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The Role of Patient Participation in Drug Approvals:

Lessons from the Accelerated Approval of Eteplirsen

KYLE T. EDWARDS*

ABSTRACT

In September 2016, the Food and Drug Administration (FDA) controversially approved Exondys 51 (eteplirsen) for the treatment of Duchenne muscular dystrophy (DMD). Submitted under FDA's Accelerated Approval pathway, eteplirsen is the first drug approved to treat DMD, a rare and fatal genetic disorder characterized by progressive loss of muscle function. Just five months earlier, FDA's scientific advisory committee had voted against approval over the objections of a crowd of more than one thousand patients and advocates who had arrived to observe and provide testimony during the committee's public hearing. Despite anecdotal accounts from patients and their caregivers of the drug's benefits, the committee determined that Sarepta's twelve-person trial had failed to present substantial evidence of the drug's effectiveness. FDA's internal scientific review team agreed. Yet, in the face of significant pressure from patients and their advocates, FDA reversed the negative recommendations of the advisory committee and its internal review team and approved the drug. This Article presents an account and critical appraisal of the role that patients and their advocates played in securing eteplirsen's approval, using the case to understand FDA's attempts to meet congressional demands over the past few decades for greater patient involvement and expanded expedited review programs. In light of the 21st Century Cures Act's recent directive to FDA to significantly develop both its patient involvement and expedited approval programs, the lessons of the eteplirsen approval are particularly timely.

INTRODUCTION

On April 25, 2016, dozens of young boys in wheelchairs, accompanied by their families and doctors, crowded into a hotel ballroom in Hyattsville, Maryland. Their host, the Food and Drug Administration (FDA), relocated the meeting to the hotel due to unusually high expected attendance: by eight in the morning, over one

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thousand patients and their advocates had settled into the at-capacity ballroom.[1] They had come to provide testimony and witness the deliberations of an independent scientific advisory committee, which had been appointed by FDA to recommend for or against the approval of eteplirsen, a new drug for the treatment of Duchenne muscular dystrophy (DMD). DMD is a rare but devastating genetic disorder that primarily affects boys and is characterized by progressive loss of muscle function.[2] Typically, the disease manifests before age five, necessitates the use of a wheelchair by the patient's early teens, and results in death during his twenties or thirties.[3] If sanctioned by FDA, eteplirsen would become the first drug specifically approved to treat patients with DMD.[4]

Over the next twelve hours, the advisory committee and the crowd heard scientific evidence about the safety and efficacy of eteplirsen from the manufacturer of the drug, Sarepta Therapeutics, and the internal review team from FDA's Center for Drug Evaluation and Research (CDER). Sarepta touted the results of its four-year clinical study, arguing that the results "show[ed] a dramatic positive effect" on participants' retention of the ability to walk.[5] But the CDER review team expressed concern that the study only included twelve boys and was not well controlled: it did "not appear possible to conclude" based on Sarepta's data set "that differences in physical performance between eteplirsen treated patients and external control [patients] resulted from an effect of eteplirsen instead of from other differences and influences."[6]

In addition to the scientific presentations, the advisory committee heard testimony from fifty-two public speakers, including DMD patients, their parents and siblings, doctors, and scientists. "I'm going to beat this bloody disease," one fifteen-year old patient stated, "but I need your help . . . . FDA, please don't let me die early."[7] "As a physician," one doctor testified, "I want the option to prescribe eteplirsen. We cannot withhold a safe drug from even one boy who may benefit."[8] And the mother of a boy

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[1] Aaron S. Kesselheim & Jerry Avorn, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 316 J. AM. MED. ASS'N 2357, 2357 (2016), http://jamanetwork.com/journals/jama/fullarticle/2572614; Andrew Pollack, *Advisers to F.D.A. Vote Against Duchenne Muscular Dystrophy Drug*, N.Y. TIMES, Apr. 25, 2016), http://www.nytimes.com/2016/04/26/business/muscular-dystrophy-drug-fda-sarepta-eteplirsen.html?_r=0; CTR. FOR DRUG EVALUATION & RESEARCH, FDA, SUMMARY MINUTES OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING 2 (Apr. 25, 2016), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM509870.pdf.

[2] Press Release, FDA, FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy (Sept. 19, 2016), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm [hereinafter FDA Eteplirsen Press Release].

[3] *Id.*

[4] Rebecca Voelker, *First DMD Drug Gains Approval*, 316 J. AM. MED. ASS'N 1756 (2016).

[5] CTR. FOR DRUG EVALUATION & RESEARCH, FDA, TRANSCRIPT OF MEETING OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE 121 (Apr. 25, 2016), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM510390.pdf [hereinafter Advisory Committee Transcript].

[6] *Id.* at 253–54.

[7] *Id.* at 359.

[8] *Id.* at 334.

with DMD claimed, "We have witnessed the efficacy of this drug. We are not just desperate parents, as often described in the media."[9]

At the end of the long day, the advisory committee publicly voted to recommend against approval of eteplirsen.[10] While members noted that they were deeply moved by patient and family member testimonials, the majority concluded that Sarepta had not provided "*substantial evidence*, that is evidence from adequate and well-controlled studies . . . , that eteplirsen is effective for the treatment of DMD," the statutory standard for approval.[11] But the committee clearly struggled in deciding how to weigh the patient testimony alongside the scientific evidence presented by Sarepta and FDA: one member—who ultimately voted in favor of approval—noted, "I can't really reconcile the difference between the testimony that was given suggesting . . . the boys' recovering abilities . . . [and] this study . . . [which] doesn't provide what I think is adequate evidence to support all this testimony that I'm seeing and hearing."[12]

Taking the advisory committee's negative recommendation into account, the CDER review team assigned to evaluate eteplirsen determined that the drug should not be approved at the present time due to the lack of substantial evidence of effectiveness.[13] In its final memo, the review team echoed the advisory committee, stating that they "were unable to reconcile the patient testimonies with the data collected by the applicant: the testimonies spoke of *improvement*; the data showed *progressive worsening*."[14]

So it came as a surprise to many when the Director of CDER overturned the recommendation of the independent advisory committee and her own review team in announcing the approval of eteplirsen.[15] In her decision, Dr. Janet Woodcock concluded, in contrast to her subordinates, that the evidence submitted by Sarepta met the statutory standard for accelerated approval.[16] She acknowledged the "seriously deficient" aspects of the drug's development and stated that her decision "represents the greatest flexibility possible for FDA while remaining within its statutory framework."[17]

The high-level reversal was highly unusual and generated significant internal turmoil at FDA. The director of the review team privately warned Dr. Woodcock that, "to [his] knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness

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[9] *Id.* at 352.

[10] *Id.* at 556.

[11] *Id.*

[12] *Id.* at 557.

[13] Office Director Decisional Memorandum from Dr. Ellis F. Unger, Dir., Office of Drug Evaluation-I, at 2 (July 15, 2016), *in* SUMMARY REVIEW OF APPLICATION 206488, at 2 (2016) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf [hereinafter Unger Decisional Memorandum].

[14] *Id.* at 35.

[15] FDA Eteplirsen Press Release, *supra* note 2; Center Director Decisional Memorandum from Dr. Janet Woodcock, Dir., Center for Drug Evaluation and Research (July 14, 2016), *in* SUMMARY REVIEW OF APPLICATION 206488, at 12 (2016), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf [hereinafter Woodcock Decisional Memorandum].

[16] Woodcock Decisional Memorandum, *supra* note 15, at 1.

[17] *Id.* at 11–12.

has been demonstrated."[18] The same director invoked a rarely-used scientific dispute appeal process to contest Dr. Woodcock's decision. In his appeal, he argued that Dr. Woodcock's reversal was based not on scientific evidence of efficacy but on "external pressures, from both patient advocacy groups and Congress."[19] He warned that approval would "send the signal that political pressure and even intimidation—not science—guides FDA decisions," and would "strongly encourag[e] public activism and intimidation as a substitute for data," which is not the "type of activism . . . envisioned for patient-focused drug development."[20] However, when the appeal reached the top of the agency, the FDA Commissioner, Dr. Robert Califf, ultimately decided to defer to Dr. Woodcock's decision, noting that "the history of the FDA includes a consistent precedent of final decision-making about medical products at the Center level."[21]

Patients rejoiced,[22] FDA employees resigned,[23] and Sarepta—its shares rising seventy-four percent after the approval—announced to investors that it would price the drug at approximately $300,000 per patient per year.[24]

The eteplirsen case illustrates the expanding role and power of patients in the drug approval process, as well as FDA's internal struggle to incorporate the patient perspective as a factor in its highly technical, safety and efficacy-based review framework. Although the agency's struggle to integrate patients into the drug approval process dates back at least to the 1980s, the passage of the 21st Century Cures Act in December 2016—just a few months after eteplirsen's approval—

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[18] Letter from Dr. Luciana Borio, Acting Chief Scientist, to Dr. Robert Califf, Comm'r of Food and Drugs, (Aug. 8, 2016, at 14), *in* SUMMARY REVIEW OF APPLICATION 206488, at 14 (2016). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf (citing an email from Dr. Ellis Unger, Dir. of Office of Drug Evaluation I, to Dr. Janet Woodcock, Dir. of Ctr. for Drug Evaluation and Research, July 5, 2016) [hereinafter Borio Appeal Memorandum].

[19] *Id.* at 10.

[20] Agency Scientific Dispute Appeal Memorandum from Dr. Ellis F. Unger, Dir., Off. of Drug Evaluation-I, to G. Matthew Warren, Dir., Off. of Scientific Integrity (July 18, 2016), *in* SUMMARY REVIEW OF APPLICATION 206488, at 23–24, (2016), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf [hereinafter Unger Appeal Memorandum].

[21] Commissioner's Decision from Dr. Robert M. Califf, Comm'r of Food and Drugs (Sept. 16, 2016), *in* SUMMARY REVIEW OF APPLICATION 206488, at 6 (2016), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf [hereinafter Califf Appeal Decisional Memorandum].

[22] Press Release, Muscular Dystrophy Association, MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy (Sept. 19, 2016), https://www.mda.org/mda-celebrates-fda-accelerated-approval-eteplirsen-treatment-duchenne-muscular-dystrophy ("This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen. Throughout this process we have seen the undeniable strength of our community . . . .This is an important victory, and we are honored to stand shoulder-to-shoulder with everyone who has fought to make this day a reality.").

[23] Toni Clarke & Natalie Grover, *Bowing to Pressure, FDA Approves Sarepta's Duchenne Drug*, REUTERS (Sept. 19, 2016, 4:26 PM), http://www.reuters.com/article/us-sarepta-fda-idUSKCN11P1HK (reporting the resignation of Dr. Ronald Farkas, the supervisor of FDA's clinical review team for eteplirsen).

[24] Rita Rubin, *Now that FDA Has Approved Muscular Dystrophy Drug Against Advisors' Recommendation, What's Next?*, FORBES (Sept. 19, 2016, 2:54 PM), http://www.forbes.com/sites/ritarubin/2016/09/19/now-that-fda-has-approved-muscular-dystrophy-drug-against-advisors-recommedation-whats-next/#36a6b06147ce.

renews the emphasis on developing patient involvement pathways at FDA.[25] The Act, passed overwhelmingly by both the House and the Senate, has been lauded for increasing the budget of the National Institutes for Health (NIH) and providing a large amount of funding for a series of science and medicine initiatives, like former Vice President Joe Biden's Cancer Moonshot.[26] But it also directs FDA to create guidance on the submission of "patient experience data" and to explain how the agency will incorporate such information into the drug approval process.[27] Patient experience data are that "collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers)" that "are intended to provide information about patients' experiences with a disease or condition"—much like the testimonials provided at the eteplirsen public hearing.[28] Furthermore, the Act requires FDA "to establish a program to evaluate the potential use of real world evidence" to support the approval of a new indication for an already-approved drug or to satisfy post-approval requirements, like the ones eteplirsen must now meet.[29] Real world evidence is defined as "data regarding the usage or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials," which could include observational or anecdotal evidence from patients and caregivers.[30]

Given Congress's directive to FDA to develop new programs and practices for incorporating the patient perspective over the coming years, the lessons from the controversy over the eteplirsen approval are particularly timely. The case illuminates both promising avenues for patient input and warns against those practices that permit or encourage agency officials to bend to political or patient-group pressure without evidence of efficacy, lessons that both FDA and Congress should take into account when crafting patient involvement mechanisms in the future. This article critiques the eteplirsen case as an example of FDA's evolving approach to incorporating patients and the non-traditional evidence that they introduce into the drug approval process. Part I explains two important historical developments that bear heavily on the eteplirsen decision: the increase in opportunities for patient involvement in the drug approval process and the creation of new tools for speeding the approval of drugs that treat rare and life-threatening diseases. Part II presents an in-depth account of the eteplirsen decision, drawing on the transcript of the advisory committee meeting and public hearing, briefing documents from FDA and Sarepta about the clinical trial and the safety and efficacy of the drug, and internal documents that FDA decided to make public from the scientific dispute appeal process. Part III

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[25] Mike DeBonis, *Congress Passes 21st Century Cures Act, Boosting Research and Easing Drug Approvals*, WASH. POST (Dec. 7, 2016), https://www.washingtonpost.com/news/powerpost/wp/2016/12/07/congress-passes-21st-century-cures-act-boosting-research-and-easing-drug-approvals/?utm_term=.b7bc38bbc1f6; *see also* Juliet Eilperin & Carolyn Y. Johnson, *Obama, Paying Tribute to Biden and Bipartisanship, Signs 21st Century Cures Act Tuesday*, WASH. POST. (Dec. 13, 2016), https://www.washingtonpost.com/news/powerpost/wp/2016/12/13/obama-paying-tribute-to-biden-and-bipartisanship-signs-21st-century-cures-act-tuesday/?utm_term=.1044766365f2.

[26] DeBonis, *supra* note 25.

[27] 21st Century Cures Act, Pub. L. No. 114-255, § 3001, 130 Stat. 1033 (2016).

[28] *Id.*

[29] *Id.* § 3022.

[30] *Id.*

draws out key lessons from the eteplirsen case for the future of patient involvement in drug approvals.

I. THE RISE OF PATIENT INVOLVEMENT PATHWAYS AND EXPEDITED DRUG APPROVAL PROGRAMS AT FDA

The pre-1962 FDA looked very different from the agency that exists today: drug manufacturers did not need to seek pre-marketing approval—they could sell drugs within sixty days of notifying FDA so long as the agency did not object—and FDA had no statutory authority to demand that drugs marketed to the public were *effective*, as opposed to merely safe.[31] In the 1950s, a new sleeping pill called thalidomide was licensed in Germany and across Europe, and quickly became popular among pregnant women due to its additional capacity to reduce morning sickness.[32] It was not until 1961 that scientists connected an increase in severe birth defects to use of the drug: it is estimated that 10,000 children worldwide were affected by the international tragedy.[33] But the United States was largely spared because one FDA reviewer, Frances Kelsey, objected repeatedly to the manufacturer's pre-marketing notification, each time demanding that the company resubmit their notification with new data, thus restarting the sixty-day clock.[34]

Senator Estes Kefauver, the chair of the Subcommittee on Antitrust and Monopoly, had recently introduced amendments to the Food, Drug and Cosmetics Act (FDCA) to put a check on the considerable power of the pharmaceutical industry.[35] Recognizing the opportunity, he harnessed the power of the thalidomide tragedy and Kelsey's overnight fame to push through the Kefauver-Harris Amendments of 1962.[36] The Amendments successfully ushered in a "new regime of drug development and approval."[37] The two key changes were 1) that manufacturers were now required to show "substantial evidence" of safety *and* efficacy through "adequate and well-controlled investigations," and 2) the approval process switched from one in which a drug could be marketed so long as FDA did not object, to one in which a drug had to receive affirmative approval from FDA before it could be distributed.[38] The Act defined "substantial evidence" of effectiveness as:

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[31] Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Amendments at 50*, 367 NEW ENG. J. OF MED. 1481, 1481 (2012); *50 Years: The Kefauver-Harris Amendments*, FDA (Feb. 26, 2016), http://www.fda.gov/Drugs/NewsEvents/ucm320924.htm.

[32] John Frisbee, *Thalidomide*, ENCYCLOPEDIA OF WOMEN'S HEALTH 643–44 (Sana Loue & Martha Sajatovic eds., 2004).

[33] Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, 35 FDA CONSUMER (2001), http://permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/features/2001/201_kelsey.html. On the history of the thalidomide tragedy and its seminal impact on the modern processes of FDA, *see generally* DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 228–97 (2014).

[34] Bren, *supra* note 33.

[35] CARPENTER, *supra* note 33, at 231, 234.

[36] *Id.* at 242, 258–59 (describing how Senator Kefauver leaked details of Kelsey's story to the Washington Post, starting "an avalanche of publicity" that he would later draw on in urging for the passage of the 1962 Amendments).

[37] CARPENTER, *supra* note 33, at 270.

[38] 21 U.S.C. § 355(d), (e).

[E]vidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have . . . .[39]

These statutory amendments were fleshed out by FDA regulations that, among other things, introduced the now-standard concepts of randomized, controlled trials, informed consent, and Phase I, Phase II, and Phase III clinical trials.[40]

Though the Kefauver-Harris Amendments are generally lauded for vastly increasing FDA's ability to protect public safety and health by switching the U.S. from a pre-marketing notification regime to a licensing regime, there has been a growing sense in the half-century since, that FDA may have swung too far toward the other end of the drug approval spectrum. If too many unsafe and ineffective drugs made it to market before 1962, many have voiced concerns that, today, too many safe and effective drugs are held up in FDA's review process or, worse, denied approval.[41] A common way of framing the issue describes the problem on one end of the spectrum as a Type I error—a false positive, where a drug is approved but is not, in fact, safe and effective—and the problem on the other end as a Type II error—a false negative, where a drug is not approved despite being safe and effective.[42] Patient groups urge that the opportunity cost of such delays and denials can mean the difference between life and death for patients with rapidly progressing diseases.[43]

On the basis of these concerns, patients and their advocates—often with the support of drug manufacturers—began to lobby for two key changes to the drug approval process: first, a greater voice for affected patients in the process, and second, speedier approval pathways for drugs treating severe and life-threatening diseases. Though the 21st Century Cures Act is the most recent step in this direction, the rise and formalization of patient involvement and the proliferation of pathways for accelerated drug approval long predate it. This section documents the rise of these two trends at FDA, both of which set the stage for the eteplirsen controversy. The eteplirsen case, approved through the agency's Accelerated Approval pathway and after significant patient involvement, provides a lens through which to view the implementation and effects of these developments on the agency's processes and approval decisions.

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[39] 21 U.S.C. § 355(d).

[40] CARPENTER, *supra* note 33, 275–80 (citing the 1963 Investigational New Drug (IND) rules as "some of the most important federal regulations ever to be issued by the Administration").

[41] *See, e.g.*, VINCENT T. DEVITA & ELIZABETH DEVITA-RAEBURN, THE DEATH OF CANCER 8, 298 (2015); RICHARD A. EPSTEIN, OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION 237–38 (2008).

[42] Daniel Carpenter & Michael M. Ting, *The Political Logic of Regulatory Error*, 4 NATURE REVS. DRUG DISCOVERY 819 (2005), http://www.nature.com/nrd/journal/v4/n10/full/nrd1850.html.

[43] *See, e.g.*, THOMAS J. PHILIPSON & ERIC SUN, COST OF CAUTION: THE IMPACT ON PATIENTS OF DELAYED DRUG APPROVALS (2010), http://www.manhattan-institute.org/pdf/fda_02.pdf; Roxanne Nelson, *Delays in Cancer Drug Approvals Cost Lives*, MEDSCAPE, (Sept. 8, 2015), http://www.medscape.com/viewarticle/850632.

A. The Formalization of Patient Involvement

The 1962 Amendments ushered in a new era of paternalism in drug regulation: the requirement that a sponsor demonstrate a drug's efficacy before consumers can access it removes the choice from patients and their physicians of whether to take a risk on a drug that might offer important benefits but has not been adequately proven to do so.[44] The seminal attack on this ideology came from AIDS activists in the 1980s.[45] In the face of a new and fatal disease without any approved treatment options, AIDS patients argued that they ought to be able to access promising drugs still in clinical trials.[46] With painful and rapid decline and death as the alternative, many AIDS patients were willing to take substantial risks on a small chance of slowing the disease's progression.[47] FDA's explanation that they weren't permitted to do so for their own safety seemed, to many, an unacceptable exercise of medical paternalism.[48] Activists mobilized, applying substantial political pressure through protests, op-eds, and unlikely partnerships with the pharmaceutical industry and conservative think tanks; in one historic protest, AIDS patients laid like corpses on the grounds outside FDA's headquarters, with tombstone-like posters declaring "I got the Placebo."[49]

The persistent political pressure succeeded. In 1987, FDA published its first formal set of regulations governing treatment investigational new drug (treatment IND) applications, which allowed limited patient access to drugs still under investigation.[50] And in 1990, FDA created its parallel track policy, which allowed even earlier access to AIDS and HIV treatments for patients who could not

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[44] Harold Edgar & David J. Rothman, *New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process*, 68 MILBANK Q. 111, 121 (1990) (describing drug approval regulations as "an island of ideological paternalism in a sea of autonomy" that characterized the rest of American medicine in the 1960s and 1970s).

[45] Jonathan J. Darrow et al., *New FDA Breakthrough-Drug Category—Implications for Patients*, 370 NEW ENG. J. MED. 1252, 1253 (2014) ("Pressure from physicians and patients intensified with the AIDS crisis of the 1980s, a pivotal episode in the evolution of the FDA drug-approval policies). *But see* CARPENTER, *supra* note 33, at 445 (describing the important role that cancer advocates in the 1970s played in initiating compassionate use programs, which laid the groundwork for the developments of the 1980s).

[46] The FDA Action Handbook released by AIDS Coalition to Unleash Power (ACT UP) was particularly impactful. In it, ACT UP argues that "[t]he imperatives of science, law, bureaucracy and corporate property, which result in a 8-10 year testing period for most drugs, must yield to a synthesis with the needs of seropositives and [people with AIDS] who, untreated, will often live far less long." JIM EIGO ET AL., FDA ACTION HANDBOOK (1988), http://www.actupny.org/documents/FDAhandbook1.html#Introduction.

[47] STEVEN EPSTEIN, IMPURE SCIENCE: AIDS, ACTIVISM, AND THE POLITICS OF KNOWLEDGE 222 (1996) (citing statement of Larry Kramer, an ACT UP founding member, that "AIDS sufferers, who have nothing to lose, are more than willing to be guinea pigs").

[48] *See id.* ("Martin Delaney, executive director of the San Francisco-based Project Inform, struck a chord that resonated deeply with U.S. political culture by painting the FDA as a would-be "Big Brother" and insisting on the individual's basic right to choose."); CHRISTINE GRADY, THE SEARCH FOR AN AIDS VACCINE 48 (1995) ("The FDA was accused by AIDS activists of being too slow, restrictive, and paternalistic . . . . They rejected the paternalism and risk-averse attitudes of the FDA, claiming that as long as a drug is safe, it should be available to anyone who wants it, even if it is medically worthless.").

[49] Edgar & Rothman, *supra* note 44, at 124.

[50] *Id.* Though FDA had operated similar "compassionate use" programs since the 1960s, "these programs had no written rules and were flexibly applied." *Id.*

participate in clinical trials.[51] These two pathways are distinct from the expedited approval pathways discussed below, in that they do not declare a new drug effective but rather allow limited and controlled access to drugs that are still pending approval. Nevertheless, they served as the first major softening of the sea change in U.S. drug regulation that was the 1962 Amendments.

FDA's approach to patients and interest groups evolved in light of the public scrutiny brought on by AIDS activism. The agency found it was able to "defuse much of the political pressure surrounding" groups like the AIDS Coalition to Unleash Power (ACT UP) "simply by incorporating the group into its functions, including formal and informal meetings and an invited seat to Advisory Committee meetings."[52] FDA reports that it has included the patient perspective in its broad set of disease-area Advisory Committees since 1991.[53] Following the success of the AIDS community in lobbying FDA, other disease-specific patient communities have attempted to replicate the model, working both from outside FDA, by harnessing the media and lobbying Congress, and from the inside, by engaging with FDA officials in drug development meetings and public hearings.[54] The common interest in faster drug approvals shared by pharmaceutical companies and many patient groups facing a life-threatening disease with no effective treatment options means that patient advocacy groups often work closely with and receive substantial funding from pharmaceutical manufacturers and their lobbying organizations.[55]

In the Food and Drug Administration Safety and Innovation Act of 2012, Congress issued a strong directive to FDA to better involve, listen, and respond to patients and their advocates.[56] There, Congress created a new section of the FDCA on "Patient Participation in Medical Product Discussion."[57] That section directed

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[51] *Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS*, FDA (Aug. 7, 2014), http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm134331.htm ("The policy differs from the treatment IND primarily in that it applies only to AIDS and HIV-related diseases, and that investigational drugs could be made available earlier in the development process.").

[52] CARPENTER, *supra* note 33, at 448. *See also id.* at 458 (describing how, in the wake of the 1980s and early 1990s protests, FDA "institutionalized audiences," by "br[inging] many of the agency's critics from the drug lag era and the cancer wars into an institutional fold").

[53] *Learn About Patient Engagement at the FDA*, FDA (Oct. 7, 2016), http://www.fda.gov/ForPatients/PatientEngagement/default.htm.

[54] Daniel Carpenter, *The Political Economy of FDA Drug Review: Processing, Politics, and Lessons for Policy*, 23 HEALTH AFF. 52, 58 (2004), http://content.healthaffairs.org/content/23/1/52.full (noting that "unorganized disease communities, witnessing the political and economic successes of the AIDS and breast cancer advocacy coalitions, have been motivated to form their own groups and to enter the political arena").

[55] Susannah L. Rose et al., *Patient Advocacy Organizations, Industry Funding, and Conflicts of Interest*, 177 J. AM. MED. ASS'N INTERNAL MEDICINE 344 (2016), http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2598094 (finding that 67 percent of non-profit patient advocacy organizations report receiving funding from for-profit companies like pharmaceutical and device companies).

[56] *See, e.g.*, Lewis A. Grossman, *FDA and the Rise of the Empowered Consumer*, 66 ADMIN. L. REV. 627, 672–73 (2014); Alexander Gaffney, *Is FDA Listening Enough to Patients? Agency Wants Feedback*, REG. FOCUS (Nov. 3, 2014) ("When Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) into law in 2012, its patient-centered provisions were among the biggest changes set to impact the culture of the US Food and Drug Administration.").

[57] Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-114, § 1137, 126 Stat. 993 (2012).

FDA to "develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions."[58] As a former FDA Commissioner explained, the patient-centered provisions at the heart of the FDA Safety and Innovation Act were "intended to tap the patient perspective."[59]

FDA has made significant efforts to implement the patient participation mandate of the Act, building on some existing programs and creating new ones. Though "[a]s recently as the 1970s, patients played virtually no role in the U.S. Food and Drug Administration's process for approving drugs"—a process that was "the exclusive domain of government bureaucrats, scientific experts, and the pharmaceutical industry"[60]—the agency now boasts a panoply of "opportunities that patients and caregivers can get involved in at the FDA": the FDA Patient Network, the FDA Patient Representative Program, the Safety and Innovation working group, the FDA and European Medicines Agency Patient Engagement Cluster, the Patient Engagement Initiative, patient reported outcomes, the Patient Focused Drug Development Initiative, the Device Patient Preference Initiative, and the Patient Engagement Advisory Committee.[61]

Yet, these various opportunities embody substantially different philosophies about how and why patients should be involved in the drug approval process, suggesting the extent to which FDA is still working through these fundamental questions. The Patient Network is "a one-stop-shop of FDA resources" for patients and their families: its purpose is to provide information about FDA and upcoming meetings, and to circulate a bimonthly patient-oriented newsletter.[62] While importantly increasing access to information, the Network represents a relatively one-way flow of information from the agency to patients, a practice more closely resembling public communication than true involvement.[63]

The Patient Representative Program, by contrast, operates a database of 200 patients and caregivers that serve on FDA decision-making committees to bring "the patient voice" to deliberations.[64] The program matches patients with decision-making committees that consider the patient's condition area, thus allowing patients a seat at the table and the opportunity to make their perspectives heard during the process. Yet the true impact of and rationale for appointing patient representatives is not entirely clear. It certainly serves a basic intrinsic goal of providing affected groups with a voice in decisions that impact them. It may also serve an instrumental goal by

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58 *Id.*

59 Margaret A. Hamburg, *FDASIA at Year Two*, FDA VOICE (July 9, 2014), http://blogs.fda.gov/fdavoice/index.php/2014/07/fdasia-at-year-two/ ("A hallmark of FDASIA was a series of provisions intended to tap the patient perspective.").

60 Lewis A. Grossman, *FDA and the Rise of the Empowered Patient*, *in* FDA IN THE TWENTY-FIRST CENTURY (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).

61 *Learn About Patient Engagement at the FDA*, *supra* note 53.

62 FDA, PATIENT PARTICIPATION IN MEDICAL PRODUCT DISCUSSIONS: REPORT ON STAKEHOLDER VIEWS 8, http://www.fda.gov/downloads/ForPatients/About/UCM486859.pdf [hereinafter PATIENT PARTICIPATION REPORT].

63 Gene Rowe & Lynn J. Frewer, *A Typology of Public Engagement Mechanisms*, 30 SCI., TECH., & HUMAN VALUES 251, 255 (2005), http://journals.sagepub.com/doi/pdf/10.1177/0162243904271724.

64 *About the FDA Patient Representative Program*, FDA (Dec. 19, 2016), http://www.fda.gov/ForPatients/PatientEngagement/ucm412709.htm.

providing a source of information about the specific condition and available treatments. However, this input—as the perspective of just one patient representative—is far from the kind of representative data that FDA normally demands. More cynically, it may offer a token patient voice with little true impact on deliberations and decisions, as a way to "defuse" critiques of the agency's technocratic paternalism. [65]

FDA also lists "patient reported outcomes" as one of its many forms of patient engagement. Patient reported outcomes are a set of assessment measures used in clinical studies that rely upon direct patient feedback about her condition, as opposed to a clinician's or family member's judgment, to measure the success of the treatment in meeting the trial's goals.[66] By contrast to the unclear role and impact of the Patient Representative Program, patient reported outcomes offer a clear pathway for patients' input to impact drug development: clinical trial participants' own reports provide evidence as to the effectiveness of the drug. Nevertheless, a trial using patient reported outcome measures may still face criticism for failing to consult patients on which clinical outcomes matter to them and should be measured by the trial in the first place.[67]

The understanding that patients have something unique to contribute to the question of what it means for a drug to be effective—what counts as 'benefit' and 'risk' in the agency's analysis—motivates the Patient Focused Drug Development Initiative and the Device Patient Preference Initiative. Through the former, FDA has organized twenty-four meetings on specific disease areas—from autism to psoriasis—in order to "elicit patients' perspectives on their disease and on treatment approaches," including what symptoms most impact daily life and the pros and cons of existing treatment regimens.[68]

The Device Patient Preference Initiative serves a similar role for medical devices, and has introduced some of the agency's most innovative patient involvement work, with the goal of "advanc[ing] the science of measuring patient preferences to inform benefit-risk assessments used in regulatory decision-making."[69] In 2016, FDA issued guidance on the submission of patient preference information by manufacturers seeking device approval, suggesting that its reviewers may consider quantitative and qualitative measures of "patient tolerance for risk and perspective on benefit . . . in FDA's assessment of the benefit-risk profile of certain devices when the information qualifies as *valid scientific evidence*."[70] Though some of FDA's methods introduce

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[65] *See supra* text accompanying note 52.

[66] PATIENT PARTICIPATION REPORT, *supra* note 62, at 8.

[67] FDA, PATIENT PREFERENCE INFORMATION—VOLUNTARY SUBMISSION, REVIEW IN PREMARKET APPROVAL APPLICATIONS, HUMANITARIAN DEVICE EXEMPTION APPLICATIONS, AND DE NOVO REQUESTS, AND INCLUSION IN DECISION SUMMARIES AND DEVICE LABELING: GUIDANCE FOR INDUSTRY, FOOD AND DRUG ADMINISTRATION STAFF, AND OTHER STAKEHOLDERS 8−9 (2016) [hereinafter PATIENT PREFERENCE DEVICE GUIDANCE], http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/UCM446680.pdf ("While PRO measures may provide a snapshot of a patient's own assessment of various outcomes at a given point in time, they do not convey how much the patient values one specified outcome or therapy when compared to other potential outcomes and therapies.").

[68] Pujita Vaidya, Presentation, *FDA's Patient-Focused Drug Development*, FDA (Mar. 31, 2016), http://www.fda.gov/downloads/Drugs/NewsEvents/UCM493616.pdf.

[69] PATIENT PARTICIPATION REPORT, *supra note* 62, at 9.

[70] PATIENT PREFERENCE DEVICE GUIDANCE, *supra* note 67, at 2 (emphasis added).

anecdotal data into the approval process, like the Patient Representative Program and patient testimony at hearings, the Device Patient Preference Initiative promotes patient preference studies that draw on a representative sample, such that the results "can be reasonably generalized to the population at interest."[71]

These developments suggest how FDA has increasingly opened its doors both to patient input and, simultaneously, to less technical and more holistic conceptions and measurements of benefit and risk. The 21st Century Cures Act directs FDA to take the next big step forward in patient engagement at the agency through its provisions on patient experience data. Most immediately, the Act requires FDA to issue "a brief statement" with every drug approval regarding the patient experience data reviewed as part of the application.[72] Patient experience data include any data collected by anyone—from patients and their families to patient advocacy groups to manufacturers—that provide information about the experience of a disease or condition, including "the impact of such disease or condition, or a related therapy, on patients' lives" and "patient preferences with respect to treatment of such disease or condition."[73] However, it leaves most of the crucial details about how patient experience data will be developed and used in the hands of FDA: it directs FDA to develop "patient-focused drug development guidance" within the next five years. The guidance must describe methodological approaches for those seeking to collect and submit patient experience data to FDA that "ensure that such data are accurate and representative of the intended population," as well as methodological approaches for "identify[ing] what is most important to patients with respect to burden of disease, burden of treatment, and the benefits and risks in the management of the patient's disease."[74] The guidance must also address how FDA plans to use such data "with respect to the structured risk-benefit assessment framework described in section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d))," the statutory section setting out FDA's substantial evidence standard.[75]

In an interview soon after the eteplirsen decision, Richard Moscicki, Deputy Center Director for Science Operations at CDER, reflected on how dramatically the role of patient advocates in the drug approval process has developed over the past few decades:

There's been an increasing movement, both on the patient's side—patients are empowered today as never before—and I think in general from our side too. I can tell you 20 years ago when I sat across the table and said to an FDA colleague, "You really need to talk to a patient to understand what they're trying to tell you." They said, "No, just the science. Don't want to be influenced or biased." Now we're looking for it, but we understand how carefully this has to be done.[76]

Nevertheless, as FDA's hodgepodge of patient involvement initiatives and the 21st Century Cures Act's open-ended directive on patient experience data make clear, the

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[71] *Id.* at 3, 11.

[72] 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033 (2016).

[73] *Id.*

[74] *Id.*

[75] *Id.*

[76] Shayla Love, *Does the FDA Have a High Enough Standard for Drug Approvals?*, STAT NEWS (Sept. 28, 2016), https://www.statnews.com/2016/09/28/fda-drug-approval-duchenne/.

practice of patient involvement at FDA is still in its infancy, with FDA experimenting with a wide variety of methods for engaging with patients. Drawing the right lessons from the eteplirsen case thus has the potential to shape the direction of patient involvement at FDA at a crucial moment.

B. The Rise of Expedited Drug Approval Programs

As the power of patients and their advocacy groups in the drug approval process grew, so did pressure on FDA to speed access to novel, life-saving drugs. Indeed, as Daniel Carpenter and Mark Fendrick conclude, "the dominant forces driving the acceleration of FDA drug approval have been increased staffing . . . and the increasing political organization and social visibility of disease sufferers in the US."[77] In the wake of the 1962 Amendments, as political momentum grew behind the proposition that FDA took too long or was too conservative in its drug reviews, FDA promulgated rules and Congress passed amendments meant to address these concerns.[78]

In 1992, FDA introduced both its Accelerated Approval and Priority Review programs. A drug may be designated for Priority Review if it treats a serious condition and would provide a "significant improvement in safety or effectiveness."[79] Priority Review drugs are afforded a shorter review clock: FDA agrees to take action on the drug application within six months, as opposed to ten months under standard review.[80] The Accelerated Approval pathway seeks to "accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses."[81] This is the pathway under which FDA approved eteplirsen. The key innovation of the Accelerated Approval pathway is that it allows approval "on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on *a surrogate endpoint* that is *reasonably likely*, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, *to predict clinical benefit*."[82]

The use of surrogate endpoints is the subject of much debate.[83] A surrogate endpoint is a measure of the effect that a drug has on an outcome that is related to a

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[77] Daniel Carpenter & A. Mark Fendrick, *Accelerating Approval Times for New Drugs in the US*, 15 REG. AFFS. J. 411, 417 (2004).

[78] *See* Carpenter, *supra* note 54, 56–57 (observing that before the 1980s "few in media or in Congress were complaining of the agency's Type II errors," but that "[t]he rise in patient advocacy has led to a balancing of the visibility of Type II versus Type I errors").

[79] FDA, GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 25 (2014).

[80] *Id.*

[81] New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942 (Dec. 11, 1992).

[82] 21 C.F.R. 314.510 (2016) (emphasis added).

[83] For a broad range of views on the risks and benefits of using surrogate endpoints in drug approvals, see, for example, BEN GOLDACRE, BAD PHARMA: HOW DRUG COMPANIES MISLEAD DOCTORS AND HARM PATIENTS 132–34 (2014); Thomas R. Fleming & David L. DeMets, *Surrogate End Points in Clinical Trials: Are We Being Misled?*, 125 ANN. INTERNAL MED. 605, 611 (1996), http://annals.org/aim/article/710042/surrogate-end-points-clinical-trials-we-being-misled ("Effects on surrogate end points often do not predict the true clinical effects of interventions."); Anupam B. Jena et al., *The Trade-off Between Speed and Safety in Drug Approvals*, J. AM. MED. ASS'N ONCOLOGY, (Sept. 29, 2016), at E1, http://jamanetwork.com/journals/jamaoncology/article-abstract/2554758 (arguing that "the limited evidence that does exist on the trade-off between speed and safety has generally shown that the harms of delay outweigh the risks of faster drug approval," such as those conducted using surrogate endpoints);

clinically meaningful endpoint but is not in itself clinically meaningful. So, for instance, a trial may show that a new drug created to reduce the risk of heart attacks reduces blood pressure, which researchers use as a surrogate for predicting cardiovascular outcomes. Supporters note that use of surrogate endpoints allows patients to access promising drugs before the many additional years or decades it may take to show a statistically significant effect on clinically meaningful endpoints, like fewer heart attacks or reduced mortality.[84] Critics note that approval based on surrogate endpoints places drugs on the market that have not yet demonstrated the ability to produce direct benefits that are actually meaningful to patients.[85] Their usefulness ultimately depends on how reliably an effect on the surrogate endpoint predicts an effect on the clinically meaningful endpoint.[86]

FDA had approved some drugs based on the use of surrogate endpoints prior to its introduction of the Accelerated Approval pathway. However, in prior cases, the surrogate endpoint was 'validated,' meaning that there was strong evidence that the surrogate endpoint reliably predicted the clinical endpoints of reduced morbidity or mortality.[87] The novelty of Accelerated Approval lay largely in its laxer standard: the surrogate endpoint need only be "reasonably likely to predict clinical benefit." When it proposed the pathway in 1992, FDA received pushback during the notice and comment period that foreshadowed criticism levied in the wake of the eteplirsen approval. Some commenters worried that approval based on surrogate endpoints might "lead to the marketing of large numbers of clinically ineffective, but pharmacologically active, drugs," insisting that "early access to so-called 'promising' drugs is not the same as early access to safe and effective drugs."[88] In response, FDA acknowledged that "[r]eliance on a surrogate endpoint almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known."[89] Nevertheless proceeding to create the pathway, FDA cited the safeguards it had created, including a requirement of post-marketing studies to ensure that clinical benefit accrues and an expedited process for withdrawing drugs granted Accelerated Approval that fail to demonstrate clinical benefit.

Russell Katz, *Biomarkers & Surrogate Markers: An FDA Perspective*, 1 NEURORX: J. AM. SOC'Y EXPERIMENTAL NEUROTHERAPEUTICS 189, 189 (2004); and Chul Kim & Vinay Prasad, *Strength of Validation for Surrogate Endpoints Used in the US Food and Drug Administration's Approval of Oncology Drugs*, 91 MAYO CLINIC PROCS. 713, 723 (2016), http://www.sciencedirect.com/science/article/pii/S0025619616001257 (finding that the standard for approval on the basis of surrogate end points "is lax, with 56% and 37% of [Accelerated Approvals] and [Traditional Approvals], respectively, based on surrogates made without any formal analysis of the strength of the surrogate-survival correlation" and concluding that "[t]his practice should be reconsidered").

[84] *See, e.g.*, DEVITA & DEVITA-RAEBURN, *supra* note 41; *Biomarkers and Surrogate Endpoints*, PHRMA, http://phrma-docs.phrma.org/sites/default/files/pdf/biomarkers-and-surrogate-endpoints.pdf.

[85] *See, e.g.*, GOLDACRE, *supra* note 82, at 132.

[86] *See* Jeffrey K. Aronson, *Biomarkers & Surrogate Endpoints*, 59 BRITISH J. CLINICAL PHARMACOLOGY 491, 492 (2005), http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2125.2005.02435.x/full.

[87] New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. at 58944.

[88] *Id.*

[89] *Id.*

On the heels of FDA's introduction of the Accelerated Approval pathway, Congress passed the Food and Drug Administration Modernization Act of 1997. Five years earlier, Congress had created the Prescription Drug User Fee Act, which, among other things, instituted a fee on manufacturers for submission of new drug applications (NDAs), with the promise that the money would go to hiring more reviewers in an effort to increase the speed and efficiency of the drug review process.[90] Although generally lauded as successful, patient groups and manufacturers were adamant that the approval process needed more systemic change.[91] Congress responded with the FDA Modernization Act, with provisions meant to address its finding that "prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health."[92] The FDA Modernization Act codified and supported the expanded use of FDA's Fast Track designation, first introduced by the agency in 1988.[93] A product can be designated as a Fast Track product if it 1) "is intended for the treatment of a serious or life-threatening condition," and 2) "demonstrates the potential to address unmet medical needs for such a condition," which may be shown by its effect "on a surrogate endpoint that is reasonably likely to predict clinical benefit."[94] Congress directed FDA to "facilitate the development and expedite the review" of drugs that receive the Fast Track designation.[95] FDA implements this congressional directive by prioritizing Fast Track drug applications and offering more frequent meetings and written communication to ensure that the manufacturer designs clinical trials appropriately and collects adequate data.[96]

Building on the Fast Track designation model, Congress created a second innovative pathway to quicker approval in the FDA Safety and Innovation Act of 2012. The Act introduced the Breakthrough Therapy designation. A drug may be designated as a Breakthrough Therapy "if the drug is intended . . . to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies."[97] A drug that receives Breakthrough Therapy designation garners all the benefits of Fast Track and, because it promises substantial improvement over the existing standard of

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[90] Deborah G. Parver, *Expediting the Drug Approval Process: An Analysis of the FDA Modernization Act of 1997*, 51 ADMIN. L. REV. 1249, 1255 (1999), http://www.jstor.org/stable/pdf/40710059.pdf.

[91] *See, e.g.*, *Reauthorization of the Prescription Drug User Fee Act and FDA Reform: Hearing Before the Subcomm. on Health & Env't of the H. Comm. on Commerce*, 105th Cong. 72 (1997) (statement of Gordon M. Binder, Chairman & CEO, Amgen, Inc., on behalf of the Biotechnology Industry Organization and the Pharmaceutical Research and Manufacturers of America) ("As effective as PDUFA has been, much remains to be done. The 1992 law focused on the drug-review process. It did not affect the clinical-development phase of the regulatory process.").

[92] FDA Modernization Act of 1997, Pub. L. No. 105–115, § 101, 111 Stat. 2296, 2298. On other provisions of the Modernization Act that promote faster approvals, *see generally* Parver, *supra* note 89, at 1258-63.

[93] Darrow et al., *supra* note 45, at 1253.

[94] FDA Modernization Act of 1997, Pub. L. No. 105–115, § 112(a), 111 Stat. 2296, 2309.

[95] *Id.*

[96] *Fast Track*, FDA (Sept. 15, 2014), http://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm.

[97] FDA Safety & Innovation Act of 2012, Pub. L. No. 112–114, § 902, 126 Stat. 993, 1086.

care, receives "more intensive FDA guidance" and "an organizational commitment involving senior managers."[98] Drugs designated for Fast Track or Breakthrough Therapy can also seek Accelerated Approval if they meet the pathway's criteria.

The FDA Safety and Innovation Act also expanded FDA's ability to use its Accelerated Approval pathway for rare diseases. In the sixteen years after FDA introduced its Accelerated Approval pathway, FDA approved seventy-three new treatments through it, but only one for a rare genetic disease.[99] In Section 901 of the FDA Safety and Innovation Act, Congress stated clearly its "inten[t] to encourage the Secretary to utilize *innovative* and *flexible* approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."[100] It found:

> (B) During the 2 decades following the establishment of the accelerated approval mechanism, advances in medical sciences, including genomics, molecular biology, and bioinformatics, have provided an unprecedented understanding of the underlying biological mechanism and pathogenesis of disease . . . .
>
> (C) As a result of these remarkable scientific and medical advances, the FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs.[101]

Though FDA had operated the Accelerated Approval pathway since promulgating its 1992 rule, the Safety and Innovation Act indicated Congress's strong intent that FDA make greater use of it. In particular, and especially relevant to the eteplirsen decision, Congress supported the use of a broader range of novel surrogate endpoints, considering that therapies for rare diseases often have no preexisting surrogate endpoints upon which to rely. Notably, however, Section 901 also states that "[n]othing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act)."[102]

The 21st Century Cures Act continues the push for expedited drug approval. First, the Act supports the use of "real world evidence" in approval of a new indication for

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[98] *Frequently Asked Questions: Breakthrough Therapies*, FDA (June 16, 2016), https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/fdasia/ucm341027.htm.

[99] Emil D. Kakkis et al., *Accessing the Accelerated Approval Pathway for Rare Disease Therapeutics*, 34 NATURE BIOTECHNOLOGY 380, 380 (2016).

[100] FDA Safety & Innovation Act of 2012, Pub. L. No. 112–114, § 901(e) (emphasis added).

[101] *Id.* at § 901(a).

[102] *Id.* at § 901(e)(2).

a drug or to satisfy post-approval requirements. As statutorily defined, real world evidence captures an expansive set of information: any "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials."[103] Approval through the submission of such data, which the Act describes as including "ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities," may be far less onerous than conducting a randomized controlled trial.[104] As with patient experience data, the Act leaves it to FDA to sort out the intricacies of what real world evidence is and how the agency will use it: FDA must "establish a program to evaluate the potential use of real world evidence" within the next two years and produce guidance to industry on when the agency "may rely on real world evidence" in the approval process within the next five years.[105]

Second, the Act also seeks more flexible alternatives to randomized controlled trials by requiring FDA to issue guidance within the next four years on "the use of complex adaptive and other novel trial design" in the approval process.[106] This guidance must explain how and under what circumstances these new and less burdensome trial designs may nevertheless satisfy the agency's substantial evidence standard.[107]

Finally, the Act directs FDA to establish a review pathway for the "qualification of drug development tools" within the next four years.[108] The pathway will allow drug developers to submit data on novel surrogate endpoints to FDA; if the endpoint is deemed "qualified" by FDA, drug manufactures will be able to use the surrogate endpoint to show efficacy in future drug applications, raising the possibility of more drug approvals on the basis of surrogate endpoints. The Act also suggests that FDA should prioritize review of new drug development tools on the basis of "the severity, rarity, or prevalence of the disease or condition targeted by the drug," adding to the list of expedited review programs for rare and life-threatening diseases.[109] Notably, Congress disclaimed any intent to alter the substantial evidence standard by introducing these three provisions—on real world evidence, novel trial design, and qualification of drug development tools—suggesting that FDA must find ways to utilize these novel programs while not sacrificing its evidentiary standards.[110]

Each of these three innovations on the drug approval process leaves much to be sorted out in the coming years by FDA. In this moment of flux in the agency's drug approval process, President Donald Trump has signaled his desire to speed up approvals by relaxing regulatory standards. In his First 100 Days Action Plan, President Trump announced, "Reforms will also include cutting the red tape at the FDA: there are over 4,000 drugs awaiting approval, and we especially want to speed

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[103] 21st Century Cures Act, Pub. L. No. 114–255, § 3022, 130 Stat. 1033 (2016).

[104] *Id.*

[105] *Id.*

[106] *Id.* at § 3021.

[107] *Id.*

[108] *Id.* at § 3011.

[109] *Id.*

[110] *Id.* at §§ 3022, 3021, 3011.

the approval of life-saving medications."[111] And in his first address to a joint session of Congress, President Trump argued that "our slow and burdensome approval process at the Food and Drug Administration keeps too many advances . . . from reaching those in need."[112]

In light of this movement to hasten approval of life-saving treatments, the eteplirsen approval provides a valuable case study of a drug's path through the Accelerated Approval program and the agency's struggle to reconcile more flexible and speedy approval pathways with its traditional evidentiary standards. Combined with the high degree of patient advocacy and participation in the eteplirsen approval, the case sheds light on the state of these two major trends at FDA—greater patient involvement and faster drug approvals—and suggests how FDA should tackle the 21st Century Cures Act's directive to further these practices.

II. THE ETEPLIRSEN CASE

It was in the midst of FDA's major push after the FDA Safety and Innovation Act to sort out how to incorporate patient involvement in drug approvals alongside its more traditional review of clinical trial data that eteplirsen entered the scene. This Part describes four phases of the eteplirsen case, drawing out the role of patient advocacy in securing the drug's approval: 1) the clinical trial and early disagreements between Sarepta and FDA about its design and analysis, 2) the scientific advisory committee meeting and public hearing, 3) Dr. Woodcock's decision to overturn the negative recommendation of the advisory committee and her review team, and 4) the scientific dispute appeal process within FDA that culminated in the FDA Commissioner deferring to Dr. Woodcock's decision.

A. The Clinical Trial

The muscle deterioration characteristic of DMD is caused by genetic mutations in the gene responsible for producing dystrophin, a protein that strengthens and stabilizes muscle fibers.[113] In patients with DMD, one or more parts of the gene are deleted such that the gene is incapable of producing functional dystrophin.[114] This is in contrast to less severe forms of muscular dystrophy, like Becker muscular dystrophy, in which some parts of the gene are deleted but it is still able to produce functional—albeit less effective—dystrophin.[115] Eteplirsen was designed to smooth

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[111] DONALD J. TRUMP, DONALD TRUMP'S CONTRACT WITH THE AMERICAN VOTER, at 2. https://assets.donaldjtrump.com/_landings/contract/O-TRU-102316-Contractv02.pdf; *see also* Jeff Tollefson et al., *Tracking the Trump Transition, Agency by Agency*, NATURE (Nov. 30, 2016), http://www.nature.com/news/tracking-the-trump-transition-agency-by-agency-1.21032 ("Widespread speculation that Trump will push to relax drug approval standards at the Food and Drug Administration (FDA) has sent pharmaceutical stocks rising and set consumer watchdogs on edge.").

[112] Sheila Kaplan, *Trump Derides 'Slow and Burdensome' Approval Process at FDA*, STAT NEWS (Feb. 28, 2017), https://www.statnews.com/2017/02/28/trump-address-rare-disease-drugs/.

[113] *Duchenne Muscular Dystrophy (DMD)*, MUSCULAR DYSTROPHY ASS'N, https://www.mda.org/disease/duchenne-muscular-dystrophy.

[114] *What Is Exon Skipping and How Does It Work?*, MUSCULAR DYSTROPHY UK, http://www.musculardystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/.

[115] *Id.* Individuals with Becker's muscular dystrophy experience less severe symptoms and are usually able to continue walking into their 40s and 50s. *Id.*

over a common 'gap' in the gene of DMD patients, thereby permitting the gene to create functional dystrophin. The deletion that eteplirsen targets affects 13 percent of all DMD patients,[116] which works out to an estimated 2,000 to 2,500 patients in the United States.[117]

Incorporated in 1980, Sarepta had not placed a drug on the market prior to eteplirsen. In 2011, the CEO "decided . . . to bet Sarepta's few remaining chips on eteplirsen."[118] The gamble appeared to pay off: in October 2012, Sarepta announced that its Phase IIb trial of eteplirsen showed a statistically significant increase in the production of dystrophin and on the distance that eteplirsen-treated participants registered on the '6-minute walk test.' The 6-minute walk test is an assessment frequently used to evaluate functional capacity in testing the efficacy of treatments for cardiopulmonary diseases.[119] However, with just twelve boys participating, the trial was exceptionally small, a feature that the CEO attributed to the company's funding constraints: "We had a limited amount of drug and no capacity to make more . . . . So we took what we had and did the best small trial we could design."[120]

Twelve boys with DMD between the ages of seven and thirteen were enrolled.[121] Four boys were randomly assigned to receive a lower dose of eteplirsen on a weekly basis through a double-blind study, four to receive a higher dose, and four to receive a placebo.[122] The four assigned to placebo were reassigned to receive either the high or low dose of eteplirsen at Week 24 of the trial. Muscle biopsies were taken at Weeks 12, 24, and 48 to measure dystrophin levels, and the 6-minute walk test was administered at Weeks 32, 36, and 48. After 48 weeks, the participants continued to receive eteplirsen through an unblinded extension of the study for the following four years.[123]

Two boys in the low-dose group became unable to walk soon after the start of the study. Sarepta noted that "[b]ased on the evolving understanding that it may take 24 weeks of eteplirsen-treatment for significant dystrophin production, these two boys may have received eteplirsen too late in the course of their disease for an impact on the [6-minute walk test]."[124] On this basis, the two were excluded from the analysis of the drug's effectiveness. After 48 weeks, the results from the remaining ten boys showed positive effects on both the 6-minute walk test and dystrophin production.

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[116] *Id.*

[117] Kesselheim & Avorn, *supra note* 1, at 2357.

[118] Paul M. Barrett, *Moms, Regulators, Biotech Startups, and the Battle over a Potentially Life-Saving Drug*, BLOOMBERG (Oct. 30, 2014, 6:03 AM), https://www.bloomberg.com/news/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug.

[119] *Sarepta Therapeutics Announces Eteplirsen Meets Primary Endpoint of Increased Novel Dystrophin and Achieves Significant Clinical Benefit on 6-Minute Walk Test After 48 Weeks of Treatment in Phase IIb Study in Duchenne Muscular Dystrophy*, SAREPTA THERAPEUTICS (Oct. 3, 2012), http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1741044 [hereinafter Sarepta October 2012 Press Release].

[120] Barrett, *supra* note 117.

[121] Sarepta October 2012 Press Release, *supra* note 118.

[122] *Id.*

[123] SAREPTA THERAPEUTICS, ETEPLIRSEN BRIEFING DOCUMENT 18, 39 (2016), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervous SystemDrugsAdvisoryCommittee/UCM497064.pdf.

[124] *Id.*

The study group published the results in a much-heralded paper in *Annals of Neurology*, citing an increase to 52 percent of normal dystrophin-positive fibers using a qualitative, immunofluorescence test: a massive effect.[125]

However, FDA later publicly raised doubts about the validity of these results. After inspecting the facility and methods under which the biopsies were analyzed, FDA identified "[s]ignificant methodological concerns . . . which cast serious doubt on the reliability of assessments from the first three biopsies."[126] In particular, FDA criticized the group's use of the immunofluorescence test, arguing that this method overestimates dystrophin production. To compensate, the agency requested a fourth biopsy taken 3.5 years after the start of the study and compared it to biopsies taken pre-treatment.[127] Using a different, quantitative measure of dystrophin production called Western blot analysis, FDA concluded that the best and most reliable estimate of eteplirsen's effect after 3.5 years was an increase to 0.9 percent of normal dystrophin, a marked difference from the publication's finding.[128] Furthermore, because the 6-minute walk test results relied on "post hoc . . . analyses" and "post-randomization exclusion of two patients," and because the open-label design introduced the possibility that expectation bias influenced the effort exerted by the boys during the walk test, FDA indicated that the 6-minute walk test data "did not provide interpretable evidence of benefit."[129]

Though FDA expressed a preference for a new randomized, placebo-controlled trial, Sarepta cited the difficulty of—and ethical objections to—recruiting patients for a placebo-controlled trial given that the perceived benefits of the drug had been widely touted.[130] Therefore, FDA agreed to consider an externally controlled study, with the caveat that data from such a study might prove difficult to interpret.[131] Sarepta decided to implement one kind of externally controlled study: a historical control study. It compared all data from its ongoing, extension study of the ten boys (by this time at Week 144), to data obtained from a 'historical control group.' Here, the control group was composed of patients selected from one Italian and one Belgium DMD patient registry who had not received any therapeutic treatment when their data was collected.

An externally controlled study "compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal

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[125] Jerry R. Mendell et al., *Eteplirsen for the Treatment of Duchenne Muscular Dystrophy*, 74 ANNALS NEUROLOGY 637, 637 (2013); Anne Steele, *Sarepta Cites Positive Muscular Dystrophy Drug Trial Results*, WALL ST. J. (Nov. 17, 2015, 11:12 AM), http://www.wsj.com/articles/sarepta-cites-positive-muscular-dystrophy-drug-trial-results-1447776751.

[126] FDA, FDA BRIEFING DOCUMENT: NDA 206488 ETEPLIRSEN 4 (2016), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM497063.pdf [hereinafter FDA BRIEFING DOCUMENT].

[127] *Id.* at 5. In fact, pre-treatment biopsies were only available for three of the participants. As such, Sarepta used data from patients who were not enrolled in the study.

[128] *Id.* at 6.

[129] *Id.* at 8.

[130] *Id.*

[131] *Id.* at 9.

control group consisting of patients from the same population."[132] Long-standing FDA regulations explain why historical control studies are suboptimal and thus "reserved for special circumstances": "historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations."[133] This makes it more difficult to ensure that the purpose of requiring "adequate and well-controlled clinical studies" is met, that purpose being "to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[134] In other words, historical control groups raise the possibility that any effect seen in the treatment group may be due to underlying differences in the treatment and control populations or the way their data were collected, rather than due to the treatment itself. Randomized controlled trials have acquired their 'gold standard' status in drug approvals in part because this concern is mitigated through the random assignment of individuals from the same population to either the treatment or the control group.

On the basis of the historical control study, Sarepta concluded that eteplirsen had a statistically significant effect on the 6-minute walk test. But FDA found Sarepta's historical control group flawed for a number of reasons that made it difficult to confirm that the results could be attributed to the drug rather than other confounding influences. First, control group patients and Sarepta-trial patients used physical therapy programs and steroid treatment to different degrees, both of which might independently bolster boys' performances on the walk test. Second, performance on Sarepta's walk test could have been influenced by "expectation bias, motivation, and coaching," while such influences were less likely in the external control group because those boys were not in a study receiving an investigational drug. Third, patient selection criteria for the Italian and Belgium registries were chosen after data from the Sarepta trial were already available, introducing the possibility of bias in selecting those criteria.[135] These factors led FDA to question whether there was "a true difference in disease course between eteplirsen-treated patients and the control group."[136]

B. The Scientific Advisory Committee Meeting

In the face of these conflicting accounts of eteplirsen's efficacy, FDA called a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. It is at the discretion of the agency whether to require advisory committee review of NDAs, and committees produce only recommendations and not binding decisions.[137] Nevertheless, "[i]n the vast majority of cases, FDA accepts the recommendation of the advisory committee for approval, further testing[,] or outright disapproval."[138] The key voting issues posed to the committee were: 1) "Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen

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[132]FDA, GUIDANCE FOR INDUSTRY: E10 CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS 6 (2001), http://www.fda.gov/downloads/Guidances/UCM073139.pdf.

[133]21 C.F.R. § 514.117 (b)(4)(iv) (2016).

[134]*Id.*§ 514.117(a).

[135]FDA BRIEFING DOCUMENT, *supra* note 126, at 10.

[136]*Id.* at 12.

[137]PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 723 (3d ed. 2007).

[138]*Id.* at 724.

induces production of dystrophin to a level that is reasonably likely to predict clinical benefit," and 2) "Do the clinical results of the single historically-controlled study [the 6-minute walk study] . . . provide substantial evidence . . . that eteplirsen is effective for the treatment of DMD."[139] The first question concerned whether eteplirsen should be approved under the Accelerated Approval pathway, with dystrophin production as the surrogate endpoint, while the second question—because the 6-minute walk test is considered a standard clinical endpoint—concerned whether eteplirsen met FDA's normal approval standard.

Prior to the meeting of the advisory committee and public hearing, members of Congress weighed in on the matter. In a letter to Dr. Woodcock signed by 109 congressmen and women, signatories pointed explicitly to Congress's intent—as evidenced by the FDA Safety and Innovation Act—both that FDA approve new drugs for life-threating conditions with all possible haste and that it draw more heavily on patient perspectives in its decision making.[140] "[W]e write to underscore the focus [the FDA Safety and Innovation Act] has on accelerating the approval of drugs that treat unmet medical needs, prioritizing the patient perspective in evaluating new drugs and treatments, and providing regulators with flexibility when evaluating drugs for a life-threatening illness."[141] In particular, the letter "urge[d] the FDA to consider . . . the testimony and experiences of . . . patient representatives on the advisory committee and patients and expert clinicians who treat them as they testify during the open public hearing portion of the upcoming advisory committee meeting."[142]

While Congress members attempted to tip FDA's hand towards approval by appealing to congressional intent for flexibility, a group of medical academics published a letter to Dr. Billy Dunn, the Director of the Office of Drug Evaluation-I's Division of Neurology Products responsible for reviewing eteplirsen, which drew on the researchers' clinical experience to advocate for approval.[143] Though the group recognized the flaws in the study design, they highlighted that "4 of 4 (100%) boys" in the eteplirsen trial "remained ambulant past the age of 14." On this basis, they concluded that the eteplirsen-treated boys were "clearly performing better than our collective clinical experience and the published literature would predict," clinical experience that they stressed includes "a group of physicians who have observed over 5,000 DMD Patients . . . over an average of more than 15 years."[144]

At the advisory committee meeting, the committee received presentations from Sarepta and CDER, and then heard brief, prepared statements from patients and members of the public during the open public hearing portion of the day. CDER

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[139]FDA, PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING QUESTIONS 3 (2016), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM500817.pdf.

[140]Letter from Members of Congress to Janet Woodcock, Dir., Ctr. for Drug Evaluation & Research 1 (Feb. 17, 2016), http://freepdfhosting.com/97bd221cd8.pdf.

[141]*Id.* at 1.

[142]*Id.* at 2.

[143]Letter from Duchenne Muscular Dystrophy Researchers to Billy Dunn, Dir., Div. of Neurology Prods. 1 (Feb. 24, 2016), http://www.cdmd.ucla.edu/files/view/FDA_ETEPLIRSEN_LETTER_02242016.pdf.

[144]*Id.* at 2.

started off by describing the demands of Accelerated Approval. Dr. Dunn warned that "[a]ccelerated approval is not a rescue strategy for suggestive data that are insufficient for conventional approval."[145] His account of Accelerated Approval teased out a crucial statutory requirement: while Accelerated Approval allows the use of a surrogate endpoint that is reasonably likely to predict clinical benefit, it does not lower the statutorily-mandated evidentiary standard for effectiveness, that of "substantial evidence." In other words, as he stated, "Accelerated approval concerns the *character* of the endpoints, not the *strength* of the results on those endpoints."[146]

Sarepta was not in disagreement on this legal point, but rather urged that it had demonstrated substantial evidence of eteplirsen's effectiveness on the surrogate endpoint of dystrophin production.[147] Sarepta representatives noted that "research in the field suggests that even small amounts of dystrophin can have a clinical effect" and that the eteplirsen trial "[was] the first time that a therapeutic has demonstrated an unequivocal increase in dystrophin expression."[148] CDER representatives, by contrast, cited their finding that eteplirsen produced an increase in dystrophin to a mere 0.9 percent of normal, calling Sarepta's results "very disappointing and far lower than estimates presented earlier by the applicant."[149] Sarepta also held up the results of the 6-minute walk test, in which the eteplirsen-treated boys showed a "striking" 162-meter benefit.[150] While CDER representatives agreed that Sarepta's results on the 6-minute walk test "if demonstrated in an adequate and well-controlled study, would provide evidence of effectiveness," they explained to the advisory committee that the study's design raised serious concerns.[151]

Sarepta offered part of its presentation time to the Jett Foundation, an organization committed to improving the lives of DMD patients. The executive director, also the mother of a boy receiving eteplirsen, described how the Foundation had met with CDER "to bring context and perspective to FDA on outcomes that are meaningful to patients."[152] After a meeting in which she offered anecdotal accounts of boys' progress on eteplirsen, CDER asked if she would produce video evidence of these improvements. The Foundation responded with "videos of boys who were jumping into pools, walking their dog, and participating in sports."[153] CDER also asked the Foundation to "quantify outcomes important to patients."[154] The Foundation produced quantitative data based on caregiver reports of daily falls, the ability to regain ambulation after a leg fracture (often the end of walking ability in DMD patients), reduced fatigue, and activities of daily living, like lifting a spoon to eat or brushing one's teeth. Comparing the improvements that she saw in these areas to the endpoints of the clinical trial, the Jett director noted, "[W]hile this boy's 6-minute

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[145] Advisory Committee Transcript, *supra* note 5, at 37.

[146] *Id.* at 36 (emphasis added).

[147] *Id.* at 54.

[148] *Id.* at 55–56.

[149] *Id.* at 261.

[150] *Id.* at 52.

[151] *Id.* at 264–65.

[152] *Id.* at 123–24.

[153] *Id.* at 124.

[154] *Id.*

walk test remains stable, it didn't capture the improvements that we saw. He stopped falling, and his fatigue was reduced. Just looking at the 6-minute walk test you wouldn't see the improvements in these other important outcome measures."[155]

After presenting a gloomy overview of CDER's findings, the Deputy Director of the Division of Neurology Products announced his intention to "speak directly to the study participants and their families" in the room: recalling his sister's congenital disability, he remarked that his parents "would have done anything, anything to create a brighter future" for her and that he would do the same for his children.[156] Nevertheless, he stated, "My role, regardless of the pressure that has been placed on my division, and in particular on the eteplirsen review team, is to present our scientific review and conclusions . . . . We are a science-based organization. That review has been very careful. Really, it has been exhaustive . . . ."[157]

During the following public hearing portion, patients and advocates engaged in three, often overlapping tactics in their attempt to sway the advisory committee: 1) emotional appeals, 2) engagement with the statutory provision for flexibility, and 3) engagement with the evidence for the drug's efficacy. Appealing on an emotional level to the committee, a father with a son in eteplirsen's new confirmatory trial stated, "Eteplirsen has given us hope for his future. We no longer plan his funeral. Now, when Peyton talks about driving, attending college and becoming a scientist . . . we believe it's possible."[158] Another father, who had lost a child, described his state of "reliv[ing] the agony of missing the threshold for inclusion in this clinical trial . . . . As a parent who has lost a son to Duchenne, I don't need a reminder of how time passes so quickly. We wait and watch as function is lost never to be regained. Each of us asks, how much longer."[159] The two boys from the Sarepta trial who had lost the ability to walk and had been excluded from the analyses arrived with their mother, who noted, "My boys became known as the kids who were making the data messy."[160] But the two boys assured the committee, "We claim victory because our lives improved while on [the] drug. Our hearts and lungs performed normally . . . . Duchenne patients don't die from not walking, they die from heart and lung failure."[161]

Representative of the second strategy, that of highlighting the statutory provision for flexibility, a congressman and member of the Congressional Rare Disease Caucus spoke to congressional intent to allow flexibility in cases like eteplirsen:

> The accelerated approval pathway outlined in Section 901 of the Act, allows demonstrably safe therapies that treat an unmet medical need, and appear to be efficacious, even with some uncertainty, to avoid the years of regulatory barriers and become accessible earlier to patients who otherwise have no other option.[162]

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[155] *Id.* at 130–31.

[156] *Id.* at 272–73.

[157] *Id.* at 273.

[158] *Id.* at 430.

[159] *Id.* at 405, 407–08.

[160] *Id.* at 398.

[161] *Id.* at 396.

[162] *Id.* at 299.

Similarly, the mother of a child with DMD waiting to access eteplirsen asked, "If not you to . . . honor the tools give[n] to you by Congress and FDASIA [the FDA Safety and Innovation Act] to demonstrate flexibility, then who will? It's time to stop talking about flexibility and to show us."[163] And, returning as a public speaker, the executive director of the Jett Foundation asked "that the agency utilize flexibility in the tools it has to approve a remarkably safe drug while pursuing confirmatory trials," assuring FDA that, "[i]f as a result of those trials, it becomes clear that eteplirsen is not working, we will stand behind the agency should it decide to remove it from the market. You see, we only want drugs that work."[164]

The third strategy, that of engaging with the evidence for eteplirsen's efficacy, saw patients and parents attempting to appeal to the advisory committee on its own terms, that of scientific and clinical evidence. One DMD patient, referring to the level of dystrophin production, stated:

I hear you say that 0.9 percent is disappointing. In order to use a word like that to describe making dystrophin in a disease like Duchenne, I can only guess that you don't know anything about Duchenne. Making 0.9 percent is amazing. It lets me feed myself. It keeps [my brother] walking. It gives us a chance. 0.9 percent is not perfect, but it is life changing.[165]

Inverting the classic conception of scientific expertise, the same patient urged, "It's time to listen to the real experts. So to make that easier for you, we brought them all here today. Please use them," referring to himself and the other DMD patients and caregivers in attendance.[166] One mother of an eteplirsen-treated boy described how she had "relied on casual observation to draw [her] conclusions" about her son's progress in a previous drug trial, and thus "had nothing definitive to say" at its conclusion when the drug was ultimately denied approval. When her son got on eteplirsen, she "was not going to rely on observation" and "wanted to be objective" in her measure of its success. She kept a daily log of collapses and took regular videos of how he performed basic tasks: "So I am not standing up here with anecdotes about how strong my son was on [the] drug and simply asking you to trust me . . . . I captured data regularly in a rigorous way."[167]

Only one of the 52 public speakers spoke out against approval. Laura Gottshalk, on behalf of the National Center for Health Research, stated:

> You're hearing from many patients and family members today who believe in this drug. Your role on the advisory committee is to pressure the company to provide scientific evidence before approval, not to pressure the FDA to ignore the lack of scientific evidence. Your decision today will send a message about whether scientific standards should matter to the FDA. I am very sorry to say that approval of eteplirsen based on today's data would set a dangerously low bar for drugs in the future.[168]

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[163] *Id.* at 417.

[164] *Id.* at 310.

[165] *Id.* at 346.

[166] *Id.* at 346–47.

[167] *Id.* at 442.

[168] *Id.* at 328.

Though all other speakers' statements were met with applause from the audience, the room was silent as she left the podium, and she was later accosted at her car as she left the meeting.[169]

At the conclusion of the day, many of the advisory committee members were clearly unsure of how to vote and, more fundamentally, about what their role in the approval process was. Although asked a list of intermediate questions to vote upon, the defining voting questions were whether Sarepta's results provided substantial evidence of effectiveness, either through the surrogate endpoint of dystrophin production or through the clinical endpoint of the 6-minute walk test.[170] Tellingly, one advisory committee member asked the FDA representatives, "To what extent are we to incorporate into this question the testimony of the families, the boys and their families? . . . From my reading of the question, it would seem narrowly worded toward the actual statistical results. So I just want some clarification on that point."[171] To the applause of the audience, Dr. Woodcock responded, "Well, we are instructed, as people said, to take the use [sic] of the patient community into account . . . . [T]he statutory standard is more or less as described [in the question], but there is flexibility, and that's where we should take the views of the community into account."[172] Another committee member reflected that he "would have two different answers to the questions. One would be objective; one would be subjective. And it's how to reconcile both in the same question here that . . . is the issue."[173]

The vote came down to six yeses and seven nos on whether eteplirsen's effects on dystrophin met the standard for Accelerated Approval and three yeses, seven nos, and three abstentions on whether eteplirsen's effects on the 6-minute walk test met the standard for approval. One member who voted yes on the surrogate endpoint question noted that he was "very troubled" by his lack of understanding of what a clinically significant amount of dystrophin production would be, but stated, "I'm not sure at what level I'm supposed to say this, but I've been extraordinarily influenced and impressed by the people who spoke about this drug earlier and their observations."[174] Other yes voters cited their conclusion that the clinical results from the 6-minute walk test and those results described anecdotally by patients in the audience provided reason to think that eteplirsen's effect on dystrophin is reasonably likely to predict clinical benefit. The nos thought either that the studies were not well controlled or that, even though the results provided strong evidence of some dystrophin production, Sarepta had not produced sufficient evidence that the small production was likely to produce clinical benefit.

On the 6-minute walk test question, the three who abstained noted respectively that they were "just torn between my mind and my heart," that while the study design was unconvincing "I'm still quite sympathetic and persuaded by the public's presentations," and that "as a scientist, I cannot say this study—and answer the question as written—was adequate and well controlled . . . . But I was also moved by

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[169] *Id.* at 329; David Crow, *US Healthcare: Power to the Patients?*, FINANCIAL TIMES (MAY 22, 2016), https://www.ft.com/content/59587d78-1dbc-11e6-a7bc-ee846770ec15.

[170] Advisory Committee Transcript, *supra* note 5, at 547–48.

[171] *Id.* at 548–49.

[172] *Id.* at 549.

[173] *Id.* at 553.

[174] *Id.* at 486–87.

the testimony."[175] Those who voted yes did so because of "the testimony . . . given suggesting . . . the boys' recovering abilities," or because they were fully convinced that "there's substantial evidence."[176] The nos were largely concerned that the study was not well-controlled, due to uncertainties arising from the use of the historical control group. Two no voters, however, noticed the fact that the audience was citing improvements that were not and could not have been measured in the study given the endpoints that were selected: "[U]nfortunately, what I would consider meaningful evidence or testimony from the families is not properly measured in the study. So I hope that in the future that the field will incorporate measures of function."[177]

The audience's disappointment was apparent: the discussion leader, after threatening to "adjourn the meeting prematurely" given the audience outcry, struggled to provide his concluding remarks over repeated audience interruptions.[178]

C. The Reversal

In the wake of the dramatic meeting and the advisory committee's negative recommendations, the CDER review team was responsible for issuing a final decision. In the decision, Dr. Unger stated the team's conclusion that Sarepta had met neither the Accelerated Approval standard (with respect to dystrophin as a surrogate endpoint) nor the conventional approval standard (with respect to the 6-minute walk test).[179] The scientific bases for these conclusions were largely on par with the CDER presentation at the advisory committee meeting, though they incorporated the teams' findings with respect to some newly-submitted data. In particular, Dr. Unger and his team were convinced that new data from Sarepta on the effect of eteplirsen on dystrophin were the result of adequate and well-controlled studies. However, the new results were even less impressive than the 0.9 percent of normal considered at the scientific advisory committee meeting: the results showed a mean of 0.3 percent of normal dystrophin production, with a range from 0 to 1.3 percent.

On the patient testimony at the advisory committee meeting, Dr. Unger noted, "[D]espite the claims of improvement made at the microphone . . . the review team did not find any patients . . . with consistent improvement in physical performance as assessed by formal testing . . . . These tests have shown moderate to extreme declines in physical function for <u>all</u> patients."[180] And with respect to dystrophin production, he noted that while "[t]he unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise . . . the effect size seems insufficient at the tested doses."[181] He questioned "the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic," because of the possibility that "[p]atients who might

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[175] *Id.* at 556–59.

[176] *Id.* at 557–58.

[177] *Id.* at 561–62.

[178] *Id.* at 564.

[179] Unger Decisional Memorandum, *supra* note 13, at 2.

[180] *Id.* at 35.

[181] *Id.* at 39.

receive a lifesaving therapy (i.e., a higher dose) would die because the dose is too low."[182]

Looking beyond the present case, Dr. Unger noted that approving eteplirsen and thus lowering the Accelerated Approval standard would lead to "a world where traditional clinical trials are abandoned in favor of small proof-of-concept studies designed to show any level of production of a target protein," in a way that "would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments."[183] He lamented that rather than trying a higher dose, Sarepta had continued to rely on its twelve-patient study, had convinced the DMD community that the drug was effective, and had "unleash[ed] a public media campaign (with the support of many politicians) to approve the drug."[184] In issuing his team' negative decision, he stated that FDA "do[es] not—and should not—make approval decisions based on patient anecdotes or campaigns through social media."[185]

In overturning the review team's decision in a memorandum finalized *before* Dr. Unger's final decision was issued, Dr. Woodcock "disagree[d] with certain of [the team's] findings and c[a]me to a different conclusion," namely that eteplirsen met the accelerated approval standard based on dystrophin production, a surrogate endpoint she concluded "is reasonably likely to predict clinical benefit."[186] Like the review team, she found that eteplirsen leads to an increase in dystrophin, "albeit at a low level."[187] On the sufficiency of the surrogate endpoint, she posed the statutory question slightly differently: "What amount of increase in dystrophin production is reasonably likely to predict clinical benefit (*even small benefits*)," because, she reasoned, "[t]here is no question that, for DMD patients and their families, small improvements in function or delays in loss of function are meaningful benefits."[188] Reviewing the existing literature on dystrophin levels and clinical expression of muscular dystrophy, she concluded—contrary to the review team—that "the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit."[189] In particular, while the review team relied on findings that "a minimum of 10% [of normal dystrophin] would be necessary for detectable clinical benefit,"[190] she concluded that "protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation."[191]

On this basis, Dr. Woodcock approved eteplirsen under the Accelerated Approval standard despite "flaws in the eteplirsen development program [that] led to severe challenges in regulatory review."[192] In relying on "the greatest flexibility possible for

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[182] *Id.* at 40.

[183] *Id.* at 39.

[184] *Id.* at 40.

[185] *Id.*

[186] Woodcock Decisional Memorandum, *supra* note 15, at 1.

[187] *Id.* at 3.

[188] *Id.* at 5 (emphasis added).

[189] *Id.* at 9.

[190] Unger Decisional Memorandum, *supra* note 13, at 39.

[191] Woodcock Decisional Memorandum, *supra* note 15, at 9.

[192] *Id.* at 11.

FDA while remaining within its statutory framework" to make the approval, she pointed to FDA's determination that "[p]hysicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses than they would accept from products that treat less serious illnesses," and reasoned that "acceptable risks include greater uncertainty about the effects of the drug."[193]

D. The Scientific Dispute Appeal

After Dr. Woodcock released her decision, Dr. Unger filed a scientific dispute appeal, used infrequently to resolve scientific disagreements within the agency. In his appeal letter, Dr. Unger stressed that "the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her . . . memo makes this case."[194] He stressed that approval would expose patients to the risks of treatment with no assurance of benefit, may offer false hope to patients and families in exchange for unjustified risk-taking and financial costs, and may lead patients to forego current treatments like steroids. Looking beyond the effects on DMD patients, he worried that approval would set a problematic precedent by indicating that patient-group and political pressure can trump the results of rigorous scientific analysis.[195] He also noted the notorious difficulty of withdrawing a drug that has been approved, even after confirmatory trials show a lack of efficacy: "FDA has not succeeded in withdrawing the marketing of a single drug for lack of verification of clinical benefit following accelerated approval."[196]

Turning from the substantive dispute about the sufficiency of Sarepta's application, Dr. Unger also raised serious concerns about process. He claimed that "the Center Director's direct involvement with this drug, compared to other development programs, has been unprecedented."[197] In particular, he noted that Dr. Woodcock "made clear her intent to approve the drug at a briefing with the review team . . . before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already ' . . . reached a different conclusion . . . .' than the review team."[198]

Upon receiving Dr. Unger's appeal, Dr. Luciana Borio, the chair of the Agency Scientific Dispute Process Review Board convened the committee to determine whether, per the agency's policies, "the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels."[199] The review process, as this objective makes clear, largely provides oversight of the agency's procedural safeguards, and does not interrogate the substantive conclusions of scientific disputes. In the process of conducting the appeal, the Board reviewed the

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[193] *Id.* at 11–12 (citing 21 C.F.R. § 312.80).

[194] Unger Appeal Memorandum, *supra* note 20, at 20.

[195] *Id.* at 23−24.

[196] *Id.* at 22.

[197] *Id.* at 26.

[198] *Id.*

[199] Borio Appeal Memorandum, *supra* note 18, at 1.

administrative file and interviewed Dr. Unger, Dr. Woodcock, an anonymous member of the review team, and the Ombudsman for CDER.

The Board learned from both Dr. Unger and the anonymous team member that Dr. Woodcock was unusually involved in the review process from an early stage and that, "at Dr. Woodcock's direction, the review team also joined her in meetings with patient advocacy groups for DMD on multiple occasions," which were " 'intense,' 'personal,' and 'intimidating.'"[200] Both Dr. Unger and the anonymous team member reported that Dr. Woodcock "was inclined to grant approval from very early on in the process."[201] Indeed, the Board reported that Dr. Woodcock "conceded . . . that she was leaning toward granting approval in light of the available data as early as 2014," even though Sarepta's NDA was not formally submitted until 2015, and that her meetings with the review team were "to convince them to come around to her more flexible way of thinking about the data."[202] Dr. Woodcock also suggested to the Board that she had considered "the broader picture" of drug development, noting that "Sarepta in particular 'needed to be capitalized'" and that "if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline."[203] The anonymous reviewer said that "the review team was never sure whether they were discussing science, policies, or politics," as Dr. Woodcock was focused on external pressures from patient groups and Congress.[204]

The Board also determined that "[Dr. Woodcock's] involvement here appears to have upended the typical review and decision-making process":

> Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science . . . . Review teams should have the opportunity to conduct their reviews without preemption by the Center Director. As noted above, the SDR Board believes that Center Directors should have a role in shaping policy, expressing concerns, and resolving issues once they are ripe for their review, but we caution that care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.[205]

In terms of addressing the evidence, the Board determined that Dr. Woodcock had "provided a very limited rationale," basing her judgment that dystrophin between undetectable and 10 percent of normal levels is enough to satisfy the accelerated

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[200] *Id.* at 9.

[201] *Id.* at 10.

[202] *Id.* at 10-11.

[203] *Id.* at 16.

[204] *Id.* at 10.

[205] *Id.* at 23.

approval standard essentially on her conclusion that the existing scientific literature is unreliable in this context.[206]

Nevertheless, the Board concluded that Dr. Unger had had an adequate opportunity to present his views—the only strictly relevant determination for the procedurally-oriented Scientific Dispute Appeal process.

Though the Board's decision technically cleared Dr. Woodcock's actions, Dr. Borio, who is also the Acting Chief Scientist, took the unusual step of appending an extra set of comments in submitting the Board's decision to the FDA Commissioner. She stressed that eteplirsen fails the Accelerated Approval standard "[b]y any meaningful objective standard."[207] Asking the FDA Commissioner to conduct a scientific review, given the limited procedural scope of the Board's work, Dr. Borio's note suggests her beliefs about the political pressures at play: "The agency's value centers on its ability to . . . maintain[] objectivity, even in the face of political pressure . . . . [A]pproving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients."[208]

The final say came down to FDA Commissioner Dr. Robert Califf. Ultimately "defer[ing]" to Dr. Woodcock's decision, he framed the case largely as an issue of conflicting scientific expert opinion and judgment: "I conclude that qualified experts with extensive experience in FDA decision-making and stellar track records can assimilate the same scientific evidence and disagree about the extrapolation to whether the evidence supports a conclusion that the treatment has an effect that is 'reasonably likely' to predict clinical benefit."[209] He also noted that "[o]verruling the Center Director is exceedingly rare" and would only be appropriate if the decision "could not be supported by the available data and information."[210]

Dr. Califf rejected the suggestion by Dr. Unger, Dr. Borio, and others that Dr. Woodcock had been politically influenced, concluding that she did not "succumb[] to pressure from the patient community, the public, the press, or others."[211] This conclusion was particularly apt, in Dr. Califf's opinion, given that "our understanding about how to include patients in the regulatory process is evolving."[212] In a footnote, Dr. Califf highlighted a particular concern of his flowing from Dr. Woodcock's statements to the Board, namely that the approval decision may have been "inappropriately motivated by concerns over the sponsor's financial well-being."[213] He indicated that he spoke directly to Dr. Woodcock on this statement, who said that while "she was aware of the financial pressures on the company . . . her decision was based on the science."[214]

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[206] *Id.* at 23-24.

[207] *Id.* at 25.

[208] *Id.* at 26.

[209] Califf Appeal Decisional Memorandum, *supra* note 21, at 5.

[210] *Id.* at 6.

[211] *Id.* at 8.

[212] *Id.* at 12.

[213] *Id.* at 8 n.23.

[214] *Id.*

III. LESSONS FOR PATIENT INVOLVEMENT IN DRUG APPROVALS

Although drug companies and patient interest groups have generally lauded the eteplirsen decision for demonstrating flexibility for potentially life-saving treatments,[215] many scientific researchers and broader consumer and public interest groups have decried the decision.[216] Beyond the CDER review team itself, Aaron Kesselheim, a prominent medical researcher and health law scholar who served on eteplirsen's advisory committee, has lamented that the drug has created "a worrisome model" for drug approvals: "demonstrate a slight difference in a laboratory test, activate the patient community, win approval, and charge high prices, while relying on limited regulatory follow-up."[217] Michael Carome, the Director of Public Citizen's Health Research Group, charged that "Woodcock's decision to overrule so many agency experts represents a dangerous, unparalleled capitulation to pressure from politicians and patients and a stunning disregard of the scientific evidence."[218]

The stark split in opinion between DMD patient groups and their supportive Congress members, on the one hand, and many scientists and consumer watchdogs, on the other, illustrates two markedly different perspectives on the eteplirsen approval. On the one hand is the view that FDA has taken a real step towards implementing Congress's directive for more flexible approval standards, as well as towards engaging in a more deliberative process with citizens directly affected by approval decisions. On the other is the view that FDA crumbled under pressure from Congress and patient groups, allowing raw political and interest group pressures to overwhelm the scientific consensus of FDA's career experts. These two perspectives suggest fundamentally different accounts of what role patient input and preferences

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[215] *Jett Foundation's Response to the Duchenne Community on the Accelerated Approval of Eteplirsen*, JETT FOUNDATION (Sept. 19, 2016), http://www.raredr.com/news/duchenne-thank-you. ("Today is a huge victory for rare disease drug development, for patient input and perseverance, for constructive and educated advocacy, for scientific innovation and integrity, and, most importantly, for Duchenne families."); *MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy*, MUSCULAR DYSTROPHY ASS'N (Sept. 19, 2016), https://www.mda.org/mda-celebrates-fda-accelerated-approval-eteplirsen-treatment-duchenne-muscular-dystrophy.

[216] *See, e.g.*, *Bad Medicine*, ECONOMIST (Oct. 13, 2016), http://www.economist.com/news/leaders/21708726-approving-unproven-drug-sets-worrying-precedent-bad-medicine ([T]he [eteplirsen] decision bodes ill for drug discovery in America."); Editorial, *Patient Need Versus Evidence: A Balancing Act*, 388 THE LANCET 1350 (2016)), http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)31765-2.pdf ("[R]aising hope, perhaps unrealistically, by approving drugs on such uncertain evidence is not the answer, and could even be counterproductive by jeopardizing the ability to undertake placebo-controlled trials."); Derek Lowe, *Sarepta Gets An Approval – Unfortunately*, SCI. TRANSLATIONAL MED. (Sept. 20, 2016), http://blogs.sciencemag.org/pipeline/archives/2016/09/20/sarepta-gets-an-approval-unfortunately ("[I]n the end, I think that the FDA's job is to approve drugs that work, and no one knows if this one works or not.").

[217] Aaron Kesselheim & Jerry Avorn, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 316 J. AM. MED. ASS'N 2357, 2358 (2016).

[218] Michael Carome, *Outrage of the Month: FDA Senior Leader Ignores Science, Approves Ineffective Drug for a Rare Disease*, PUBLIC CITIZEN (Oct. 2016), https://www.citizen.org/our-work/health-and-safety/outrage-of-the-month-fda-senior-leader-ignores-science-approves-ineffective-drug-for-a-rare-disease.

should play in drug approval decisions at FDA—how, in other words, patients and their advocates can legitimately influence decisions at the agency.

As FDA expands its patient involvement and expedited drug approval mechanisms in light of the 21st Century Cures Act, the eteplirsen case may help sort through this question of how patients can meaningfully and legitimately affect FDA's approval decisions. First, the agency must create strong internal checks to identify and block the approval of drugs based solely on patient or political pressure where substantial evidence of effectiveness is lacking. Section A identifies significant procedural failures in the eteplirsen approval that should serve in the future as warning signs that approval stems not from factors and evidence relevant to the statutory risk-benefit analysis but rather from pressures external to the scientific assessment. And, second, FDA must tailor its public engagement pathways to suit the demands of representativeness and generalizability embodied in the substantial evidence standard. Section B illustrates the incompatibility of the method by which patients were involved in the eteplirsen approval and the agency's effectiveness standard, and suggests alternative methods by which patients may have legitimately affected the drug development and approval process.

A. Internal Checks on the Influence of Patient and Political Pressure

In support of his decision to accept Dr. Woodcock's approval of eteplirsen, Dr. Califf noted that two scientific experts can assess the same data and reasonably disagree about whether it constitutes substantial evidence of effectiveness. Precisely because experts can disagree on such technical conclusions, it is often difficult to identify when a controversial decision is made on the scientific merits or when it is instead unduly influenced by external pressures from patient groups or the political branches. Existing doctrines of administrative law that invalidate agency action that is "arbitrary and capricious" provide guidance for identifying when decisions may be based on such undue influences. This Section draws on some of those judicial doctrines to illustrate the numerous red flags raised that Dr. Woodcock's reversal was based on pressure from patients and politicians, and not on the evidence.

Importantly, while a number of the events in the course of the eteplirsen decision might suggest the legal invalidity of the decision under these administrative law doctrines, the judiciary provides a relatively weak check on FDA's drug approval standards. Though coalitions interested in preserving FDA's high standards for efficacy exist, like Public Citizen and the National Center for Health Research, the decision to approve a drug like eteplirsen has rarely been subject to legal challenge.[219] This is due in large part to the substantial hurdle that standing poses to appealing decisions like the eteplirsen approval. While standing for the *denial* of a drug application can rest on the injury that a patient will suffer from not having access to that drug, it is difficult to articulate injury-in-fact for parties that do not

[219]Peter Barton Hutt et al., FOOD AND DRUG L. 731 (3d ed. 2007) ("An FDA decision to approve a drug has seldom been contested in court."). *But see*, *id*. at 731-32 ("In fact, challenges to denials are relatively rare because manufacturers recognize their poor prospects in court: courts tend to give only "perfunctory scrutiny of FDA[] denial[s]" and "[n]o sponsor has successfully sought reversal of an FDA refusal to approve its drug.").

have DMD who are challenging an approval.[220] The claimed 'harm' by public interest and consumer protection groups—an erosion of FDA's general standards of safety and efficacy or the increase of ineffective drugs on the market—is likely too diffuse to sustain under current law. A DMD patient concerned about the inability to tell whether the only drug approved to treat his disease is effective would have a slightly better standing claim; but even then a court might reasonably conclude that the 'injury'—use of an ineffective drug—is not actual or threatened given that the patient could choose not to take eteplirsen. An insurance company might claim injury from having to pay steep fees for a drug that is of dubious effectiveness, and if a law required them to cover the drug, that claim might succeed. But, as the decision of Anthem to deny coverage of eteplirsen shows,[221] insurance companies have a considerable amount of discretion to decide which drugs to cover.

The unique nature of drug approvals, then, shields the agency from judicial challenges that a drug approval was issued on the basis of patient or political pressure, even where such claims might have purchase in other administrative contexts. Therefore, application of these administrative law doctrines to the eteplirsen case are used here not to suggest litigation strategy but rather the kind of internal checks that the agency must itself create to insulate its evidence-based decisions on safety and efficacy.

American administrative law focuses on whether an agency has given adequate reasons for its decisions.[222] An agency is deemed to have breached this duty of reason-giving—and to have thus acted "arbitrarily and capriciously"—if it "has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise."[223] The standard account of administrative reason-giving holds that 'political' considerations are insufficient on their own to justify action. In *State Farm*, the Court concluded that the National Highway Traffic Safety Administration (NHTSA) had failed to provide a sufficient justification for rescinding a rule that required all new cars to be equipped with passive restraints.[224] The majority rested this decision exclusively on short-comings in NHTSA's technical reasoning.[225] But, in a partial dissent, Justice Rehnquist observed that NHTSA's decision in fact appeared to reflect a change in

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[220] *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560 (1992) ("[O]ur cases have established that the irreducible constitutional minimum of standing contains three elements. First, the plaintiff must have suffered an 'injury in fact'—an invasion of a legally protected interest which is (a) concrete and particularized and (b) 'actual or imminent, not 'conjectural' or 'hypothetical.'").

[221] Ed Silverman, *Anthem Declines to Cover Sarepta Drug for Duchenne, Citing Doubts Over Data*, STAT NEWS, (Oct. 7, 2016), https://www.statnews.com/pharmalot/2016/10/07/anthem-duchenne-sarepta-fda/.

[222] *See, e.g.*, Jerry L. Mashaw, *Small Things Like Reasons Are Put in a Jar: Reasons and Legitimacy in the Administrative State*, 70 FORDHAM L. REV. 17 (2001); Martin Shapiro, *The Giving Reasons Requirement*, 1992 U. CHI. LEGAL F. 179 (1992).

[223] *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29, 42-43 (1983).

[224] *Id.* at 31.

[225] *Id.* at 53-54.

political administrations: the rule was passed under the Carter administration and rescinded under the Reagan administration, which had very different views on the value of regulatory intervention. Though Justice Rehnquist believed that "[a] change in administration brought about by the people casting their votes is a perfectly reasonable basis for an executive agency's reappraisal of the costs and benefits of a program,"[226] the majority's exclusive focus on the technical rationale for the rescission led to the widespread conclusion that "agencies should explain their decisions in technocratic, statutory, or scientifically driven terms, *not* political terms."[227]

Though pressure from patient advocacy may initially seem distinct from this standard conception of political pressure, close examination reveals that patient pressure can yield similar effects on agency action. The literature considering the role of 'political' considerations in agency decisions defines political influences as those "influences aimed at agencies coming from executive and legislative actors, including the President, members of Congress, and those who speak for and act for the President"[228] or as "reasons communicated from a particular source (rather than reasons with a particular content)," namely "those contributed by or adhered to by the President and the politically-appointed executive officials who oversee the administrative process and who answer most closely to the President."[229] On these definitions, it is clear that the lobbying of patient interest groups is not a political influence as such, though the pressure on FDA from members of Congress seen in the eteplirsen decision might count.

But these accounts often distinguish between legitimate political considerations, that might reasonably play a role in agency decisions, and illegitimate ones. Kathryn Watts, for example, argues that "legitimate political influences" are those that "seek to further policy considerations or public values, whereas illegitimate political influences can be thought of as those that seek to implement raw politics or partisan politics unconnected in any way to the statutory scheme being implemented."[230] This distinction suggests that the true concern about political influences on agency decisions is not, in fact, the source of the reason (e.g. the President or a member of Congress) but rather the content of the reason (e.g. "you should approve this drug because a group that supported my campaign wants access").[231] Legitimate political reasons are similarly acceptable because of their content: they are not deemed to be "raw politics" because they are connected to the statutory scheme being implemented

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[226] *Id.* at 59 (Rehnquist, J., dissenting).

[227] Kathryn A. Watts, *Proposing a Place for Politics in Arbitrary and Capricious Review*, 119 YALE L. J. 2, 5 (2009); *see also* Elena Kagan, *Presidential Administration*, 114 HARV. L. REV. 2245 (2001).

[228] Watts, *supra* note 227, at 8-9.

[229] Nina A. Mendelson, *Disclosing 'Political' Oversight of Agency Decision Making*, 108 MICH. L. REV. 1127, 1128 (2010).

[230] Watts, *supra* note 227, at 8-9.

[231] "T]he Department of Health and Human Services (HHS) would be allowed to rely upon a public statement issued by President Obama articulating his pro-choice agenda and his pro-choice policy initiatives if HHS chose to rescind a Bush-era rule that forbids medical facilities that receive federal money from discrimination against health care providers who refuse, on religious grounds, to perform abortions. Conversely, it would mean that HHS could not legitimately justify a decision to rescind the same Bush-era 'provider conscience' rule by simply saying: 'President Obama directed us to rescind the rule in order to reward various pro-choice organizations for their endorsement of him during his campaign.'" *Id.* at 9.

and concern public values. The distinction this draws between raw political justifications and public-regarding ones squares with theories on checking the power of interest groups in the regulatory process. Cass Sunstein, for instance, has argued that rationality review "attempts to ensure that representatives have acted to promote the public good and not solely in response to political pressure," and that administrative law doctrines similarly "attempt to diminish the authority of powerful private groups over the regulatory process, ensuring that regulatory decisions are reached through a process of deliberation about statutorily relevant factors."[232]

The real concern with 'political' influences then is not that they come from the President or Congress per se. Rather, the worry is that they result in agency decisions that are based on the power of certain individuals or interest groups instead of on the reasoned application of the statutory factors to the case at hand. In this sense, the source of the pressure in the eteplirsen case—that it came from a strong patient group and their congressional allies rather than traditional 'political' institutions like the White House—is less important than the content of FDA's justifications. If FDA is statutorily mandated to base its decision on scientific evidence, then an approval based on the grounds that "the scientific evidence isn't there but the patients told us to grant it" is no better than "the scientific evidence isn't there but the President told us to grant it."

This Section considers three doctrinal grounds for concluding that political influences may have distorted an agency decision: irrational departure from settled agency practice, prejudgment, and bias. Application to the eteplirsen case illustrates the presence of these features, which in other contexts may be sufficient to invalidate agency action.

1. Departure from Settled Agency Procedures

Much of the criticism of the eteplirsen approval, both within FDA and from the broader scientific community and the public, has focused on procedural irregularities of the decision. Dr. Unger, Dr. Borio, and the anonymous reviewer interviewed for the Scientific Dispute Appeal raised concerns that Dr. Woodcock was involved unusually early and often in the review process and that she seemed focused on patient and congressional pressures rather than on the science. Dr. Woodcock herself told the Board that she was leaning toward approval before Sarepta even filed its NDA, that she was trying to bring the reviewers around to her "more flexible" way of interpreting the data, and that she had written her final decision approving the drug before receiving the review team's decision. These procedural irregularities—particularly the "upending" of FDA's typical, hierarchical decision making process[233] by Dr. Woodcock's reversal of both the advisory committee and her review staff—are reminiscent of the agency's Plan B approval controversy, one of the more notorious FDA decisions in recent memory. The case illustrates how the court used marked and unexplained departures from FDA's standard practices to reach the conclusion that FDA's refusal to move Plan B to over-the-counter status was motivated by political pressures and not scientific evidence.

In the Plan B case, the Center for Reproductive Rights filed a citizen petition urging FDA to switch Plan B and similar emergency contraceptives from

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[232]Cass R. Sunstein, *Interest Groups in American Public Law*, 38 STAN. L. REV. 29, 85 (1985).

[233]Borio Appeal Memorandum, *supra* note 18.

prescription only to over-the-counter status, and the Plan B manufacturer submitted an application to the same effect.[234] After an advisory committee voted to recommend approval, the review team at CDER began to work towards a final recommendation. However, members of the review team were told "that the decision was to be made at the level of CDER Director or at the Commissioner's level" and that "the White House had been involved in the decision."[235] The review team nevertheless persisted and produced a draft memorandum tentatively recommending approval of Plan B for over-the-counter status. But a week later, before the team had finished the full evaluation process, the CDER Director announced that he would deny the application, a decision reached in concert with the Commissioner's office.[236]

Coincidentally, it was Dr. Woodcock, then the Acting Deputy Commissioner, who told the review team that "there were a lot of constituents who would be very unhappy with . . . an over-the-counter Plan B, and . . . [there] was part of the public that needed to have the message that we were taking adolescents and reproductive issues seriously."[237] She later told the Office Director responsible for the review team "that this was the only way to go to issue a non-approval letter to appease the [present] administration's constituents."[238]

Judge Korman, in vacating FDA's denial of the citizen petition and remanding the decision to FDA, found evidence "of a lack of good faith and reasoned agency decision-making."[239] After overt political pressure from the White House and other channels, Judge Korman noted that "the record is clear that the FDA's course of conduct . . . departed in significant ways from the agency's normal procedures."[240] In particular, he cited the facts that "FDA upper management, including the Commissioner, wrested control over the decision-making on Plan B from staff that normally would issue the final decision," that the denial "went against the recommendation of a committee of experts it had empanelled to advise it," and that "the Commissioner—at the behest of political actors—decided to deny . . . before FDA scientific review staff had completed their reviews."[241]

On remand, then-Commissioner Margaret Hamburg announced that FDA was prepared to approve Plan B for over-the-counter use by women of all ages.[242] However, Secretary of Health and Human Services Kathleen Sebelius ordered Hamburg to deny the application.[243] While the FDCA technically gives the Secretary of HHS discretionary control over approval decisions by FDA, the Secretary had

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[234]Lisa Heinzerling, *The FDA's Plan B Fiasco: Lessons for Administrative Law*, 102 GEO. L. J. 927, 940 (2014).

[235]*Tummino v. Torti (Tummino I),* 603 F. Supp. 2d 519, 529 (E.D.N.Y. 2009).

[236]*Id*. at 532.

[237]*Id.* at 529-30.

[238]*Id.* at 530 (insertion in original).

[239]*Id.* at 523.

[240]*Id.*

[241]*Id*. A scathing report from the Government Accountability Office, produced after undertaking an investigation at the behest of members of Congress, highlighted many of the same concerns in concluding that the denial was "unusual." *Id.* at 537.

[242]Heinzerling, *supra* note 234, at 947.

[243]*Id.* at 947-48.

always previously deferred to the judgment of FDA. When the plaintiffs returned to court, Judge Korman found again that FDA had departed from its own established policies and practice. Citing *INS v. Yang*, he noted that where an agency "announces and follows—by rule or by settled course of adjudication—a general policy by which its exercise of discretion will be governed, an irrational departure from that policy (as opposed to an avowed alteration of it)" may be set aside as agency action that is arbitrary, capricious, or an abuse of discretion.[244] He ordered the agency to approve the citizen petition and make Plan B available over the counter for women of all ages. His reasoning was heavily guided by Sebelius's intervention, which he called "[p]erhaps the most significant departure from agency practice."[245]

The eteplirsen case is not fully analogous to the Plan B controversy. Most significantly, the eteplirsen approval was an intra-agency dispute from start to finish: the reversal of mid-level staff and the advisory committee was made by the CDER Director and sanctioned by the Commissioner, with no apparent involvement of FDA's parent agency, HHS, or the White House. But Judge Korman's concerns about the departure from settled agency practice are still highly relevant to the eteplirsen case. In his review of the first denial of the citizen petition, Judge Korman focused on the way in which higher-ups wrested control of the decision from the reviewers responsible for engaging with the evidence, overturned the decision of the expert advisory committee, and reached a decision before the review team had finalized its recommendation. All of these features—which Judge Korman concluded show a departure from FDA's settled policies and practices that was arbitrary and capricious—are reflected in the eteplirsen approval. These procedural irregularities raise the concern that pressure in the case distorted the agency's decision making.

2. Prejudgment

During the scientific dispute appeal process, both Dr. Unger and the anonymous member of the review team interviewed by the Board claimed that Dr. Woodcock had decided to approve eteplirsen before the review team had finished its assessment of the data. Indeed, Dr. Woodcock herself admitted to the Board that she had been "leaning toward granting approval" in 2014, long before all of the evidence on eteplirsen was submitted.[246] And after the advisory committee voted against approval, she told the distressed audience, "It's possible to reach different conclusions based on the data presented today . . . . Failing to approve a drug that actually works in devastating diseases—these consequences are extreme."[247]

In *Cinderella Career and Finishing Schools, Inc. v. FTC*, the leading case on the invalidation of agency action due to evidence of prejudgment, the D.C. Circuit lambasted one of the Commissioners of the Federal Trade Commission for failing to recuse himself from a case that the court ruled he had prejudged.[248] There, the Commission was considering whether the Cinderella Career and Finishing School

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[244] *Tummino v. Hamburg (Tummino II),* 936 F. Supp. 2d 162, 169 (E.D.N.Y 2013).

[245] *Id.* at 170.

[246] *See supra* text accompanying note 202.

[247] Ed Silverman, *FDA Approves Sarepta's Controversial Drug for Duchenne Muscular Dystrophy*, STAT NEWS, (Sept. 19, 2016), https://www.statnews.com/pharmalot/2016/09/19/sarepta-wins-dmd-drug-approval/.

[248] 425 F.2d 583, 591 (D.C. Cir. 1970).

was engaging in unfair and deceptive practices. Among other allegedly false representations, the Cinderella School advertised that its instruction would qualify students to become airline stewardesses.[249] While the case was before him, the Commissioner gave a speech to the National Newspaper Association, questioning the ethics of newspaper advertising practices:

What about carrying ads that offer college educations in five weeks, fortunes by raising mushrooms in the basement, getting rid of pimples with a magic lotion, *or becoming an airline's hostess by attending a charm school*? . . . Without belaboring the point, I'm sure you're aware that advertising acceptance standards could stand more tightening by many newspapers.[250]

On this basis, the D.C. Circuit ruled that the Commissioner met the test for disqualification for adjudicatory decisions on the basis of prejudgment, which is a determination that "a disinterested observer may conclude that (the agency) has in some measure adjudged the facts as well as the law of a particular case in advance of hearing it."[251] Dr. Woodcock's public statements, particularly to the crowd at the public hearing, seem to approach this objective observer test for prejudgment, and her private revelations to the Board lend credence to this interpretation.

In *Cinderella*, the Court framed the Commissioner's prejudgment as a denial of due process, suggesting that the problem with a decision maker prejudging a case lies in the harm to litigants who "are entitled to an impartial tribunal."[252] In a decision *approving* a drug, no parties' due process rights are violated by prejudgment: Sarepta met its objective of gaining approval, arguably *because* Dr. Woodcock reached a conclusion before all the facts were in. Nevertheless, evidence of prejudgment belies the objectivity required for FDA approval decisions, just as it illuminates impartiality in other contexts, and is thus a useful tool for FDA in checking the role of powerful external influences on approval decisions. Prejudgment suggests that a decision has been made without reference to all the relevant considerations, namely the hard evidence on a drug's safety and efficacy that the review team in the eteplirsen case was still analyzing when Dr. Woodcock reached her decision.

3. Bias

Dr. Woodcock was also under heavy pressure from Congress. Dr. Unger testified to the Board that "Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress."[253] A letter from 109 members of Congress to Dr. Woodcock sent in advance of the advisory committee meeting stated, "As Members of Congress representing constituents battling Duchenne, we wholeheartedly agree with this viewpoint [that flexibility is warranted for life-threatening diseases] and urge the FDA to ensure this flexibility is applied in reviewing all Duchenne candidate therapies."[254] In the midst of the eteplirsen review, a Senate committee convened a hearing on 'Connecting Patients to New and

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[249] *Id.* at 584 n.1.

[250] *Id.* at 590 (emphasis added).

[251] *Id.* at 591.

[252] *Id.* at 590, 592.

[253] *See supra* note 19 and accompanying text.

[254] Letter from Members of Congress to Janet Woodcock, *supra* note 139, at 1.

Potential Life Saving Treatments.' One of the five witness called was Laura McLinn, the mother of a boy with DMD. She testified, "Sometime in the next few months there will be patients testifying in front of an FDA adcom panel and asking the panel members to endorse the approval of [eteplirsen] . . . . Now we want to see the FDA use the tools in FDASIA to grant accelerated approval to potentially life-saving treatment, starting with eteplirsen."[255] And, after the advisory committee meeting, two senators sent a letter "to express disappointment in the committee's vote against approval of the new drug" and to "encourage [Dr. Califf] to fully employ the flexibilities and considerations available to the Food and Drug Administration (FDA) when making a final determination with respect to this drug," suggesting their desire that the agency overturn the recommendation of the advisory committee.[256]

This congressional input reveals not just general pressure to use the expedited pathways ratified by Congress in the FDA Modernization Act and the FDA Safety and Innovation Act but pressure to approve a specific drug application before the agency at the time. In *Pillsbury Co. v. FTC*, the Fifth Circuit reasoned that where a congressional hearing "focuses directly and substantially upon the mental processes of a Commission in a case which is pending before it, Congress is no longer intervening in the agency's legislative function, but rather in its judicial function."[257] Like the prejudgment pronouncement in *Cinderella*, the court in *Pillsbury* vacated the FTC's decision because the hearings threatened "the appearance of impartiality, which cannot be maintained unless those who exercise the judicial function are free from powerful external influences."[258]

In *Pillsbury*, a Senate subcommittee subjected a number of FTC Commissioners to hostile questioning during a hearing about the agency's interpretation of an amendment Congress had intended to slow the number of mergers. The questioning focused in particular on why the agency had failed to apply the new amendment as Congress intended in a case that was still before the FTC. While the court recognized that Congress often and legitimately "call[s] [agencies] to task for failing to adhere to the 'intent of Congress' in supplying meaning to the often broad standards from which the agencies derive their authority," it focused on the fact that questioning concerned the application of that general intent to a specific and ongoing case.[259]

Congressional involvement in the eteplirsen case—both the letters sent to Dr. Woodcock and Dr. Califf, the Senate committee hearing that raised the eteplirsen case, and the public testimony of a senator during the advisory committee meeting—similarly stressed Congress's intent that the flexibility it had attempted to provide through amendments to the FDCA be utilized in the eteplirsen approval. In this

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[255] *Testimony for the HSGAC Hearing – Laura McLinn & Jordan McLinn, Testimony for the HSGAC Hearing—Connecting Patients to New and Potential Life Saving Treatments,: Hearing Before the Sen. Homeland Sec. & Gov't Affairs Comm.*, 114th Cong., at 3, (2016) (statement of Laura McLinn & Jordan McLinn), http://www.hsgac.senate.gov/hearings/connecting-patients-to-new-and-potential-life-saving-treatments.

[256] Letter from Sen. Ron Johnson, Chairman, Sen. Comm. on Homeland Security and Governmental Affairs, and Sen. Dan Coats, to Robert Califf, Comm'r of Food and Drugs, (May 20, 2016), https://www.hsgac.senate.gov/media/majority-media/johnson-coats-ask-fda-to-utilize-authorities-granted-by-congress-to-provide-patients-hope.

[257] 354 F.2d 952, 964 (5th Cir. 1966).

[258] *Id.*

[259] *Id.* at 963.

sense, congressional pressure may have intervened in FDA's adjudicatory function. As in *Pillsbury*, the degree of pressure placed upon FDA raises the concern that Dr. Woodcock's decision simply provides a showing of flexibility to Congress regardless of the factual conclusions about whether eteplirsen met the statutory standards for Accelerated Approval.

Although the agency likely cannot be held accountable for it in court, the eteplirsen case exhibits these three signs of capitulating to external pressures, each of which is enough to invalidate administrative decisions in other contexts—departure from settled agency practice, prejudgment, and bias. Precisely because standing prevents a judicial check on unduly influenced drug approvals, FDA must develop its own internal checks against officials' succumbing to pressure from patients or Congress, particularly as patient groups accumulate political power. Most importantly, FDA must sustain its hierarchical decision-making process for drug approvals; though higher-level officials like Dr. Woodcock may exercise substantial authority in setting broader policies with respect to expedited drug approval and patient participation, the scientific team responsible for reviewing a specific drug application should be insulated from those pressures in the early stage of a drug approval, which should be focused on the objective evaluation of the safety and efficacy evidence. Such reviewers should never, as one reviewer in the eteplirsen case stated, be unsure of "whether they [are] discussing science, policies, or politics."[260]

Decisions of a Center Director to overturn the joint recommendation of a review team and advisory committee should be subject to careful scrutiny. In considering scientific dispute appeals, the Scientific Dispute Process Review Board and the FDA Commissioner should explicitly consider factors that suggest the presence of strong external influences. Where there is evidence of departure from settled practices, prejudgment, or bias in a disputed approval—like Dr. Woodcock's unusually early involvement in the process and decision to approve before the review team reached its conclusion, or the uniquely strong congressional and patient advocacy from the DMD community—the deference that Dr. Califf afforded in the eteplirsen case may not be appropriate. The Commissioner may need to assign the case to another Center Director or Deputy Director within FDA with the ability to review the evidence or, as Dr. Borio suggested, convene a special scientific review panel, in order to ensure that such reversals are properly based in the evidence and not on external pressures.

These kinds of internal checks target largely procedural problems in the course of an approval: they seek to ensure that decision-makers are somewhat insulated from pressures—from patients and politicians—that might sway their decision against that demanded by the evidence. But the eteplirsen case also illustrates deficiencies in the substantive determination that substantial evidence supported the approval, considered in the next Section.

B. Patient Input and the Substantial Evidence Standard

The amendments that Congress has made to the FDCA to speed drug approvals and increase patient participation have placed FDA under two increasingly conflicting mandates. On the one hand, since 1962, FDA has been statutorily

[260] *See* Letter from Dr. Luciana Borio, *supra* note 18, at 10.

required to ensure that, for each drug approval, there is "*substantial evidence* that the drug will have the effect it purports or is represented to have."[261] And by law, substantial evidence is that from "*adequate and well-controlled investigations*, by *experts qualified by scientific training* and experience to evaluate the effectiveness of the drug involved."[262] On the other hand, through the FDA Modernization Act, the FDA Safety and Innovation Act, and the 21st Century Cures Act, Congress has demanded more flexibility in approvals and a greater role for patients.

Each time Congress has amended the Act to provide FDA with new tools to get drugs to patients faster, it has tacked on a "rule of construction" that preserves the substantial evidence standard. So, when it passed the FDA Safety and Innovation Act—making clear its intent that FDA use more "innovative and flexible approaches" in accelerating the approval of drugs that treat serious diseases with unmet need—it added: "Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act."[263] The Cures Act's provision for the use of real world evidence and patient experience data provides the same caveat.[264]

As FDA staff explained during the eteplirsen approval process, there exist some opportunities to introduce the flexibility mandated by the statutory amendments while still abiding by the substantial evidence requirement. During the public hearing, Dr. Dunn explained one such opportunity: altering the *character* of the endpoint studied—by using surrogate endpoints like dystrophin production rather than clinical endpoints like mobility—while still requiring "[s]ubstantial evidence of an effect" on that endpoint.[265] Even then, the surrogate nature of the endpoint introduces greater *uncertainty* into the judgment that it "could fairly and responsibly be concluded by . . . 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."[266] Indeed, the Accelerated Approval pathway reflects flexibility by responding to the more acute need of patients with a serious or life-threatening disease for which there is no approved treatment by permitting the special use of non-validated surrogate endpoints despite this increased uncertainty.

What Congress and patient advocates asked for in the eteplirsen decision, and what Dr. Woodcock granted in approving the drug, appears to double dip into this uncertainty exception allowed for serious and life-threatening diseases. In her decisional memorandum, Dr. Woodcock recognized the "seriously deficient" aspects of the eteplirsen drug development process and admitted that her decision to grant approval represented "the greatest flexibility possible for FDA while remaining within its statutory framework."[267] To justify nevertheless approving the drug despite

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[261] 21 U.S.C. § 355(d) (2012) (emphasis added).

[262] *Id.* (emphasis added).

[263] Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-114, § 901, 126 Stat. 993, 1086.

[264] 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096 (2016).

[265] *See* Advisory Committee Transcript, *supra* note 5 at 36.

[266] 21 U.S.C. § 355(d) (2012).

[267] Woodcock Decisional Memorandum, *supra* note 15, at 12.

the flawed trials and shaky evidence, she cited "the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children."[268] Yet these justifications are the very ones that permitted Sarepta to use a non-validated surrogate endpoint through the Accelerated Approval pathway in the first place. Dr. Woodcock's decision thus allows a second layer of uncertainty over that already afforded by the use of a non-validated surrogate endpoint.

The accumulation of layers of uncertainty in the eteplirsen decision threatens a change in the default rule on uncertainty for drug approval. Whereas the standard for drug approvals has since 1962 placed a burden of proof on manufacturers to show affirmative evidence of effectiveness, the standard in the eteplirsen decision looks more like a 'when-in-doubt-approve' standard. Members of Congress seemed to urge this result, even while pointing to amendments creating expedited programs that explicitly purport to *preserve* the agency's important substantial evidence standard.[269]

A major contributor to this apparent conflict is the incompatibility of the substantial evidence standard and the role that patient participation played in the eteplirsen case. As discussed in Part I, the great push for patient participation in FDA approval decisions, particularly after the FDA Safety and Innovation Act, has introduced a plethora of patient engagement pathways at FDA, which experiment with different ways of fitting patient input into the approval decision.[270] In the eteplirsen approval, patients and their advocates were strongly represented at the public hearing: they offered their understanding of the disease and its treatments, drawing on anecdotal accounts of how the drug had benefited them in ways not captured by the data.[271]

These contributions from patient involvement—what kinds of improvements represent meaningful benefit as drawn from patients' and caregivers' lived experiences—are vitally important in creating and approving effective drugs. Yet they are incompatible with the late stage of drug development at which an advisory committee and review team are tasked with evaluating safety and efficacy. Per the statute, the question that FDA must answer at this point in the approval process is inescapably technical in nature: the FDCA properly demands "well-controlled investigations" carried out by "experts qualified by scientific training" to demonstrate effectiveness, because marketing to the broader public must be based on generalizable and unbiased data, not on anecdote or non-blinded, ad hoc observations from family and caregivers.

The incompatibility of the patient testimony at the hearing as an 'input' into the advisory committee's judgment of whether Sarepta had met the Accelerated Approval standard is patent in the members' struggle to integrate the testimony with the scientific evidence. As one member asked, "To what extent are we to incorporate into this question the testimony of the families, the boys and their families? . . . From my reading of the question, it would seem narrowly worded toward the actual

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[268] *Id.*

[269] *See supra* notes 140-42, 253-56 and accompanying text.

[270] *See* discussion *supra* Part I.A.

[271] *See* discussion *supra* Part II.B.

statistical results."[272] Contrary to Dr. Woodcock's response that "the statutory standard [for substantial evidence of effectiveness] is more or less as described . . . but there is flexibility, and that's where we should take the views of the community into account," the Act and its amendments explicitly do not permit an alteration of the evidentiary standard. The flexibility and patient involvement mandated by recent amendments to the FDCA must influence the approval process at a different point than the determination of whether the substantial evidence standard has been met.

Indeed, the public hearing does illustrate an ideal—though missed—opportunity for patient involvement and agency flexibility in the drug approval process. Speaker after speaker came to the microphone attributing to eteplirsen their child's sustained ability to pick up a book or give a hug or feed himself.[273] As one advisory committee member noted:

Now, when you listen to the testimony from the families, one of the things that was highlighted is opening cans, opening packages, lifting things, and none of that is captured by the [6-minute walk test] . . . . So you have an unfortunate discrepancy between what the families are describing as tangible benefits and what is actually measured.[274]

This question—about what counts as a meaningful benefit of treatment that should be measured in testing a promising new drug—is one where patient involvement can valuably and demonstrably influence the approval of new drugs, unlike the question of whether the statutory standard of substantial evidence has been met. Of the broad array of patient involvement pathways at FDA, this lesson from the eteplirsen case lends support to ones—like the Patient Focused Drug Development Initiative and the Device Patient Preference Initiative—that seek to systematically collect data on how patients understand the benefits and risks of treatment options given their lived experience of the disease. Patients and their caregivers are better placed than scientists to determine what kinds of improvements are meaningful in living with a condition: in the eteplirsen case, patients would have been able to tell designers of the clinical trial that, for example, being able to continue to feed oneself would represent a substantial benefit, which would necessitate an entirely different clinical endpoint than the 6-minute walk test.

But to inform these kinds of decisions about trial design, patient involvement must occur far further upstream in the drug development process. This suggests that in developing its guidance on patient experience data as instructed by the 21st Century Cures Act, FDA should focus not only on methodological approaches for collecting such data, but also how such data—once reliably and representatively collected—can meaningfully inform drug development. Patient experience data, submitted as a supplement to clinical trial results in an attempt to show substantial evidence of effectiveness, will not be successful unless the data were also used in the early stages of the development process such that their influence on trial design is captured in the clinical trial data. It also suggests that FDA should seek a far greater role in the pre-clinical stages of drug development than it currently occupies, to ensure that the

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[272] *Id.* at 548-49.

[273] *See* discussion *supra* Part II.B.

[274] Advisory Committee Transcript, *supra* note 5, at 549.

measurements of benefit and risk used in testing are responsive to this patient experience data.

Expanding initiatives like the Patient Focused Drug Development Initiative and striving for patient-centered risk-benefit analysis, rather than relying on researchers' or clinicians' judgments of risk and benefit factors, allows FDA to meet the statutory demands for flexibility and patient involvement in a way that upholds the substantial evidence standard, the preservation of which is vital for ensuring that marketed drugs are safe and effective.

CONCLUSION

Since Senator Kefauver first introduced the requirement that manufacturers demonstrate substantial evidence of effectiveness before marketing a drug, FDA has seen a growing movement for patient involvement at the agency and, as patients gained political power, for faster approval for drugs that target the most serious conditions. There is no doubt that these two goals are paramount to FDA's mission. Nevertheless, as the eteplirsen case illustrates, patient involvement and expedited approvals—if not carefully implemented—can be carried out in a way that conflicts with the fundamental requirement that drug manufacturers demonstrate substantial evidence of a drug's effectiveness before it is placed on the market. Weakening FDA's standards by capitulating to pressure—be it from patients, Congress, or drug companies—in the absence of positive evidence not only risks delivering exorbitantly expensive and ineffective treatments to patients affected by the immediate decision but also erodes FDA's longer-term reputation and ability to function as a science-driven organization that produces evidence-based decisions. As FDA works to meet the requirements of the 21st Century Cures Act's patient involvement and expedited approval provisions, it would do well to attend to the lessons of the eteplirsen approval: it must develop stronger internal checks against patient and political pressure to approve drugs in the absence of substantial evidence of effectiveness, and must tailor its patient involvement pathways to give patients a real opportunity to influence the process while preserving the substantial evidence requirement.