatment IND’s, as the regulations specifically permit access under this type of IND for drugs that are “not being developed.” *See* § 312.315. The statute requires that, not only sponsors be “actively pursuing marketing approval,” but that they at least be in the midst of a clinical trial in order for the FDA to allow expanded access through a treatment IND. *See* 21 U.S.C.A. § 360bbb(c)(3). The statute does not mention IND’s for “intermediate-size patient populations,” and the only seeming definitional difference in the regulations is that intermediate-size patient populations are “smaller than that typical of a treatment IND or treatment protocol.” *See* 21 C.F.R. § 312.315 (2014).

101. § 312.320; 21 U.S.C.A. § 360bbb(c)(3). The FDA may also grant “single-patient IND’s” for individual patients who are unable to obtain the drug through a treatment IND or clinical protocol, provided certain conditions are met. § 312.310. *See* 21 U.S.C.A. § 360bbb(a) for similar requirements. The threshold conditions are relaxed for “emergency use.” *See* 21 C.F.R. § 312.310(d); 21 U.S.C.A. § 360bbb(a). It may also grant IND’s for “intermediate-sized patient populations,” even if all the requirements for treatment IND’s may not be met. *See* 21 C.F.R. § 312.315.

102. 21 U.S.C.A. § 360bbb(c)(3).

103. *See* Rossen, *supra* note 8, at 216.

reimbursement for “direct costs” under certain conditions,¹⁰⁴ the regulations define the term narrowly, and it probably does not capture all true financial direct costs.¹⁰⁵ Furthermore, investigators must report adverse drug events to the sponsor, under any form of expanded access, and sponsors must in turn inform the FDA of this information through IND safety reports.¹⁰⁶ Such data may expose them to potential liability,¹⁰⁷ and may affect the label or the probability of approval.¹⁰⁸ In fact, the FDA explicitly stated that expanded access data “can be useful to a drug’s safety assessment,” but that it is “very unlikely that an expanded access IND would yield [useful] effectiveness information.”¹⁰⁹ The sponsor therefore incurs the risk of acquiring adverse event data, which would likely be biased against the drug, but acquires little or no benefit from the data.¹¹⁰

Finally, expanded access often interferes with the approval process, as patients would prefer to access an experimental drug through a Treatment IND than through a clinical trial.¹¹¹ Accordingly, it would not be in the interest of drug sponsors who were conducting clinical trials to permit any delay in, or interference with, the clinical trial process.¹¹² Especially as industry disincentives has always been a major, if not the primary, obstacle to expanded access,¹¹³ it is unlikely that treatment IND’s can be the ultimate answer to the problem of delayed access.

104. See Leibfarth, *supra* note 1, at 1289 (noting that the section was meant to “eliminate[e] the economic disincentive”).

105. See Rossen, *supra* note 2, at 218. See also *id.* at 217-218 (noting that biotechnology companies are often small start-ups that “face enormous pressure to complete clinical trials and obtain an approved product as quickly as possible” and are therefore in worse position to provide expanded access than more secure pharmaceutical companies).

106. See 21 C.F.R. § 312.305(4), (5) (2014); 74 Fed. Reg. 40905 (August 13, 2009).

107. Rossen, *supra* note 2, at 216.

108. See 74 Fed. Reg. 40905 (stating that “adverse events first identified during expanded access use of certain drugs have been included in the drugs’ approved product labeling”).

109. *Id.* This is not necessarily true, at least in the case of orphan drugs. See Aaron S. Kesselheim, Institute of Medicine (IOM), *Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs*, RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT, at 307 (The Nat’l Academies Press 2011) (finding that “[a] substantial number of pivotal efficacy trials for orphan drugs were open label”).

110. One cited comment, made during the notice-and-comment period for the proposed amendments, noted that a sponsor providing expanded access “runs the risk of being adversely affected by unfavorable safety observations,” but receives “no commensurate benefit...from favorable efficacy observations in the expanded access population.” The commentator also noted that patients under expanded access protocols will likely be often sicker or “otherwise not representative” of the clinical trial population. This should bias the data against the drug’s favor. See 74 Fed. Reg. 40905.

111. Greenberg, *supra* note 42, at 319.

112. *Id.* at 319-320. One drug sponsor explained that it could not make its cancer therapy available on an expanded access basis because, “for every patient [it] took on a compassionate use basis, it would mean one less patient [it] could take in a clinical trial.” Rossen, *supra* note 2, at 218 (citing a statement by Rick Harem, general counsel and vice president at Dendreon).

113. *Id.* at 217.

2. *The Orphan Drug Act*

Congress addressed the second harm, that of disincentives to development of orphan therapies, by using a package of economic incentives through the Orphan Drug Act. Congress passed the Act in 1983 based on the recognition that drugs indicated for rare conditions were highly unprofitable and that few were brought to market.¹¹⁴ To obtain the benefits of the Act, a sponsor must request the FDA to designate the drug as an “orphan” before it submits the NDA.¹¹⁵ An orphan drug must be indicated for a “rare disease or condition,” or one that impacts a patient population of under 200,000 or that otherwise supports “no reasonable expectation” that costs would be recouped.¹¹⁶

The Act operates by granting three primary benefits to designated orphan drugs.¹¹⁷ First, sponsors receive a tax credit that covers 50% of clinical research costs.¹¹⁸ Secondly, they may receive some federal assistance, in the form of grants or funding to obtain contracts with public or private entities, for qualified clinical trial costs.¹¹⁹ Finally, and most importantly,¹²⁰ if a designated orphan drug is approved, the sponsor would enjoy seven years of market exclusivity, or a guarantee that the FDA would not approve another “such drug for such disease or condition” during that period.¹²¹

The Act appeared to have some success, particularly in the years immediately following its passage; however, the extent of its effect today is a matter of significant debate.¹²² Regardless, it cannot fully substitute for

114. David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, 31 AM. J.L. & MED. 365, 367 (2005) (noting that, because the “increased complexity of the clinical trial process significantly increased the cost associated with bringing a discovered drug to market,” drug sponsors “focused efforts on drugs that would have large markets waiting after clinical trials.”) Many potential drugs for rare diseases were unpatentable, and it simply was not economically viable for a sponsor to take drugs for rare diseases through the entire, expensive approval process. David B. Clissold, *Prescription for the Orphan Drug Act: The Impact of the FDA's 1992 Regulations and the Latest Congressional Proposals for Reform*, 50 FOOD & DRUG L.J. 125, 126 (1995).

115. 21 U.S.C.A. § 360bb(a)(1).

116. § 360bb(a)(2).

117. David Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 128 (2000).

118. *Id.*; 26 U.S.C.A. § 45C.

119. Rohde, *supra* note 117, at 128 (citing 21 U.S.C.A. § 360ee).

120. *Id.* at 130 (“Of the three primary incentives incorporated in the Act, the most significant is the seven-year grant of market exclusivity”).

121. 21 U.S.C.A. § 360cc(a)(2) (West 2002). This is subject to the condition that, if it can be shown that the holder of the NDA “cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated,” or if the holder consents, the drug may be subject to shared exclusivity. § 360cc(b)(2).

122. Rohde, *supra* note 117, at 142 (noting that “[t]en times the number of orphan products were approved in the decade following the Act than in the decade preceding Act,” but it is highly debated

reforms that address the evidentiary requirements. For one, it does not address the practical difficulties in acquiring “gold standard” data for orphan drugs.¹²³ Orphan drug studies are often severely underpowered, due to the difficulty in acquiring a sufficient sample size. If a study cannot acquire a sufficiently large sample, it may not be able to report a finding of statistical significance, even if the therapy has an actual effect.¹²⁴ For extremely rare diseases, it is often nearly impossible to recruit enough patients to even use quantitative analysis; and some diseases affect fewer than ten people.¹²⁵

More fundamentally, the Act only crudely incentivizes the production of orphan drugs and results in significant unwanted consequences.¹²⁶ If the Act’s goal was to compensate for economic disincentives for orphan drugs, it may have undershot and “mis-shot” in achieving this goal. It may have mis-shot because the possibility for off-label use opens the door for potential misapplication of the Act, whether intentional or not.¹²⁷ Because a drug may be used off-label for different indications, a sponsor may reap the benefits of the Act by having the drug approved for an orphan indication but sold on a significantly wider market.¹²⁸ On the other hand, if the relevant disease is truly rare and the potential for profit significantly small, market exclusivity would provide little additional incentive to market the drug.¹²⁹

Furthermore, sponsors face significant uncertainties as to whether they would be the first to obtain market exclusivity and as to what may qualify as the “same” drug under the Act.¹³⁰ In short, in applying crude, general

whether the Act continues to efficiently incentivize orphan drug research, for numerous reasons). For more information on the relevant concerns, *see id.* at 131-142,

123. Kesselheim et al., *Characteristics*, *supra* note 64, at 2321 (discussing the difficulties in conducting controlled clinical trials on orphan populations).

124. IOM, *Summary*, *supra* note 73, at 1.

125. *See id.* (noting that some rare conditions have “reported cases in the single or low double digits”).

126. Rohde, *supra* note 117, at 131-132.

127. A drug manufacturer only need to prove efficacy with respect to “the conditions of use prescribed, recommended, or suggested in the labeling,” *see* 21 C.F.R. §514.4 (2014); however, doctors are free, and frequently do, prescribe drugs under different conditions of use and for completely different indications, *see* Michael J. Malinowski & Grant G. Gautreaux, *All That Is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development*, 45 CORNELL INT’L L.J. 185, 191-192 (2012).

128. Loughnot, *supra* note 114, at 370-1 (describing how several orphan drugs became “blockbuster drugs,” and noting that the method of “salami slicing,” or using a subgroup of a larger disease as the orphan indication, is one of the major criticisms of the Orphan Drug Act”).

129. Dov Greenbaum, *Incentivizing Pharmacogenomic Drug Development: How the FDA Can Overcome Early Missteps in Regulating Personalized Medicine*, 40 RUTGERS L.J. 97, 124 (2008).

130. Clissold, *supra* note 114, at 131; Loughnot, *supra* note 114, at 376 (stating that, while the Act prohibits the FDA from granting market exclusivity for the “same” orphan drug designation during a protected period, “due to the complexity of the biochemical structure of most orphan drugs, the distinction between ‘same’ and ‘different’ became more uncertain.”); Rohde, *supra* note 117, at 134, 136 (stating, “The risk of being locked out of the market after a substantial investment in, and the successful

economic incentives across the board, the Orphan Drug Act succeeds in partially incentivizing the development of orphan drugs, but fails to precisely target critically-needed orphan therapies in a focused, dependable manner.

PART IV. CHALLENGING THE CURRENT EVIDENTIARY REGIME

Therefore, the approaches that Congress and FDA have taken to address the unintended costs of the “substantial evidence” requirement, while mitigating the harms, fail to adequately restore incentives to develop critically-needed drugs with high risk and low market potential. Because the FDA’s flexibility is discretionary and unpredictable, the articulated “gold standard” approach still stands as a hurdle to the development of critically-needed drugs. Case-by-case flexibility, expanded access, and the Orphan Drug Act are not enough; the FDA must act consistently and clarify that a reduced standard applies, at a minimum, to orphan drugs for serious or life-threatening conditions.

1. *Challenging the Gold Standard*

First, the FDA should not require gold standard data for critically-needed drugs. Although the “gold standard” may be theoretically ideal, what is ideal in theory is often not ideal in practice.¹³¹ Assuming certain assumptions are met, no other design compares to the blinded RCT in its ability to isolate the effect of the drug.¹³² However, RCT’s merely test the average effect of a drug across the trial participant population, and a finding of statistical significance says nothing about how the drug is effective, nor among

development of, an orphan drug is an unintended barrier to innovation not contemplated initially by the Act”).

131. See Evans, *supra* note 3, at 435 (admitting that RCTs “are correctly regarded as the highest-quality evidence of drug efficacy,” if efficacy is defined as “how well a drug works for carefully chosen trial subjects in the ideal setting of a clinical trial,” because of its ability to eliminate biases.... but arguing that “that RCTs may not provide a complete picture of a drug’s effectiveness,” where effectiveness is “how well it works in real patients in the actual health-care setting”).

132. In other words, an ideal study should minimize or eliminate the possibility of confounding or bias. David Grimes & Kenneth Schulz, *Bias and Causal Associations in Observational Research*, 359 LANCET 248, 249 (2002). A “confounding factor” is any factor other than the intervention that differs between the two groups and can explain a difference in the outcome. *Id.* at 249-50. Bias, more generally, may be considered anything that “undermines the internal validity” of the study, such as selection bias and information bias. Examples of biases include selection bias, where the treatment and control group are not comparable due to the method of selection, and differential information bias, where the exposure or outcome is misclassified or misrepresented based on the method of collecting information. Information bias goes beyond the well-known “placebo effect” but can include the bias of the observing clinicians in making subjective assessments, participant bias that can result from altered behaviors because of the knowledge of treatment, etc. *Id.* at 248-49. Random assignment practically eliminates confounding and selection bias, and double-blinding practically eliminates information bias. See Evans, *supra* note 3, at 433.

whom.¹³³ Often, a drug is effective only among patients with a certain characteristics, genetic or phenotypic.¹³⁴ Therefore, it may be highly effective among a small subgroup in a trial, but the entire trial would be a failure if the average effect is not statistically significant.¹³⁵

Furthermore, data from RCT's are not often generalizable, or translatable, to the various uses and populations in the real world.¹³⁶ Aside from the fact that a significant portion of drug use is off-label,¹³⁷ RCT's are conducted on an artificially-defined population that is often healthier than the population intended to receive the drug.¹³⁸ With potential "wide gaps between clinical data and clinical use of pharmaceuticals," the medical profession may have to rely on data from patient experience, which is exactly what pre-approval clinical trials are supposed to prevent.¹³⁹

Finally, RCT's shed little light on safety. In fact, Phase III trials do not specifically test for drug safety.¹⁴⁰ For this reason, reports of successful Phase III trials may be misleading to consumers, and perhaps even doctors, for the supposition that the expensive trials are a powerful source of safety data.¹⁴¹

Furthermore, with the dawn of personalized medicine and a myriad of other technological advances, the ability to reliably provide sound efficacy evidence outside of the gold standard is not merely becoming more of a reality, but, as some argue, a necessity.¹⁴² In 1962, drugs were, and still are to a large extent today, identified by a process of random screening.¹⁴³ Without a prior understanding of for whom and under what conditions the drug may be effective, it might have once been necessary to cast a broad net

133. See Malinowski & Gautreaux, *Drug Development*, *supra* note 14, at 368-9 (criticizing the "gold standard" design for its "focus[]on ascertaining statistically significant variations based upon group averages," which he argues is inappropriate in light of human variability).

134. Matthew Avery, *Personalized Medicine and Rescuing "Unsafe" Drugs with Pharmacogenomics: A Regulatory Perspective*, 65 FOOD & DRUG L.J. 37, 40 (2010).

135. Evans, *supra* note 3, at 468.

136. See *id.* at 446, 448. Generalizability is the extent to which study results can be applied to a population beyond that of the study. *Id.* at 448.

137. In fact, according to a recent (2000) study, most cancer and AIDS patients receive off-label drug therapy. Malinowski & Gautreaux, *supra* note 127, at 191-92.

138. Evans, *supra* note 3, at 450. This is the not only for ethical and commercial reasons, *id.*, but because researchers try to enhance the homogeneity of the study population to better isolate the effect of the drug. That is, if a diverse study population has multiple illnesses, it is more likely that even a randomized study would suffer from "chance confounding." See Grimes & Schulz, *supra* note 132, at 250.

139. Malinowski & Gautreaux, *supra* note 127, at 194.

140. Based on an underlying principle of hypothesis testing, RCT's must be designed to test for a prespecified endpoint. Since drugs can cause numerous, unknown side effects, many which may not be detectable until later in life, it is virtually impossible to design an RCT that specifically tests for drug safety. Evans, *supra* note 3, at 440-41.

141. *Id.*

142. See, e.g., Greenbaum, *supra* note 129, at 101-15.

143. See *id.* at 111 (observing that the classical method of drug identification is "somewhat stochastic," and "random[]").

in a clinical trial.¹⁴⁴ However, technological advances are better enabling researchers to engage in “rational drug design,” or the use of “genetic and molecular knowledge of the disease,” to identify compounds that target particular proteins or other biological products.¹⁴⁵ In particular, the field of pharmacogenomics is becoming increasingly prominent, where scientists may identify “disease-causing genes...or their eventual protein product” as specific targets.¹⁴⁶ This in turn is giving rise to a world of personalized medicine and targeted therapies.¹⁴⁷ With rational drug design and targeted therapies, clinical trials are rendered less meaningful and useful.¹⁴⁸

Additionally, technological advances in recording, storing, and analyzing data increase the reliability of post-approval studies.¹⁴⁹ In 1962, it was slow, costly, and cumbersome to record and analyze patient data in an observational study. Today, however, it is possible to record minute details in large databases.¹⁵⁰

This increased ability to identify and control for confounding variables, along with more comprehensive data sets, narrows the gap between gold standard clinical trials and observational studies.¹⁵¹

Granted, regardless of these improvements, observational data is far less verifiable and more incomplete than Phase III data,¹⁵² and post-approval studies can never be guaranteed to be free from bias.¹⁵³ Also, while Phase III trials may not fit a regime of individualized medicine, personalized medicine is still in the early stages.¹⁵⁴ Today, gold standard data has at least some value, but its value seems to be increasingly limited.

144. *Id.*

145. *Id.*

146. *Id.* at 110.

147. See Leigh Ann Simmons et al., *Personalized Medicine is More Than Genomic Medicine: Confusion Over Terminology Impedes Progress Towards Personalized Healthcare*, 9 PERS. MED. J. 85, 86–87 (2011) (defining “targeted therapies” as those “designed to impact specific metabolic components or pathways found to be responsible for a particular disease,” and personalized medicine more generally as “the application of personalized medicine tools...to components of patient care.”)

148. See Greenbaum, *supra* note 129, at 114.

149. See, e.g., Andrew Grove, *Rethinking Clinical Trials*, 333 SCIENCE, SEPT. 23, 2011, 1679.

150. *Id.*; Evans, *supra* note 3, at 438–39.

151. See Grimes & Schulz, *supra* note 132, at 250 (noting that confounding can be “corrected, provided that confounding was anticipated and the requisite information gathered,” although it may not be possible to correct selection bias or information bias after the fact.)

152. D.W. Borhani & J.A. Butts, *Rethinking Clinical Trials: Biology’s Mysteries*, 334 SCIENCE 1346, 1346–1347 (2011).

153. See Grimes & Schulz, *supra* note 132, at 250 (noting that selection and information bias result in “irreparable damage” to an observational study).

154. See Greenbaum, *supra* note 129, at 102.

2. Challenging the Application of the Gold Standard to Critically-Needed Drugs

However, a separate, more fundamental objection to the “gold standard” approach can be made with respect to patients with serious illnesses. Regardless of what provides the best evidence of efficacy, there is less reason to require efficacy data for critically-needed drugs, at least when no comparable therapy is available.

Congress introduced the efficacy requirement largely for economic reasons, to address the problem of drug companies’ “misleading and unsupported claims” and unjustly high prices.¹⁵⁵ In addition, pre-approval evidence of efficacy may also increase safety. Since every new drug comes with the risk of adverse effects, some argue that it would be unethical to distribute drugs without “valid statistical evidence of efficacy.”¹⁵⁶

However, the entire risk/benefit analysis is significantly different for patients who suffer from serious diseases.¹⁵⁷ Delayed access may mean little to those seeking “lifestyle drugs,” but it may be a matter of life and death to those with a life-threatening illness.¹⁵⁸ The cost of the “substantial evidence” requirement is further amplified if the disease is also an untreated orphan condition; the ultimate cost being that few or no drugs are developed.

Not only are the costs of the “substantial evidence” requirement increased, but the benefits are reduced.¹⁵⁹ Safety is a relative term, and severely ill patients who have exhausted all alternatives are clearly and understandably willing to take significant risks for any chance of hope.¹⁶⁰ Similarly, the value of efficacy data diminishes, because patients would be willing to incur the risks of a new therapy with even the smallest chance of efficacy.¹⁶¹

Finally, such patients are arguably in a better position, and may have a fundamental right, to decide whether and how they want to attempt to improve their conditions or save their lives.¹⁶² Once it comes to a matter of

155. Frederick Beckner, III, *The FDA's War on Drugs*, 82 GEO. L.J. 529, 550-51. See also Guidance, *supra* note 20, at 2.

156. Borhani & Butts, *supra* note 152, at 1347.

157. Leibfarth, *supra* note 1, at 1288.

158. See Greenberg, *supra* note 42, at 315.

159. *Id.* at 296 (stating, “For a group of individuals facing imminent death..., the possibility that an experimental treatment could be unsafe or ineffective became largely irrelevant”).

160. Leibfarth, *supra* note 1, at 1288.

161. *Id.*

162. See Hayes Edwards, *Risky Business: How the FDA Overstepped Its Bounds by Limiting Patient Access to Experimental Drugs*, 22 GEO. MASON U. C.R. L.J. 389, 393 (2012); Lois K. Perrin, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and*

life and death, the “value of scientific rigor may become secondary to the value of personal therapeutic choice.”¹⁶³ This is particularly true in the case of orphan drugs for serious diseases. It is one thing to argue for strong pre-approval evidence if it simply meant a temporary delay to access, however; it makes little sense to require such evidence if it could mean that no drug would be developed. Accordingly, the clearest case for a lowered standard for efficacy evidence is a drug indicated for a serious or life-threatening orphan condition. The true cost of the gold standard is at its highest here, since the disincentives to drug production is higher in the case of orphan drugs, and the resulting harm is at its greatest.

This does not necessarily mean the gold standard approach should be completely abolished. However, the marginal benefits of gold standard data simply do not exceed its costs in the case of serious and life-threatening illnesses. Instead, a greater reliance on post-marketing studies may be more appropriate in these cases.¹⁶⁴ Since early-phase data is generally more powerful today than in 1962, and since many new drugs for serious or life-threatening illnesses are targeted therapies,¹⁶⁵ early-phase data may be sufficient to release the drugs to these patients.

PART V: THE EX ANTE PERSPECTIVE

Nonetheless, it is not enough to convince the FDA that orphan drugs for serious or life-threatening diseases should be subject to lowered standards of approval because, as demonstrated by its approval history, the FDA may already recognize this to some degree. However, it does not uniformly apply a lowered standard, nor does it offer a clear indication of when it will apply a reduced standard or what that might mean. By taking this approach, the FDA fails to address one crucial component of the problem, ex ante disincentives.

Early Approval for New Drugs, 69 S. CAL. L. REV. 105, 149 (1995) (claiming that patients with terminal illnesses have a “fundamental right” to choose what risks to take).

163. *Id.* at 150 ([A]rguing that any government interest should give way to the “value of personal therapeutic choice” for terminally ill patients because : “(1) The freedom to care for one’s health is of a highly personal nature that should ultimately rest with the individual; (2) a regulation denying access to unapproved drugs severely interferes with the lifestyle of the terminally ill individual; and (3) only the terminally ill person is affected by the decision to choose unapproved drugs”).

164. See Steven R. Salbu, *The FDA and Public Access To New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, Aids, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 143-50 (1999).

165. See Steven T. Walker, *Should Congress Amend FDCA to Create Earlier Patient Access to New Treatments for Serious and Life-Threatening Conditions?* FDLI’S FOOD AND DRUG POLICY FORUM, at 1 (Ap.11, 2011), <http://abigail-alliance.org/docs/FDLISteveWalker.pdf>.

1. The Economic Perspective

As in any other industry, pharmaceutical and biotechnology companies must compare expected revenue to expected cost before deciding whether to pursue a particular venture. Given the nature of drug investments, it is critical that drug sponsors be able to make reasonable projections of these figures at an early point in time.¹⁶⁶ Sponsors and investors use the concept of “net present value” (NPV) in their development and investment decisions.¹⁶⁷ Important factors that affect NPV include total cost, time, and the discount rate. The discount rate, or the required return on investment, is critically affected by the risk of the investment.¹⁶⁸ Estimations of total outlay, time, and risk are especially crucial in the drug development context.¹⁶⁹

A clarified reduction in evidentiary requirements should have the following effects on the ex ante estimate of NPV. First, it would reduce total expected direct costs. Phase III trials account for as much as ninety percent (90%) of the development costs of drugs that are ultimately approved,¹⁷⁰ therefore, a simple expectation that Phase III trials would not be required should dramatically affect the NPV estimation. Secondly, it would reduce the estimated time of approval. According to a recent study, it takes an average of 7.2 years to bring a drug from IND filing to eventual approval, and an average of almost nine years for neuropharmacologic and cancer drugs,¹⁷¹ in addition to 3 or more years of preclinical research prior to IND filing.¹⁷² Not only do longer trials incur higher accounting costs, the time

166. See P. Honig & R. Lalonde, *The Economics of Drug Development: A Grim Reality and a Role for Clinical Pharmacology*, 87 CLIN PHARMACOL & THER. 247, 248 (2010), <http://www.aacp.org/meetingsandevents/pastmeetings/Documents/Lalonde%20clpt2009298a.pdf>

167. *Id.* at 248.

168. The classic equation for NPV include the following variables: the time of the cash flow (t), the total time (n), the discount rate (r), the net cash flow (C_t) and the initial capital outlay C₀ . :

$$NPV = \sum_{t=1}^n \frac{C_t}{(1+r)^t} - C_0$$

The discount rate in this equation is “reflective of and significantly determined by the risk or probability of success (POS) of the project.” *Id.*

169. See *id.* (characterizing the “dominant concerns of the industry” as that of cost, time, and risk). See also J.A. DiMasi et al., *Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs*, 87 CLIN PHARMACOL THER. 272, 272 (2010), <http://www.readcube.com/articles/10.1038/clpt.2009.295> (“Many factors affect the cost of drug development, but two of the key basic elements are time and risk.”).

170. This data is based on findings from a recent study on development costs for drugs that are ultimately approved in four major areas of disease. Phase III trials account for 40% of R&D expenditures in general, but this figure is higher because it is based on drugs that are ultimately approved. Roy, *supra* note 4, at 2.

171. The study was conducted on drugs approved in the period 2003-2007. Critically, since these time periods measure the period since the IND filing, they do not include the period of preclinical testing, discovery, and research. See Kenneth Kaitin, *Deconstructing the Drug Development Process: The New Face of Innovation*, 87 CLIN PHARMACOL THER. 356, 357-58 (2010), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2953249/>.

172. Rossen, *supra* note 2, at 187.

value of money is particularly implicated in any investment with a significant delay between the initial investment and eventual return.¹⁷³ The expected time-to-approval component may be especially critical in the biotechnology industry, given the time pressure from its heavy reliance on venture capital,¹⁷⁴ and the FDA should note that reliably shortening the expected time-to-approval could markedly impact the development of important therapies in this sector.

Another critical factor affecting the development decision is the anticipated risk. A reduced evidentiary standard may or may not lower the probability of failure significantly, depending on exactly how the FDA applies the standard. However, it clearly impacts the cost of failure, or the magnitude of the risk. This cost is extremely high in the context of a decade-long development process. According to a recent study, only sixteen percent (16%) of self-originating drugs were approved in the U.S. during the period 1999-2004.¹⁷⁵ Late-stage failure is particularly detrimental, as a significant amount of time and money had already been invested in the drug.¹⁷⁶ Investors also face the risk of late-stage “economic failure,” which includes the risk that a sponsor will realize the market is overcrowded only after it is well into the clinical trial process. On average, these decisions occur 3.7 years after the beginning of clinical trials, when development costs are at the highest.¹⁷⁷

Accordingly, if an investment is characterized by high risk and high outlay, it may only be worth it if there is a chance of significant gain. For this reason, rational drug developers often choose to develop “blockbuster therapies,” or those targeted to large patient populations.¹⁷⁸ On average, only thirty percent (30%) of new drugs are actually profitable; therefore, sponsors are particularly incentivized to aim for blockbuster drugs in hopes that one success would offset the other losses.¹⁷⁹ Innovative, critically-needed drugs with low expected revenue and uncertain efficacy certainly do not fit this model. However, by decreasing expected time and costs, a lowered

173. Honig & Lalonde, *supra* note 166, at 248. The concept behind the time value of money is that a given unit of money is valued more in the present than in the future.

174. Composed primarily of small, young companies with little assets, the industry relies heavily on venture capital financing, for the purpose of developing product and licensing them out. Accordingly, they “face enormous pressure to complete clinical trials and obtain an approved product as quickly as possible.” Rossen, *supra* note 2, at 217-18.

175. DiMasi, *supra* note 169, at 272.

176. Honig & Lalonde, *supra* note 166, at 249 (noting that late phase failures “incur tremendous direct, indirect, and opportunity costs, and serve to significantly destroy company valuations as well as erode the credibility of the R&D leadership in the eyes of investors”).

177. Kaitin, *supra* note 171, at 358.

178. Rossen, *supra* note 2, at 201.

179. Kaitin, *supra* note 171, at 356.

evidentiary standard would reduce the cost of failure and encourage the investment.

Finally, predictability plays an important role in these economic decisions. It is important to note that the variables in the NPV equation are all *ex ante* estimates of expected value, and each estimate has a certain level of variance, or range of possible values, associated with it. The narrower the range, the more confident an investor or sponsor would be of their projections.

Case-by-case flexibility expands the range of possible estimates, but it does not reliably lower the cost estimate. Given the FDA's unpredictable approach, the possibility of high costs still remains, and will be seriously considered by pharmaceutical companies and investors. The non-negligible possibility of having to conduct two large Phase III trials will be factored into the analysis and may act as a deal-breaker. Accordingly, it is not enough to reduce the time or cost of a given trial; the FDA must more generally reduce reliable *ex ante* estimates of the expected time and cost.

2. *The Ex Ante Perspective of Current Reforms*

Therefore, a clarified reduction in evidentiary standards would accomplish what the existing reform measures could not. For one, it would not carry many of the infirmities of the Orphan Drug Act. Instead of over- and under-shooting, it directly targets a primary disincentivizing factor, the cost of the evidentiary standards. If early approval is accompanied by restricted access, this would address the problem of misapplication of the Act for off-label use.¹⁸⁰ It would not impose the unintended side effects of market exclusivity; and, financially, it would be essentially costless.

Secondly, it would add the necessary piece of predictability to the FDA's current approach. Even if the FDA has recently been more open about the fact that it often exercises flexibility,¹⁸¹ it does not clearly say how it will, or even whether it will. The FDA still reveals a significantly risk-averse

180. See Roy, *supra* note 4, at 8 (advocating for a system of early "conditional approval [for] patients most in need" of the drug, which would permit a "modest amount of revenue").

181. For each of the fiscal years 2011 and 2012, the FDA issued reports on the year's "innovative drug approvals." The reports speak positively of the scientific flexibility that the FDA exercised in the year's approvals, and of its support for finding new, innovative means of assessing a drug's safety and effectiveness. In fact, the FDA explicitly notes that it "often allows non-traditional approaches to establishing safety and effectiveness" for orphan drugs, due to the "small numbers of patients who suffer from each disease." See FDA, *FY 2012 Innovative New Drug Approvals: Bringing Life-Saving Drugs to Patients Quickly and Efficiently*, FDA.GOV, at 8 (Dec. 2012), <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM330859.pdf>. In fact, the FDA explicitly notes that it "often allows non-traditional approaches to establishing safety and effectiveness" for orphan drugs, due to the "small numbers of patients who suffer from each disease." *Id.* at 9.

side,¹⁸² and it appears to be sending mixed messages, likely due in part to a “divergence” within the agency.¹⁸³

Furthermore, neither vague statements of intentions, nor isolated reports of select cases of evidentiary flexibility, can reliably lower cost estimates. The FDA may be willing to announce its intention to “innovate” the drug approval process and provide “timely access to innovative and life-saving drugs.”¹⁸⁴ However, such statements do not give a sponsor a solid indication whether a reduced standard will apply, to the extent practicable, nor what that might mean.¹⁸⁵

Admittedly, a lowered efficacy standard comes with its own costs. Neither the FDA nor prescribing doctors would be as confident that the marketed drugs are safe and effective. However, because the FDA already exercises flexibility in a significant number of cases, it is already imposing the “cost” of this approach on the public. In other words, the patient population is already bearing the cost of reduced standards of efficacy in many cases, without the concomitant benefit of ex ante incentivization. Therefore, if the FDA is to apply a reduced standard anyway, it should announce this intention ahead of time to obtain the benefits of incentivization.

This is also not to deny that the measures that Congress and the FDA took had any positive impact on ex ante incentives.¹⁸⁶ However, they leave

182. See e.g. Roy, *supra* note 4, at 9 (stating that “[t]he FDA is averse to all risk”); Henry I. Miller & David R. Henderson, *The FDA’s Risky Risk-Aversion*, POLICY REVIEW, no. 145 (Oct. 2, 2007), <http://www.hoover.org/research/fdas-risky-risk-aversion> (stating that “drug regulation in the United States in recent years has actually become progressively more risk-averse,” and referencing Genentech’s statement that the FDA arbitrarily delayed approval of the cancer drug Avastin).

183. Walker, *supra* note 165, at 4.

184. FDA, *FY 2012*, *supra* note 181, at 9.

185. See Sasinowski, *supra* note 63, at 5 (calling for a “statement from FDA as to how that flexibility finds expression”).

186. It should be noted that Congress took one measure that does focus on the predictability of evidentiary standards, although it cannot completely address ex ante concerns. Under “special protocol assessment” provision of FDAMA, the FDA must meet with a sponsor who “makes a reasonable written request” to come to an “agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim.” If an agreement is reached, the FDA is bound to the agreement unless the sponsor agrees otherwise in writing, or if the director of the reviewing division determines “that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.” See 21 U.S.C.A. § 355(b). However, the “special protocol assessment” provision does not guarantee that an agreement would be reached. See FDA, *Guidance for Industry: Special Protocol Assessment*, FDA.GOV, at 2, (May 2002), www.fda.gov/downloads/Drugs/Guidances/ucm080571.pdf (noting, “If ...the parties cannot agree that the trial design is adequate to meet the goals of the sponsor, the Agency will clearly state the reasons for the disagreement in a letter to the sponsor.”) Also, the agreement would generally take place too late to impact early ex ante decisions, as the sponsor can only make the request as a part of the IND once the drug is in “advanced clinical development,” and once product characterization and the protocol are complete. See *id.* at 2, 4-6. However, it can take about 3 years to acquire the preclinical data for an IND. See Rossen, *supra* note 2, at 187. This would be far long after sponsor and investors make the initial cost-based decision to develop the therapy, the point at which cost estimates are crucial.

significant room for improvement.¹⁸⁷ A proposal to change the evidentiary standards would not replace any of these reforms; rather, it would be complementary. In addition to the broad measures that Congress has already taken, a tailored efficacy requirement would more precisely, and powerfully, incentivize the development of the most critically-needed drugs.

3. Proposals

How to specifically go about doing this is not an easy task. Various proposals have been made to strengthen expanded access, modernize the evidentiary standards, or adjust the standards based on the need for the drug. Congress and the FDA can draw elements from these proposals to more precisely target ex ante incentives for critically-needed drugs.

For instance, Steven Walker proposes that Congress amend the statutory definition of “substantial evidence” to take into account the severity of the disease.¹⁸⁸ If Congress alters the definition to explicitly allow, or perhaps require, the FDA to take into account the need for the drug, it gives the FDA leeway to announce the lowered standards, without running afoul of statute. The FDA then should, through regulations and guidances, clarify as much as practicable the reduced standard of efficacy for qualified drugs.

However, given the concern for off-label use, and the concern that sponsors would have little incentive to pursue additional clinical studies, the FDA may choose to adjust this proposal by offering a type of provisional approval. Avik Roy proposes a system of “conditional approval” that would permit “limited marketing authorization” for drugs after Phase II to patients who most need it.¹⁸⁹ The ability to reap marginal revenue can support funding for Phase III trial(s) and mitigate the risk that a “company would lose everything” if a Phase III trial fails or is not pursued.¹⁹⁰ More dramatically, Andrew Grove proposes that the FDA only require Phase I safety data prior to marketing, and that a post-marketing “e-trial” system be utilized to establish efficacy.¹⁹¹

187. See Honig & Lalonde, *supra* note 166, at 247 (recognizing the “remaining unmet medical needs in most all therapeutic areas”); Radcliffe, *supra* note 77 (claiming that “far too many patients with [rare] diseases still have no treatments”).

188. Specifically, he proposes that, instead of “adequate and well-controlled investigations,” the text should read: “adequate scientific and medical investigation(s) that reasonably establish the safety and effectiveness of a new drug or treatment indication for its intended use, considering not only the risks and benefits of the drug, but also the risks posed by the disease and the adverse public health effect of delaying availability of a new treatment.” See Walker, *supra* note 165, at 7.

189. See Roy, *supra* note 4.

190. See *id.* (suggesting also that the FDA “retain[] the option to revoke that approval later on, should unexpected data come to light”).

191. See Grove, *supra* note 149, at 1679.

If Congress is unwilling to apply these proposals to all drugs, it may implement a system of conditional approval tailored to the level of need. Along these lines, the proposed ACCESS Act would create a “three-tiered scheme” that ties the ability to access an early-stage drug to the severity of the need.¹⁹² The third tier would be equivalent to the current scheme, while the first tier would function as a more dependable version of expanded access, allowing qualified terminally ill patients to access a drug based on Phase I data.¹⁹³ However, the proposed Act envisions that the sponsor continue in clinical trials, as it must be “actively pursuing marketing approval with due diligence” to charge for the drug.¹⁹⁴ This may be modified to allow sponsors the option to continue clinical trials, which would give the concomitant benefit of wider marketing opportunities, but allow adequate returns on an investment even at the first tier. If the definition of “substantial evidence” is amended, this multiple-tiered system may be modified to provide for early approval, rather than expanded access.

Gleaning from these proposals, the FDA could provide one or more levels of restricted, provisional approval and condition these upon agreements to conduct post-marketing stud(ies). The model may allow for the option of Phase III studi(es) that would permit broader marketing requirements. This ensures that, if a sponsor does not believe it is economically worthwhile to bring a drug through clinical trials, it may invest up to the “first tier.” Accordingly, sponsors would receive adequate incentives to reach any “tier” of approval.

Whatever the specific solution, Congress and the FDA should tailor the evidentiary standards to the need for the drug, clarify these standards as much as possible, and allow an economically-sustainable scheme of approval that supports it. Granted, this clarification would be imperfect, and the FDA naturally would not be able to guarantee what specific types of evidence would necessarily qualify. However, any added clarification should narrow the range of cost estimates. At a minimum, a Congressional acknowledgement that a lowered standard of efficacy actually applies would have an enormous impact, not simply in assuring sponsors, but in giving the FDA license to clarify a lowered standard without having to make the difficult argument that “the same statutory standard” applies. Similarly, although the standards will undoubtedly go through some evolution, any added clarification through regulations and guidances would in-

192. See Leibfarth, *supra* note 1, at 1309 (citing Access, Compassion, Care, and Ethics for Seriously Ill Patients Act, S. 1956, 109th Cong. (2005)).

193. *Id.*

194. See Compassionate Access Act of 2010, H.R. 4732, 111th Cong. (2010), at 11. The Act would also require that any patient accessing the drug have failed in an attempt to enter a clinical trial. See *id.* at 9.

crease predictability. Although precise guarantees are impossible, the FDA should move in the direction of transparency and clarity.

CONCLUSION

The FDA must fulfill its statutory directive to ensure that any drug brought to the market is “safe and effective” for its intended use. However, in doing so, it cannot forget its overarching goal, “to promote and protect the public health.”¹⁹⁵ To best fulfill this goal, both Congress and the FDA must prioritize the incentivization of critically-needed drugs. Through the existing reform measures, they have displayed a willingness to fight the unintended costs of “substantial evidence” requirement. However, for the most part, they have done so from a current perspective, focusing on identifiable drugs and identifiable costs. To locate and target the hidden costs of undeveloped drugs, they must take a new perspective, an *ex ante* one. Case-by-case flexibility, expanded access, and the Orphan Drug Act may help, but they are not the answer. Only by openly recognizing the relative value of “substantial evidence,” and by consistently applying a tailored standard, may the FDA truly fulfill a critical aspect of promoting the public health, delivering important new therapies to those who most need it.

APPENDIX A

Below is a list of examples of drug approvals that were included in the 2011 NORD report.

- 1983: The FDA approved Panhematin (hemin) to treat attacks caused by certain porphyria’s based on six small open-label studies. Each had about twenty subjects; most lasted a few days; and none utilized concurrent controls. As no data on the patients’ prior conditions had been provided, the studies did not appear to even have historical controls.¹⁹⁶

- 1985: The FDA approved Moctanin (monoctanoin) for dissolving gallstones in the bile duct based on published clinical data, animal and *in vitro* studies, and one multicenter study that involved no concurrent or historical control group. Both the published literature and the multicenter study reported success for only about a third of participants, and the published literature also reported a “high incidence of adverse effects.”¹⁹⁷

195. See FDA, *Advancing Regulatory Science for Public Health*, October 2010, at 2, available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf> (stating that the FDA’s agency’s “fundamental mission” is “to promote and protect the public health”); see also Leibfarth, *supra* note 1, at 1282.

196. Sasinowski, *supra* note 63, at 16. (NORD acknowledges the possibility that the FDA may have relied on poorly documented historical controls, although it could not find any reference to such controls, nor could it ascertain whether any prior patient data was recorded or provided to the FDA.)

197. *Id.* at 20.

- 1989: The FDA approved Cytovene (ganciclovir sodium) for the treatment of cytomegalovirus retinitis in AIDs patients based on a retrospective case-series analysis of forty-one patients treated by the same physician, and analyzed in a post-hoc manner.¹⁹⁸
- 1995: The FDA approve WinRho (rho (D) immune globulin intravenous) for the treatment of immune thrombocytopenic purpura, based on four clinical trials that each failed to show a statistically significant improvement on any of the several employed endpoints.¹⁹⁹
- 1996: The FDA approved Cystadane (betaine HCL) for the treatment of homocystinuria based solely on data from published literature and a double-blinded controlled trial that failed.²⁰⁰
- 1997: The FDA approved sclerosol (sterile talc powder) based only on evidence from published literature. The designs of the various studies different in crucial aspects, from dose to the identity of the control group, and the statistical reviewer stated that it was impossible to determine how exactly the patients were treated.²⁰¹
- 1997: The FDA approved Antizol (fomepizole) to treat methanol or ethylene glycol poisoning, based on historical data and two small, open-label studies that the medical and statistical reviewer described as “uncontrolled.”²⁰² The statistical reviewer found the data unsuitable for statistical analysis and “inconclusive” because most patients in the treatment group were also treated with ethanol and/ or hemodialysis. This made it nearly impossible to isolate Antizol’s effect from that of the other treatments.²⁰³
- 1998: FDA approved Thalomid (thalidomide) based on an open-label pivotal study that was uncontrolled and retrospective.²⁰⁴ The statistical reviewer claimed that “[v]irtually no adverse event data [were recorded,]” that the study was not “adequate [or] well-controlled,” and that “due to the total absence of any safety and adverse event data, no benefit to risk

198. *Id.* at 16.

199. *Id.* at 21-22.

200. *Id.* at 12.

201. *Id.* at 23.

202. *Id.* at 15-16. (citing FDA, *Statistical Review and Evaluation: Antizol*, October 16, 1997, at 3-4).

203. *Id.* at 16. (citing FDA, *Statistical Review and Evaluation: Antizol*, [WWW.RAREDISEASES.ORG](http://www.rarediseases.org), at 4-5, Oct. 16, 1997) <https://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovalforphandrugs.pdf>.

204. *Id.* at 23. The Statistical Review also mentioned another small controlled study, disregarding it as too small to support statistical analysis. See Brenda Vaughan, FDA, *Statistical Review and Evaluation: Thalidomide*, NDA no. 20-785, at 1-2, (Jun. 16, 1997), http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020785s000_Thalidomide_StatR.pdf.

evaluation [could] be made.”²⁰⁵ (This is the same thalidomide that gave rise to the 1962 drug amendments.²⁰⁶)

- 2003: The FDA approved Aldurazymje (laronidase) for the treatment of mucopolysaccharidosis-I, despite the fact that the single pivotal trial failed to have a statistically significant effect on one of the two pre-specified primary endpoints and on three of the four pre-specified secondary endpoints.²⁰⁷

- 2004: The FDA approved DTPA (diethylenetriamine pentaacetic acid) based on an uncontrolled, retrospective review of patient data in a government database, using rates of radiation elimination as the primary endpoint, and without the benefit of animal data.²⁰⁸

- 2005: The FDA approved Revlimid (lenalidomide) based on a single-armed, non-randomized pivotal trial that used same-patient data as nominal controls. However, the method of selection suffered from severe design defects such that the controls were arguably meaningless.²⁰⁹

- 2005: The FDA approved Exjade (deferasirox), relying mainly on a single non-inferiority trial that failed to meet the pre-specified non-inferiority margin for the study population. The FDA allowed the sponsor to engage in post-hoc subgroup analysis to achieve this margin for certain subgroups, an act that both the FDA and statistical community strongly frown upon as a form of “data-picking.”²¹⁰

205. Vaughan, *supra* note 204, at 36-37.

206. Aaron. S. Kesselheim & Daniel. H. Solomon, *Incentives for Drug Development—The Curious Case of Colchicine*, 362 N ENGL J MED 2045, 2046 (2010).

207. Sasinowski, *supra* note 63, at 17.

208. Drugs that treat severe or life-threatening effects of certain forms of toxic exposures may fall under a highly specific exception to the human efficacy data requirement, provided in 21 C.F.R. §314, Subpart I, given that such trials would be “unethical or unfeasible.” However, Subpart I requires animal data, *see* § 314.610, but the FDA “did not require the sponsor to conduct such animal studies either pre- or post-approval” in this case. *Id.* at 15.

209. The sponsor claimed that it was able to use same-patient data as historical controls, comparing a treatment “success” of any 8-week period of transfusion dependence against a comparator 8-week period. However, as NORD points out, the sponsor was able to select any eight-week period of transfusion independence, in an unblinded fashion, as the “treatment period,” and compare it to the 8-week run-in period that served as the control. Given the inclusion criteria, the patient could not be transfusion-independent during the comparator period; so the control period took place during a time in which it could not report a “success.” *Id.* at 18.

210. One of the fundamental tenants of statistical analysis is that the statistical criteria must be specified ahead of time; otherwise, it is possible to engage in “data picking” [or other phrase]. The statistical community severely criticizes post-hoc subgroup analysis because almost any study can achieve “statistical significance” for a particular subgroup, identified after the fact. For this reason, the FDA generally is extremely strict on this point, requiring a detailed statistical protocol ahead of time. *See* § 314.126(b)(1); *see also* Kulynych, *supra* note 7, at 142 (noting that the “FDA generally takes a dim view of post hoc “fishing” in data for subgroup effects, reflecting the traditional concern of statisticians that post hoc data analysis artificially inflates statistical significance” and that “FDA will consider only effectiveness data that has been analyzed “in accordance with the plan prospectively stated in the protocol”). *Id.* at 15.