Redressing the Harm of Accelerated Approval

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The accelerated approval pathway of the United States Food and Drug Administration (FDA) enables drugs to come to market more quickly than would be possible under a traditional FDA approval pathway. Accelerated approval is based upon the agency's determination that changes in a surrogate or intermediate clinical endpoint are "reasonably likely" to predict a clinical benefit meaningful for patients. In essence, the pathway affords sick patients earlier access to potentially beneficial drugs while trials to confirm clinical benefit continue. Accelerated approval has been likened to a social compromise in which promising drugs enter the market sooner in exchange for a sponsor's promise to undertake so-called confirmatory trials—that is, postmarketing trials to "verify and describe" the predicted clinical benefit. This Article argues that patients, too, are expected to engage in a compromise when they take drugs approved under the pathway: patients must accept the risk that a drug will ultimately confer no meaningful benefit in exchange for the chance of treatment. But must the compromise end there?

This Article deconstructs the harms that result from the accelerated approval pathway and explores how those harms should be remedied. For purposes here, the focus is on therapies later withdrawn from the market due to a sponsor's inability to verify clinical benefit or its decision not to pursue confirmatory trials to completion. Patients and payers incur great expense during what the FDA has termed the "period of uncertainty," the span of time between a therapy's approval under the pathway and verification of clinical benefit or lack thereof. Moreover, therapies approved under accelerated approval, the bulk of which are immunotherapies to treat various types of cancer, often have serious side effect profiles. This means that patients who consume later-withdrawn therapies may suffer serious adverse effects or even a hastened death from a drug that ultimately yields them little to no benefit—in essence, a "toxic placebo."

This Article proposes a tort alternative modeled on the National Vaccine Injury Compensation Program to "make whole" patients harmed by accelerated approval's "toxic placebos." The proposed administrative compensation scheme, funded through a combination

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of prescription drug user fees and mandatory contributions from sponsors of later-withdrawn accelerated approval drugs, would allow patients to recover medical expenses, out-of-pocket costs for the accelerated therapy itself, compensation for side effects causally linked to a later-withdrawn drug, lost wages, pain and suffering, and wrongful death. This Article does not stand as a criticism of the accelerated approval pathway, which has successfully yielded a plethora of new cancer therapies, among others. Rather, it addresses why an administrative compensation scheme is a necessary adjunct to the pathway and preferable to the status quo in which patients harmed by accelerated approval typically remain without redress through the civil tort system. Finally, it counters the notion that the defense of assumption of risk should bar recovery for patients who incur harm from therapies approved under the pathway.

INTRODUCTION

The United States Food and Drug Administration's (FDA) accelerated approval pathway creates a lottery of sorts: sick patients are given early access to as-yet unproven drugs.[1] Many will benefit, but a few will be harmed. Despite initial approval based on a surrogate endpoint or intermediate clinical endpoint, mere proxies for clinical benefit, most accelerated approval drugs will confer benefits meaningful to patients such as relief of symptoms, improved functioning, or prolonged survival.[2] In those cases, accelerated approval fulfills the program's highest purpose. Rather than wait years for completion of confirmatory trials, patients reap the benefits of promising new treatments sooner while confirmatory trials are still underway.[3] For some small fraction of drugs approved under accelerated approval, however, the hoped-for benefit does not materialize: a drug's early promise does not come to fruition through clinical trials, and the FDA or the pharmaceutical sponsor determines that there is no longer a sufficient basis to believe that the drug's benefits outweigh its risks.[4] In that small fraction of cases,

1. *See Accelerated Approval*, U.S. FOOD & DRUG ADMIN. (Feb. 24, 2023), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval [perma.cc/3RFA-4X6D].

2. *See* U.S. FOOD & DRUG ADMIN., EXPEDITED PROGRAM FOR SERIOUS CONDITIONS—ACCELERATED APPROVAL OF DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY 4 (2024) [hereinafter ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY].

3. *See id.*

4. *See Accelerated Approval*, *supra* note 1.

the drug's indication initially approved under accelerated approval will be withdrawn.[5]

Staff at the FDA conceives of this latter subset of drugs "not as a failure of accelerated approval but rather as an *expected trade-off* in expediting drug development that benefits patients with severe or life-threatening diseases."[6] Surely, a trade-off is involved. However, there is a latent misconception in such a sanguine view of accelerated approval. Patients prescribed an accelerated therapy for which the benefits could not be proven do not end up in a neutral position relative to their condition ex ante. Instead, many end up worse off. They have taken a therapy that may have caused severe or life-threatening side effects, and in many cases, they have incurred high out-of-pocket drug costs, all in exchange for no meaningful difference to their overall clinical picture. They may have experienced no alleviation of symptoms, no improvement in functioning, and no prolongation of overall survival. Worse yet, they may have suffered serious adverse effects or even a hastened death. These patients, losers in the accelerated approval lottery, are not well served by the FDA's expedited pathway. The harms they suffer from accelerated approval typically go unnoticed and almost certainly uncompensated.

The accelerated approval pathway has received a great deal of scholarly attention recently: some have argued that it relies on too lax a standard for early market access. Others have criticized the use of surrogate endpoints, imperfect proxies for clinical benefit, as the basis for "converting" an accelerated approval to a traditional approval.[7] And many have bemoaned delays in completion of confirmatory trials.[8] However, this Article argues that the primary defect in accelerated approval as a regulatory pathway is the absence of a mechanism to compensate patients—risk-takers in the accelerated approval lottery—when the very basis of an early approval—a "reasonable likelihood" to treat a condition—ultimately does not pan out.

The accelerated approval pathway has been likened to a social compromise in which promising drugs enter the market sooner in exchange for a sponsor's promise to undertake so-called confirmatory trials.[9] However, patients too are implicitly

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5. According to a recent government investigation, thirty-five of 278 drug applications granted accelerated approval were withdrawn since the accelerated approval pathway was first initiated in 1992. OFF. OF INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUM. SERVS., OEI-01-21-00401, DELAYS IN CONFIRMATORY TRIALS FOR DRUG APPLICATIONS GRANTED FDA'S ACCELERATED APPROVAL RAISE CONCERNS 2–3 (2022) [hereinafter U.S. DEP'T OF HEALTH & HUM. SERVS., DELAYS IN CONFIRMATORY TRIALS]. Current listings by the FDA indicate that upwards of forty indications have been withdrawn across drug categories. *See Accelerated Approval Program*, U.S. Food & Drug Admin. (Dec. 24, 2024), https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program [perma.cc/L36R-KX74]. In some cases, manufacturers choose to withdraw indications approved under accelerated approval after determining that additional studies are not worth the financial investment due to poor sales; this category of withdrawals is also of concern because patients who took a drug prior to such a voluntary withdrawal never have the benefit of confirmation of clinical efficacy or the certainty of a favorable benefit-risk profile.

6. Julia A. Beaver & Richard Pazdur, Perspective, *"Dangling" Accelerated Approvals in Oncology*, 384 NEW ENG. J. MED. e68(1), e68(4) (2021) (emphasis added).

7. For the meaning of "convert" in this context, see ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY, *supra* note 2, at 3 ("The Agency sometimes refers to this determination [conclusion of confirmatory trial requirements following satisfactory verification of clinical benefit] informally as *conversion* of a product to traditional approval.").

8. *See infra* notes 32–34.

9. *See infra* note 103 and accompanying text.

expected to engage in a compromise: they must accept the risk that a drug will confer no meaningful benefit in exchange for the chance of treatment. When sponsors do not make good on their end of the bargain—that is, when sponsors decide that completion of confirmatory trials is not worth the cost or when confirmatory trials fail to demonstrate clinical benefit—this Article argues that patients should have a means for redress and that an administrative compensation scheme is best suited to the unique circumstances accelerated approval foists on patients.

Part I frames the discussion by highlighting the recent scholarly and regulatory attention paid to the accelerated approval pathway, including common criticisms and suggestions for reform. Part II considers the oft-mentioned trade-off that forms of the crux of accelerated approval—exactly what is being traded off and by whom? And who has acquiesced to the bargain? Part III argues that absent from current conceptions of accelerated approval as a social compromise is the very party accelerated approval was designed to benefit: the patient. Implicit in the accelerated approval bargain is the foundational premise that patients appreciate the risks they undertake—a notion that may not align with reality. Drawing on scholarship and case law that developed and critiqued the doctrine of assumption of risk within tort law, Part IV makes the case that although patients are presumed to have voluntarily chosen to face the risks of accelerated approval, in fact, those risks are largely invisible to patients and therefore not undertaken voluntarily. The high cost of drugs, especially cancer therapies, and the uniqueness of the accelerated approval bargain warrant a means for redress when accelerated approval does not fulfill its intended purpose as a regulatory pathway. Part V proposes an administrative compensation program, modeled on the National Vaccine Injury Compensation Program, to make whole patients harmed by withdrawn accelerated approval drugs.

I. A CONTESTED APPROVAL PATHWAY

Now that the pandemic phase of COVID-19 has subsided, few issues have been as contentious in the medical and scientific community as accelerated approval. Thrust into the public vernacular as a result of the disputed approval of Biogen's Alzheimer's therapy Aduhelm (aducanumab),[10] accelerated approval has been the target of considerable empirical investigation and scrutiny.[11] The pathway is among four nonexclusive expedited programs by which a new drug or biologic can gain approval or licensure in the United States.[12] First introduced in 1992, accelerated approval provides a means to expedite FDA approval and market entry of drugs to treat "serious or life-threatening" diseases and conditions on the basis of a surrogate endpoint or intermediate clinical endpoint considered "reasonably

10. *See, e.g.*, Pam Belluck, *House Committees Demand F.D.A. Records on Alzheimer's Drug Approval*, N.Y. TIMES (Sept. 2, 2021), https://www.nytimes.com/2021/09/02/health/aduhelm-fda.html [perma.cc/E6ZJ-N4TQ]; Kerry Dooley Young, *Will Medicare Cover It? Drugs Like Aduhelm Are Challenging Its Standard*, STAT (May 25, 2023), https://www.statnews.com/2023/05/25/medicare-aduhelm-cms-fda-pharmaceuticals [perma.cc/8QYZ-XXVE]; Aaron S. Kesselheim, Perspective, *Aducanumab and Accelerated Approval: Where Do We Go from Here?*, 111 CLINICAL PHARMACOLOGY & THERAPEUTICS 726, 726–27 (2022).

11. *See infra* notes 31–40 and accompanying text.

12. *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, U.S. FOOD & DRUG ADMIN. (June 12, 2023), https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review [perma.cc/A2N3-MU7S].

likely" to translate into a clinical benefit.[13] For cancer drugs, which constitute the overwhelming majority of recent accelerated approvals,[14] common surrogate endpoints include tumor size, progression-free survival,[15] and response rate.[16] These metrics translate variably to outcomes that matter most to patients, such as prolonged overall survival or improved quality of life.[17] However, surrogate endpoints offer the benefit of earlier assessment and permit smaller sample sizes,[18] thus enabling earlier drug access that forms the cornerstone of the pathway.

The FDA has identified the "principal risk" of accelerated approval, namely the risk of exposing patients to a drug that may not ultimately confer a clinical benefit.[19] FDA staff has referred to a "period of uncertainty" between the date of

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13. 21 U.S.C. § 356(c)(1)(A). Accelerated approval was first introduced through FDA regulation and later codified in the Prescription Drug User Fee Amendments of 1997. *See* Peter B. Hutt, *The Evolution of Federal Regulation of Human Drugs in the United States: An Historical Essay*, 44 AM. J.L. & MED. 403, 436 (2018). For the final rule establishing accelerated approval, see New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942, 58942 (Dec. 11, 1992) (codified as amended at 21 C.F.R. pts. 314, 601).

14. *See* Ginny Beakes-Read, Madison Neisser, Patrick Frey & Mara Guarducci, *Analysis of FDA's Accelerated Approval Program Performance December 1992–December 2021*, 56 THERAPEUTIC INNOVATION & REGUL. SCI. 698, 699 (2022) (computing that hematology-oncology therapeutics accounted for 83% of approvals under the accelerated approval pathway from 2012 to 2021).

15. Progression-free survival, as its name implies, is time without worsening of disease, which is typically measured by time to tumor progression (i.e., a certain increase in tumor size or detection of a new lesion) or death. *See* U.S. FOOD & DRUG ADMIN., CLINICAL TRIAL ENDPOINTS FOR THE APPROVAL OF CANCER DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY 10 (2018) [hereinafter CLINICAL TRIAL ENDPOINTS, GUIDANCE FOR INDUSTRY]; Amy E. McKee, Ann T. Farrell, Richard Pazdur & Janet Woodcock, *The Role of the U.S. Food and Drug Administration Review Process: Clinical Trial Endpoints in Oncology*, 15 THE ONCOLOGIST 13, 16 (2010).

16. Response rate is the percentage or proportion of patients experiencing a partial or complete response to treatment, where a partial response is a reduction in tumor burden and a complete response is no detectable tumor burden. *Objective Response Rate*, NAT'L CANCER INST., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/objective-response-rate [perma.cc/C2FA-TGF7]; CLINICAL TRIAL ENDPOINTS, GUIDANCE FOR INDUSTRY, *supra* note 15, at 9–10. A pitfall of response rate as a clinical trial endpoint is that it does not capture stable disease. *See* McKee et al., *supra* note 15, at 16.

17. *See* Christopher M. Booth & Elizabeth A. Eisenhauer, Comments and Controversies, *Progression-Free Survival: Meaningful or Simply Measurable?*, 30 J. CLINICAL ONCOLOGY 1030, 1031 (2012).

18. CLINICAL TRIAL ENDPOINTS, GUIDANCE FOR INDUSTRY, *supra* note 15, at 6.

19. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 16 (2014); *see also* Lola A. Fashoyin-Aje, Gautam U. Mehta, Julia A. Beaver & Richard Pazdur, *The On- and Off-Ramps of Oncology Accelerated Approval*, 387 NEW ENG. J. MED. 1439, 1441 (2022) (referring to "delayed withdrawals" resulting from postponed or overdue confirmatory trials as "the greatest risk to patients"). A 2009 report on accelerated approval by the Government Accountability Office (GAO) summarized the same risk as follows:

> [R]eliance on . . . [surrogate] endpoints may introduce uncertainty regarding the risks and benefits of a drug, and may lead to the adoption of useless or even harmful therapies. This can arise if the effect on a surrogate endpoint does not accurately predict whether treatments provide benefits to patients, or if the drug has a smaller than expected benefit and a larger than expected adverse effect . . . . For example, several large trials assessing drugs based on surrogate endpoints found those drugs to be clinically ineffective, and in some cases, identified unexpected adverse effects such as increased rates of death.

U.S. GOV'T ACCOUNTABILITY OFF., GAO-09-866, NEW DRUG APPROVAL: FDA NEEDS TO ENHANCE ITS OVERSIGHT OF DRUGS APPROVED ON THE BASIS OF SURROGATE ENDPOINTS 9 (2009) [hereinafter GAO REPORT, FDA NEEDS TO ENHANCE ITS OVERSIGHT].

accelerated approval and confirmation of clinical benefit or lack thereof.[20] By statute, the FDA may require sponsors to undertake postapproval studies (i.e., confirmatory trials) to confirm clinical benefit,[21] and as a practical matter, these studies are generally required. When the FDA grants a license to market a new drug or biologic therapy, it issues an approval letter to the drug's sponsor that summarizes the sponsor's postmarketing commitments, including requirements to complete postapproval studies. As a result of recent changes to Section 506(c) of the Federal Food, Drug & Cosmetic Act (FDCA), as amended by the Food and Drug Omnibus Reform Act of 2022, the agency must "specify the conditions" for postmarketing studies, which could encompass factors such as targets for trial enrollment and trial milestones, including a "target date" by which postapproval studies must be completed.[22] If a sponsor does not fulfill its obligations to conduct postapproval studies with "due diligence," including meeting the target completion date specified by the agency,[23] the Secretary is authorized to withdraw approval but need not do so as a matter of law.[24] Prior to withdrawal of an accelerated therapy, a sponsor must be provided with notice, an explanation for the proposed withdrawal, a public comment period, an opportunity for both a written appeal and a meeting with the Commissioner or a designee, and the input of an advisory committee at the sponsor's request.[25]

As a practical matter, withdrawal procedures have been infrequently invoked, with a notable exception being the withdrawal of bevacizumab (Avastin) for treatment of patients with HER2-negative metastatic breast cancer in combination with paclitaxel.[26] The FDA's arduous withdrawal of Avastin and its sluggishness in

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20. Fashoyin-Aje et al., *supra* note 19, at 1441 ("The time between [accelerated approval] and verification or refutation of clinical benefit is a period of uncertainty.").

21. 21 U.S.C. § 356(c)(2)(A)(i); 21 C.F.R. § 314.510 ("Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome."); 21 C.F.R. § 601.41 (providing the same for biologics).

22. 21 U.S.C. § 356(c)(2)(C).

23. According to the FDA's recent draft guidance on accelerated approval, the agency interprets "due diligence" to mean that a sponsor must devote "sufficient resources" to conduct confirmatory trials "expeditiously[,] so that a determination of whether the drug provides the expected clinical benefit can be made as soon as possible." ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY, *supra* note 2, at 12.

24. *Id.* 21 U.S.C. § 356(c)(3)(A) ("The Secretary *may withdraw* approval of a product approved under accelerated approval . . . if—(i) the sponsor fails to conduct any required postapproval study of the product with due diligence, including with respect to conditions specified by the Secretary under paragraph 2(C) . . . ." (emphasis added)). For corresponding implementing regulation, see 21 C.F.R. § 601.43, providing withdrawal procedures for biologic products, and 21 C.F.R. § 314.530, providing the same for new drugs.

25. 21 U.S.C. § 356(c)(3)(B)(i)–(iv). Whereas previously an annual report was required to update the agency on a sponsor's progress toward fulfillment of its postapproval commitments, among other things, that timeframe has been changed to 180 days after approval and no more than 180-day increments thereafter. *Id.* § 356b(a)(2). The agency must publicly report on its website the information received from sponsors. *Id.* According to the more detailed procedures for withdrawal announced in the FDA's recent draft guidance for industry, a sponsor's request to convene an advisory committee should not be granted if a committee has already been convened for purposes of advising the agency on the proposed withdrawal. ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY, *supra* note 2, at 21.

26. Final Decision on Withdrawal of Breast Cancer Indication for AVASTIN (Bevacizumab) Following Public Hearing, 77 Fed. Reg. 11554, 11554 (U.S. Food and Drug Admin. Feb. 27, 2012) (announcing the withdrawal of the metastatic breast cancer indication for Avastin, effective November

policing confirmatory trials have led some to argue that withdrawal is too onerous and ought to be simplified, if not triggered automatically.[27] Automatic withdrawal could shorten the "period of uncertainty" and ameliorate harm from ineffective accelerated products. The FDA currently has authority to initiate withdrawal procedures under certain delineated circumstances.[28] Yet, procedural safeguards such as notice and the right to appear before the agency help protect the due process rights of pharmaceutical sponsors who stand to lose a valuable marketing license if accelerated approval is withdrawn.[29]

Central to the debate over accelerated approval is the fact that many sponsors do not complete required clinical trials intended to verify clinical benefit, as required by statute and FDA regulation,[30] in a timely manner. The Office of Inspector General of the Department of Health and Human Services (HHS), which undertook an examination of accelerated approval in response to the controversy over aducanumab, found that confirmatory trials were incomplete for more than one-third of drug applications granted accelerated approval.[31] Of those applications,

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18, 2011, following a public hearing on June 28 and 29, 2011); *see infra* notes 70–78 and accompanying text. More recently, the FDA withdrew approval of Makena (hydroxyprogesterone caproate) for prevention of preterm birth, following a hearing before the agency. *See FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena*, U.S. FOOD & DRUG ADMIN. (Apr. 6, 2023), https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena [perma.cc/F95C-NF3L].

27. For literature proposing automatic withdrawal upon failure of a confirmatory trial, see Bishal Gyawali, Joseph S. Ross & Aaron S. Kesselheim, Viewpoint, *Fulfilling the Mandate of the US Food and Drug Administration's Accelerated Approval Pathway: The Need for Reforms*, 181 JAMA INTERNAL MED. 1275, 1276 (2021).

28. Those circumstances include the following: (1) a sponsor's failure to conduct "any required postapproval study . . . with due diligence," (2) findings from a confirmatory trial that "fail[] to verify and describe" the predicted effect or benefit, (3) "other evidence . . . that the product is not shown to be safe or effective under the conditions of use," and (4) dissemination of false or misleading promotional materials for a product. 21 U.S.C. § 356(c)(3)(A).

29. Automatic withdrawal may raise due process concerns if holders of a license to market an accelerated product received no notice or opportunity to appear before the agency in connection with a marketing license withdrawal. Courts have considered, and the FDA has not disputed, drug makers' property interest in abbreviated new drug applications (ANDAs), *see* Mallinckrodt Inc. v. U.S. Food and Drug Admin., No. 14-3607, 2015 WL 13091366, at *15–16 (D. Md. July 29, 2015), and similar reasoning would recognize a property interest in new drug applications and biologics license applications. At a minimum, therefore, manufacturers would be entitled to notice and some kind of hearing in connection with withdrawal of a license to market their drug for a particular use. *Cf.* Board of Regents v. Roth, 408 U.S. 564, 570–71, 576–77 (1972) (recognizing as property interests those interests for which a claimant possesses a legitimate claim of entitlement, the deprivation of which is sufficient to trigger procedural due process); Mathews v. Eldridge, 424 U.S. 319, 333–35 (1976) (holding that whether a pre-deprivation hearing is constitutionally required would depend on the outcome of a balancing of various interests, including the private interest impacted by the deprivation, the risk of an erroneous deprivation, and the government's interest in expediency).

30. *See* 21 C.F.R. § 601.41 (providing for postapproval study requirements for biologic products); *id.* § 314.510 (providing the same for new drug products).

31. U.S. DEP'T OF HEALTH & HUM. SERVS., DELAYS IN CONFIRMATORY TRIALS, *supra* note 5, at 1–2. More than ten years earlier, in 2009, the GAO undertook a study of accelerated approval and found that, of 90 applications for accelerated approval granted by the agency based on surrogate endpoints between 1992 and 2008, the FDA required 144 postapproval studies, of which the agency deemed 64% (92 of 144) "closed," meaning that studies were completed or the agency regarded them as no longer necessary or feasible. GAO REPORT, FDA NEEDS TO ENHANCE ITS OVERSIGHT, *supra* note 19, at 15, 18. Thirty-six percent (52 of 144) of required studies were considered open, which included ten delayed studies and two which had been terminated. *See id.* at 19–21. Notably, almost one-third of completed studies (23 of 71) took more than five years to complete. *See id.* at 19–20.

more than one-third remained incomplete beyond their target date of completion, in rare cases exceeding five years.[32] A study of all hematology-oncology drugs approved under the pathway from 1992 to 2017 found that just over half had completed postmarketing requirements and confirmed clinical benefit, while 40% had not.[33] Delays in completion of confirmatory trials lengthen the time to conversion or withdrawal, effectively prolonging the "period of uncertainty" when a drug's definitive clinical benefit is unsettled and its risk-benefit profile equivocal.

Proposals for reform to accelerated approval have focused on three primary domains: first, incentives for timely completion of confirmatory clinical trials and penalties for noncompliance;[34] second, reductions in payment or restrictions on coverage of accelerated therapies until clinical benefit is verified;[35] and third,

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32. U.S. DEP'T OF HEALTH & HUM. SERVS., DELAYS IN CONFIRMATORY TRIALS, *supra* note 5, at 1–2.

33. Julia A. Beaver, Lynn J. Howie, Lorraine Pelosof, Tamy Kim, Jinzhong Liu, Kirsten B. Goldberg, Rajeshwari Sridhara, Gideon M. Blumenthal, Ann T. Farrell, Patricia Keegan, Richard Pazdur & Paul G. Kluetz, *A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review*, 4 JAMA ONCOLOGY 849, 851 (2018). A more recent study of all accelerated approval indications from the inception of the pathway through December 2021 reached a similar result: half of accelerated approvals converted to a traditional approval, whereas 38% had not yet converted. *See* Beakes-Read et al., *supra* note 14, at 699–701. Research has shown that those indications that convert do so rather quickly (with a median time of just over three years from the date of accelerated approval, *see id.* at 699), whereas withdrawals occur after a lag (in some cases exceeding a decade, although this timeframe is decreasing), *see id.* at 700.

34. For literature in support of a requirement that sponsors begin confirmatory trials prior to the granting of accelerated approval, see Beaver et al., *supra* note 33, at 851 (finding a longer median time to verification of clinical benefit when a trial was not underway at the time of accelerated approval); Fashoyin-Aje et al., *supra* note 19, at 1441 (finding the same); Mahnum Shahzad, Huseyin Naci & Anita K. Wagner, *Association Between Preapproval Confirmatory Trial Initiation and Conversion to Traditional Approval or Withdrawal in the Accelerated Approval Pathway*, 329 JAMA 760, 761 (2023) (finding more rapid conversion to traditional approval or withdrawal when a confirmatory trial was in progress at the time of accelerated approval). For literature in support of penalties for noncompliance with FDA deadlines, see Steven Woloshin, Lisa Schwartz, Brian White & Thomas J. Moore, *The Fate of FDA Postapproval Studies*, 377 NEW ENG. J. MED. 1114, 1116 (2017).

35. *See, e.g.*, Jeromie Ballreich, Mariana Socal, Charles L. Bennett, Martin W. Schoen, Antonio Trujillo, Andrew Xuan & Gerald Anderson, *Medicare Spending on Drugs with Accelerated Approval*, 175 ANNALS INTERNAL MED. 938, 939, 943 (2022) (suggesting reimbursement caps on accelerated approval indications in the Medicare program, or alternatively, lower Medicare reimbursement for drugs prescribed for indications that were granted accelerated approval, until conversion to traditional approval); Rachel E. Sachs, Shelley A. Jazowski, Kyle A. Gavulic, Julie M. Donohue & Stacie B. Dusetzina, *Medicaid and Accelerated Approval: Spending on Drugs With and Without Proven Clinical Benefit*, 47 J. HEALTH POL. POL'Y & L. 673, 687 (2022) [hereinafter Sachs et al., *Medicaid and Accelerated Approval*] (discussing a proposal by the Medicaid and CHIP Payment and Access Commission to raise rebates on as-yet unverified accelerated approval drugs in the Medicaid program); Leonard M. Fleck, *Alzheimer's and Aducanumab: Unjust Profits and False Hopes*, 51 HASTINGS CTR. REP. 9, 11 (2021) (arguing for a limit on the price of aducanumab to cost of production plus 5% profit, "given the uncertainty around . . . [the drug's] safety and effectiveness"); Robert A. Bohrer, *A Better Balance Between Accelerated Access and High-Priced New Drugs, A New Conditional Approval Option*, HEALTH AFFS. (Mar. 20, 2017), https://www.healthaffairs.org/content/forefront/better-balance-between-accelerated-access-and-high-priced-new-drugs-new-conditional [perma.cc/3CBU-XHPB] (suggesting a "conditional approval distribution price" of 25% of a drug's initial price for accelerated approval therapies); Jonathan J. Darrow, *The Perils of Increasing Medicaid Rebates for Drugs with Accelerated Approval*, 2 JAMA HEALTH F. 1, 2 (2021) (suggesting that revenue from accelerated approval drugs could be placed in escrow until the time of verification of clinical benefit); Gyawali, Ross & Kesselheim, *supra* note 27, at 1276 (proposing as a reform a policy excepting accelerated approval drugs from Medicaid's coverage mandate). Other proposals have focused on limiting use of accelerated therapies

changes to the standard for accelerated approval to incorporate more precise evidence-based criteria and greater rigor around primary endpoints in studies to support traditional approval.[36] To be sure, federal programs and private payers spend very large sums on accelerated approval drugs during the so-called "period of uncertainty." Research has shown that the Medicaid program, for example, incurred approximately $707 million in gross spending on as-yet unconverted accelerated approval indications in 2019, $2.9 billion in gross spending on accelerated therapies overall, and $2.2 billion in net spending on accelerated therapies after accounting for mandatory rebates and the Medicaid inflation penalty.[37] Medicare spending on accelerated approval indications was estimated to reach $1.8 billion in 2019, including $187 million for later-withdrawn indications.[38] The majority of drugs approved under accelerated approval, however, are eventually converted to a traditional approval.[39] It is the small subset of indications withdrawn

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prior to verification of benefit through formulary design and other utilization management tools and expanding the availability of such tools in federal programs. *See* Sachs, *supra*, at 674; Darrow, *supra*, at 2; Rachel E. Sachs, Julie M. Donohue & Stacie B. Dusetzina, Special Communication, *Reforming Reimbursement for the US Food and Drug Administration's Accelerated Approval Program to Support State Medicaid Programs*, 3 JAMA HEALTH F. 1, 4–5 (2022) [hereinafter Sachs et al., *Reforming Reimbursement*]. Of course, access restrictions through coverage exclusion, for example, would undo the very benefits that expedited access is designed to foster and could give rise to serious equity concerns if applied to the Medicaid program in particular.

36. *See, e.g.*, Thomas R. Fleming, *Surrogate Endpoints and FDA's Accelerated Approval Process*, 24 HEALTH AFFS. 67, 73, 77 (2005) (recommending that Phase III trials be based on either "true clinical efficacy measure[s]" or validated surrogate endpoints, rather than non-validated surrogates, as is commonly the case now); Spencer Phillips Hey, Bishal Gyawali, Elvira D'Andrea, Manoj Kanagaraj, Jessica M. Franklin & Aaron S. Kesselheim, *A Systematic Review and Meta-Analysis of Bevacizumab in First-Line Metastatic Breast Cancer: Lessons for Research and Regulatory Enterprises*, 112 J. NAT'L CANCER INST. 335, 340 (2020) (calling for "greater guidance . . . about what degree of evidence is needed to satisfy the 'reasonably likely' standard, as well as what endpoints should be considered clinically beneficial"); Bishal Gyawali, Spencer Phillips Hey & Aaron S. Kesselheim, *Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval*, 179 JAMA INTERNAL MED. 906, 910 (2019) (criticizing the use of the same surrogate endpoint in confirmatory trials as was used in trials to support accelerated approval and arguing that such evidence merely "corroborat[es] the effect on the surrogate measure"); Bishal Gyawali, Benjamin N. Rome & Aaron S. Kesselheim, *Regulatory and Clinical Consequences of Negative Confirmatory Trials of Accelerated Approval Cancer Drugs: Retrospective Observational Study*, 374 BRITISH MED. J. 1, 6 (2021) (recommending that the FDA mandate the use of clinically meaningful primary endpoints such as overall survival in confirmatory trials for cancer therapies). *But see* Beaver et al., *supra* note 33, at 854 (defending the use of progression-free survival and response rate as primary endpoints for postapproval studies, on the grounds that overall survival and quality of life can present logistical and ethical difficulties when used as primary endpoints).

37. *See* Sachs et al., *Medicaid and Accelerated Approval, supra* note 35, at 683.

38. *See* Ballreich et al., *supra* note 35, at 942. By another estimate, between 2017 and 2019, Medicare spent $171 million on four withdrawn accelerated approval indications and $569 million on ten indications for which confirmatory trials failed to show an overall survival benefit. Mahnum Shahzad, Huseyin Naci & Anita K. Wagner, *Estimated Medicare Spending on Cancer Drug Indications with a Confirmed Lack of Clinical Benefit After US Food and Drug Administration Accelerated Approval*, 181 JAMA INT. MED. 1673, 1673–74 (2021). Although the authors equate spending on drugs that do not improve overall survival to "waste," *id.*, practical challenges such as crossover in randomized studies to assess overall survival may complicate study results. *See* Ramzi Dagher, John Johnson, Grant Williams, Patricia Keegan & Richard Pazdur, *Accelerated Approval of Oncology Products: A Decade of Experience*, 96 J. NAT'L CANCER INST. 1500, 1508 (2004).

39. *See* Kenji Omae, Akira Onishi, Ethan Sakher & Toshi A. Furukawa, *US Food and Drug Administration Accelerated Approval Program for Nononcology Drug Indications Between 1992 and 2018*, 5 JAMA NETWORK OPEN 1, 4 (2022) (finding that 43 of 57 (75%) non-oncology indications approved under accelerated approval from 1992 to 2018 received regular approval); Beaver et al., *supra* note 33,

when confirmatory trials fail to meet primary endpoints or when manufacturers determine that further study to confirm clinical benefit is not worth the cost for which drug spending arguably amounts to squandered resources.

Now, some would contest this proposition on the grounds that the number of withdrawn accelerated therapies understates the number of therapies that *ought* to be withdrawn from the market due to delays in completion of confirmatory trials, use of surrogate markers that are poor measures of clinical benefit as primary endpoints in confirmatory trials, and the FDA's sluggish response to negative confirmatory trials. For example, the disputed approval of the Alzheimer's therapy aducanumab despite uncertain evidence of efficacy drew attention to potential weaknesses in the FDA's implementation of accelerated approval,[40] and recently, aducanumab's manufacturer chose to discontinue development and sales of the therapy.[41] But even assuming the aforementioned points of contention to be true, a product cannot retain market access with unverified clinical benefit forever; the FDA's system of oversight will ensure that such products eventually gain traditional approval, are withdrawn, or receive the tacit approval of the agency to remain marketed.[42] For purposes of identifying redressable injury from the accelerated

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at 851 (finding that 51 of 93 (55%) oncology accelerated approval indications during the first twenty-five years of the pathway's existence received verification of clinical benefit through confirmatory trials); Joshua J. Skydel, Alexander C. Egilman, Joshua D. Wallach, Reshma Ramachandran, Ravi Gupta & Joseph S. Ross, *Spending by the Centers for Medicare & Medicaid Services Before and After Confirmation of Benefit for Drugs Granted US Food and Drug Administration Accelerated Approval, 2012 to 2017*, 3 JAMA HEALTH F. 1, 4 (2022) (finding that 22 of 38 drugs (58%) granted accelerated approval from 2012 to 2017 had received traditional approval by 2020, and one indication was withdrawn during the study period). Yet even among those drugs that gain traditional approval, spending by federal payers can be substantial where clinical benefit is verified on the basis of surrogate rather than clinical endpoints, a point of much contention among physicians and researchers. *See id.* at 6 (reporting that, of $62.1 billion in spending by the Centers for Medicare and Medicaid Services on accelerated approval drugs that were converted to traditional approval during the study period, more than 60% of spending [$39.4 billion] was for indications whose benefits were confirmed using surrogate endpoints).

40. Controversy surrounding approval of aducanumab prompted the HHS Office of Inspector General to undertake an examination of a sample of twenty-four drugs approved under accelerated approval, including ten drugs for which stakeholders identified concerns. *See* OFF. OF INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUM. SERVS., OEI-01-21-00400, HOW THE FDA USED ITS ACCELERATED APPROVAL PATHWAY RAISED CONCERNS IN 3 OF 24 DRUGS REVIEWED 7–8 (2025). The examination confirmed earlier congressional investigation findings demonstrating aberrancies in the review process and gaps in the administrative record for aducanumab. *See id.* at 14–15. For additional background on aducanumab's controversial approval, see Laura Karas, *FDA's Revolving Door: Reckoning and Reform*, 34 STAN. L. & POL'Y REV. 1, 8–11 (2023).

41. *See Biogen to Realign Resources for Alzheimer's Disease Franchise*, BIOGEN (Jan. 31, 2024), https://investors.biogen.com/news-releases/news-release-details/biogen-realign-resources-alzheimers-disease-franchise [perma.cc/66NU-E8SR].

42. The agency, for its part, has renewed its commitment to ensuring that confirmatory trials are completed in a timely manner. For example, the FDA's recent draft guidance for industry on accelerated approval made clear the agency's intention to require that confirmatory trials have been initiated prior to granting accelerated approval, an authority that the agency possesses by statute and that it may exercise at its discretion. *See* ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY, *supra* note 2, at 12; 21 U.S.C. § 356(c)(2)(D). The FDA's guidance further states that confirmatory trials should generally be in progress at the time of marketing application *submission*, *see* ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY, *supra* note 2, at 12, a time point that antedates approval and is likely to facilitate timely confirmatory trials.

The guidance also elaborates on the FDA's procedure surrounding withdrawal of accelerated products, *id.* at 15–22, suggesting the agency may initiate withdrawals with greater frequency. The FDA implemented its withdrawal procedures most recently in 2023 when it began efforts to withdraw

approval pathway, it is arguably the population of product indications *ultimately withdrawn* from the market that should be of greatest concern.

To be sure, minimization of the "period of uncertainty" for any product approved under the pathway, whether or not the product is ultimately withdrawn, is a valid policy goal in itself, and to this end, reform that would discount or withhold payment during the "period of uncertainty"[43] has appeal on its face. Before efficacy has been verified, the argument goes, accelerated therapies do not warrant payment on par with that of traditionally approved drugs. Currently, manufacturers can set drug prices without regard to whether clinical benefit has been confirmed, and payment is not made contingent on confirmation of clinical benefit in any uniform manner.[44] As a result, drug companies lack economic incentives for timely completion of confirmatory trials, especially when those trials are unlikely to confirm previously predicted benefits. It may be in a company's economic interest to delay completion of confirmatory trials if the outcome of those trials would likely result in a product's withdrawal from the mass market. But reductions in payment for all accelerated approval indications across the board is too blunt an instrument; it risks undercompensating efficacious drugs for which clinical benefit is soon to be verified, while non-efficacious drugs remain overcompensated, even under a scheme of reduced reimbursement.[45] Although the statutory standard for accelerated approval is that a product must have "an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint . . . that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit,"[46] each accelerated product differs in just how likely it is that

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melphalan flufenamide (Pepaxto) following the drug's failure to meet primary endpoints in a confirmatory trial and evidence that the drug decreased overall survival. Final Decision on Withdrawal of PEPAXTO (melphalan flufenamide) Following Appeal of the Proposal to Withdraw Approval, 89 Fed. Reg. 27766, 27766-67 (U.S. Food and Drug Admin. Apr. 18, 2024) [hereinafter Final Decision on the Proposal to Withdraw PEPAXTO]; Final Decision on the Proposal to Withdraw Approval of Pepaxto (melphalan flufenamide) for Injection, Docket No. FDA-2023-N3167, at 1–2 (Feb. 23, 2024) [hereinafter Final Decision on the Proposal to Withdraw Pepaxto]. The drug's manufacturer appealed, and ultimately, the Director of the Center for Biologics Evaluation and Research, acting as the FDA Commissioner's designee, issued a final decision in favor of withdrawing the drug for lack of safety or effectiveness under the drug's conditions of use. *See* Final Decision on the Proposal to Withdraw PEPAXTO, *supra*, at 1–2.

43. *See* sources cited *supra* note 35. The Center for Medicare and Medicaid Innovation is in the process of developing a new payment model for accelerated approval involving adjustments to payment under Medicare Part B for drugs approved via the pathway, with the goal of incentivizing timely completion of confirmatory trials. *See* Liz Fowler, Vinod Mitta & Laurie McWright, *CMS Innovation Center's One-Year Update on the Executive Order to Lower Prescription Drug Costs for Americans*, CTR. MEDICARE & MEDICAID SERVS. BLOG (Oct. 11, 2023), https://www.cms.gov/blog/cms-innovation-centers-one-year-update-executive-order-lower-prescription-drug-costs-americans [perma.cc/9SUG-386E]; XAVIER BECERRA, U.S. DEP'T OF HEALTH & HUM. SERVS., A REPORT IN RESPONSE TO THE EXECUTIVE ORDER ON LOWERING PRESCRIPTION DRUG COSTS FOR AMERICANS 14–16 (2023) [hereinafter REPORT, LOWERING PRESCRIPTION DRUG COSTS]. The proposal acknowledges the challenge of adjusting price for particular indications approved under the pathway given that Medicare Part B payments are not indication specific. *See id.* at 16.

44. *See* Sachs et al., *Reforming Reimbursement*, *supra* note 35, at 3–4.

45. This Article takes the view that a non-efficacious drug merits no compensation, even during the "period of uncertainty." Hence, the need for post hoc remedies to provide recompense for patients' out-of-pocket costs for withdrawn accelerated approval therapies.

46. 21 U.S.C. § 356(c)(1)(A).

clinical benefit will be confirmed.[47] Any payment-based policy measure that applies uniformly to all drugs approved under the pathway is therefore overbroad.

Payment adjustments during the "period of uncertainty" and compensation for harm due to accelerated therapies whose approval is ultimately withdrawn are not mutually exclusive. This Article, however, takes the position that the more precise approach is a post hoc corrective measure, one that retrospectively compensates those individuals—the focus here being patients rather than payers, though the argument can be extended—who have incurred out-of-pocket costs and potentially suffered harm from accelerated products later withdrawn from the market. Although drug manufacturers who sell later-withdrawn therapies arguably externalize the costs of those products on payers and consumers, this Article limits its focus to compensating patients who suffer the dual harms of exposure to ineffective and even harmful products and monetary injury from products whose promised benefits could not be demonstrated.

II. UNDERSTANDING THE TRADE-OFF OF ACCELERATED APPROVAL

The FDA has argued in favor of the success of the accelerated approval pathway,[48] a position that this Article does not contest.[49] In so doing, the agency has taken the view that the eventual withdrawal of a small fraction of accelerated approval indications is part of an "expected tradeoff" involved in expedited drug development,[50] and the time until clinical benefit is confirmed constitutes an "accepted tradeoff."[51] But exactly what is being traded off in the accelerated approval bargain? And by whom has this trade-off been accepted? Some have suggested that the pathway balances speed—and its corollary, access—with

47. A manufacturer's estimation of the likelihood of verification of clinical benefit may affect how expeditiously it completes confirmatory trials. Relatedly, time to verification of clinical benefit or withdrawal may be a function of the likelihood of verification of clinical benefit. This can help explain the observed phenomenon, *see supra* note 33, that those therapies that convert, convert quickly, and those that are ultimately withdrawn typically undergo withdrawal after a lag.

48. *See, e.g.*, Beaver et al., *supra* note 33, at 855 (noting earlier patient access to accelerated approval drugs on the scale of years and finding that in only 5% of indications for malignant hematology-oncology drugs was clinical benefit not verified).

49. Others, however, have directly challenged the agency's statements on the success of accelerated approval. *See, e.g.*, Sarah S. P. DiMagno, Aaron Glickman & Ezekiel J. Emanuel, *Accelerated Approval of Cancer Drugs—Righting the Ship of the US Food and Drug Administration*, 179 JAMA INTERNAL MED. 922, 923 (2019) (charging that a "low rate of withdrawals is not a valid measure of success" of the accelerated approval pathway, given that the "FDA decides when to withdraw approval for drug indications and is very reluctant and slow to do so"); Elizabeth A. Richey, E. Alison Lyons, Jonathan R. Nebeker, Veena Shankaran, June M. McKoy, Thanh Ha Luu, Narissa Nonzee, Steven Trifilio, Oliver Sartor, Al B. Benson III, Kenneth R. Carson, Beatric J. Edwards, Douglas Gilchrist-Scott, Timothy M. Kuzel, Dennis W. Raisch, Martin S. Tallman, Dennis P. West, Steven Hirschfeld, Antonio J. Grillo-Lopez & Charles L. Bennett, *Accelerated Approval of Cancer Drugs: Improved Access to Therapeutic Breakthroughs or Early Release of Unsafe or Ineffective Drugs?*, 27 J. CLINICAL ONCOLOGY 4398, 4403 (2009) (presenting research findings that "suggest an alternative, less positive, interpretation of the most recent experience with [accelerated approval]").

50. Beaver & Pazdur, *supra* note 6, at e68(4).

51. Beaver et al., *supra* note 33, at 855 ("The time between [accelerated approval] and verification of clinical benefit is the . . . accepted tradeoff for the [accelerated approval] program and highlights the importance of completing trials with due diligence.").

evidence.[52] Others have argued that accelerated approval trades safety for access,[53] and still others perceive of the trade-off as a detriment,[54] ultimately permitting approval on the basis of evidence that is incomplete,[55] premature,[56] or lacking.[57]

Understanding the accelerated approval trade-off is quite critical from a policy perspective, as it provides the compass by which to assess and make adjustments to the expedited pathway to best fulfill its purposes. As in other areas of regulatory science, what appears at first to be a heated dispute over evidence in fact comes down to a debate over the wisdom of policy.[58] Physicians and researchers who have

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52. *See, e.g.*, Robert M. Califf, Editorial, *Balancing the Need for Access with the Imperative for Empirical Evidence of Benefit and Risk*, 318 JAMA 614, 614 (2017); Holly Fernandez Lynch & Alison Bateman-House, *Facilitating Both Evidence and Access: Improving FDA's Accelerated Approval and Expanded Access Pathways*, 48 J.L. MED. & ETHICS 365, 368–69 (2020) (highlighting that accelerated approval can make enrollment in clinical trials—sometimes termed accrual—more challenging postmarketing, thereby deterring the very evidence generation on which the accelerated approval pathway relies); Edward Susman, *Accelerated Approval Seen as Triumph and Roadblock for Cancer Drugs*, 96 J. NAT'L CANCER INST. 1495–96 (2004) (recognizing a similar concern regarding the impact of early marketing on subsequent clinical trials). *But see* Huseyin Naci, Olivier J. Wouters, Radhika Gupta & John P.A. Ioannidis, *Timing and Characteristics of Cumulative Evidence Available on Novel Therapeutic Agents Receiving Food and Drug Administration Accelerated Approval*, 95 MILBANK Q. 261, 264–65, 284–85 (2017) (providing evidence that trials evaluating accelerated therapies as part of combination therapies and as a "background treatment" are undertaken concurrently with trials to confirm efficacy, thereby undercutting the notion that there are too few willing patients for randomized trials to confirm clinical benefit after a grant of accelerated approval).

53. *See, e.g.*, Anupam B. Jena, Jie Zhang & Darius N. Lakdawalla, Viewpoint, *The Trade-Off Between Speed and Safety in Drug Approvals*, 3 JAMA ONCOLOGY 1465, 1465 (2017).

54. *See* Maximilian Salcher-Konrad, Huseyin Naci & Courtney Davis, *Approval of Cancer Drugs with Uncertain Therapeutic Value: A Comparison of Regulatory Decisions in Europe and the United States*, 98 MILBANK Q. 1219, 1221 (2020) (referring to an "evidence vs. access conundrum"); *When the Evidence Is Weak, Caution Should Be Applied*, 11 LANCET ONCOLOGY 805, 805 (2010) (commenting on a perceived "trend towards lowering the evidence threshold" for accelerated approval); Stephen L. George, Editorial, *Selection Bias, Phase II Trials, and the FDA Accelerated Approval Process*, 95 J. NAT'L CANCER INST. 1351, 1351 (2003) (labeling as "the most fundamental concern" with the accelerated approval pathway the use of "evidence that is less reliable than that required for full approval").

55. *See, e.g.*, Salcher-Konrad et al., *supra* note 54, at 1221 ("[G]ranting approval on the basis of incomplete evidence shows greater willingness to accept uncertainty about a new drug's therapeutic value.").

56. *See, e.g.*, Naci et al., *supra* note 52, at 264 ("Therapeutic agents granted accelerated approval have premature data on their clinical benefits and harms at the time of market entry.").

57. *See, e.g.*, Sachs et al., *Reforming Reimbursement*, *supra* note 35, at 3 ("The [accelerated approval] program imposes no limitations on pricing while confirmatory trial results are pending despite the lack of evidence regarding clinical benefits."); *see also* Fleck, *supra* note 35, at 10 (referring to aducanumab's benefits as "only . . . alleged," not proven). Of note, the FDA takes the position that "[d]rugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval." ACCELERATED APPROVAL, GUIDANCE FOR INDUSTRY, *supra* note 2, at 9.

58. Policies at the interface of medicine and public health that rely on scientific evidence are often falsely portrayed as having clear-cut answers when in fact evidence only informs decisions in the manner and to the extent that it guides the weighing of competing values. *See, e.g.*, Sarah C. Dupont & Sandro Galea, Perspective, *Science, Competing Values, and Trade-Offs in Public Health—The Example of COVID-19 and Masking*, 387 NEW ENG. J. MED. 865, 867 (2022) ("[I]t would behoove public health practitioners to stop suggesting in social media posts that nuanced questions have universally correct answers. . . . [T]he primary objective of public health institutions during a pandemic—after the early crisis stage has passed—should be to provide data and decision-making frameworks that local partners can use in diverse contexts to weigh various trade-offs."). The underacknowledged role that values play in policy choices that touch on science and the more overt reliance on scientific facts and determinations often presented as conclusive or incontrovertible can obscure policy choices and interfere with the public's understanding and acceptance of those choices. For a thoughtful discussion

become accustomed to a certain level of evidence supporting drug approvals may disagree when that evidence base is adjusted or evidence gathering shifted into the period following market entry. But accelerated approval as a policy matter is a value-laden choice: the forms and level of evidence supporting a drug approval is but one factor among many in the ultimate policy choice to move drugs for certain conditions to market more quickly. In the view of the author, accelerated approval does not compromise the evidentiary standard or lower the quality or quantity of evidence supporting approval. In other words, it is not that the evidence supporting accelerated products is lacking or the evidentiary threshold too low;[59] rather, the nature of the evidence is, by design, preliminary and predictive. It is based on the reliability of the prediction that the effect on a surrogate marker will ultimately lead efficacy to outweigh risks that the agency's decision to market a product must be judged.

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of the less apparent but no less important role that values play in ostensibly scientifically grounded environmental law and regulation and approaches to better incorporate values in the context of environmental regulatory policymaking, see Alyson C. Flournoy, *Coping with Complexity*, 27 LOY. L.A. L. REV. 809, 811, 816–19 (1994) (suggesting that "better tools for coping with complex and uncertain questions . . . may reduce the pressure on agencies to justify as 'science' decisions that science does not demand," *id.* at 824).

59. Early proposals for accelerated approval conceptualized the use of pathway as furthering a more "flexible interpretation of the statutory requirement of efficacy." *Council on Competitiveness and FDA Plans to Alter the Drug Approval Process at FDA, Hearing Before the Hum. Res. & Intergovernmental Rels. Subcomm. of the H. Comm. on Gov't Operations*, 102d Cong. 31 (1992) [hereinafter *Council on Competitiveness, 1992 Hearing*] (letter from Louis Lasagna, Dir., Ctr. for the Study of Drug Dev., Tufts University). Therefore, a conception of accelerated approval as involving a less rigorous efficacy standard is not without some merit. Nonetheless, any perceived adjustment to the bar for efficacy is essentially a policy choice, designed to achieve offsetting benefits, among them the need for fewer pre-approval clinical trials and a faster drug review process. *See id.* (discussing, in reference to accelerated approval, that the "FDA will significantly reduce both the number of clinical studies required prior to approval and the amount of time [the] FDA requires to grant approval for drugs to treat life-threatening or severely debilitating conditions"). Notably, reform proposals for accelerated approval envisioned no restrictions on coverage by insurers or federal payers. *See id.* at 32. Yet perceptions of accelerated approval drugs as "experimental" continue to drive efforts to restrict coverage. In 2018, Sarepta brought suit against the Arkansas Department of Human Services for its decision to deny coverage of Sarepta's therapy Exondys 51 (eteplirsen) after the Department determined that the lack of verified clinical benefit made the drug "'unproven' and 'experimental' and thus not 'medically necessary.'" Ark. Dep't of Hum. Servs. v. Sarepta Therapeutics, Inc., 2021 Ark. App. 330, 2021 WL 4186665, at *2 (Ark. Ct. App. Sept. 15, 2021). Exondys 51 received approval under the accelerated approval pathway for treatment of DMD in 2016; clinical benefit remains unverified. *FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy*, U.S. FOOD & DRUG ADMIN. (Sept. 19, 2016), https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy [perma.cc/8GLU-83EB]; *Exondys 51 (eteplirsen) Prescribing Information*, U.S. FOOD & DRUG ADMIN. (Jan. 2022), https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/206488s027s028s029lbl.pdf [perma.cc/9V4E-JPPK]. The Court of Appeals of Arkansas affirmed a lower court's grant of summary judgment for Sarepta, holding that the Arkansas Department of Human Services, as a participant in the Medicaid Drug Rebate Program, was obligated under federal law to cover therapies prescribed for FDA-approved uses, subject to certain narrow exceptions not applicable in this case. *Ark. Dep't of Hum. Servs.*, 2021 WL 4186665, at *11. In contrast, Sarepta was held to lack standing to challenge a denial of reimbursement for Exondys 51 by the State of Washington's Health Care Authority (HCA), which deemed the drug's level of evidence "only weak or inconclusive" in the HCA's evidence-based rating system. Sarepta Therapeutics, Inc. v. Wash. Health Care Auth., 497 P.3d 454, 459–60, 463 (Wash. Ct. App. 2021). There, the court drew a distinction between coverage (i.e., *eligibility* for reimbursement) and guaranteed payment for covered drugs, the latter of which the court regarded as not assured despite the coverage mandate of the Medicaid Drug Rebate Program. *Id.* at 462–63.

The perceived trade-off between speed and evidence, on the one hand, and speed and safety, on the other, are both in effect true. Evidence generation takes time, and time (and scale) uncovers safety risks. The so-called "period of uncertainty" carries three forms of risk: first, the risk that the marketed drug will prove inefficacious or less efficacious than formerly predicted based on the surrogate or intermediate clinical endpoint; second, the risk that the drug will cause previously unknown harms (a risk attendant to all drug approvals); and third, the risk that the drug's known and unknown harms together will outweigh the benefit ultimately conferred on patients.

The genesis of the accelerated approval pathway during the HIV-AIDS crisis helps illuminate the sense of urgency that both precipitated the adoption of the pathway and that underlay the willingness of the public and the agency to embrace the trade-off at the heart of accelerated approval. Frustrated at the prospect of a six- to eight-year timetable for new drug approvals and faced with staggering death rates, the AIDS community, including organized AIDS advocacy groups, placed pressure on the agency to alter the traditional process of clinical trial testing, including by permitting "conditional approval" of drugs that promised some semblance of efficacy.[60] Faster approval would require substituting new measures of efficacy for traditional ones, such as prolonged survival.[61] But from its inception, the accelerated approval pathway was a source of controversy,[62] and split advisory committee votes on HIV-AIDS therapies highlighted the difficulty of drawing conclusions about likely efficacy.[63] In newspaper coverage of the crisis, Dr. David Kessler,

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60. *See* Warren E. Leary, *F.D.A. Pressed to Approve More AIDS Drugs*, N.Y. TIMES, Oct. 11, 1988, at C5; Warren E. Leary, *Panel Seeks to Streamline F.D.A. for Cancer and AIDS Drugs*, N.Y. TIMES, Jan. 5, 1989, at B12; Robert Pear, *As AIDS Money Is Parceled Out, Political Questions*, N.Y. TIMES, Feb. 7, 1993, at E3 (noting a doubling of the number of AIDS cases from nearly 118,000 in 1989 to more than 242,000 in 1992); Mark Mascolini, *AIDS Task Force Grapples with Faster Access to Protease Drugs*, 1 J. INT'L ASS'N PHYSICIANS AIDS CARE 6, 9 (1995) (commenting that, in the view of the head of one advocacy group, "too many advocates are ready to toss aside confirmatory requirements in a single-minded drive to rapid approval"); *see also The FDA and the Future of American Biomedical and Food Industries, Hearing Before the Sen. Comm. on Lab. & Hum. Res.*, 104th Cong. 102 (1995) [hereinafter *The FDA and the Future of American Biomedical and Food Industries, Hearing*] (statement of David A. Kessler, Comm'r, U.S. Food & Drug. Admin.) (referring to accelerated approval as a "conditional approval"). AIDS advocacy groups also took measures to encourage drug manufacturers to make use of the accelerated approval pathway. *See* Mascolini, *supra*, at 6 (discussing a consensus statement sent from "[a] dozen advocacy organizations, including Project Inform, the San Francisco AIDS Foundation, and several ACT UP chapters . . . urging Abbott, Merck, and Hoffman-LaRoche to file for accelerated approval of their protease inhibitors by the second quarter").

61. *See* Leary, *supra* note 60, at B12; Johns S. James, *Fewer AIDS Deaths: San Francisco Information*, AIDS TREATMENT NEWS, Dec. 6, 1996, at 3 (commenting that "'survival endpoint trials' often take years," and suggesting that a "decline in published obituaries of AIDS-related deaths" could be used as an indicator of overall survival, though not "scientific").

62. *See, e.g.*, *Council on Competitiveness and FDA Plans to Alter the Drug Approval Process at FDA: Hearing Before the Hum. Res. and Intergovernmental Rels. Subcomm. of the Comm. on Gov't Operations*, H.R., 102d Cong. 12 (1992) (statement of Sidney M. Wolfe, Dir., Pub. Citizen Health Rsch. Grp.) (citing the comments of a survey of FDA medical officers on the Quayle Council proposals for reforms to the FDA's review process, including the statement by one officer: "I am particularly concerned about being forced to accept certain unproven surrogate endpoints for drug effectiveness that may ultimately bear little relation to clinical benefit").

63. For example, the Antiviral Drugs Advisory Committee of the FDA reached a 4-4 vote on whether to approve delavirdine; four members recommended approval despite "variable effects on CD4 count and viral load," Mark Mascolini, *FDA Advisory Committee Deadlocks on Delavirdine*, AIDS TREATMENT NEWS, Dec. 6, 1996, at 3, whereas another four members "remained unconvinced that

Commissioner of the FDA for much of the 1990s, was said to "bluntly acknowledge[] that the desire to put drugs on the market quickly—based on virologic and immunologic markers—could mean that minimally effective or even ineffective drugs may slip through the approval net."[64] Then-Director of the Center for Drug Evaluation and Research at the FDA, Carl Peck, framed the agency's action in approving DDI, an early antiretroviral therapy, in risk-based terms; when the agency grants accelerated approval, it is "tak[ing] a regulatory risk," the assessment of which would depend on what subsequent data show.[65]

The judgment that the FDA makes when it grants accelerated approval to a particular drug for use to treat a serious or life-threatening condition involves, as do all approvals, a weighing of risks and benefits.[66] Accelerated approval carries a different package of risks than does an ordinary approval because it involves greater uncertainty with respect to benefit and, to some extent, greater uncertainty with respect to safety risks.[67] As the agency has recognized, the precise balance of risks

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delavirdine's impact on CD4 cells and circulating virus would translate into slower HIV disease progression," *id.* at 4.

64. Mascolini, *supra* note 60, at 9.

65. *Food and Drug Administration Oversight (Part 2): Hearing Before the Subcomm. on Health & the Env't of the H. Comm. on Energy & Com.*, 102d Cong. 72 (1992) [hereinafter *Food and Drug Administration Oversight (Part 2), Hearing*] (statement of Carl Peck, Dir., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin.); *see id.* at 73.

66. Indeed, as Commissioner Kessler opined, in reference to accelerated approval: "In the end, . . . it is really nothing new. . . . [W]e are back to a risk-benefit equation. When there is greater potential benefits, we can act in light of greater risks and greater unknown risk and less data. The situation calls for it. The equation allows for it." *Id.* at 72 (statement of David Kessler, Comm'r, U.S. Food & Drug Admin.). Speaking before a Senate committee on various drug reform proposals, including an early proposal for accelerated approval of breakthrough drugs, former Secretary of the Department of Health, Education, and Welfare Joseph Califano stated: "What we ask with respect to each drug, and command and mandate under the law, is that a benefit-risk ratio determination be made. . . . Where the benefits outweigh the risks in a particular situation, that is the standard we would use to determine the safety of the drug." *Regulation Reform Act of 1978; Hearing Before the S. Subcomm. on Health & Sci. Rsch. of the Comm. on Hum. Res.*, 95th Cong. 253 (1978) (statement of Joseph Califano, Sec'y, Dep't of Health, Educ., & Welfare).

67. The FDA has noted, in literature, that the "safety database is usually larger than the efficacy database supporting [accelerated approval]," and "many of the [accelerated approval] indications are efficacy supplements of already-approved drugs with large safety information and postmarketing safety data." Beaver et al., *supra* note 33, at 855. In some cases, accelerated therapies may have a well-established safety profile. This fact takes on importance for this Article's argument in favor of redressing the harms of accelerated approval drugs because, in many cases, well-established adverse effects may allow for an inference of causation to be drawn from patient injury. Take, for example, the drug duvelisib (brand name Copiktra). The drug's manufacturer has advertised the drug's safety profile as "established," noting that more than 70% of patients experienced serious adverse reactions, including serious and sometimes fatal colitis, pneumonitis, and cutaneous reactions, in studies. *See Copiktra Has an Established Safety Profile for Patients with CLL/SLL*, COPIKTRA (DUVELISIB), https://copiktrahcp.com/cll-sll/safety [perma.cc/R8DT-3MR6]. In 2018, duvelisib was approved under accelerated approval for treatment of relapsed or refractory follicular lymphoma and under traditional approval for other cancer indications. *See* Letter from Richard Pazdur, Dir., Ctr. for Drug Evaluation and Rsch., to Mary Matthew, Vice President Regul. Affs., Verastem Inc. (Sept. 24, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/211155Orig1s000ltr.pdf [perma.cc/535U-A7DY]. The manufacturer withdrew the indication for follicular lymphoma in 2021, concluding that "the logistics, cost and timing of the postmarketing requirements . . . for COPIKTRA in [follicular lymphoma] was no longer merited." *Secura Bio Announces Copiktra (duvelisib) Strategic Focus on T-cell Lymphoma and Voluntary U.S. Withdrawal of the Relapsed or Refractory Follicular Lymphoma Indication*, CISION PR NEWSWIRE (Dec. 3, 2021, 4:30 PM), https://www.prnewswire.com/news-releases/secura-bio-announces-copiktra-duvelisib-strategic-focus-on-t-cell-lymphoma-and-voluntary-us-withdrawal-of-the-r

versus benefits turns on the existence—that is, the verification—of the benefits that changes in a surrogate marker predict.[68] The next Section considers the consequences for patients when those predictions are not borne out during confirmatory trials.

A. The Dangers of a "Toxic Placebo"

What result when a therapy approved via accelerated approval does not work? That is, when the therapy turns out *not* to have a demonstrable clinical benefit in postapproval studies? Therapies approved under the pathway, the bulk of which are immunotherapies to treat various types of cancer, often have serious side effect profiles, which means that some patients will suffer serious adverse effects, or even a hastened death, from a drug that ultimately yields them little to no benefit—in effect, a "toxic placebo."[69] Perhaps the most striking example of such an undesirable outcome occurred with the approval and subsequent withdrawal of Genentech's Avastin for treatment of metastatic breast cancer. First approved for the treatment of metastatic colorectal cancer in 2004,[70] Avastin was later approved to treat metastatic breast cancer in combination with paclitaxel under the accelerated approval pathway in 2008. Avastin's approval to treat metastatic breast cancer was based on statistically significant, sizeable improvements in median progression-free survival seen in a Phase III trial.[71] At the time of approval for treatment of breast cancer, the drug was known to carry a risk of serious side effects, including bleeding, gastrointestinal perforation, arterial and venous thromboembolic events, and treatment-related death.[72] Its withdrawal three and a half years later marked a point

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elapsed-or-refractory-follicular-lymphoma-indication-301436834.html [perma.cc/DV26-AE8M]. Many of those who took the drug for treatment of follicular lymphoma from 2018 to 2021 may have experienced adverse reactions, potentially without concomitant benefit.

68. New Drug, Antibiotics, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 13234, 13238 (U.S. Food and Drug Admin. Apr. 15, 1992) ("Without the assurances regarding demonstration of actual clinical benefit . . . , the risk/benefit assessment for these drugs changes significantly.").

69. *See* George, *supra* note 54, at 1351 ("The purpose of accelerated approval is to provide rapid access to potentially effective agents in serious or life-threatening diseases when no other effective therapies exist. Unfortunately, no drug is completely safe. The risk of approving a 'toxic placebo' increases as the standards of approval are lowered."); Antonio J. Grillo-Lopez, Editorial, *The ODAC Chronicles: Part 4. Hurdles Pre and Post Accelerated Approval*, 5 EXPERT REV. ANTICANCER THERAPY 197, 198 (2005) ("[A] toxic agent with very limited or no activity could be approved.").

70. *Fact Sheet: Avastin (bevacizumab) in Metastatic Colorectal Cancer*, GENENTECH, https://www.gene.com/download/pdf/avastin_crc_factsheet.pdf [perma.cc/PW7S-H9M8].

71. *See* Andrew Pollack, *F.D.A. Extends Avastin's Use to Breast Cancer*, N.Y. TIMES (Feb. 23, 2008), https://www.nytimes.com/2008/02/23/business/23drug.html [perma.cc/UVZ3-UCHA]; Kathy Miller, Molin Wang, Julie Gralow, Maura Dickler, Melody Cobleigh, Edith A. Perez, Tamara Shenkier, David Cella & Nancy E. Davidson, *Paclitaxel Plus Bevacizumab Versus Paclitaxel Alone for Metastatic Breast Cancer*, 357 NEW ENG. J. MED. 2666, 2670–71 (2007); *Avastin (bevacizumab) Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125085s145lbl.pdf [perma.cc/W9QY-7NAR] (displaying bevacizumab's efficacy results, including a statistically significant 5.5-month improvement in progression-free survival in the bevacizumab arm and a slight, non-statistically significant increase in overall survival); Ralph B. D'Agostino, Perspective, *Changing End Points in Breast-Cancer Drug Approval—The Avastin Story*, 365 NEW ENG. J. MED., e2(1), e2(2) (2011) (summarizing study results).

72. *See, e.g.*, D'Agostino, *supra* note 71, at e2(2) (noting that "there was a clear indication of increased risk of cardiovascular disease and treatment-related death in the bevacizumab-and-paclitaxel group" but that "incomplete follow-up confounded both efficacy and safety analyses"); Jeanne Lenzer,

of tension between the agency and the drug company: postapproval studies did not replicate the improvement in progression-free survival seen in the trial on which accelerated approval was based, and neither did they show an improvement in overall survival,[73] leading the agency to conclude that the drug's metastatic breast cancer indication should be withdrawn.[74] Genentech, however, held fast to its position that the drug indeed worked in the treatment of breast cancer.[75]

FDA Committee Votes to Withdraw Bevacizumab for Breast Cancer, 343 BRITISH MED. J. 1, 1 (2011) (commenting on a higher rate of gastrointestinal perforation and bleeding, among other serious side effects, in the bevacizumab treatment group of the E2100 study). At the time of bevacizumab's approval for metastatic breast cancer, the drug carried a black box warning of potentially fatal gastrointestinal perforation, wound dehiscence, and pulmonary hemorrhage. *See Avastin (bevacizumab) Label*, *supra* note 71, at 1–2.

73. Two randomized, controlled confirmatory studies—the AVADO and RIBBON-1 trials—failed to confirm the 5.5-month improvement in progression-free survival seen in E2100, the trial on which accelerated approval was based. *See* D'Agostino, *supra* note 71, at e2(2)–(3); Harold J. Burstein, Editorial, *Avastin for Breast Cancer, 2005-2011: Requiescat in Pacem?*, 9 J. NAT'L COMPREHENSIVE CANCER NETWORK 1321, 1321 (2011) (explaining that "[c]onfirmatory trials were expected to show, at a minimum, similar improvements in [progression-free survival] in both magnitude and hazard ratio," but that such improvements did not materialize). AVADO showed only a 0.9-month increase in median progression-free survival (1.9 months on subsequent analysis), and RIBBON-1 showed a 2.9-month median increase. *See* Pre-Hearing Summary of Evidence and Arguments of Genentech, Inc. in Support of Maintaining the Accelerated Approval of AVASTIN (Bevacizumab) in Combination with Paclitaxel for the First-Line Treatment of HER2-Negative Metastatic Breast Cancer, No. FDA-2010-N-0621, at 8 (May 13, 2011) [hereinafter Pre-Hearing Summary, No. FDA-2010-N-0621]. And neither E2100 nor the two postapproval studies showed improvements in overall survival between the bevacizumab groups and the control. *See* D'Agostino, *supra* note 71, at e2(2)–(3). However, it is notable that, according to Genentech, the FDA did not require the company to demonstrate improvements in overall survival as the anticipated basis for conversion to traditional approval; instead, confirmation of improvements in progression-free survival and no impairment in overall survival would have sufficed. *See* Pre-Hearing Summary, No. FDA-2010-N-0621, *supra*, at 7–8. The company reported that AVADO and RIBBON-1 were not powered to detect improvements in overall survival, *see id.* at 9, and that such a study "could require a lengthy accrual period, thousands of participants, and several years to generate data," *id.* at 28.

74. Memorandum from Richard Pazdur, MD, Dir., Off. of Oncology Drug Products, to Janet Woodcock, MD, Dir., Ctr. for Drug Evaluation & Rsch. 2 (Dec. 15, 2010) ("The modest benefit observed with Avastin together with the substantial adverse reactions observed in breast cancer trials to date fail to provide a favorable risk-benefit profile to support continued marketing of Avastin for a first-line metastatic breast cancer indication. It is the conclusion of [the Office of New Drugs] that the breast cancer indication for Avastin be withdrawn."); *see id.* at 6 ("After reviewing data from the four studies described above, the Agency concluded that women who took Avastin did not live any longer than women who did not receive the drug, and yet were at risk of experiencing severe side effects, including side effects that are unique to this drug and death.").

75. *See* Pre-Hearing Summary, No. FDA-2010-N-0621, *supra* note 73, at 16–17, 23 (attributing the smaller increase in progression-free survival seen in AVADO and RIBBON-1 to the "chemotherapy partner" with which bevacizumab was paired, *id.* at 16–17, and arguing that bevacizumab's breast cancer indication should be maintained while the company undertakes another trial of bevacizumab with paclitaxel, *id.* at 23). Notably, patients appeared before the FDA during Genentech's hearing on Avastin to argue in favor of the drug's efficacy and against withdrawal. *See, e.g.*, Transcript of FDA Public Hearing, Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin), at 30–32 (June 28, 2011) [hereinafter FDA Public Hearing, Avastin] (statement of Nancy Haunty, metastatic breast cancer patient) (offering a personal testimonial of Avastin's efficacy); Andrew Pollack, *Breast Cancer Patients Plead for Avastin Approval*, N.Y. TIMES (June 28, 2011), https://www.nytimes.com/2011/06/29/business/29drug.html [perma.cc/52MF-UE5X]. However, as some have noted, apparent public support for the drug among patients may have reflected a selection bias in which those harmed by the drug were less able or willing to advocate for its withdrawal. *See* Agnes Vitry, Tuan Nguyen, Vikky Entwistle & Elizabeth Roughead, *Regulatory Withdrawal of Medicines Marketed with Uncertain Benefits: The Bevacizumab Case Study*, 8 J. PHARM. POL'Y & PRAC. 1, 7 (2015).

After a two-day hearing before the agency, then-Commissioner Margaret Hamburg issued a decision withdrawing Avastin's indication for breast cancer,[76] an outcome that was met with mixed reactions.[77] At the time of the withdrawal decision, 17,000 women were undergoing bevacizumab treatment, and the drug was reported to cost $88,000 annually.[78] Avastin is not the only example of a therapy approved under accelerated approval and later withdrawn for lack of efficacy or

76. *See* Proposal to Withdraw Approval for the Breast Cancer Indication for Avastin (Bevacizumab), Decision of the Comm'r, U.S. Food & Drug. Admin., No. FDA-2010-N-0621, at 2–3 (Nov. 18, 2011), https://downloads.regulations.gov/FDA-2010-N-0621-0544/attachment_1.pdf [perma.cc/MQ5R-67RB] (determining that "[t]he early promise suggested by E2100 has not been verified," *id.* at 38, and concluding that "the lesser benefit shown in the confirmatory trials presented by Genentech does not justify the risks associated with this drug in this patient population," *id.* at 40); *see also id.* at 41 (stating that "the evidence that use of the drug by metastatic breast cancer patients will harm some of those patients is undeniable").

77. *See, e.g.*, Opinion, *A Reasonable Decision on Avastin*, N.Y. TIMES (Nov. 21, 2011), https://www.nytimes.com/2011/11/22/opinion/a-reasonable-decision-on-avastin.html [perma.cc/CH3C-DXZU]; Opinion, *The Avastin Denial*, WALL ST. J. (Nov. 19, 2011) (calling the decision "an awful turn for anticancer progress and innovation") https://www.wsj.com/articles/SB10001424052970203611404577046133283707236; Shari Roan, *FDA Withdraws Approval of Avastin to Treat Breast Cancer*, L.A. TIMES (Nov. 18, 2011, 12:00 AM), https://www.latimes.com/nation/la-xpm-2011-nov-18-la-he-avastin-breast-cancer-20111119-story.html (commenting that the National Breast Cancer Coalition was in support of the FDA's decision to withdraw the drug but that patient groups generally were divided).

78. *See* Alina Selyukh & Anna Yukhananov, *FDA Revokes Approval of Avastin for Breast Cancer*, REUTERS (Nov. 18, 2011, 11:38 AM), https://www.reuters.com/article/us-fda-avastin/fda-revokes-approval-of-avastin-for-breast-cancer-idUSTRE7AH1Q120111118 [perma.cc/F2BW-WHG9].

serious safety risks: ponatinib,[79] gefitinib, [80] tositumomab,[81] gemtuzumab,[82] and umbralisib[83] are other notable examples. In other cases, drugs approved under the

79. *See* Justin F. Gainor & Bruce A. Chabner, Editorial, *Ponatinib: Accelerated Disapproval*, 20 THE ONCOLOGIST, 847, 847 (2015) (discussing the withdrawal of ponatinib in 2013 after discovery of a fairly high incidence of arterial thrombosis not observed in Phase I studies and the drug's subsequent reintroduction in 2014 for a narrowed indication).

80. Gefitinib (trade name Iressa), an oral anticancer therapy, was on the market from 2003 to 2012 as a third-line treatment for locally advanced or metastatic non-small cell lung cancer. Within roughly two years of its approval, the FDA restricted access to the drug following studies that did not demonstrate improvements in overall survival, permitting access only to those who had previously taken the drug or who showed a benefit. *See* Andrew Pollack, *F.D.A. Restricts Access to Cancer Drug, Citing Ineffectiveness*, N.Y. TIMES (June 18, 2005), https://www.nytimes.com/2005/06/18/business/fda-restricts-access-to-cancer-drug-citing-ineffectiveness-232386.html [perma.cc/3K8P-G5RV]; A.A. Armour & C.L. Watkins, *The Challenge of Targeting EGFR: Experience with Gefitinib in Nonsmall Cell Lung Cancer*, 117 EUR. RESPIRATORY REV. 186, 190 (2010). The drug was known at the time of approval to carry a rare but serious risk of pulmonary toxicity, and that, in conjunction with negative Phase III trial results, led some public health advocates to petition the FDA for withdrawal. *See* Letter from Elizabeth Barbehenn, Rsch. Analyst, Pub. Citizen, Peter Lurie, Deputy Dir., Pub. Citizen, and Sidney Wolfe, Dir., Pub. Citizen Health Rsch. Grp., to Lester Crawford, Acting Comm'r, U.S. Food & Drug Admin. (Mar. 4, 2005), https://www.citizen.org/article/petition-to-remove-cancer-drug-gefitinib-iressa-from-the-market [perma.cc/84EM-2FZ6]. The drug's maker, AstraZeneca, requested withdrawal of the drug from the market in 2011, characterizing the request as a "business decision." Withdrawal of Approval of a New Drug Application for IRESSA, 77 Fed. Reg. 24723, 24723 (U.S. Food and Drug Admin. Apr. 25, 2012). Yet, the drug turned out to have benefit in patients with certain epidermal growth factor receptor mutations detectable by companion diagnostic testing, leading to the drug's unconditional approval in 2015 and prompting some to argue that the drug exemplifies the success of biomarker research and surrogate endpoints in cancer treatment. *See IRESSA Approved by US FDA for First-Line Treatment of Patients with Advanced EGFR Mutation-Positive Non-small Cell Lung Cancer*, ASTRAZENECA (July 13, 2015), https://www.astrazeneca.com/media-centre/press-releases/2015/iressa-fda-approved-non-small-cell-lung-cancer-treatment-13072015.html [perma.cc/J3GY-5M2Z]; Paul Howard, *Why the FDA Rejected a Drug that Helps Cure Lung Cancer—And What We Can Do to Fix It*, FORBES (Nov. 6, 2015, 1:01 AM), https://www.forbes.com/sites/theapothecary/2015/11/06/attacking-the-21st-century-cures-act [perma.cc/2X3C-GEQ2].

81. *See* Vinay Prasad, Viewpoint, *The Withdrawal of Drugs for Commercial Reasons: The Incomplete Story of Tositumomab*, 174 JAMA INTERNAL MED. 1887, 1887–88 (2014). Tositumomab's manufacturer voluntarily withdrew the drug, not due to a failure of confirmatory trials but due to waning sales and the existence of alternative therapies for relapsed lymphoma. *See id.* at 1887. However, the drug had serious safety concerns, which may have precipitated its withdrawal. *See id.* ("Although tositumomab's benefits are unknown, its potential harms are clear. Tositumomab can cause severe allergic reactions at the time of infusion and prolonged and severe cytopenias. Secondary malignant neoplasms were reported in 10% of the patients enrolled in the clinical trials leading to its approval and in 3% of patients in the extended access program. Safety concerns may have contributed to the drug's dwindling use.").

82. Gemtuzumab, sold under the brand name Mylotarg, was on the market for ten years before its withdrawal in 2010 due to a lack of demonstrated clinical benefit in a confirmatory trial and higher rates of death in the treatment arm. *Pfizer Receives FDA Approval for MYLOTARG™ (gemtuzumab ozogamicin)*, PFIZER (Sept. 1, 2017, 7:38 AM), https://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_fda_approval_for_mylotarg_gemtuzumab_ozogamicin [perma.cc/NY3M-VFKJ]; Kelly J. Norsworthy, Chia-Wen Ko, Jee Eun Lee, Jiang Liu, Christy S. John, Donna Przepiorka, Ann T. Farrell & Richard Pazdur, *FDA Approval Summary: Mylotarg for Treatment of Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia*, 23 THE ONCOLOGIST 1103, 1103–04 (2018). A black box warning was also added postmarketing to warn of the risk of hepatoxicity and potentially fatal hepatic veno-occlusive disease. *Id.* at 1104; *MYLOTARG™ Boxed Warning (gemtuzumab ozogamicin)*, PFIZER, https://www.pfizermedicalinformation.com/en-us/mylotarg/boxed-warning [perma.cc/P8AE-VAB9]. The drug was later reintroduced and gained marketing approval at a lower dose, which largely ameliorated the severe adverse effects seen at the dosing regimen associated with the drug's initial indication. Norsworthy et al., *supra*, at 1105.

pathway have been withdrawn after manufacturers were unable to complete confirmatory trials, often due to difficulty enrolling study participants, but these drugs, too, often have had known and serious safety risks.[84] Some have argued that withdrawn products are merely outliers. But as the FDA has emphasized, withdrawal is an expected regulatory outcome of the accelerated approval pathway. Though infrequent, "toxic placebos" constitute an anticipated byproduct of a regulatory scheme founded on predictions of clinical benefit.

B. Disaggregating Accelerated Approval's Net Social Benefit

The trade-offs frequently referenced and discussed in the context of accelerated approval[85] operate at a societal level. Although often not explicit in discussions of accelerated approval, the pathway is presumed to be good policy because of its effects in the aggregate.[86] In some cases, the justification even resembles a utilitarian calculus: provided that more patients benefit from earlier entry of a therapy than are harmed by it, the decision to approve was the correct one and the pathway is working as it should.[87] Yet, utilitarian calculus necessarily falls short when it elides heterogeneity in preferences, fails to account for various incommensurables, and neglects to weigh in the balance the distribution of benefits and burdens. As behavioral economist and professor Cass Sunstein has noted, "[p]eople care not simply about how many lives are saved, but also about whether risks are involuntarily incurred, especially dreaded, inequitably distributed,

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83. Umbralisib, sold under the brand name Ukoniq, was withdrawn in 2022, sixteen months after its approval under the accelerated approval pathway for treatment of relapsed or refractory marginal zone and follicular lymphomas, due to Phase III study findings indicating an increased risk of death. *See FDA Withdrew Its Approval for the Cancer Medicine Ukoniq (umbralisib) Due to Safety Concerns*, U.S. FOOD & DRUG ADMIN. (July 7, 2022), https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-withdrew-its-approval-cancer-medicine-ukoniq-umbralisib-due-safety-concerns [perma.cc/FDR4-WSCM].

84. For example, panobinostat (Farydak) and idelalisib (Zydelig), both of which were withdrawn due to difficulty enrolling patients in confirmatory trials, had black box warnings at the time of accelerated approval for serious and sometimes fatal hepatoxicity, pneumonitis, and colitis in the case of idelalisib, and severe diarrhea and cardiac toxicity in the case of panobinostat. *See Zydelig (idelalisib) Prescribing Information*, U.S. FOOD & DRUG. ADMIN. (2014), https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205858lbl.pdf [perma.cc/PY4F-QQXB]; *Farydak (panobinostat) Prescribing Information*, U.S. FOOD & DRUG ADMIN. (2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf [perma.cc/7MGZ-CUFD].

85. *See supra* notes 50–59 and accompanying text; FDA Public Hearing, Avastin, *supra* note 75, at 142 (statement of Abby Brandel, Att'y, Off. of Chief Couns., U.S. Food & Drug Admin.) ("The tradeoff for providing patients with earlier access to drugs, however, was and is uncertainty about whether a drug's clinical benefit will be verified in the post-approval studies.").

86. Hence the plethora of studies looking at the percentage of accelerated therapies for which clinical benefit was confirmed versus the percentages withdrawn and pending confirmation of benefit, and the time to these events. *See, e.g.*, Beaver et al., *supra* note 33, at 851–54; Gyawali, Rome & Kesselheim, *supra* note 36, at 3–5 (focusing on those therapies for which post-approval trials failed to confirm benefit); Beakes-Read et al., *supra* note 14, at 699–701 (concluding that the pathway is "working effectively" based on rates of confirmation of clinical benefit and echoing the FDA's sentiment that "[t]he small percentage of drugs whose clinical benefit is ultimately not confirmed . . . represent an expected trade-off," *id.* at 701).

87. *Cf.* Grillo-Lopez, *supra* note 69, at 199 ("One must consider how many patients have benefited from the early availability of the agent and then weigh risk versus benefit. These unusual cases should not stand in the way of early approvals that can benefit thousands of patients."); Prasad, *supra* note 81, at 1888 ("[T]here are no data on whether tositumomab harmed more patients than it helped.").

potentially catastrophic, faced by the current or by future generations, and so forth."[88]

Perhaps more common is an implicit cost-benefit analysis: The FDA's predictions regarding which drugs carry a favorable benefit-risk profile justify earlier market entry when, on balance, those predictions confer a net social benefit.[89] Yet the cost-benefit calculus at a societal level and at an individual level necessarily differ. Certainly, many patients will benefit from early access to therapies approved under accelerated approval that allow them to live longer or experience diminished symptoms of disease (or, at the least, halt the growth or spread of a malignancy in some cases.)[90] Other patients, however, derive little to no benefit from accelerated products and yet may suffer serious adverse effects requiring hospitalization, extra clinic visits, additional pharmaceutical therapies, added morbidity, and earlier mortality.[91] Accompanying these costs are myriad other costs: the out-of-pocket cost of the therapy itself, which for some may exhaust personal financial resources;[92] the opportunity cost of a forgone, more effective therapy; lost wages that may result from ineffective treatment of the target condition or occurrence of adverse effects; and other more subjective costs such as a diminished quality of life and emotional distress due to continued illness. Accelerated approval, then, can produce a net social benefit while also inflicting a net harm on a small number.

The FDA's task in approving new drugs through accelerated approval embodies two simultaneous and often conflicting moral commitments[93]: first, to

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88. Cass R. Sunstein, *Health-Health Tradeoffs*, 63 U. CHI. L. REV. 1533, 1537 (1996).

89. Government agencies, including the FDA, are required to conduct cost-benefit analyses of new regulations and must not take regulatory action "unless the potential benefits to society for the regulation outweigh the potential costs to society." Exec. Order No. 12,291, 3 C.F.R. § 127 (1981); *see* W. Kip Viscusi, *Regulating the Regulators*, 63 U. CHI. L. REV. 1423, 1430 (1996) (discussing President Reagan's executive order that first introduced the requirement for cost-benefit analysis by agencies and subsequent changes during the Clinton Administration). An agency must set its regulatory priorities "with the aim of maximizing the aggregate net benefits to society." Exec. Order No. 12,291, 3 C.F.R. § 127 (1981). For a succinct overview of cost-benefit analysis, see Viscusi, *supra*, at 1436–39.

90. *See* Beakes-Read et al., *supra* note 14, at 703 n.10.

91. *See, e.g.*, *FDA Withdrew Its Approval for the Cancer Medicine Ukoniq (umbralisib) Due to Safety Concerns*, *supra* note 83.

92. A study of thirteen oral anticancer drugs—including two with indications approved under accelerated approval and later withdrawn—found that mean annual out-of-pocket spending in 2019 was $10,470, an increase from $8,794 in 2010. *See* Stacie B. Dusetzina, Haiden A. Huskamp & Nancy L. Keating, *Specialty Drug Pricing and Out-of-Pocket Spending on Orally Administered Anticancer Drugs in Medicare Part D, 2010 to 2019*, 321 JAMA 2025, 2026 (2019). A $10,000 expense for a drug that does not confer clinical benefit is arguably an unreasonable burden. Notably, as a result of changes to Medicare Part D under the Inflation Reduction Act, Part D enrollees no longer have a coinsurance requirement in the catastrophic phase. *See* Juliette Cubanski & Tricia Neuman, *Changes to Medicare Part D in 2024 and 2025 Under the Inflation Reduction Act and How Enrollees Will Benefit*, KAISER FAM. FOUND. (Apr. 20, 2023), https://www.kff.org/medicare/issue-brief/changes-to-medicare-part-d-in-2024-and-2025-under-the-inflation-reduction-act-and-how-enrollees-will-benefit [perma.cc/STV8-2989].

93. *Cf.* Eric A. Posner & Cass R. Sunstein, Essay, *Moral Commitments in Cost-Benefit Analysis*, 103 VA. L. REV. 1809, 1810–14 (2017) (discussing the way in which government regulation can help protect and realize moral commitments). Should patients' willingness to pay for cancer therapies approved under accelerated approval be considered in assessing the pathway? Professors Eric Posner and Cass Sunstein have advocated incorporating into cost-benefit analysis of government regulation private willingness to pay to protect moral commitments. *See* Posner & Sunstein, *supra*, at 1814–15. Applying a welfarist account of cost-benefit analysis, one might conclude that people suffer a welfare loss when they must wait a few additional years to get access to therapies that could slow disease

enable rapid access to therapies where there is an unmet need, and second, to ensure protection of the public from therapies that are unsafe or inefficacious, including the "toxic placebos." The FDA recognized the risk of harm latent in accelerated approval and the simultaneous pull of these conflicting moral commitments:

> Some day, we may approve a drug under accelerated approval that does not benefit patients and may even harm them. That is the risk we are taking. But when it comes to getting therapies to dying patients, the riskiest thing we can do is to be unwilling to take any risks.[94]

The trade-off at the heart of accelerated approval can be usefully conceptualized as a *health-health trade-off*, a conceptual schema advanced by Professor Sunstein that refers to the creation or exacerbation of one health risk by regulation designed to address or ameliorate another.[95] Sunstein has written insightfully about the existence and prevalence of health-health trade-offs as a consequence of regulatory action.[96] Reducing morbidity and mortality from unmet health needs through expedited approval programs such as accelerated approval creates an "ancillary risk" that some subset of patients will experience added morbidity and mortality as a regulatory byproduct of the predictive judgments that form the basis of expedited approval.

In a sense, expedited approval carries risks that are the inverse of those associated with "drug lag," the delay in entry of drugs to the U.S. market as a consequence of the FDA's review of a drug's safety and efficacy. The term "drug lag" has been ascribed various meanings in connection with the FDA's drug approval process, but it historically refers to lengthier periods before marketing approval of new drugs in the United States and a consequent appearance of a lag or

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progression or extend life by even a few months. Yet no restraints on access to drugs that have not yet demonstrated safety or measurable efficacy would violate the moral commitments of the FDA, which have been set out in statute and regulation, to protect the public's health. To the extent that facets of accelerated approval not codified in statute afford the agency discretion, such as choice of acceptable endpoints in pivotal and confirmatory studies, willingness to pay for marginal extensions of life might provide some guide to assessing those regulatory choices. *Cf. id.* at 1833–34 (inferring that when statutes afford agencies discretion in fulfilling moral commitments and do not prescribe specific regulatory outcomes, willingness to pay can provide a useful tool in choosing regulations that protect those commitments). Yet there might be danger in looking to willingness to pay for drugs when patients suffer severe or life-threatening conditions. Although research has estimated that cancer patients' willingness to pay for cancer therapies often far exceeds the total cost of the drugs themselves, including patients' out-of-pocket costs and costs to payers, *see* Dana P. Goldman, Anupam B. Jena, Darius N. Lakdawalla, Jennifer L. Malin, Jesse D. Malkin & Eric Sun, *The Value of Specialty Oncology Drugs*, 45 HEALTH SERVS. RSCH. 115, 123 (2010), these measures are aggregate figures and may not reflect misperceptions about efficacy, *see* David H. Howard, Peter B. Bach, Ernst R. Berndt & Rena M. Conti, *Pricing in the Market for Anticancer Drugs*, 29 J. ECON. PERSPS. 139, 142 (2015) (noting that "willingness-to-pay estimates must be interpreted cautiously in light of the fact that most patients mistakenly believe that anticancer drugs cure cancer"); *see also* Posner & Sunstein, *supra*, at 1824 (acknowledging that "net benefits or net costs . . . may greatly understate or overstate the actual effects of regulation on people's lives, because people's willingness-to-pay judgments may be a product of inadequate information or behavioral biases").

94. *The FDA and the Future of American Biomedical and Food Industries, Hearing*, *supra* note 60, at 99 (statement of David A. Kessler, Comm'r, U.S. Food & Drug. Admin.).

95. *See* Sunstein, *supra* note 88, at 1535–36.

96. *See id.* at 1539–42. Sunstein refers to "regulated risk" as a risk that regulation aims to control and an "ancillary risk" as a risk spawned or aggravated by regulation. *See id.* at 1539.

diminution in drug approvals.[97] The term was popularized in the 1970s in response to increases in new drug application review times following the agency's 1962 mandate (in the Kefauver-Harris amendments to the FDCA) to review new drug applications for efficacy as well as safety and make determinations of approval based on substantial evidence derived from well-controlled trials.[98] Prior to 1963, new drug applications enjoyed automatic approval sixty days after submission unless the FDA took action to block approval, and evidence of efficacy was not required.[99] Whereas drug lag risks death and suffering while patients await further clinical testing and FDA review of later-phase clinical trial results, accelerated approval ameliorates that risk while simultaneously generating a new risk: some of the therapies approved on the basis of proxies for clinical benefit will ultimately confer no benefit and instead inflict harm on the class of patients who consume them.

Now, some might argue that the package of risks in accelerated approval is not all that different from the risks that accompany a drug approved in the ordinary manner: No drug is entirely safe, and any given drug is not guaranteed to work in all patients. Patients may take a drug only to experience a side effect without accompanying benefit, or a side effect that outweighs the drug's benefits to that individual. As some practitioners have observed, "[e]fficacy measured in clinical trials does not necessarily translate into effectiveness in clinical practice."[100] Yet, accelerated approval *is* different, and it is different in a manner fundamental to a proper understanding of therapeutic choice and regulatory risk.

A traditional approval carries a message: this drug has been shown to work for the treatment of a certain disease or condition, and the FDA has determined that

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97. *See* Harold M. Shmeck Jr., *Medical Experts Debate "Drug Lag,"* N.Y. TIMES, Sept. 28, 1974, at 12; Donald Kennedy, Special Communication, *A Calm Look at 'Drug Lag,'* 239 JAMA 423, 423 (1978) (referring to "drug lag" as a term coined by FDA critics "to express what they argue is a relative delay in the introduction of new chemical entities in the United States"); William M. Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499, 502–03 (1978); Dale H. Gieringer, *The Safety and Efficacy of New Drug Approval*, 5 CATO J. 177, 178–79 (1985); Stuart L. Nightingale, *Drug Regulation and Policy Formulation*, 59 MILBANK MEM'L FUND Q. 412, 438–39 (1981) (discussing former FDA Commissioner Donald Kennedy's response to the charge that there was a "drug lag" in the United States, namely that although new drug approvals in the United States had decreased, the same was true of other nations, and numbers alone could not capture the quality of drugs approved).

98. *See* Hutt, *supra* note 13, at 417, 419–20.

99. *See id.* at 412; *see also* Kennedy, *supra* note 9798, at 424–25 (making the case that the decline in new drugs was more attributable to the "drying up of . . . [a] spring" of scientific knowledge that drove a flurry of new drug approvals in the 1940s and 1950s, *id.* at 424–25, and "a vastly increased flow of knowledge about what must be done to test drugs adequately," *id.* at 425, than to the FDA's new efficacy mandate). Of course, today, the U.S. market is a key market for global multinational pharmaceutical companies, and many companies prefer to launch drugs first in the United States due to the ability to garner higher launch prices. *See* Kerstin N. Vokinger, Thomas J. Hwang, Paola Daniore, ChangWon C. Lee, Ariadna Tibau, Thomas Grischott, Thomas J. Rosemann & Aaron S. Kesselheim, *Analysis of Launch and Postapproval Cancer Drug Pricing, Clinical Benefit, and Policy Implications in the US and Europe*, 7 JAMA ONCOLOGY 1, 4 (2021).

100. Erick H. Turner & Robert Rosenthal, Editorial, *Efficacy of Antidepressants*, 336 BRIT. MED. J. 516, 517 (2008). Drugs may be less efficacious in certain populations or under certain conditions. *See, e.g.*, A. Amery, W. Birkenhäger, R. Brixko, C. Bulpitt, D. Clement, M. Deruyttere, A. De Schaepdryver, C. Dollery, R. Fagard, F. Forette, J. Forte, R. Hamdy, J.F. Henry, J.V. Joossens, G. Leonetti, P. Lund-Johansen, K. O'Malley, J.C. Petrie, T. Strasser, J. Tuomilehto & B. Williams, *Efficacy of Antihypertensive Drug Treatment According to Age, Sex, Blood Pressure, and Previous Cardiovascular Disease in Patients Over the Age of 60*, 328 THE LANCET 589, 591 (1986).

there is substantial evidence of the drug's effectiveness sufficient to warrant approval.[101] Accelerated approval, on the other hand, should carry the message that a drug *may* work (or is *reasonably likely* to work) for the treatment of a disease or condition, but that studies to confirm the drug's benefit continue. Patients should reasonably expect a drug approved by the ordinary FDA approval process to be effective, even if the drug may be effective for only some of the patients who receive it. By contrast, recipients of an accelerated therapy *as a class* should not reasonably expect to benefit with the same degree of certainty as those who receive a drug approved by the ordinary course because there exists some likelihood that later phase trials (those ordinarily complete at the time of a traditional approval) will fail to verify predicted benefits.

Critically, however, patients are often not aware of whether a drug was approved by the ordinary course or by an expedited pathway for the particular use for which a patient takes a drug. Nor are most patients familiar with the meaning and the risk implications of accelerated approval.[102] Without that critical knowledge, a patient may agree to undergo treatment with a particular therapy, and so forgo the chance to try an alternative treatment if one exists, without realizing the different package of risks she has assumed. This begs the question, by whom has the trade-off of accelerated approval been accepted? The FDA and drug manufacturers, active participants in accelerated approval, ostensibly have accepted the trade-off. But the everyday cancer patient, for example, may have little understanding of the regulatory trade-off of which she could become collateral damage. Parts III and IV examine more closely the role of patients in the accelerated approval bargain and the role that assumption of risk should—or should not—play in understanding the risks patients undertake when they receive therapies approved under the pathway.

III. RECENTERING PATIENTS IN THE ACCELERATED APPROVAL COMPROMISE

The accelerated approval pathway has been analogized to a social contract or compromise between drug manufacturers and the FDA[103]: The agency grants early market entry to therapies based on evidence of improvement in a surrogate or

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101. The FDCA defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, . . . on the basis of which it could fairly and responsibly be concluded . . . 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." 21 U.S.C. § 355(d).

102. *See infra* notes 137 to 145 and accompanying text.

103. *See* Ballreich et al., *supra* note 35, at 942 (referring to "[t]he social contract of accelerated approval"); Bishal Gyawali & Aaron S. Kesselheim, *Reinforcing the Social Compromise of Accelerated Approval*, 15 NATURE REVS. CLINICAL ONCOLOGY 596, 597 (2018) ("Timely planning and completion of postmarketing trials is part of the essential compromise that underlies the accelerated approval pathway . . . ."); *see id.* at 596 ("To fulfil the social compromise [of accelerated approval], regulators should ensure that confirmatory trials testing clinically meaningful end points are already underway at the time of approval."); Jennifer Gill & Vinay Prasad, *A Reality Check of the Accelerated Approval of Immune-Checkpoint Inhibitors*, 16 NATURE REVS. CLINICAL ONCOLOGY 656, 656 (2019) (discussing accelerated approval as a "social contract" in which the "FDA . . . promises that provisional approvals are necessary, postmarketing commitments will be pursued and approval statuses will be updated on the basis of clinical outcomes from these confirmatory studies"); Daniel Carpenter, Aaron S. Kesselheim & Steven Joffe, *Reputation and Precedent in the Bevacizumab Decision*, 365 NEW ENG. J. MED. e3(1), e3(2) (2011) ("The accelerated approval mechanism thus creates a contract between the FDA and a pharmaceutical company: in return for promises of further clinical studies, the company receives provisional approval and rapid market access.").

intermediate clinical endpoint. In exchange, drug manufacturers agree to undertake trials to confirm the clinical benefit of the drugs they market, according to terms agreed upon by the drug manufacturer and the agency. Earlier market entry, of course, provides a financial return to drug manufacturers. In a 1992 congressional hearing on the Prescription Drug User Fee Act, it was estimated that introducing a drug just one month faster would yield $13 million in profits, and a one-year reduction in the duration of FDA review could reduce by three to four years the "breakeven time" until a drug's revenue outstrips costs of research and development.[104] It is reasonable to expect drug manufacturers to fulfill their obligations—now requirements—for postapproval studies, especially in light of the financial benefits manufacturers accrue from earlier marketing. The FDA, to keep its end of the bargain, must provide proper oversight of postapproval studies and either shepherd drugs to traditional approval or take steps to withdraw indications where warranted. Much has been made of the apparent laxity with which drug manufacturers and the agency have approached their respective obligations.[105]

Absent from current conceptions of accelerated approval as a social compromise is the very party accelerated approval was designed to benefit—the patient. Yet patients, too, are implicitly expected to engage in a compromise: They must accept the risk that a drug will not ultimately work in exchange for the chance of treatment. The unfortunate reality is that not all who take accelerated approval drugs find themselves better off. Although scholars have paid close attention in recent years to the costs of accelerated therapies to federal programs,[106] costs incurred by individuals—including out-of-pocket drug costs, the cost of the forgone opportunity to take another therapy with a more favorable risk-benefit profile, and costs associated with adverse effects including pain and suffering, medical expenses, and loss of life—tend to be overlooked. Certainly, these costs can be more difficult to measure but are no less significant.

Critical to the compromise patients undertake is the high cost of drugs approved under the pathway.[107] Cancer therapies are among the highest-priced drugs,[108] and attendant costs of cancer care, such as frequent disease monitoring,

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104. *User Fees for Prescription Drugs: Hearing Before the Subcomm. on Health & the Env't of the H. Comm. on Energy & Com.*, 102d Cong. 14 (1992) (memo to accompany comments of Mary Jo Veverka, Senior Advisor for Mgmt. and Sys., U.S. Food & Drug Admin.).

105. By this author's count, there have been upwards of a dozen editorials focused specifically on accelerated approval in the academic literature since 2017, many of which call for greater vigilance from both the agency and drug manufacturers with respect to fulfillment of their respective obligations under the pathway. *See, e.g.*, Gill & Prasad, *supra* note 103104, at 648; Gyawali & Kesselheim, *supra* note 103, at 597; Kesselheim, *supra* note 10, at 727; DiMagno, Glickman & Emanuel, *supra* note 49, at 92.

106. *See supra* notes 37–38 and accompanying text.

107. Even the first HIV drugs were expensive by the day's standards. *See* Irvin Molotsky, *U.S. Approves Drug to Prolong Lives of AIDS Patients*, N.Y. TIMES, Mar. 21, 1987, at A1 (noting that Retrovir (AZT), an early AIDS drug, was priced at $8,000 to $10,000 annually, raising concern that the cost would "force many people to exhaust their savings and go on the welfare rolls, relying on programs such as Medicaid to pay for the drug"). And HIV drugs, which have remained among the top revenue-earning drugs in the United States in recent years, continue to be unaffordable for many who need them. Douglas Krakower, Kenneth Katz & Julia L. Marcus, *Will the Newest Pill for HIV Prevention Fuel Progress—or Profits?*, STAT (Feb. 26, 2020), https://www.statnews.com/2020/02/26/newest-prep-pill-hiv-prevention-fuel-progress-or-profits [perma.cc/925S-YNEG] (citing Truvada's (emcitritabine/tenofovir) list price of $24,000 per year in 2020 as an obstacle to HIV prevention for many).

108. Cancer drugs commonly exceed $100,000 for one year of treatment, and prices tend to increase over time, often outpacing inflation. *See* Sham Mailankody & Vinay Prasad, Research Letter,

hospitalizations, and doctor's visits, leave many cancer patients and their families in financial straits, a phenomenon that has been dubbed financial toxicity.[109] The manifold burden of cancer tends to be especially weighty for younger cancer survivors, racial and ethnic minorities, and the uninsured.[110] The financial impact of cancer drugs can be significant, but the impact is that much greater when the benefits patients would find most meaningful—and those benefits they expect to receive from a drug, such as prolonged survival or relief of symptoms—have not been confirmed but rather predicted.

The high profitability of accelerated therapies and the financial returns that follow from early market entry lend further support to the argument in favor of an administrative compensation scheme. Disgorgement of profits from therapies for which

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Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs, 1 JAMA ONCOLOGY 539, 540 (2015) (reporting a median annual price of more than $116,000 for 21 cancer therapies with novel mechanisms of action approved between 2009 and 2013, and a median annual price of nearly $120,000 for 30 next-in-class cancer therapies); Miloš D. Miljković, Jordan E. Tuia, Timothée Olivier, Alyson Haslam & Vinay Prasad, *Association Between US Drug Price and Measures of Efficacy for Oncology Drugs Approved by the US Food and Drug Administration from 2015 to 2020*, 182 JAMA INTERNAL MED. 1319, 1319 (2022) (reporting a median annual treatment cost of $196,000 for cancer drugs approved between 2015 and 2020); Vokinger et al., *supra* note 99, at 4 (finding that, over the period from 2009 to 2019, nearly three-quarters of 65 cancer drugs examined had price increases exceeding the rate of inflation); Juliette Cubanski & Tricia Neumann, *Prices Increased Faster Than Inflation for Half of All Drugs Covered by Medicare in 2020*, KAISER FAM. FOUND. (Feb. 25, 2022), https://www.kff.org/medicare/issue-brief/prices-increased-faster-than-inflation-for-half-of-all-drugs-covered-by-medicare-in-2020 [perma.cc/V5SN-JSBA] (demonstrating that many cancer drugs are among the top drugs by total spending in Medicare Part B, and noting the prevalence of price increases exceeding the rate of inflation).

109. *See Financial Toxicity and Cancer Treatment (PDQ)—Health Professional Version*, NAT'L CANCER INST. (May 29, 2024), https://www.cancer.gov/about-cancer/managing-care/track-care-costs/financial-toxicity-hp-pdq [perma.cc/V6GV-TF5Q] (describing financial toxicity as "the phenomenon of adverse financial effects of cancer treatment" and highlighting that financial toxicity assumes many forms ranging from high out-of-pocket expenses and lost productivity to bankruptcy and feelings of distress); Noam Levey, *She Was Already Battling Cancer. Then She Had to Fight the Bill Collectors*, NPR (July 9, 2022, 5:00 AM), https://www.npr.org/sections/health-shots/2022/07/09/1110370391/cost-cancer-treatment-medical-debt [perma.cc/AA2M-NSNS]; Thomas G. Knight, Allison M. Deal, Stacie B. Dusetzina, Hyman B. Muss, Seul Ki Choi, Jeanette T. Bensen & Grant R. Williams, *Financial Toxicity in Adults with Cancer: Adverse Outcomes and Noncompliance*, 14 J. ONCOLOGY PRAC. e665, e667 (2018) (finding that cancer patients who reported financial toxicity were more likely to experience medication noncompliance and delayed or forgone care); Sue J. Fu, Liam Rose, Aaron J. Dawes, Lisa M. Knowlton, Kathryn J. Ruddy & Arden M. Morris, *Out-of-Pocket Costs Among Patients with a New Cancer Diagnosis Enrolled in High-Deductible Health Plans vs Traditional Insurance*, 4 JAMA NETWORK OPEN 1, 5–8 (2021) (quantifying the financial burden of a new cancer diagnosis on patients with private insurance and finding that cancer patients with high-deductible health plans faced substantially higher monthly out-of-pocket costs—in excess of $860 more per month—than those with traditional insurance, *id.* at 7); Ezekiel J. Emanuel, *Cancer Patients Shouldn't Be Responsible for Out-of-Pocket Costs*, STAT (May 23, 2023), https://www.statnews.com/2023/05/23/financial-toxicity-cancer-costs-cost-sharing [perma.cc/BP4M-M7QC] (describing the "uniquely American" problem of financial toxicity and recommending as a solution that public and private insurers do away with patient cost-sharing for cancer treatment).

110. *See* K. Robin Yabroff, Emily C. Dowling, Gery P. Guy Jr., Matthew P. Banegas, Amy Davidoff, Xuesong Han, Katherine S. Virgo, Timothy S. McNeel, Neetu Chawla, Danielle Blanch-Hartigan, Erin E. Kent, Chunyu Li, Juan L. Rodriguez, Janet S. de Moor, Zhiyuan Zheng, Ahmedin Jemal & Donatus U. Ekwueme, *Financial Hardship Associated with Cancer in the United States: Findings from a Population-Based Sample of Adult Cancer Survivors*, 34 J. CLINICAL ONCOLOGY 259, 261–63, 264 (2016); Knight et al., *supra* note 109, at e667 (finding that black race, unmarried status, and low education were "statistically significant independent predictors of financial toxicity").

confirmatory studies fail to show benefit might be an extreme measure.[111] But equity weighs in favor of setting aside funds from the revenue streams of later-withdrawn drugs to enable patients to recover out-of-pocket drug costs and medical expenses resulting from drug-induced adverse effects. Important to this discussion is the fact that many therapies initially approved under accelerated approval and later withdrawn remain on the market even *after* withdrawal because they continue to be sold for other approved uses.[112] This author's examination of accelerated approval oncology drugs for which an indication was withdrawn revealed that roughly half (8 of 17 drugs, corresponding to a total of 20 withdrawn indications) remained on the market after withdrawal.[113] A single cancer drug often treats many cancer types; withdrawal of one indication after failure or infeasibility of a confirmatory trial has no impact on the drug's other approved indications, which means that a therapy

111. Suppose an accelerated product is withdrawn from the market after a drug manufacturer decides not to complete confirmatory trials required by the FDA. The product, however, has been on the market for a number of years, and the drug manufacturer has received on the order of millions of dollars in payment for the now-withdrawn indication. Some might argue that the drug manufacturer has been unjustly enriched. Unjust enrichment, an equitable doctrine, requires that the defendant appreciated some benefit, which was conferred on the defendant by the plaintiff, and the retention of which by the defendant in the absence of payment would be unjust. *See* Everhart v. Miles, 422 A.2d 28, 31 (Md. Ct. Spec. App. 1980) (citing WILLISTON ON CONTRACTS s 1479 (3d ed. 1970)). Courts have described unjust enrichment as "a fiction of law adopted to achieve justice where no true contract exists." Lord & Stevens, Inc. v. 3D Printing, Inc., 756 N.W.2d 789, 792 (N.D. 2008) (quoting B.J. Kadrmas, Inc. v. Oxbow Energy, LLC, 727 N.W.2d 270, 273 (N.D. 2007)); Schenck v. K.E. David, Ltd., 666 A.2d 327, 328–29 (Pa. 1995) ("Where unjust enrichment is found, the law implies a contract, referred to as either a *quasi contract* or a contract implied in law, which requires that the defendant pay to plaintiff the value of the benefit conferred.").

Does the approval letter setting out a drug company's postapproval trial requirements constitute a valid and enforceable contract between the drug company and the FDA? If so, then restitution damages for unjust enrichment would generally not be available. *See* RESTATEMENT (THIRD) OF RESTITUTION AND UNJUST ENRICHMENT § 2(2) (AM. L. INST. 2011). However, if it does not constitute an express contract, one could argue that there is a contract implied in law, such that a state Medicaid program, for example, that paid many millions of dollars for a drug with an unconfirmed benefit could sue the drug company to recover damages on a theory of unjust enrichment. This is a novel theory, but one that merits exploration.

A state Medicaid program may not be considered a party to the implied contract between the FDA and the drug company, but it would have conferred a benefit on the drug company in the form of reimbursement for the accelerated approval drug—a benefit unjustly conferred as a result of the company's failure to complete postapproval studies as it had promised. To the extent that there is a valid and enforceable agreement between the FDA and the drug company, or to the extent that statute establishes the available remedies in the case that a drug company fails to comply with postapproval requirements, *see* 21 U.S.C. § 356(c)(3)(A), that could displace a claim for unjust enrichment. *See* Associated Mgmt. Servs., Inc. v. Ruff, 424 P.3d 571, 595–96 (Mont. 2018). (In addition, some courts require absence of a remedy at law as an element of an unjust enrichment claim. *See e.g.*, Hayden v. Medcenter One, Inc., 828 N.W.2d 775, 781 [N.D. 2013]). But, even so, statutory provisions on withdrawal arguably do not address the consequences to *payers* of a material breach of the obligation to conduct postapproval studies, thereby potentially salvaging a viable claim for unjust enrichment by a payer such as a state Medicaid program. *See Associated Mgmt. Servs*., 424 P.3d at 596 (noting the "availability of unjust enrichment where governing contract . . . does not address aftermath of a material breach").

112. *See, e.g.*, *Gilead Provides Update on U.S. Indication for Trodelvy in Metastatic Urothelial Cancer*, GILEAD (Oct. 18, 2024), https://www.gilead.com/company/company-statements/2024/gilead-provides-update-on-us-indication-for-trodelvy-in-metastatic-urothelial-cancer [perma.cc/87SH-N57K] ("This decision [to voluntarily withdraw Trodelvy for its urothelial cancer indication in the United States] does not affect the other approved Trodelvy indications within or outside of the U.S.").

113. Data on file with author.

may continue to generate revenue (and many do) after a particular indication's withdrawal.

Take, for example, durvalumab, which is sold under the brand name Imfinzi. In 2017, the FDA approved durvalumab under the accelerated approval pathway for the treatment of locally advanced or metastatic urothelial cancer (the most common form of bladder cancer) with disease progression during or after platinum-based chemotherapy.[114] The drug's approved uses were expanded to include treatment of stage III non-small cell lung cancer in 2018 and extensive-stage small-cell lung cancer in 2020.[115] In 2021, drug maker AstraZeneca withdrew durvalumab's indication in the United States for treatment of urothelial cancer after a Phase III trial failed to meet its primary endpoints.[116] In fact, the drug was found to produce a shorter progression-free survival relative to chemotherapy, the opposite of the hoped-for benefit.[117] Yet, in the year 2020, prior to durvalumab's voluntary withdrawal for urothelial cancer, the drug produced $1.185 billion in sales revenue in the United States alone and over $2 billion worldwide.[118] Even after the indication's withdrawal, AstraZeneca saw annual growth in sales of Imfinzi, which increased to more than $1.5 billion in the United States in 2022, as a result of the

114. *Durvalumab (Imfinzi)*, U.S. FOOD & DRUG ADMIN. (May 1, 2017), https://www.fda.gov/drugs/resources-information-approved-drugs/durvalumab-imfinzi [perma.cc/547J-CMK3]. The approval was based on a single-arm trial of 182 patients. *Id.*

115. *See FDA Expands Approval of Imfinzi to Reduce the Risk of Non-Small Cell Lung Cancer Progressing*, U.S. FOOD & DRUG ADMIN. (Feb. 16, 2018), https://www.fda.gov/news-events/press-announcements/fda-expands-approval-imfinzi-reduce-risk-non-small-cell-lung-cancer-progressing [perma.cc/RQ74-AKQ5]; *FDA Approves Durvalumab for Extensive-Stage Small Cell Lung Cancer*, U.S. FOOD & DRUG ADMIN. (Mar. 30, 2020), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-extensive-stage-small-cell-lung-cancer [perma.cc/2W7D-JRG4]. More recently, the drug was approved for treatment of locally advanced or metastatic biliary tract cancer, unresectable hepatocellular carcinoma, and certain forms of endometrial cancer. *FDA Approves Durvalumab for Locally Advanced or Metastatic Biliary Tract Cancer*, U.S. FOOD & DRUG ADMIN. (Sept. 2, 2022), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-locally-advanced-or-metastatic-biliary-tract-cancer [perma.cc/SV64-HJYL]; *Imfinzi Plus Chemotherapy Approved in the US for Mismatch Repair Deficient Advanced or Recurrent Endometrial Cancer*, ASTRAZENECA (June 17, 2024), https://www.astrazeneca.com/media-centre/press-releases/2024/imfinzi-approved-in-the-us-for-endometrial-cancer.html [perma.cc/4MHY-X5GF]; *Imfinzi (durvalumab) Prescribing Information*, U.S. FOOD & DRUG ADMIN. (Feb. 2025), https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761069s051lbl.pdf [perma.cc/B7M6-J7CV].

116. *See Voluntary Withdrawal of Imfinzi Indication in Advanced Bladder Cancer in the US*, ASTRAZENECA (Feb. 22, 2021, 7:00 AM), https://www.astrazeneca.com/media-centre/press-releases/2021/voluntary-withdrawal-imfinzi-us-bladder-indication.html [perma.cc/EH8L-YRJU]; Matthew Stenger, *DANUBE Trial Reports No Survival Benefit with First-Line Durvalumab in Metastatic Urothelial Carcinoma*, THE ASCO POST (Nov. 10, 2020), https://ascopost.com/issues/november-10-2020/danube-trial-reports-no-survival-benefit-with-first-line-durvalumab-in-metastatic-urothelial-carcinoma [perma.cc/H54W-9QM3].

117. *See* Stenger, *supra* note 116.

118. ASTRAZENECA, 2022 ANNUAL REPORT & FORM 20-F INFORMATION 149 (2022) [hereinafter ASTRAZENECA, 2022 ANNUAL REPORT]. Imfinzi's U.S. sales revenue was $564 million in 2018 and just over $1 billion in 2019. *See* AstraZeneca, 2020 ANNUAL REPORT & FORM 20-F INFORMATION 187 (2020). Imfinzi's sales also included sales of the drug for unresectable, stage III non-small cell lung cancer and extensive stage small-cell lung cancer, both of which were traditional approvals. *See Imfinzi (durvalumab) Label*, U.S. FOOD & DRUG ADMIN. (Nov. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761069s023s024s025lbl.pdf [perma.cc/K8AF-2KAF].

drug's use to treat other cancer types, in addition to possible off-label use for urothelial cancer.[119]

Durvalumab's trajectory is fairly typical. Cancer drugs commonly earn $50 million or more in product sales in the year prior to an indication's withdrawal, and product sales may be on the order of many billions of dollars for blockbuster drugs that treat a wide variety of cancers.[120] In fact, drug manufacturers may attempt to increase their chances of commercial success with a cancer therapy by seeking accelerated approval for treatment of a variety of different cancers on the basis of surrogate endpoints. The mechanisms of action of many new cancer immunotherapies lend themselves to just that approach.[121] In this regard, seeking accelerated approval for many cancer types is akin to seeking multiple patents on a new technology; some may prove to be of little value, but with each, the holder increases her likelihood that one among the many will have commercial significance.[122]

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119. *See* ASTRAZENECA, 2022 ANNUAL REPORT, *supra* note 118120, at 149. Drug sales post -withdrawal come from three possible sources: First, durvalumab may continue to be used off-label in the United States for urothelial cancer, despite the failed confirmatory trial and the drug's withdrawal for that indication. *See, e.g.*, Burstein, *supra* note 73, at 1323 (describing continued use of Avastin for metastatic breast cancer after its withdrawal for that indication in 2011). Second, durvalumab remains approved for treatment of other types of cancer. *See supra* note 117 and accompanying text. Third, when an indication is withdrawn from the U.S. market, drug manufacturers often do not take corresponding action to withdraw the indication from markets in other countries, permitting continued sales and revenue generation abroad. *See* Amol Akhade, Bhawna Sirohi & Bishal Gyawali, Comment, *Global Consequences of the US FDA's Accelerated Approval of Cancer Drugs*, 23 LANCET ONCOLOGY 201, 202 (2022) (discussing a persistent global spillover effect in which withdrawn drugs continue to be marketed and sold abroad).

120. This author's examination of oncology products approved under accelerated approval since the inception of the accelerated approval pathway through June 2023 for which one or more indications has been withdrawn revealed that product sales exceeded $1 billion in the year prior to an indication's withdrawal for five drugs—Keytruda (pembrolizumab), Tecentriq (atezolizumab), Opdivo (nivolumab), Imfinzi, and Avastin—and exceeded $50 million for an additional three drugs—Istodax (romidepsin), Blenrep (belantamab mafodotin-blmf), and Lartruvo (olaratumab). Data on file with author.

121. By targeting a common pathway involved in the body's response to cancer and inflammation, immune checkpoint inhibitors, including anti-PD-1 antibodies such as nivolumab and anti-PD-L1 therapies such as atezolizumab, have proven useful for treatment of a variety of different cancers. *See* Arlene H. Sharpe & Kristen E. Pauken, Review, *The Diverse Functions of the PD1 Inhibitory Pathway*, 18 NATURE REVS. IMMUNOLOGY 153, 153–54 (2018).

122. Akin to forms of intellectual property such as patents on new inventions, regulatory licenses to market pharmaceutical products harbor elements of uncertainty. At the time of issuance, a patent's commercial significance is largely unknown, and the patent's scope and the extent of the legal rights conferred may be hashed out only later when alleged infringers challenge a patent's validity or scope. *See* Mark A. Lemley & Carl Shapiro, *Probabilistic Patents*, 19 J. ECON. PERSPS. 75, 76 (2005). Similarly, an accelerated product's commercial significance is indeterminate at the time accelerated approval is granted; the product's efficacy and consequent risk-benefit profile, and the full scope of its adverse effects, become known only later with the passage of time and the results of postapproval studies. Patents issued on an obvious invention or one that is not novel over prior art "cause social costs without offsetting benefits," *id.* at 77, just as does accelerated approval of a drug whose benefit is ultimately not confirmed. In each case, there is a degree of uncertainty or prediction entailed in the government's judgment to confer a valuable right, and the costs of a miscalculation are ultimately borne by society. With drugs as with patents, it is not sufficient to consider net social benefit of the system in the aggregate; rather, we must consider the impact of regulatory misfires and what turn out to be mistaken predictions.

When an accelerated product does not live up to its promise of clinical benefit, it arguably does not merit the revenue earned during the "period of uncertainty." And a drug manufacturer that reaps the monetary benefits of earlier market access but does not fulfill its promises of postapproval trials arguably cannot lay claim to the full extent of the profits accelerated approval brought about. Part V will propose a policy involving a tax on drug companies with a new drug or biologics license application that was granted accelerated approval and later withdrawn, measured as some percentage of an accelerated product's revenue, to be held in trust for the benefit of patients harmed by accelerated approval's "toxic placebos."

IV. ACCELERATED APPROVAL AND ASSUMPTION OF RISK

A potential objection to an administrative compensation scheme for withdrawn accelerated approval drugs, or for any accelerated approval drug for that matter, is that patients have assumed the risk the drug may not work, that it may cause harm, and that its harms may ultimately outweigh its benefits. Therefore, if a patient should ultimately not benefit, incur costs, or worse yet, suffer harm, the risk of which she was aware, an argument might be made that she should not be entitled to redress. The doctrine of assumption of risk as it was classically conceived barred recovery for a plaintiff who knowingly placed herself in harm's way—that is, a plaintiff who, knowing of a risk, voluntarily proceeded to encounter it.[123] Important to the defense of assumption of risk is that the plaintiff's act must be a voluntary one, actuated "with full knowledge and apprehension of the risk incurred."[124]

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123. One of the classic articulations of this doctrine, encapsulated in the maxim *volenti non fit injuria* ("no wrong is done to one who consents," RESTATEMENT [SECOND] OF TORTS § 496A cmt. b [AM. L. INST. 1965]) can be found in the dissenting opinion of Judge Allen in *Eckert v. Long Island Railroad Co.*, 43 N.Y. 502 (N.Y. 1871):

> It is a well established rule, that no one can maintain an action for a wrong, when he consents or contributes to the act which occasions his loss. One who with liberty of choice, and knowledge of the hazard of injury, places himself in a position of danger, does so at his own peril, and must take the consequences of his act.

Id. at 507. The modern doctrine, recognized to contain greater conceptual nuance, blends into the doctrine of contributory negligence, in which a plaintiff's failure to take reasonable care, or unreasonable action in failing to avoid a danger he knows or should know was created by the defendant's negligence, contributes to his injury. RESTATEMENT (SECOND) OF TORTS §§ 466, 496A cmt. d (AM. L. INST. 1965). Like assumption of risk, contributory negligence under classical doctrine was a bar to recovery. The Restatement (Second) of Torts has described the distinction between the two doctrines as follows: "[A]ssumption of risk rests upon the voluntary consent of the plaintiff to encounter the risk and take his chances, while contributory negligence rests upon his failure to exercise the care of a reasonable man for his own protection." *Id.* § 496A cmt. d. Or as one court put it: "[t]he essence of contributory negligence is carelessness; of assumption of risk, venturousness. Thus an injured person may not have acted carelessly; in fact, may have exercised the utmost care, yet may have assumed, voluntarily, a known hazard. If so, he must accept the consequence." Hunn v. Windsor Hotel Co., 193 S.E. 57, 58 (W. Va. 1937).

124. *Eckert*, 43 N.Y. at 508; *see also* Ind. Nat. Gas & Oil Co. v. O'Brien, 65 N.E. 918, 920 (Ind. 1903) ("Freedom of the will, in fact, is the thing emphasized by the principle asserted in the maxim volenti non fit injuria."); Clayards v. Dethick, [1848] 12 Q.B. 439, 443 (Eng.) ("[I]f the plaintiff had persisted in running upon a great and obvious danger, his action could not be maintained."); Dahlin v. Sherwin, 132 Ill. App. 566, 569 (Ill. App. Ct. 1907) ("One who attempts to do work which exposes him to obvious and known dangers assumes the risk."); Sparks v. River & Harbor Improvement Co., 74 N.J.L. 818, 821 (N.J. 1907) ("While a servant assumes the risk of injury from obvious defects or dangers, he does not assume the risk of injury from defects and dangers which are not obvious and of which he had no knowledge, and could not observe and know by the exercise of ordinary care."). Some courts

Voluntariness requires knowledge of the hazard: Where a plaintiff does not know of the risks involved or where a plaintiff cannot appreciate their magnitude and extent, a plaintiff cannot be said to assume the risks.[125] Yet knowledge of risk is not enough; there must be *consent* to accept risk.[126] A common example illustrates the role of consent in assumption of risk: A passenger in a vehicle driven recklessly who remains in the vehicle even after being given the opportunity to exit and avoid injury impliedly assents to the risks of the reckless driving. But one who has had insufficient time since the onset of the reckless driving to object and so rectify the driver's conduct or to extricate himself from the dangerous conditions will not be taken to have impliedly assented to the conduct.[127] Modern conceptions distinguish between express assumption of risk, grounded in contract, and implied assumption of risk, in which an agreement on the part of the plaintiff to accept risk is implied rather than explicit.[128]

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have held that knowledge of a hazard must be specific rather than generalized. *See* Hogenson v. Serv. Armament Co., 461 P.2d 311, 315 (Wash. 1969).

125. RESTATEMENT (SECOND) OF TORTS § 496D cmt. b (AM. L. INST. 1965) ("[A plaintiff] will not be found . . . to assume any risk unless he has knowledge of its existence. This means that he must not only be aware of the facts which create the danger, but must also appreciate the danger itself and the nature, character, and extent which make it unreasonable."); *id.* § 496C cmt. i ("[T]he plaintiff must . . . be held to assume only the risk he appreciates, and not the risk which he does not.").

126. *Id.* § 496C cmt. h; Edwards v. Kirk, 288 N.W. 875, 877 (Iowa 1939) ("[M]ere knowledge of the risk does not necessarily involve consent to the risk, and . . . the maxim [*volenti non fit injuria*] does not apply on the mere showing of knowledge of the danger, but only where the circumstances are such as warrant the inference that the plaintiff encountered the risk freely and voluntarily with full knowledge of the nature and extent thereof.").

127. *See, e.g.*, Fay v. Thrasher, 66 N.E.2d 236, 241–42 (Ohio 1946); *Kirk*, 288 N.W. at 878–79 (affirming the lower court's striking of the defense of assumption of risk in an action to recover damages for the death of a motorcycle passenger, reasoning that the passenger had "no time for deliberation; no opportunity to choose" and "[t]o jump would have been certain injury," such that the decedent was "suddenly caught in a trap not of his own choosing").

A plaintiff's assumption of risk is not voluntary where a defendant's conduct has left the plaintiff with "no reasonable alternative course of conduct." RESTATEMENT (SECOND) OF TORTS § 496E(2) (AM. L. INST. 1965). This is reminiscent of the meaning of voluntariness as it is understood in the context of the defense of duress in contract law. Elsewhere, I have argued that a drug manufacturer's conduct in setting unreasonable prices for pharmaceutical therapies that obstruct access to those very therapies often leaves patients with no reasonable alternative but to accept the conditions manufacturers, in effect, demand as a means to access, which often require sharing of protected health information. *See* Laura Karas, *Privacy as the Price of Drug Access*, 23 COLUM. SCI. & TECH. L. REV. 50, 85–87, 86 n.174 (2021); *see also id.* at 74–75. Here, by contrast, it is not a drug manufacturer's conduct in connection with the accelerated approval pathway that limits the alternative courses of conduct (i.e., therapeutic options) for a patient who chooses to take an accelerated approval drug; rather, patients taking accelerated therapies are "driven by . . . [their] own necessities to accept a danger." RESTATEMENT (SECOND) OF TORTS § 496E cmt. b (AM. L. INST. 1965). Therefore, the way to defeat assumption of risk as a defense, if it were raised, in the setting of liability arising from accelerated approval is on the grounds of a plaintiff's lack of knowledge—awareness and appreciation of the nature, character, and extent—of the risks involved.

128. ROBERT E. KEETON, LEWIS D. SARGENTICH & GREGORY C. KEATING, TORT AND ACCIDENT LAW: CASES AND MATERIALS 538, 554 (4th ed. 2004). Implied assumption of risk can be further subdivided into primary implied assumption of risk, equivalent to a statement that defendant owed no duty, *see id.* at 538, and secondary implied assumption of risk, in which a plaintiff voluntarily and unreasonably proceeded to encounter a risk created by the defendant's negligence, *see* Robert E. Keeton, *Assumption of Products Risks*, 19 SW. L.J. 61, 67 (1965). Many jurisdictions have recognized the merger of secondary implied assumption of risk with comparative negligence, though courts have taken varying positions on whether and to what extent a comparative fault regime subsumes assumption of risk. *See* Davenport v. Cotton Hope Plantation Horizontal Prop. Regime, 508 S.E.2d 565, 571–72 (S.C.

Even since the pathway's inception discussions of accelerated approval have been imbued with language evocative of assumption of risk.[129] Speaking before the House Committee on Energy and Commerce in 1992, Commissioner Kessler alluded to the notion that patients are "willing to accept [the] risk" of accelerated approval:

> [W]hen one is dealing with diseases, devastating diseases, life-threatening diseases, the American public, I believe, is willing to accept risk, assuming they are fully informed. The package insert for DDI had something like, 40 cautions. It was probably the longest package insert ever, because we wanted to make sure. If we are going to have accelerated approval, we have an obligation to the clinicians prescribing it and to patients, to let them know the basis of what was done.[130]

Former FDA Commissioner Robert Califf, in a medical journal editorial in 2017, expressed a similar sentiment: "[P]eople with serious or life-threatening illnesses that lack effective treatments are willing to take greater risk for earlier access to novel therapies."[131] Yet, to be truly *willing* to take the risks of a drug, one must know a priori what those risks are—just as to assume risks, one must have knowledge of them. Indeed, former Commissioner Kessler's comment was predicated on the assumption that patients are "fully informed" of a drug's risks. This assumption, however, is likely a faulty one in the context of accelerated approval for the reasons discussed below. And simply because sick patients may have a greater willingness to try a drug that *might* work to alleviate their suffering or extend their life does not necessarily mean they appreciate—let alone accept—the full sweep of the risks involved.

1998). South Carolina, for example, declines to recognize secondary implied assumption of risk as an absolute bar to recovery, reasoning that "it would be incongruous to absolve the defendant of all liability based only on whether the plaintiff assumed the risk of injury." *Id.* at 573. Instead, a plaintiff's assumption of risk is weighed in the balance of relative faults. *Id.* at 573–74. One who knowingly and voluntarily encounters a negligently created risk can do so reasonably or unreasonably. *Id.* at 571. Primary implied assumption of risk, in contrast to secondary implied assumption of risk, entails a risk "not created by the defendant's negligence, but by the nature of the activity," such that "the plaintiff enters into the relationship knowing that the defendant will not protect him against the risk." Ferguson v. Cincinnati Gas & Elec. Co., 590 N.E.2d 1332, 1333 (Ohio Ct. App. 1990). For primary implied assumption of risk to apply, risks must be "so inherent in some activit[y] that they cannot be eliminated." Collier v. Northland Swim Club, 518 N.E.2d 1226, 1228 (Ohio Ct. App. 1987). Whereas a spectator's risk of being hit by a fly ball at a baseball game often supplies the paradigmatic example of primary implied assumption of risk, the risk of being injured diving into a shallow pool has been deemed "not so inherent as to relieve pool operators from any duty whatsoever to all divers." *Id.* at 1229; *see id.* at 1228–29. Instead, the pool operator maintains a duty to act reasonably in its management of the risks, which includes a responsibility to provide "proper instruction, warnings and supervision." *Id.* at 1229. So too with manufacturers of drugs approved under accelerated approval. The risks associated with taking an accelerated product are not so inherent as to relieve drug companies of their duty to supply proper warnings, instructions, and supervision; consequently, primary implied assumption of risk cannot serve as a defense to a drug company's negligence in this context.

129. For a recent example of such a reference, see Gill & Prasad, *supra* note 103, at 658 ("Patients and providers are willing to undertake risk in accepting drugs that have limited evidence of efficacy because they have an assurance that the FDA will take all steps necessary to reduce harms and guarantee benefit in a timely manner.").

130. *Food and Drug Administration Oversight (Part 2), Hearing*, *supra* note 65, at 72 (statement of David Kessler, Comm'r, U.S. Food & Drug Admin.).

131. *See* Califf, *supra* note 52, at 614–15.

The FDA has taken steps to inform patients of the risks they may assume when they take any drug or biologic therapy via disclosures on drug labels.[132] Current regulation obligates drug manufacturers to convey accelerated approval-related risk information in a label's Indication and Usage section: Manufacturers must provide a "succinct description of the limitations of usefulness" of a drug or biologic approved on the basis of a surrogate endpoint and "any uncertainty about anticipated clinical benefits."[133] That description, according to agency guidance, should include a statement that an indication was approved under accelerated approval, the clinical trial endpoints that supported accelerated approval, and a statement that continued approval may depend on confirmation of benefit in clinical trials.[134] The mandated disclosures promote informed consent; physicians have a duty to convey risk information to patients, and greater disclosure from drug manufacturers enables doctors, and thus patients, to "know the basis of what was done" to secure approval, in Kessler's words.[135]

Despite required disclosures on drug labels, it is unlikely that meaningful information about the actual risks of accelerated approval consistently finds its way to patients. Several factors point to this conclusion. First, recent research has demonstrated that compliance with the FDA's labeling guidelines for accelerated approval is high, but not universal.[136] Second, and critically, patients rely on health care providers to know and relay the thrust of drug labels, such as the conditions for which a drug is approved and the risks associated with treatment.[137]

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132. *See, e.g.*, *Project Confirm*, U.S. FOOD & DRUG ADMIN. (Dec. 4, 2024), https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm [perma.cc/LUQ2-86XX] (including as a Frequently Asked Question the following query: "How does the FDA let patients and providers know that a product was approved under accelerated approval?" and the associated answer: "If a product is approved under accelerated approval, this status is described in the Indications and Usage Section . . . of the [drug's label]").

133. 21 C.F.R. § 201.57(c)(2)(i)(B) (2015).

134. U.S. FOOD & DRUG ADMIN., LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS APPROVED UNDER THE ACCELERATED APPROVAL REGULATORY PATHWAY: GUIDANCE FOR INDUSTRY 3–4 (2019). The FDA offers model language, to which most drug companies adhere. For example, before it was given traditional approval, Leqembi (lecanemab) had the following disclosure on its label: "This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial." *Leqembi (lecanemab) Prescribing Information*, EISAI-BIOGEN, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s000lbl.pdf [perma.cc/Z2JC-5S5V].

135. *Food and Drug Administration Oversight (Part 2), Hearing*, *supra* note 65, at 72 (statement of David Kessler, Comm'r, U.S. Food & Drug Admin.).

136. Jeromie Ballreich, Mariana Socal, Charles L. Bennett, Andrew Xuan, Antonio Trujillo & Gerard Anderson, *Accelerated Approval Drug Labels Often Lack Information for Clinical Decision-Making*, 43 PHARMACOTHERAPY 300, 301–02 (2023). Across 110 indications approved by accelerated approval (corresponding to 62 drugs), 12 of 110 (11%) made no mention of accelerated approval, and 6 of 110 (6%) failed to identify the surrogate or intermediate clinical endpoint on which approval was based. *Id.*

137. *See* William Shrank, Jerry Avorn, Cony Rolon & Paul Shekelle, *Effect of Content and Format of Prescription Drug Labels on Readability, Understanding, and Medication Use: A Systematic Review*, 41 ANNALS PHARMACOTHERAPY 783, 786 (2007) (summarizing the findings of studies examining physician-patient communication about drugs). A low level of literacy can further compound patients' reliance on physicians for proper interpretation of a drug's risks and safe administration. *See, e.g.*, Terry C. Davis, Michael S. Wolf, Pat F. Bass III, Mark Middlebrooks, Estela Kennen, David W. Baker, Charles L. Bennett, Ramon Durazo-Arvizu, Anna Bocchini, Stephanie Savory & Ruth M. Parker, *Low Literacy*

Manufacturers may satisfy their duty to warn of a drug's risks through adequate drug label information, directed to the provider as a learned intermediary.[138] Yet, many health care providers remain unfamiliar with the specifics of drug labels and so may not be attuned to a therapy's accelerated approval status in the first place.[139] Even those providers who stay current with on-label indications and evidence supporting on- and off-label uses may still lack a fundamental understanding of the meaning of FDA designation and approval terminology.[140] A statement that an indication was

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Impairs Comprehension of Prescription Drug Warning Labels, 21 J. GEN. INTERNAL MED. 847, 850 (2006).

138. *See, e.g.*, Tracy v. Merrell Dow Pharms., Inc., 569 N.E.2d 875, 878 (Ohio 1991) ("Where a prescription drug has been prescribed for a patient by the patient's physician, the manufacturer has been held to discharge its duty to warn if the manufacturer adequately warns the physician. . . . The rationale behind these holdings is that the physician stands between the manufacturer and the patient as a learned intermediary. The physician has the duty to know the patient's condition as well as the qualities and characteristics of the drugs or products to be prescribed for the patient's use. The physician is in the best position, therefore, to balance the needs of patients against the risks and benefits of a particular drug or therapy, and then to supervise its use."); Carlin v. Superior Court, 920 P.2d 1347, 1354 (Cal. 1996) ("[I]n the case of prescription drugs, the duty to warn runs *to the physician*, not to the patient."); Davis v. Wyeth Lab'ys, Inc., 399 F.2d 121, 130 (9th Cir. 1968) ("Ordinarily in the case of prescription drugs warning to the prescribing physician is sufficient."); Centocor, Inc. v. Hamilton, 372 S.W.3d 140, 157 (Tex. 2012) ("[A] prescription drug manufacturer fulfills its duty to warn end users of its product's risks by providing adequate warnings to the intermediaries who prescribe the drug and, once fulfilled, it has no further duty to warn the end users directly."). Importantly, the learned intermediary doctrine assigns the ultimate "task of weighing the benefits of any medication against its potential dangers" to the prescribing physician by virtue of the physician's expertise, medical judgment, and "knowledge of both patient and palliative." *Centocor*, 372 S.W.3d at 159 (quoting Reyes v. Wyeth Lab'ys, 498 F.2d 1264, 1276 (5th Cir. 1974)). In addition, states have adopted statutory presumptions of an adequate product warning when the warning has been approved by the FDA. *See, e.g.*, N.J. STAT. ANN. § 2A:58C-4 (creating a "rebuttable presumption . . . that the warning or instruction is adequate" if the FDA "approved or prescribed" the warning or instruction under the FDCA or the Public Health Service Act, 42 U.S.C. § 201 *et seq.*). The FDA also conveys information on drug risks and benefits to patients through the patient package insert, first required with oral contraceptive pills in 1970. Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAG., Jan.-Feb. 2006, at 4.

139. *See* Donna T. Chen, Matthew K Wynia, Rachael M. Moloney & G. Caleb Alexander, *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094, 1098 (2009) (surveying a national sample of primary care physicians and psychiatrists and finding that respondents accurately identified the level of evidence supporting a particular prescription drug's use (e.g., on-label, off-label but strong evidence, off-label and ineffective, etc.) only about half of the time).

140. *See* Aaron S. Kesselheim, Steven Woloshin, Wesley Eddings, Jessica M. Franklin, Kathryn M. Ross & Lisa M. Schwartz, *Physicians' Knowledge About FDA Approval Standards and Perceptions of the "Breakthrough Therapy" Designation*, 315 JAMA 1516, 1517 (2016) (finding that more than half of physicians surveyed mistakenly believed that the FDA requires strong evidence ("randomized trials evaluating clinical outcomes") rather than preliminary evidence ("uncontrolled studies or studies testing surrogate outcomes") for its "breakthrough" designation). Other research has suggested that, like physicians, the public may attach mistaken, lay interpretations to commonly used FDA jargon, such as the breakthrough designation. *See* Tamar Krishnamurti, Steven Woloshin, Lisa M. Schwartz & Baruch Fischhoff, *A Randomized Trial Testing US Food and Drug Administration "Breakthrough" Language*, 175 JAMA INTERNAL MED. 1856, 1857–58 (2015) (describing a lay perception of higher efficacy and evidentiary strength with use of the term "breakthrough" and "promising" in a description of a hypothetical new drug—a so-called "breakthrough effect"). Physicians' understanding of regulatory terminology may be increasing, but a sizeable proportion of physicians remains misinformed. A more recent survey of physicians' familiarity with the breakthrough designation found that 65% correctly associated the breakthrough designation with a preliminary evidence base, while 34% associated the designation with strong rather than preliminary evidence. *See* Ryan S. Paquin, Vanessa Boudewyns,

"approved under accelerated approval" will have little chance of being conveyed to patients if providers lack familiarity with what accelerated approval entails. Thus, exclusive reliance on providers as learned intermediaries to reliably and accurately convey information to patients on the risks of accelerated approval may be misplaced.

The concept of a "surrogate" endpoint and its potential disconnect with outcomes that matter most to patients may also be beyond the ken of the average patient. Research has shown that the lay public harbors misconceptions about the meaning of a traditional approval of a drug by the FDA.[141] In one study, nearly 40% of adults surveyed believed that the "FDA only approves prescription drugs that are extremely effective," and 25% believed that the "FDA only approves drugs that do not have serious side effects."[142] Correcting baseline misconceptions about the drug approval process would be an arduous task in itself, let alone conveying the nuances of an expedited regulatory pathway. To the extent that patients' beliefs about a drug's safety and effectiveness are tied to a therapy's FDA approval, patients will tend to overestimate the benefits and underestimate the risks of drugs "approved" under accelerated approval.[143]

Unfortunately for consumers, other signals of uncertain efficacy are largely lacking, making a therapy's accelerated approval status effectively unobservable if not conveyed by providers or manufacturers directly.[144] A therapy's price, for instance, has not been a factor differentiating accelerated approval from a regular approval,[145] although, of course, patients are often shielded from the full impact of

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Amie C. O'Donoghue & Kathryn J. Aikin, *Physician Perceptions of the FDA's Breakthrough Therapy Designation: An Update*, 27 THE ONCOLOGIST e85, e86–e87 (2022).

141. *See* Lisa M. Schwartz & Steven Woloshin, *Communicating Uncertainties About Prescription Drugs to the Public: A National Randomized Trial*, 171 ARCHIVES INTERNAL MED. 1463, 1465 (2011).

142. *Id.*

143. An apt analogy is the "therapeutic misconception," the mistaken belief among research participants that their involvement in a clinical study entails deliberate treatment in the participant's best interest rather than experimentation designed with research ends in mind. *See* Richard S. Saver, *Medical Research and Intangible Harm*, 74 U. CIN. L. REV. 941, 988 (2006); Franklin G. Miller & Steven Joffe, *Evaluating the Therapeutic Misconception*, 16 KENNEDY INST. ETHICS J. 353, 353–54 (2006). This fallacy leads research participants to misperceive and overestimate the benefits that they may derive as a result of their participation in the research process. *See* Saver, *supra*, at 988. Although informed consent is the traditional antidote to the therapeutic misconception, the questionable effectiveness of informed consent tends to erode its reliability both as a bulwark against these misperceptions and as a process that should be accorded legal weight.

144. One notable exception is the existence of a coverage restriction, which may signal a therapy's uncertain risk-benefit profile. Some private insurers have limited coverage of accelerated approval drugs, such as aducanumab, pending confirmatory trial results. *See, e.g.*, Robert King, *Major Insurers Won't Pay for Biogen's Alzheimer's Drug Until They Get More Proof that It Works: Bloomberg Survey*, FIERCE HEALTHCARE (Nov. 22, 2021, 6:00 PM), https://www.fiercehealthcare.com/payer/bloomberg-survey-major-insurers-question-if-controversial-alzheimer-s-drug-medically [perma.cc/63JY-CRX6]. But federal payers' requirements for coverage have made this an uneven signal and one that is not relevant among those who do receive coverage. In addition, some accelerated products may continue to be covered by insurers for a withdrawn indication, as was the case with bevacizumab for the treatment of metastatic breast cancer. For challenges to state coverage restrictions for accelerated therapies, *see* discussion *supra* note 59.

145. At other points in the pharmaceutical supply chain, the effective price of accelerated therapies may vary from their non-accelerated counterparts due to rebates and other discounts negotiated by purchasers. However, such price differences do not trickle down to patients. *See* Erin Trish, Katrina Kaiser & Geoffrey Joyce, *How Would Sharing Rebates at the Point-of-Sale Affect Beneficiary Cost-Sharing in Medicare Part D?*, USC SCHAEFFER CTR. HEALTH POL'Y & ECON. 1–2

drug prices by public or private insurance coverage.[146] Any given cancer therapy frequently has indications approved under accelerated approval and the ordinary approval process. The blockbuster therapy pembrolizumab (Keytruda) is a prime example.[147] First approved in 2014 under the accelerated approval pathway for unresectable or metastatic melanoma,[148] pembrolizumab is now indicated for more than twenty types of cancer, only a small number of which currently carry a notation regarding accelerated approval.[149] Yet, no price differential typically exists among pembrolizumab's various uses based on accelerated approval status. To the extent that patients feel the price impact of these drugs, that provides no indicator of the preliminary and predictive nature of the evidence supporting them. What is more, high drug prices may bolster mistaken beliefs about a therapy's efficacy or curative potential.

Where a certain characteristic of a product is unobservable and could lead consumers to systematically understate risk or to rely on misunderstandings of legal standards (such as the belief that the FDA only approves highly effective drugs with no serious risks, for example), scholars have asked how the legal standard might be modified to account for consumers' mistaken expectations.[150] This line of inquiry

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(2020) (explaining that patient cost-sharing for drugs in Medicare Part D is based on a drug's list price, set by drug manufacturers, rather than downstream net or post-rebate prices). A new oncology drug approved under accelerated approval will typically have a list price on par with other oncology drugs, and for any given drug with both accelerated and traditionally approved uses, patients will not see a difference in price depending on the use for which the drug was prescribed.

146. *See* Howard et al., *supra* note 93, at 142–45 (noting that, as a result of cost-sharing, "patients may be indifferent between a drug that costs $20,000 and one that costs $100,000," *id.* at 144). For physician-administered drugs under Medicare Part B, coinsurance is calculated based on 20% a drug's cost. *See* Juliette Cubanski, Nolan Sroczynski & Tricia Neuman, *Medicare Part B Drugs: Cost Implications for Beneficiaries in Traditional Medicare and Medicare Advantage*, KAISER FAM. FOUND. (Mar. 15, 2022), https://www.kff.org/medicare/issue-brief/medicare-part-b-drugs-cost-implications-for-beneficiaries-in-traditional-medicare-and-medicare-advantage [perma.cc/H8LB-54VP]. Although a supplemental insurance plan may cover all or part of this cost-sharing, by recent measures one in twenty Medicare beneficiaries (approximately 3.2 million individuals) lack supplemental coverage. Nancy Ochieng, Juliette Cubanski & Tricia Neuman, *A Snapshot of Sources of Coverage Among Medicare Beneficiaries*, KAISER FAM. FOUND. (Sept. 23, 2024), https://www.kff.org/medicare/issue-brief/a-snapshot-of-sources-of-coverage-among-medicare-beneficiaries [perma.cc/MMK9-25BH].

147. *See Keytruda (pembrolizumab) Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s172lbl.pdf [perma.cc/LU3E-SYPV].

148. *See Merck Receives Accelerated Approval of KEYTRUDA (Pembrolizumab), The First FDA-Approved Anti-PD-1 Therapy*, MERCK (Sept. 4, 2014, 2:15PM), https://www.merck.com/news/merck-receives-accelerated-approval-of-keytruda-pembrolizumab-the-first-fda-approved-anti-pd-1-therapy [perma.cc/Q4NE-LDZK].

149. Indications that were approved under accelerated approval include: gastric and gastro-esophageal junction adenocarcinoma; certain solid tumors; and a particular dosing regimen for treatment of adult classical Hodgkin Lymphoma and primary mediastinal large B-cell lymphoma. *See Keytruda (pembrolizumab) Label*, *supra* note 147.

150. *See* Oren Bar-Gill & Kevin E. Davis, *(Mis)perceptions of Law in Consumer Markets*, 19 AM. L. & ECON. REV. 245, 248–49 (2017). Application of Professor Bar-Gill and Davis' model to accelerated approval may prove fruitful in assessing whether the standard for accelerated approval ought to be raised, as some physicians and researchers have advocated. *See* sources cited *supra* note 26. A few comments here deserve mention: Accelerated approval arguably creates a "weak liability" regime under the framework proposed by Professors Bar-Gill and Davis, *see* Bar-Gill & Davis, *supra*, at 261, in which the liability manufacturers face when accelerated therapies fall short of the legal standard is smaller than the harm incurred by patients. This is in large part due to the low likelihood that patients harmed by accelerated approval drugs—potentially quite ill at baseline and facing a poor prognosis—will seek and achieve redress. It is also, in some respect, a sanctions regime, *see id.* at 249, in which manufacturers falling

finds useful application in the context of accelerated approval. Consumers are unlikely to know the precise legal standard for accelerated approval; instead, they either conflate accelerated approval with their conception of a traditional approval, or hold beliefs that accelerated therapies are *even more* efficacious than traditionally approved drugs (due, for example, to associations with terms such as "breakthrough," which may be mistakenly taken to connote superior efficacy).[151] Consumers who are unaware of the proper legal standard for accelerated approval and its practical import will tend to overstate product quality for accelerated therapies and, consequently, demand more of them than in the counterfactual world in which the legal standard is fully and accurately perceived.[152]

In addition to consumer misperceptions of the legal standard for accelerated approval, systematic understatement of the risks associated with accelerated therapies could be an argument in favor of limiting or eliminating use of the pathway. Here, again, the underlying reasoning is that the bargain of accelerated approval only works when patients are aware of the risks they undertake. Alternatively, to address the omission of important risk information about accelerated therapies in patient-provider discussions, a duty could be placed on drug manufacturers to warn patients directly of a drug's accelerated approval status rather than provide warnings to the provider as a learned intermediary.[153] Courts, however, have rejected such an extension of a manufacturer's duty to warn in the setting of investigational drugs on the grounds that physicians, not manufacturers, have formed a relationship with patients at the point of treatment.[154] Nonetheless, the expansion of direct-to-consumer advertising of prescription drugs has arguably fostered a closer nexus between drug manufacturers and patients that could overcome the prevailing view that doctors are best positioned to warn of a product's risks.[155]

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short of the legal standard for accelerated approval may face the sanction of withdrawal—although the sanction here, rather than induce compliance with the legal standard, may instead create a disincentive to comply (i.e., the prospect of an indication's withdrawal could disincentivize completion of confirmatory studies that would otherwise permit a more definitive risk-benefit assessment of a drug).

151. *See* Krishnamurti et al., *supra* note 140, at 1856–58.

152. *See* Bar-Gill & Davis, *supra* note 150, at 248, 253–56.

153. A study undertaken to examine disclosures about accelerated approval status in drug manufacturers' direct-to-consumer websites found that 19 of 26 (73%) websites made such disclosures, though of those 19, less than half mentioned future or ongoing research. *See* Helen W. Sullivan, Amie C. O'Donoghue, Kathleen T. David & Nisha J. Patel, *Disclosing Accelerated Approval on Direct-to-Consumer Prescription Drug Websites*, 27 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1277, 1278–79 (2018). While this percentage may be heartening, especially given the lack of regulation mandating direct-to-consumer disclosure of a therapy's accelerated approval status in a form readily understood by the average consumer, there is room for improvement. Indeed, as the authors recognize, the effect of such disclosures on patients' understanding of the risks involved in accelerated approval is a separate matter that warrants further study. *See id.* at 1280.

154. *See* Tracy v. Merrell Dow Pharmaceuticals, Inc., 569 N.E.2d 875, 879–80 (Ohio 1991); *see id.* at 880 ("The use of investigational drugs may, of course, require greater warning and more physician supervision, but the status of the drug with the FDA does not alter the relationship between drug manufacturer, physician and patient."). *But see* Davis v. Wyeth Lab'ys Inc., 399 F.2d 121, 131 (9th Cir. 1968) (distinguishing a mass vaccination clinic that vaccinated all comers from prescription drugs prescribed after a provider's assessment and concluding that where a physician's judgment is not involved, a manufacturer may have a duty "to see that warnings reach the consumer, either by giving warning itself or by obligating the purchaser to give warning").

155. The Supreme Court of New Jersey has taken this tack, ruling in 1999 that "a pharmaceutical manufacturer that makes direct claims to consumers for the efficacy of its product

And finally, even if providers or manufacturers convey risk information on accelerated therapies in a manner that can be grasped by the average patient—an unlikely scenario—patients facing a grave medical condition may not properly weigh the risks, including the risk of financial harm and the risk of adverse effects, against potential benefits in reaching a treatment decision.[156] Diagnosis with a serious and life-threatening medical condition complicates and, in many ways, frustrates the process of informed treatment decision-making.[157] The perception of a lack of choices even in the face of treatment options,[158] misunderstandings about prognosis and effectiveness of treatment,[159] and the challenge of processing information about

should not be unqualifiedly relieved of a duty to provide proper warnings of the dangers or side effects of the product." Perez v. Wyeth Lab'ys Inc., 734 A.2d 1245, 1247 (N.J. 1999); *see id.* at 1263 ("Given the presumptive defense that is afforded to pharmaceutical manufacturers that comply with FDA requirements, we believe that it is fair to reinforce the regulatory scheme by allowing, in the case of direct-to-consumer marketing of drugs, patients deprived of reliable medical information to establish that the misinformation was a substantial factor contributing to their use of a defective pharmaceutical product.").

156. *See* Mark A. Hall & Carl E. Schneider, *Patients as Consumers: Courts, Contracts, and the New Medical Marketplace*, 106 MICH. L. REV. 643, 650–51 (2008) (recounting the many ways that "illness can cripple the patient as consumer").

157. *See* Wendy Netter Epstein, *Nudging Patient Decision-Making*, 92 WASH. L. REV. 1255, 1286–88 (2017) (explaining that, due to cognitive biases, patients may not exhibit preferences for those treatments most likely to benefit them and lamenting that "current law simply accepts the patient's choice without considering the implications . . . of doing so," *id.* at 1287); Barbara A. Noah & Rene Reich-Graefe, *Rational Patient Apathy*, 49 SETON HALL L. REV. 535, 538, 596–99 (2019) (describing a "rational apathy" that besets patients who confront a new diagnosis of serious or life-threatening illness, in which patients "default[] to *negative* decision-making: an affirmative choice to not make any balanced decision on the merits but rather to remain rationally ignorant of some or all aspects of the choice situation," *id.* at 538).

158. *See* Thomas W. Le Blanc, Laura J. Fish, Catherine T. Bloom, Areej El-Jawhari, Debra M. Davids, Susan C. Locke, Karen E. Steinhauser & Kathryn I. Pollak, *Patient Experiences of Acute Myeloid Leukemia: A Qualitative Study about Diagnosis, Illness Understanding, and Treatment Decision-Making*, 26 PSYCHO-ONCOLOGY 2063, 2065–67 (2017) (describing a tendency among patients with acute myelogenous leukemia (AML) to "dichotomize treatment options into either 'do or die,' when there were actually several available treatment options of varying intensity and risk," *id.* at 2065); MA Sekeres, RM Stone, D. Zahrieh, D. Neuberg, V. Morrison, DJ De Angelo, I. Galinsky & SJ Lee, *Decision-Making and Quality of Life in Older Adults with Acute Myeloid Leukemia or Advanced Myelodysplastic Syndrome*, 18 LEUKEMIA 809, 814 (2004) (reporting that nearly two-thirds of AML patients studied "denied being offered treatment options" other than their chosen treatment, even where the medical record showed otherwise).

159. *See, e.g.*, Jane C. Weeks, Paul J. Catalano, Angel Cronin, Matthew D. Finkelman, Jennifer W. Mack, Nancy L. Keating & Deborah Schrag, *Patients' Expectations About Effects of Chemotherapy for Advanced Cancer*, 367 NEW ENG. J. MED. 1616, 1619–20 (2012) (finding that a substantial proportion of surveyed patients with metastatic lung or colorectal cancer on chemotherapy treatment held false beliefs about the curative potential of chemotherapy); Kah Poh Loh, Huiwen Xu, Anthony Back, Paul R. Duberstein, Supriya Gupta Mohile, Ronald Epstein, Colin McHugh, Heidi D. Klepin, Gregory Abel, Stephanie J. Lee, Areej El-Jawhari & Thomas W. LeBlanc, *Patient-Hematologist Discordance in Perceived Chance of Cure in Hematologic Malignancies: A Multicenter Study*, CANCER 1306, 1309 (2020) (finding that, even after consultation, patients and hematologists held discrepant perceptions of prognosis in roughly half of cases); Sekeres et al., *supra* note 158, at 812–13. Research has shown that greater discordance between physician and patient estimates of survival is associated with higher odds of choosing life-extending treatments, *see* Jane C. Weeks, E. Francis Cook, Steven J. O'Day, Lynn M. Peterson, Neil Wenger, Douglas Reding, Frank E. Harrell, Peter Kussin, Neil V. Dawson, Alfred F. Connors, Joanne Lynn & Russell S. Phillips, *Relationship Between Cancer Patients' Predictions of Prognosis and Their Treatment Preferences*, 279 JAMA 1709, 1712 (1998), highlighting the danger of patients' misperceptions of prognosis for treatment-related decision-making.

complex treatments while in the throes of illness[160] cloud patients' capacity to make informed and autonomous choices.

A. Access to Investigational Therapies Among the Terminally Ill

The notion that patients assume the risks of unproven treatments figures prominently in discussions around access to investigational therapies not yet approved by the FDA.[161] A fruitful comparison can be drawn between accelerated approval and two alternative routes that enable access to investigational therapies by the terminally ill: expanded access and right to try. Expanded access, or "compassionate use," is a program of the U.S. FDA initiated during the HIV-AIDS crisis that allows a health care provider to place a *request* for drug access with the sponsor of an investigational product and later with the agency, after gaining the company's authorization, a patient's informed consent, and IRB approval.[162] The FDA conducts a review of clinical and nonclinical data on the investigational product and makes a determination regarding whether the appropriate regulatory criteria have been met, after which it may grant or decline the request.[163] Among those criteria are the following: a physician must determine that the "probable risk" of the investigational drug to her patient is "not greater than the probable risk from the disease or condition,"[164] and the agency must determine that "potential patient benefit justifies the potential risks . . . and . . . potential risks are not unreasonable" given the patient's disease or condition.[165]

The Federal Right to Try Act,[166] enacted in May 2018, permits patients with life-threatening diseases or conditions to access investigational drugs with a

160. *See* Le Blanc et al., *supra* note 158, at 2065; Ronald M. Epstein & Richard L. Street, *Shared Mind: Communication, Decision Making, and Autonomy in Serious Illness*, 9 ANNALS FAM. MED. 454, 456 (2011).

161. *See, e.g.*, Complaint at ¶ 16, Abigail Alliance for Better Access to Developmental Drugs v. McClellan, No. 1:03-cv-01601 (D.D.C. July 28, 2003) ("Terminally ill patients are typically willing to assume risks if their physicians advise them that a treatment may save or prolong their lives and if they have no other viable options."); Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 708–09 (D.C. Cir. 2007) (en banc) ("[T]he Alliance concedes that taking experimental drugs can 'involve enormous risks.' Appellants' Br. at 32. In essence, the Alliance insists on a constitutional right to assume any level of risk.").

162. *See Expanded Access*, U.S. FOOD & DRUG ADMIN. (Feb. 28, 2024), https://www.fda.gov/news-events/public-health-focus/expanded-access [perma.cc/8N62-QY8X]; Barbara Scepura, Mitchell Chan, Tamy Kim, Jessica Boehmer, Kirsten B. Goldberg & Richard Pazdur, *Oncology Expanded Access and FDA's Project Facilitate*, 26 THE ONCOLOGIST e1880, e1881 (2021); Tamy Kim, Peter Lurie & Richard Pazdur, *US Food and Drug Administration Efforts to Facilitate the Use of Expanded Access*, 33 J. CLINICAL ONCOLOGY 3979, 3979 (2015) (discussing the history of expanded access, including its inception in 1987, the introduction of expanded access for intermediate-size populations in 2009, and a less onerous physician application form released by the agency in 2015). In the process of reaching a decision on an expanded access request, the agency considers "the totality of data and information that the commercial sponsor has submitted to the FDA for the development program, including data (eg, safety/toxicity data, dosing considerations) that may not be publicly available." Amy E. McKee, André O. Markon, Kirk M. Chan-Tack & Peter Lurie, *How Often Are Drugs Made Available Under the Food and Drug Administration's Expanded Access Process Approved?*, 57 J. CLINICAL PHARMACOLOGY S136, S137 (2017).

163. *See* Scepura et al., *supra* note 162, at e1881.

164. 21 C.F.R. § 312.310(a)(1).

165. *Id.* § 312.305(a)(2).

166. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372-73 (2018).

completed Phase I clinical trial and an active development program or a filed new drug or biologics license application.[167] Unlike expanded access, the patient's physician need not seek the approval of the FDA or the involvement of an IRB, but must certify that no approved treatment options remain and that the patient is unable to participate in a clinical trial for the desired investigational therapy.[168] Unlike expanded access but similar to state right to try laws, the federal statute exempts drug manufacturers and sponsors from liability for acts or omissions in connection with their voluntary decision to permit access to investigational drugs and shields prescribers and dispensers from liability for ordinary negligence.[169]

Expanded access and right to try permit access to therapies that may be backed by exceedingly preliminary evidence—often the results of Phase I testing only[170]—and in that regard, they give rise to a core concern common to the debate over accelerated approval: Access to drugs earlier in the clinical trial testing process, before larger and lengthier trials have generated sufficient data on efficacy and adverse effects, poses a real risk that patients will receive a drug that either does not work or could cause harm.[171]

Proponents of early access to investigational treatments rely heavily on a rhetoric of patient autonomy, emphasizing a willingness among the sickest of the sick to take their chances, however low, with an investigational treatment.[172] In response,

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167. 21 U.S.C. § 360bbb-0a(a)(2).

168. *Id.* § 360bbb-0a(a)(1)(B).

169. Pub. L. No. 115-176, § 2(b), 132 Stat. 1372, 1374. Prescribers and dispensers may, however, be held liable for "reckless or willful misconduct, gross negligence, or an intentional tort." *Id.* § 2(b)(1)(B).

170. The Federal Right to Try Act and some state right to try laws require completion of a Phase I trial. *See* 21 U.S.C. § 360bbb-0a(a)(2)(A) (federal); *see, e.g.*, LA. STAT. ANN. § 40:1169.3(2)(a) (2017) (state).

171. *See, e.g.*, McKee et al., *supra* note 162, at S141 ("Expanded access provides just that: access. There is no guarantee that the product sought will be effective and/or safe, much less that it will be effective and/or safe for the particular patient . . . ."); Steven Joffe & Holly Fernandez Lynch, *Federal Right-to-Try Legislation—Threatening the FDA's Public Health Mission*, 378 NEW ENG. J. MED. 695, 696 (2018) ("There is a low probability of benefit, but a risk of worsened quality of life or accelerated death, from drugs that have progressed only through phase 1 trials—especially for frail patients or those with advanced disease."); Brief for Respondents in Opposition at 3, Abigail All. for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007) (No. 07-444) ("[P]reliminary expectations of safety and efficacy often prove to be unfounded, and drugs that initially appear promising are frequently found ineffective or even affirmatively dangerous to life and health.").

172. *See, e.g.*, Laurie McGinley, *Are Right-to-Try Laws a Last Hope for Dying Patients — Or a False Hope?*, WASH. POST (Mar. 26, 2017, 7:55 PM), https://www.washingtonpost.com/national/health-science/are-right-to-try-laws-a-last-hope-for-dying-patients--or-a-cruel-sham/2017/03/26/1aa49c7c-10a2-11e7-ab07-07d9f521f6b5_story.html [perma.cc/3FQP-AVPT] (quoting statements of Matthew Bellina, a patient with Lou Gehrig's disease after which the Federal Right to Try Act was later named, that "[a]t some point in the near future, I'm going to suffocate under the weight of my chest, so what difference does it make if we have a side effect?"); Editorial Board, *Giving Patients One More Shot*, Opinion, WALL ST. J. (Feb. 4, 2018, 3:28 PM), https://www.wsj.com/articles/giving-patients-one-more-shot-1517776111 [perma.cc/ML2N-ERWA] ("Right to try is not a miracle drug. But at minimum it would move the decision over treatment and risk closer to the patient facing a tough diagnosis or death."); *Exploring a Right to Try for Terminally Ill Patients: Hearing Before the Sen. Comm. on Homeland Sec. & Governmental Affs.*, 114th Cong. (2016) (statement of Matthew Bellina, Lieutenant Commander, U.S. Navy (retired)) ("I do not believe it is the role of interest groups or bioethicists who have never met me to dictate how I should find value in my remaining days. . . . I am willing to make informed choices with my doctor, based on the individual nature of my disease."); CHRISTINA CORIERI, GOLDWATER INST., EVERYONE DESERVES THE RIGHT TO TRY: EMPOWERING THE TERMINALLY

opponents of right to try—often scholars and public health advocates—counter with strongly worded criticisms of what they view as a degradation of the FDA's authority and power.[173] The debate over these programs illuminates the dangers of ignoring the competing values that underlie policy choices and instead conflating scientific policy with science itself. Rather than foster productive dialogue that would both advance patient autonomy and address underlying patient safety and regulatory concerns, the acrimony over early access to investigational drugs enables both sides of the debate to purport to take the moral high ground while eliding the disparate prioritization of values that inspire their positions.[174]

On one view, the critiques of expanded access and right to try are essentially equivalent to those of accelerated approval, only more acute: chances that an investigational therapy will lack efficacy are higher, data on safety are often less robust, and potential interferences with the conduct of clinical trials just as fearsome.[175] On that view, the risks foisted on patients by accelerated approval might be mitigated through a standardized informed consent procedure, in the spirit if not in the form of the informed consent required under those programs.[176]

ILL TO TAKE CONTROL OF THEIR TREATMENT 10 (2014) ("The terminally ill face a much different risk-benefit analysis than the public at large. . . . Many terminal patients who lack other treatment options may be willing, even eager, to try medications whose efficacy has not yet been established.").

173. *See* Joffe & Lynch, *supra* note 171, at 697 (criticizing Federal Right to Try legislation as "part of a broader effort to weaken medical product regulation" that risks undermining the FDA's "public health mission"); N.K. Reddy & V. Subbiah, *Right to Try, Expanded Access Use, Project Facilitate, and Clinical Trial Reform*, 32 ANNALS OF ONCOLOGY 1083, 1084–85 (2021) (characterizing the recently passed Federal Right to Try legislation as creating "a less restrictive second . . . nontrial preapproval pathway," *id.* at 1085, that "deceptively revives a hope for patients with incurable disease processes," *id.* at 1084); Lisa Kearns & Alison Bateman-House, *Who Stands to Benefit? Right to Try Law Provisions and Implications*, 51 THERAPEUTIC INNOVATION & REGUL. SCI. 170, 174 (2017) (charging that state right to try laws "masquerade as patient-friendly legislation while doing very little for patients" and arguing that "[c]ompletion of a phase I trial is too low a bar at which to allow investigational medical products to reach patients outside of clinical trials without the sort of individualized review offered by FDA oversight").

174. As an en banc decision of the U.S. Court of Appeals for the District of Columbia Circuit acknowledged in 2007, matters of "morality, quality of life, and acceptable levels of medical risk are certainly ones that can be aired in the democratic branches . . . ." Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 713 (D.C. Cir. 2007) (en banc).

175. Only one-third of drugs move from Phase II to Phase III testing, *see Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-3-clinical-research [perma.cc/NAR5-7F4J], which means a substantial winnowing of the pool of investigational drugs after Phase I testing. In some cases, the evidence available at the time of expanded access may be comparable to the evidence available at the time of accelerated approval. A study examining ninety-two expanded access programs for drugs that were ultimately granted FDA approval found that more than two-thirds of the programs were initiated within six months of the submission of a new drug application to the FDA. *See* Jeremy Puthumana, Jennifer E. Miller, Jeanie Kim & Joseph S. Ross, *Availability of Investigational Medicines Through the US Food and Drug Administration's Expanded Access and Compassionate Use Programs*, 1 JAMA NETWORK OPEN 1, 5 (2018).

176. Expanded access requires informed consent in compliance with federal regulation for protection of human subjects. *See* 21 C.F.R. § 312.305(c)(4); 21 C.F.R. §§ 50.20–50.27; U.S. FOOD & DRUG ADMIN., INFORMED CONSENT: GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS 3–20 (2023). The Federal Right to Try Act requires "written informed consent," 21 U.S.C. § 360bbb-0a(a)(1)(C), but provides no direction on what that should entail, *see* Rajiv Agarwal & Leonard B. Saltz, *Understanding the Right to Try Act*, 26 CLINICAL CANCER RSCH. 340, 341 (2020) ("What are the standards for this informed consent? . . . Presumably the treating physician, who is charged in this legislation with obtaining written informed consent, would be responsible for the completeness and

However, in addition to the inherent limitations of informed consent,[177] there are several key distinctions between those avenues for access to investigational therapies and accelerated approval that make the comparison considerably less apposite than meets the eye. Accelerated approval, in other words, raises its own distinct problems that cannot be so easily resolved.

First, single-patient expanded access requests and access under right to try are, by their very nature, quite different from broad market access granted to a drug that gains accelerated approval. Only the particular patient for whom an expanded access request is granted or for whom a sponsor makes a drug available under right to try may receive the investigational therapy. Although there are other forms of expanded access intended to treat larger populations, these, too, are limited in comparison to the wide-scale market access enabled by accelerated approval.

Second, the hurdles that both physician and patient must overcome to qualify for an investigational therapy—including paperwork, informed consent, and the request placed with the drug's sponsor—should effectively eliminate the scenario in which a patient is unaware that a drug is, in fact, investigational and that its safety and efficacy are uncertain. It is much more likely that patients receiving a drug approved under accelerated approval will be entirely unaware that the drug lacks the same degree of certainty in its risk-benefit profile as a drug approved under non-expedited review. The concept of a surrogate endpoint also entails a degree of sophistication and nuance that may be harder to convey to the average patient than would the uncertainty attendant to an investigational therapy early in the clinical testing process.

Third, and perhaps most importantly, sponsors must not promote investigational drugs, including those drugs that the sponsor may choose to make available through expanded access or right to try.[178] Promotional materials for drugs approved under accelerated approval must be submitted for FDA review.[179] Nonetheless, disclosure of accelerated approval in direct-to-consumer promotional

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accuracy of that informed consent."). State right to try laws have varying requirements with respect to the nature and specificity of the informed consent required. *Compare* Right to Try Act, MISS. CODE ANN. § 41-131-1(2)(a)(iv) (West 2020) (requiring written informed consent that is "at least as comprehensive as the consent used in clinical trials"), *and* MO. ANN. STAT. § 191.480 (1.)(1)(d) (West 2014) (requiring the same), *with* MONT. CODE ANN. § 50-12-105 (West 2015), *amended by* 2023 Mont. Laws ch. 413 (requiring that written informed consent include "a description of the potentially best and worst outcomes of using the investigational drug, biological product, or device" that must "include the possibility that new, unanticipated, different, or worse symptoms might result"), *and* Right to Try Act, LA. STAT. ANN. § 40:1169.3(1)(d)(i) (2017) (requiring only that a patient, or a parent or legal guardian of a minor or incapacitated patient, must have "given his consent in writing for the use of the investigational drug, biological product, or device").

177. As legal scholar William Sage aptly wrote: "Because of technical complexity, patient vulnerability, and the power of physicians to persuade, it is unclear whether informed consent represents true empowerment or merely the illusion of self-determination." William M. Sage, *Regulating Through Information: Disclosure Laws and American Health Care*, 99 COLUM. L. REV. 1701, 1705 n. 8 (1999).

178. 21 C.F.R. § 312.7(a) ("A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.").

179. 21 C.F.R. § 314.550 requires preapproval submission of promotional materials, including advertisements, intended to be used within 120 days following approval and, after that period, mandates submission of advertisements for drugs approved under accelerated approval thirty days prior to initial publication. *See also* 21 CFR § 601.45 (requiring the same for biologics).

advertisements is neither specifically mandated nor uniform.[180] Hence, a drug with many indications, only some of which were approved under an expedited pathway, may be promoted through direct-to-consumer advertising that omits any mention of accelerated approval but otherwise complies with the FDA's drug advertising regulations.[181] Circumstances are thus ripe for patients to receive accelerated approval therapies oblivious to the risks they have ostensibly assumed.

B. Liability under Current Regimes

This Section considers how drug manufacturers could be subject to liability for harm resulting from therapies approved under accelerated approval. Imposing liability on drug manufacturers for "defective" prescription drugs in practice has proved challenging for plaintiffs, leading one scholar to describe the state of drug products liability as one of "near-total immunity" for drug manufacturers.[182] A few preliminary doctrinal points are in order. First, drug manufacturers may in theory be sued under any of the three traditional theories of products liability—manufacturing defect, design defect, or failure to warn—though in the prescription drug context, plaintiffs most commonly prevail on a failure to warn theory.[183] Viable design defect claims for pharmaceuticals have been few and far between as a result of the venerable "comment *k*" of section 402A of the Second Restatement of Torts, which makes reference to drugs among examples of "unavoidably unsafe products" for which comment *k* dictates, in essence, immunity from strict liability for defective design that applies to other products.[184] The comment, however, does not by its terms clearly encompass all pharmaceutical therapies; instead, it indicates that unavoidably unsafe products are "especially common in the field of drugs."[185] Consequently, jurisdictions vary with respect to whether comment *k*'s immunity from strict liability extends to all drugs or only some, and where the latter approach is taken, the determination is often made on a case-by-case basis.[186]

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180. *See* Sullivan, *supra* note 153, at 1279 (finding, upon review of a random sample of thirty-seven non-internet based promotional pieces for accelerated products submitted to the FDA, that most (20 of 37, or 54%) did not mention accelerated approval).

181. *See, e.g.*, Direct-to-Consumer Prescription Drug Advertisements, 88 Fed. Reg. 80,958 (U.S. Food & Drug Admin, Nov. 21, 2023) (codified at 21 C.F.R. pt. 202). This may occur, for instance, if a drug is promoted without reference to an indication for which it received accelerated approval.

182. *See* Anita Bernstein, *(Almost) No Bad Drugs: Near-Total Products Liability Immunity for Pharmaceuticals Explained*, 77 WASH. & LEE L. REV. 3, 9 (2020); *see id.* at 11–20 (attempting a quantitative assessment of the number of U.S. drug products liability suits for design defect or failure to warn that reached jury determination relative to the total number of potentially "defective" drugs and concluding that the ratio is vanishingly small).

183. *See id.* at 16.

184. Section 402A of the Second Restatement provides for strict liability against sellers of products for harm to users and consumers, provided that the seller is "engaged in the business of selling . . . [the] product" and the product reaches the user or consumer substantially unchanged from its condition at the time of sale. RESTATEMENT (SECOND) OF TORTS § 402A (AM. L. INST. 1965). Excepted from this rule of strict liability are products considered "unavoidably unsafe"—that is, "incapable of being made safe for their intended and ordinary use." *Id.* § 402A cmt. k. Comment *k* goes on to state that "[s]uch a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous." *Id.* (emphasis added).

185. *Id.* § 402A cmt. k.

186. *See, e.g.*, Freeman v. Hoffman-La Roche, Inc., 618 N.W.2d 827, 836–37 (Neb. 2000) (noting that the majority of jurisdictions to apply comment *k* utilize a case-by-case approach for prescription drugs, and that this most commonly takes the form of a risk-utility test that involves determining

Added to the lack of clarity around comment *k*'s reach in the realm of pharmaceutical products is the decidedly different test for design defect in drugs and devices provided by section 6(c) of the Third Restatement of Torts. Drafters of the Third Restatement chose to eschew comment *k*'s muddiness in favor of a test that asks whether foreseeable risks of a drug or device are "sufficiently great" relative to foreseeable benefits such that prescribers "would not prescribe the drug or medical device for any class of patients."[187] Only then should a drug or device be subject to strict liability in design.[188] The "no net benefit in any class of patients" test is a rigorous criterion to meet, and courts have been reluctant to adopt it, instead choosing to adhere to the more familiar risk-utility tests that grew out of judicial applications of comment *k*.[189]

Section 6(c) comes just shy of (and for some, arguably too close to) imposing complete immunity on drug manufacturers for design defects, leading some to argue that its approach lends unwarranted protection to industry.[190] But it is worth considering whether the assumptions on which the Third Restatement's more rigorous test for design defect was predicated still apply today. The drafters of the Third Restatement acknowledge as rationales for the general aversion to design defect for prescription drugs the reliability of prescribers as learned intermediaries who can "see that the right drugs reach the right patients"[191] and the effectiveness of government agencies such as the FDA in detecting and withdrawing defective designs.[192] Lessons from accelerated approval should cast doubt on both of these assumptions: prescribers may often fail in their duty to consider risks attendant to accelerated approval[193] and, by some accounts, the FDA has not policed confirmatory trials critical to identifying defective designs as carefully as it should.[194]

Given the baseline judicial and doctrinal hostility to plaintiffs' drug product liability claims, any attempt to hold drug manufacturers liable for adverse effects of drugs approved under accelerated approval would be an especially difficult task, underscoring the need for a tort alternative. A hypothetical here is illustrative: In 2019, a patient with multiple myeloma begins a treatment regimen with the drug

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whether a reasonable alternative design existed); Grundberg v. Upjohn Co., 813 P.2d 89, 93–95 (Utah 1991) (providing a thorough discussion of the rationales behind jurisdictions' variable approaches to the scope of comment *k* immunity and ultimately rejecting a case-by-case approach as "unworkable," *id.* at 95); White v. Wyeth Lab'ys, 533 N.E.2d 748, 752 (Ohio 1988).

187. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6(c) (AM. L. INST. 1998).

188. *Id.*

189. *See Freeman*, 618 N.W.2d at 840 (declining to adopt section 6(c) in favor of comment *k* and reasoning that section 6(c) is "too strict of a rule, under which recovery would be nearly impossible"); Bryant v. Hoffman-La Roche, Inc., 585 S.E.2d 723, 727 (Ga. Ct. App. 2003) (summarizing common criticisms of section 6(c) and characterizing it as a "dramatic change from the product liability provisions of the Second Restatement"); Bernstein, *supra* note 182, at 25, 27–32 (reviewing section 6(c)'s underwhelming reception in case law and noting lingering reliance on comment *k*).

190. *See, e.g.*, Richard L. Cupp, Jr., *Rethinking Conscious Design Liability for Prescription Drugs: The* Restatement (Third) *Standard Versus a Negligence Approach*, 63 GEO. WASH. L. REV. 76, 99, 103 (1994) ("Under the new Restatement's approach, prescription product designs with even the smallest utility to the smallest class of patients are immune from liability even if such design decisions present no utility and great risks to the vast majority of potential patients.").

191. James A. Henderson, Jr. & Aaron D. Twerski, *Drug Designs Are Different*, 111 YALE L.J. 151, 172 (2001); *see id.* at 171–74; RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6(c) cmt. b.

192. *See* RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6(c) cmt. b.

193. *See supra* notes 139–142 and accompanying text.

194. *See supra* note 105.

panobinostat (Farydak), a therapy first approved by the FDA in 2015 for treatment of multiple myeloma after failure of two prior treatment regimens and in combination with bortezomib and dexamethasone.[195] Panobinostat was approved under the accelerated approval pathway based on improvement in progression-free survival.[196] Unfortunately, even at the time of approval, the drug was known to cause serious side effects, including serious diarrhea in one-quarter of patients, cardiac toxicity, and potentially fatal gastrointestinal and pulmonary hemorrhage.[197] All of these risks are disclosed in the drug's label, including a black box warning regarding the risk of severe diarrhea and severe and potentially fatal cardiac ischemic events.[198] Panobinostat's label also carries the FDA's required warning regarding limitations of usefulness and uncertainty of benefit, in the standard recommended format:

> This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[199]

After two years of treatment, our hypothetical patient does indeed suffer from a near-fatal heart attack and subsequently terminates use of the drug. Later that year, in 2021, panobinostat's manufacturer requests voluntary market withdrawal of the drug, citing that trials to confirm clinical benefit are no longer feasible.[200] How might our hypothetical patient-plaintiff make a case against the drug manufacturer to recover for his injury?

Let's assume for the sake of argument that the manufacturer complied in all material respects with the FDA's labeling requirements, including the language regarding the provisional nature of the drug's approval, the continuation of which was contingent on the results of confirmatory trials. The plaintiff does not concede that the manufacturer warned adequately of the specific harm he suffered, but it is undisputed that panobinostat's label carried a black box warning of potentially fatal cardiac ischemic events at the time the patient took the drug. Our hypothetical plaintiff can avail himself of state products liability law, alleging liability on various

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195. *FDA Approves Panobinostat for Some Patients with Multiple Myeloma*, NAT'L CANCER INST. (Mar. 19, 2015), [hereinafter *FDA Approves Panobinostat*], https://www.cancer.gov/news-events/cancer-currents-blog/2015/fda-approves-panobinostat [perma.cc/2PBP-9TJJ].

196. *Drug Trials Snapshot: FARYDAK (Panobinostat)*, U.S. FOOD & DRUG ADMIN. (July 29, 2020), https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshot-farydak-panobinostat [perma.cc/RRU2-FZ2G] (reporting a progression-free survival of 10.6 months in the panobinostat group as compared to 5.8 months in the control group (bortezomib and dexamethasone only), but noting that "[i]t is not known whether FARYDAK will help patients live longer or feel or function better").

197. *FARYDAK (Panobinostat) Prescribing Information*, U.S. FOOD & DRUG ADMIN. (Feb. 2015), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf [perma.cc/X6CC-LUG9]; *FDA Approves Panobinostat*, *supra* note 195. A physician of the National Cancer Institute is quoted as saying, regarding panobinostat: "Given the modest improvement seen to this point, patients should be aware of the toxicity of this drug." *Id.*

198. *FARYDAK (Panobinostat) Prescribing Information*, *supra* note 197.

199. *Id.*; *see supra* notes 134–136 and accompanying text.

200. *Secura Bio Announces U.S. Withdrawal of FARYDAK (Panobinostat) NDA*, PR NEWSWIRE (Nov. 30, 2021, 4:45 PM) https://www.prnewswire.com/news-releases/secura-bio-announces-us-withdrawal-of-farydak--panobinostat-nda-301434428.html [perma.cc/DXA9-HMV5].

theories. For the sake of argument, let us further assume that Ohio products liability law applies.[201]

First, the plaintiff could sue the drug's manufacturer under a theory of defective design, bringing both negligent design defect and strict liability design defect claims under Ohio law. In response to a strict liability claim for design defect, the manufacturer might argue that the plaintiff was harmed not by a product defect but by an "unavoidably unsafe" aspect of the drug, and according to Ohio law, a drug is not defective due to an aspect that is unavoidably unsafe if a manufacturer provides adequate warning and instruction regarding the unavoidably unsafe aspect.[202] The Ohio Supreme Court has declined to label prescription drugs "'unavoidably unsafe' *per se* under Comment *k*" and has instead adopted a case-by-case approach to determining whether a particular drug is unavoidably unsafe.[203] Important to the analysis is whether "at the time of its distribution, there existed no alternative design which would have as effectively accomplished the same purpose or result with less risk."[204] Barring evidence from the plaintiff that an alternative, safer design existed, the manufacturer is likely to argue that panobinostat was unavoidably unsafe, and therefore, the plaintiff cannot bring a claim for strict liability under defective design.[205]

Second, our hypothetical plaintiff could bring a claim for failure to warn against panobinostat's manufacturer. The plaintiff could make the argument that the manufacturer's warning, although compliant with the FDA's labeling requirements, nonetheless fell short of adequately informing prescribers of the risk that panobinostat's benefits were minimal and tenuous in relation to safety risks. And the inadequacy of that warning, the plaintiff would argue, was the actual and proximate cause of the plaintiff's injury. Our hypothetical plaintiff should emphasize here that every drug approved under accelerated approval bears a similar warning but that the warning, in the case of panobinostat, did not capture adequately the precarity of panobinostat's risk-benefit profile. That is, panobinostat carried such serious risks in such a high percentage of patients that the magnitude of the benefit needed to outweigh the drug's risks was large, and ultimately, the manufacturer did not warn adequately of the danger that those benefits might not,

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201. OHIO REV. CODE ANN. § 2307.71 *et seq.* (West 2007).

202. *Id.* § 2307.75(D).

203. White v. Wyeth Lab'ys, 533 N.E.2d 748, 752 (Ohio 1988).

204. *Id.* at 753.

205. The California Supreme Court articulates well a common policy argument against strict liability for design defect when pharmaceuticals are accompanied by proper warning and instruction:

> Public policy favors the development and marketing of beneficial new drugs, even though some risks, perhaps serious ones, might accompany their introduction, because drugs can save lives and reduce pain and suffering. If drug manufacturers were subject to strict liability, they might be reluctant to undertake research programs to develop some pharmaceuticals that would prove beneficial or to distribute others that are available to be marketed, because of the fear of large adverse monetary judgments. Further, the additional expense of insuring against such liability—assuming insurance would be available—and of research programs to reveal possible dangers not detectable by available scientific methods could place the cost of medication beyond the reach of those who need it most.

Brown v. Superior Court, 751 P.2d 470, 479 (Cal. 1988). *But see* RESTATEMENT (THIRD) OF TORTS, PRODS. LIAB. § 2 cmt. a (AM. L. INST. 1998) (recognizing strict products liability as incentivizing manufacturers to increase investment in product safety). There is, however, some irony in wielding prescription drug affordability as a justification to avoid imposing strict liability on drug manufacturers for design defects, given the high prices of many drugs today.

in fact, materialize. A nearly one-size-fits-all warning of the kind the FDA currently requires for drugs approved under accelerated approval simply does not reflect the variation among drugs in the likelihood that a favorable benefit-risk ratio will be verified. Nor does it prevent a manufacturer from providing a stronger warning as it pertains to the evidence underlying accelerated approval or the precarity of a drug's as-yet unconfirmed efficacy. Had the plaintiff's physician been warned more fully of panobinostat's risk of indeterminate efficacy in relation to its grim safety risks, the argument might go, the prescriber would not have prescribed the drug and the plaintiff would not have taken it.

Compliance with FDA regulations and the FDA's approval of a drug label or package insert do not shield a drug company from charges of failure to warn.[206] As another court has noted: "The warnings required by such agencies may be only minimal in nature and when the manufacturer or supplier knows of, or has reason to know of, greater dangers not included in the warning, its duty to warn may not be fulfilled."[207] Panobinostat's manufacturer would likely argue, in response, that a claim for failure to warn predicated specifically on panobinostat's indeterminate efficacy should be preempted by the FDA's decision to approve the drug in the first instance. After all, the agency made a preliminary determination at the time of granting accelerated approval that predicted benefits outweighed risks, one that courts are in a poor position to second-guess. The plaintiff, in turn, could argue that, under relevant Supreme Court precedent in *Wyeth v. Levine*, 555 U.S. 555 (2009), panobinostat's manufacturer cannot wield FDA approval as a complete defense to a state failure to warn claim.[208]

Third, the plaintiff can allege ordinary negligence when the drug's manufacturer did not fulfill required postmarketing confirmatory trials. Panobinostat's manufacturer agreed to complete a confirmatory study by February 2021,[209] but it was not until November 2021 that the company, which had not even initiated the postmarketing trial it promised six years earlier, requested the drug's withdrawal.[210] The argument could go something like the following: when panobinostat's manufacturer did not complete postapproval study obligations within the promised timeframe, it fell short of the duty it owed consumers of its drug and

206. Wagner v. Roche Lab'ys., 671 N.E.2d 252, 258 (Ohio 1996); Stevens v. Parke, Davis & Co., 507 P.2d 653, 661 (Cal. 1973); RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 4(b) (AM. L. INST. 1998). *But see White*, 533 N.E.2d at 755 (noting that "it was undisputed that the FDA had reviewed and given its approval to the warning in the package insert," before concluding that "[r]easonable minds could only conclude that the warning was adequate").

207. *Stevens*, 507 P.2d at 661. Interestingly, the Supreme Court of California also suggested that a manufacturer's aggressive marketing efforts, "which may have the effect of persuading the prescribing doctor to disregard the warnings given," could "erode[] or even nullif[y]" an otherwise adequate warning. *Id.*; Henderson & Twerski, *supra* note 191, at 171 n.84.

It is well-established that "[t]he manufacturer cannot be held liable if it has provided appropriate warnings and the doctor fails in his duty to transmit these warnings to the patient or if the patient relies on inaccurate information from others regarding side effects of the drug." *Brown*, 751 P.2d at 477–78. Thus, where existing warnings are adequate but a provider neglected to inform the patient of a drug's risks, the provider's negligence cannot be a source of liability for a drug company.

208. *See* Wyeth v. Levine, 555 U.S. 555, 558–59 (2009).

209. Letter from Richard Pazdur, Dir., Ctr. for Drug Evaluation & Rsch., to Jeannie Shen, Senior Assoc. Dir., Drug Regul. Affs., Novartis Pharms., (Feb. 23, 2015) https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205353Orig1s000ltr.pdf [perma.cc/328B-MNPE].

210. Withdrawal of Approval of New Drug Application for FARYDAK (Panobinostat) Capsules, 87 Fed. Reg. 16742, 16743 (U.S. Food & Drug Admin. Mar. 24, 2022).

prolonged the plaintiff's exposure to a drug with an unfavorable risk-benefit profile.[211] Furthermore, the plaintiff could argue, the manufacturer *would have* completed its postapproval study obligations in a timely manner had it anticipated favorable results in those trials. The manufacturer's failure even to initiate the promised postapproval study underscores a lack of confidence in the favorability of its drug's risk-benefit profile and an awareness that the drug was unlikely to convert to a traditional approval. This can be further supported by indirect evidence from the accelerated approval pathway: Drugs that convert do so quickly, whereas withdrawal typically occurs after a lag.[212]

Finally, scholar and products liability expert Anita Bernstein has argued in favor of a novel cause of action for drug *ineffectiveness*,[213] some variant of which may find particularly good application in the accelerated approval context. As Bernstein astutely recognizes, ineffective drugs cause harm in more ways than one: first, by exposing patients to drugs that carry certain dangers without offsetting benefits (i.e., the toxic placebos); second, by subjecting patients to what might otherwise have been avoidable suffering; third, by causing financial harm to patients and payors ("money wasted"); and fourth, by eliciting emotional distress from unmet therapeutic expectations.[214]

Under Ohio products liability law, the manufacturer can raise as a defense assumption of risk[215]: That is, the manufacturer can argue that the plaintiff knew of panobinostat's risks and that panobinostat's benefits had not yet been confirmed, and that he nonetheless voluntarily encountered the risks of the drug by choosing to undergo treatment with it.[216] Professor Kenneth Simons summarizes the various permutations of assumption of risk as it overlaps with comparative negligence.[217] A plaintiff who, acting reasonably, assumed a risk will not recover if the defendant

211. What are the causes of delays in initiation and completion of confirmatory trials? Academic literature has not focused on this question. Case law, however, has revealed that Phase III clinical trials are in some cases delayed by changes to drug dosing regimens, for example, in order to improve a drug's efficacy. *See* S'holder Representative Servs. LLC v. Shire US Holdings, Inc., No. 2017-0863, 2020 WL 6018738, at *20–21 (Del. Ch. Oct. 12, 2020). Something more than simple delays in completion of confirmatory trials would likely be needed to show negligence.

212. *See supra* note 33. For related discussion, see *supra* note 47.

213. Anita Bernstein, *Enhancing Drug Effectiveness and Efficacy Through Personal Injury Litigation*, 15 J.L. & POL'Y 1051, 1066 (2007). Bernstein argues: "Federal law proscribes the sale of ineffective drugs; courts interpreting this law declare that consumers have no right to ineffective drugs. From here, one may infer that when consumers receive drugs that, unknown to them, are ineffective, they have suffered an infringement of their rights." *Id.* Bernstein defines effectiveness "as customers seek it" to "include[] both halves of the effectiveness/efficacy division: customers want drugs to live up to the promises on their drug labels, and they want improved therapeutic outcomes." *Id.* at 1071.

214. *See id.* at 1075–82.

215. OHIO REV. CODE ANN. § 2307.711 (West 2023–24). Both express and implied assumption of risk are affirmative defenses under Ohio law. *See id.* § 2307.711(B). If a defendant proves both that a plaintiff expressly or impliedly assumed the risk and that assumption of risk was "a direct and proximate cause of harm for which the claimant seeks to recover damages," Ohio law provides a complete defense and bars a plaintiff from recovery. *Id.* § 2307.711(B)(2).

216. "[W]here a plaintiff knew of the danger a product posed and nonetheless voluntarily proceeded in his course of action, he may not recover." Monroe v. Novartis Pharms. Corp., 29 F. Supp. 3d 1115, 1123 (S.D. Ohio 2014) (quoting Allen v. Indep. Concrete Pipe Co., No. 3:04-cv-7053, 2005 WL 3274679, at *2 (N.D. Ohio Dec. 2, 2005)).

217. See Kenneth W. Simons, *Reflections on Assumption of Risk*, 50 UCLA L. REV. 481, 487–88 (2002).

either owed no duty or did not breach a duty owed.[218] A plaintiff who, acting reasonably, voluntarily and knowingly encountered a *negligently created* risk does not recover under the doctrine's traditional formulation but may under a modern approach of comparative negligence.[219] Here, our hypothetical plaintiff may argue that the risks he encountered were indeed negligently created by the drug's manufacturer when it kept panobinostat on the market without undertaking required postapproval studies. Furthermore, our hypothetical plaintiff may be wise to challenge the necessary predicates of assumption of risk—that is, whether his choice to encounter panobinostat's risks was knowing and voluntary. Here, our hypothetical plaintiff could argue that the agency's decision to create the accelerated approval pathway but inadequately police it (thereby facilitating the defendant's negligence) foisted on patients a "hard choice" of the kind Professor Robert Keeton has perceptively described.[220] Consequently, the plaintiff's seemingly voluntary decision to encounter the risks of panobinostat, even under the illusory assumption that he fully appreciated the risks he was undertaking, should not serve to bar recovery.

The purpose here is not to predict an outcome of this hypothetical suit but to demonstrate the hurdles a plaintiff would face in bringing and defending his claims. The next Part proposes a tort alternative that would obviate many of the impediments to recovery for patients injured by accelerated approval drugs.

V. AN ADMINISTRATIVE COMPENSATION SCHEME FOR WITHDRAWN ACCELERATED APPROVAL DRUGS

This Article proposes an administrative compensation scheme that would permit individuals who were prescribed later-withdrawn accelerated approval drugs to recover out-of-pocket expenses for the cost of the drug and compensation for injuries caused by the later-withdrawn drug. The proposal takes as its model the National Vaccine Injury Compensation Program,[221] enacted as part of the National Childhood Vaccine Injury Act of 1986[222] and effective since October 1, 1988. This Part begins with a discussion of the structure and features of the Vaccine Injury Compensation Program before proposing a closely analogous set of elements adapted to the accelerated approval context. The proposal here also draws lessons from a variety of other legislative enactments that have provided compensation to discrete groups of individuals harmed by drugs, biologic products, and other naturally occurring or man-made toxic substances.

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218. *See id.* at 487. This is analogous to primary implied assumption of risk, discussed in note 128, *supra*.

219. *See id.* at 488–89. Under modern terminology, a voluntary and knowing encounter of a negligently created risk falls within the doctrinal category of secondary implied assumption of risk.

220. *See* Keeton, *supra* note 128, at 71 ("Why should a negligent defendant be allowed to escape liability because the plaintiff chose to expose himself to the risk negligently created by the defendant, if the plaintiff's choice was reasonable? Should we not instead say that the defendant's negligence unfairly confronted plaintiff with a hard choice in which exposure to defendant's negligently created risk seemed the lesser evil and that, therefore, the defendant should be liable?").

221. 42 U.S.C. § 300aa-10 *et seq.*

222. 42 U.S.C. § 300aa-1 to -34.

A. The National Vaccine Injury Compensation Program

The early- to mid-1980s saw the emergence of crisis conditions in the U.S. vaccine market: Surges in vaccine-related lawsuits posed the risk of large and unpredictable jury awards for vaccine-injured plaintiffs, prompting declines in the already small number of vaccine manufacturers and sharp increases in vaccine prices that threatened further disruption of precarious market conditions.[223] The National Childhood Vaccine Injury Act, enacted in response to this market instability and largely regarded as a success,[224] blends a no-fault compensation system for injured

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223. *See* William Toreki, *National Childhood Vaccine Injury Act of 1986*, 7 TRENDS IN HEALTH CARE L. & ETHICS 1, 41 (1992) (noting a decline in the number of companies manufacturing diphtheria, tetanus, and pertussis vaccines from five in 1984 to two in 1986, with a concomitant 100-fold increase in vaccine cost per dose); *National Childhood Vaccine-Injury Compensation Act, Hearing on S. 2117 Before the Sen. Comm. on Lab. & Hum. Res.*, 98th Cong. 23–24 (1984) (Alan Hinton, Immunization Div., Ctrs. for Disease Control and Prevention) (discussing the dwindling number of vaccine manufacturers, including only three manufacturers of DPT; one manufacturer of a measles, mumps, rubella vaccine; and one manufacturer of the oral polio vaccine, as of May 1984); *see id.* at 25 (commenting that award of a government contract for federal purchase of vaccines to only one of the three then-existing DPT manufacturers "would be a disincentive to the unsuccessful bidders"); *National Childhood Vaccine Injury Compensation Act of 1985: Hearing on S. 827 Before the Sen. Comm. on Lab. & Hum. Res.*, 99th Cong. 240 (1985) (statement of Robert Johnson, President, Lederle Laboratories) (reporting to Congress that the company was "barraged with an assault of lawsuits" that led the company to face more than $2 billion in potential liability, rising insurance premiums, and a decline in insurance carriers willing to provide insurance, and that despite vaccine price increases, "[v]irtually all of the additional revenue generated . . . will be devoted to liability costs and may not be adequate for that purpose if current trends in jury verdicts continue"); Martin H. Smith, *National Childhood Vaccine Injury Compensation Act*, 82 PEDIATRICS 264, 265–67 (1988) (recounting circumstances that led to the enactment of the National Childhood Vaccine Injury Act from the perspective of the medical community, including the occurrence of cases of Guillain-Barré syndrome following mass immunization for swine flu in the late 1970s, the federal push toward a national immunization program as a prerequisite to school entry, and the DPT supply shortages and threat of market exit of Lederle Laboratories, one of two remaining DPT vaccine manufacturers in 1986).

224. *See* James R. Copland, *Administrative Compensation for Pharmaceutical- and Vaccine-Related Injuries*, 8 IND. HEALTH L. REV. 277, 285 (2011) (calling the Vaccine Injury Compensation Program (VICP) "an unqualified success" and commenting that "[t]he existence of the VICP, and the preemption of tort claims, has not seemed to deter continuing safety innovation in the vaccine market, as companies have expanded and modernized production capabilities, developed new and safer vaccine technologies (such as the safer acellular pertussis vaccine, replacing old whole-cell technology), and brought new vaccines to market (including Gardasil, the first vaccine proved to prevent cancer in humans, introduced in 2006)"); *Vaccine Injury Compensation Program*, U.S. DEP'T OF JUST. CIV. DIV. (Jan. 25, 2023), https://www.justice.gov/civil/vicp [perma.cc/XCJ4-WXKG] (reporting that the program has provided compensation of more than $4.5 billion to nearly 9,500 individuals and commenting that "the VICP has succeeded in providing a less adversarial, less expensive, and less time-consuming system of recovery than the traditional tort system"); Katherine M. Cook & Geoffrey Evans, *The National Vaccine Injury Compensation Program*, 127 PEDIATRICS S74, S77 (2011) ("The vaccine marketplace remains healthy; liability-related vaccine shortages are a distant memory, new vaccines are being licensed, and many are in various stages of development . . . . [T]he VICP continues to fulfill the intent of Congress . . . ."). *But see* Mary J. Davis, *The Case Against Preemption: Vaccines & Uncertainty*, 8 IND. HEALTH L. REV. 293, 316 (2011) (deeming the VICP only "moderately successful . . . because there are many who complain that the Program is slow, unfriendly to victims, and more restrictive in operation than was originally intended"); Mary S. Holland, *Liability for Vaccine Injury: The United States, the European Union, and the Developing World*, 67 EMORY L.J. 415, 435–47 (2018) (criticizing the three-year statute of limitations as too "rigid," *id.* at 435, and the Supreme Court's decision in *Bruesewitz v. Wyeth LLC*, 562 U.S. 223 (2011), in which it was decided that the National Childhood Vaccine Injury Act preempted state law design defect claims against vaccine manufacturers, a disincentive to innovation for vaccine safety, *id.* at 444); Nora Freeman Engstrom, *A Dose of Reality for Specialized Courts: Lessons from the*

vaccine recipients with provisions shielding vaccine manufacturers from liability. Central to the compensation program is the Vaccine Injury Table, a listing that currently includes seventeen categories of vaccines covering sixteen diseases or pathogens, along with specified covered injuries for each category, a timeframe in which symptoms must appear to qualify for compensation, and descriptive "qualifications and aids to interpretation" supplying clinical criteria for the various injuries.[225] Petitioners enjoy a legal presumption of causation if they experience a "table injury" for a qualifying vaccine within the corresponding timeframe specified within the Table.[226] Petitioners may also file a petition for compensation arising from injuries not specified within the Table, but for non-table injuries, the petitioner bears the burden of proving causation by a preponderance of the evidence.[227] One of eight special masters of the U.S. Court of Federal Claims adjudicates each petition,[228] and ultimately issues a determination regarding whether and how much compensation to award.[229] Judgments may be appealed within sixty days.[230] Importantly, petitioners retain the ability to sue in court if they are either dissatisfied with the judgment of the special master or if certain time periods have elapsed since filing,[231] but filing of a petition is a necessary precursor to a civil action.[232]

Petitioners are eligible to receive compensation for unreimbursable past and future expenses resulting from the vaccine-related injury, including medical, behavioral, custodial, and rehabilitation-related expenses; actual and anticipated lost

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VICP, 163 U. PA. L. REV. 1631, 1677–78, 1685–88 (2015) (arguing that the VICP has not lived up to the promise of consistent and expeditious awards to injured petitioners).

225. *Vaccine Injury Table*, HEALTH RES. & SERVS. ADMIN. (Jan. 3, 2022), https://www.hrsa.gov/sites/default/files/hrsa/vicp/vaccine-injury-table-01-03-2022.pdf [perma.cc/YS5M-22SK]. Specified injuries either must be shown to have first manifested themselves within the time period provided in the table, or they must be shown to have become significantly aggravated within the period provided. Recordings to the contrary do not preclude a finding by the special master that this criterion is satisfied. *See* 42 U.S.C. § 300aa-13(b)(2). The original Vaccine Injury Table contained four categories of vaccines protecting against seven childhood diseases: diphtheria, tetanus, pertussis, measles, mumps, rubella, and polio. *See id.* § 300aa-14(a). The Secretary of HHS has authority to amend the Table after notice and comment, and has periodically done so.

226. 42 U.S.C. § 300aa-11(c)(1)(C)(i).

227. *Id.* §§ 300aa-11(c)(1)(C)(ii), 300aa-13(a). With respect to eligibility for recovery, "any person who has sustained a vaccine-related injury," without age limitation, may file a petition, as can that person's legal representative if the injured individual is a minor, disabled, or deceased. *Id.* § 300aa-11(b)(1)(A). Children in utero at the time a covered vaccine was administered to the pregnant mother are considered to have received the vaccine and may petition for recovery. *Id.* §§ 300aa-11(f), 300aa-11(b)(2).

228. *Id.* § 300aa-12(d).

229. *Id.* § 300aa-12(d)(3)(A). Determinations regarding whether a petitioner met her burden by a preponderance of the evidence are made "on the record as a whole." *Id.* § 300aa-13(a)(1)(A). Throughout the adjudicative process, including during any hearings that may be conducted before the special master, an attorney of the Office of Vaccine Litigation of the U.S. Department of Justice represents the interests of HHS. *See Vaccine Injury Compensation Program*, *supra* note 224.

230. 42 U.S.C. § 300aa-12(f).

231. *Id.* § 300aa-21(a). A petitioner may choose to withdraw her petition and file a civil action if the special master fails to render a decision within 240 days of filing or if the Court of Federal Claims fails to enter a judgment within 420 days of filing. *Id.* §§ 300aa-12(g), 300aa-21(b). Once a judgment is entered on a petition, petitioners have ninety days to accept the judgment or elect to file a civil action. U.S. CT. FED. CL. SECTION IX. EXITING THE VACCINE PROGRAM AND FILING A SUBSEQUENT CIVIL ACTION 62, https://www.uscfc.uscourts.gov/sites/cfc/files/guidance_on_exiting_the_vaccine_program.pdf. [perma.cc/6K8K-AGKC].

232. 42 U.S.C. § 300aa-11(a)(2)(A).

earnings; and pain and suffering.[233] Similar to other federal programs discussed below, the Vaccine Injury Compensation Program constitutes a secondary benefit that will not compensate expenses covered by public or private payers.[234] Several key limitations on compensation exist: the award for a vaccine-related death is capped at $250,000,[235] as is the award for pain and suffering,[236] and punitive damages are prohibited.[237] Finally, petitioners may receive an award of attorneys' fees irrespective of whether compensation is awarded under the program, provided that the petition was filed in good faith and with a reasonable basis for the petitioner's claims.[238]

Petitions for compensation arising from vaccines administered prior to October 1, 1988, were initially funded from appropriations.[239] For vaccines administered thereafter, awards are disbursed from the Vaccine Injury Compensation Trust Fund,[240] which is financed by a seventy-five cent excise tax per vaccine dose.[241]

The Vaccine Injury Compensation Program was ultimately a legislative compromise, a cornerstone of which was a number of limitations on liability for vaccine manufacturers. Several of the Act's provisions set out these limitations. First, vaccine manufacturers cannot be held liable for injuries or deaths that "result[] from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings,"[242] which the Supreme Court has interpreted to expressly preempt design defect claims against vaccine manufacturers.[243] Second, vaccine warnings are presumed adequate if the manufacturer has complied with relevant federal law and regulation, including the

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233. *Id.* § 300aa-15(a).

234. *See id.* § 300aa-15(h); Robert L. Rabin, *The Vaccine No-Fault Act: An Overview*, 8 IND. HEALTH L. REV. 269, 271 (2011) ("[U]nlike the majority approach in torts, collateral sources are netted out."). Relatedly, public and private payers may not make the provision of health benefits secondary to receipt of compensation under the Vaccine Injury Compensation Program. *See id.*

235. 42 U.S.C. § 300aa-15(a)(2).

236. *Id.* § 300aa-15(a)(4).

237. *Id.* § 300aa-15(d).

238. *Id.* § 300aa-15(e).

239. *Id.* §§ 300aa-15(i)(1), 300aa-15(j).

240. 26 U.S.C. § 9510.

241. *Id.* § 4131. The federal black lung benefits program provides another precedent for an excise tax on producers to fund a trust for the benefits of those harmed by a product. *See* 26 U.S.C. § 4121 (imposing a tax on producers of coal, measured per ton of coal sold, to finance the Black Lung Disability Trust Fund). After a series of reversions to the initial tax rates, which were insufficient to fund the program, higher coal tax rates were made permanent in 2022. *See Change in Rate for Coal Excise Tax*, IRS (Sept. 11, 2024), https://www.irs.gov/businesses/small-businesses-self-employed/change-in-rate-for-coal-excise-tax [perma.cc/C9Y6-M5RV].

242. 42 U.S.C. § 300aa-22(b)(1).

243. Bruesewitz v. Wyeth, 562 U.S. 223, 231–32 (2011). The Court, based on a textual analysis, concluded that state law design-defect claims are preempted under the Act. *See id.* It also made an argument in favor of preemption in which it conceived of the Act as creating a "structural *quid pro quo*," *id.* at 239:

> [V]accine manufacturers fund from their sales an informal, efficient compensation program for vaccine injuries; in exchange they avoid costly tort litigation and the occasional disproportionate jury verdict. But design-defect allegations are the most speculative and difficult type of products-liability claim to litigate. Taxing vaccine manufacturers' product to fund the compensation program, while leaving their liability for design defect virtually unaltered, would hardly coax manufacturers back into the market.

Id. at 239–40.

requirements of the FDCA.[244] A manufacturer cannot be subject to punitive damages in a civil action unless the manufacturer committed fraud; intentionally and wrongfully withheld information, including information regarding vaccine safety or efficacy; or committed criminal or illegal activity in connection with vaccine safety or efficacy.[245] Third, and finally, manufacturers cannot be held liable solely for failing to warn directly the vaccine recipient or her legal representative of the vaccine's potential harms, a provision that effectively codifies the common law learned intermediary standard.[246]

In addition to the compensation program, the National Childhood Vaccine Injury Act put in place reporting requirements relating to the administration of covered vaccines and adverse events;[247] required the Secretary to develop vaccine information materials describing the benefits and risks of vaccination and the existence of the compensation program;[248] and mandated that health care providers supply vaccine recipients or their legal representatives with the informational materials prior to vaccination.[249]

B. A Proposal for an Accelerated Approval Compensation Program

This Section sketches the details of a no-fault compensation program for eligible recipients of drugs and biologics approved under the accelerated approval pathway and later withdrawn. In short, the program would provide a straightforward and relatively swift alternative to tort law that would enable patients to recover out-of-pocket drug expenses and compensation for injuries sustained from later-withdrawn accelerated products.[250] As with the Vaccine Injury Compensation Program, table injuries (derived from a drug's label at the time of accelerated approval and updated in accordance with label changes) would permit a presumption of causation, but petitioners may offer proof of causation for any non-table injuries they believe resulted from use of a later-withdrawn accelerated product. Awards of compensation may include lost earnings, awards for pain and suffering, and death benefits. The program would confer certain liability protections

244. 42 U.S.C. § 300aa-22(b)(2).
245. *Id.* § 300aa-23(d)(2).
246. *Id.* § 300aa-22(c); Holland, *supra* note 224, at 431.
247. 42 U.S.C. § 300aa-25(a)-(b).
248. *Id.* § 300aa-26(a)-(c).
249. *Id.* § 300aa-26(d).
250. The advantages of a no-fault system to compensate injured patients as compared with the more traditional tort scheme have been discussed at length elsewhere, but among the principal benefits are the potential for faster claims adjudication, the avoidance of costly litigation and, in particular, the costs associated with proving negligence, and a more assured route to compensation that avoids the vagaries of a lay jury. For in-depth discussions of a proposed no-fault model as applied to medical injury, see Paul C. Weiler, *The Case for No-Fault Medical Liability*, 52 MD. L. REV. 908, 919–41(1993); and David M. Studdert & Troyen A. Brennan, *Toward a Workable Model of "No-Fault" Compensation for Medical Injury in the United States*, 27 AM. J.L. & MED. 225, 229–35 (2001). For two, more limited no-fault models for medical injury in the United States, the Virginia Birth-Related Neurological Injury Compensation Program and the Florida Birth-Related Neurological Injury Compensation Plan, see VA. CODE ANN. § 38.2-5002 (West 2003), and FLA. STAT. ANN. § 766.303 (West 2021), respectively. For a proposal to extend no-fault to pharmaceutical and medical-device related injury, see JAMES R. COPLAND & PAUL HOWARD, IN THE WAKE OF *WYETH V. LEVINE*: MAKING THE CASE FOR FDA PREEMPTION AND ADMINISTRATIVE COMPENSATION 11–15 (2009) (suggesting a compensation system for "unforeseen, rather than known, side effects" of pharmaceuticals and devices, *id.* at 15), and Copland, *supra* note 224, at 287–90.

on makers of accelerated products who comply with federal labeling requirements, the FDCA, and other relevant federal law and regulation.

1. Recovery of Out-of-Pocket Drug Expenses

Under this proposal, unlike the Vaccine Injury Compensation Program, all those who were prescribed a therapy for a use approved under the accelerated approval pathway and later withdrawn would become eligible to submit a claim to HHS for recovery of out-of-pocket drug expenses. Thus, a patient need not have suffered an injury to recover out-of-pocket drug expenses. Given the proposed program's connection to pharmaceutical drugs, HHS is a natural administrator of this program. The Health Resources and Services Administration (HRSA), which administers the Vaccine Injury Compensation Program and the Countermeasures Injury Compensation Program,[251] would be a reasonable choice for an administering agency within HHS, as would the FDA. The eligible period in which out-of-pocket expenses must have been incurred would begin from the date on which the drug was approved under accelerated approval until the date the relevant indication is withdrawn. Under the proposal presented here, a patient may not recover if she chooses to take a therapy off-label for a particular indication after the therapy's withdrawal for that indication, on the grounds that the weight of the evidence no longer supports the therapy's use for that purpose. For example, those who were prescribed and received Avastin therapy for metastatic breast cancer after its withdrawal for that indication by the FDA in 2011 would not be eligible for compensation under the program.

2. Compensable Injuries

Akin to the Vaccine Injury Compensation Program, the proposed program would provide a means to petition for compensation for injuries caused by a later-withdrawn accelerated product. The Secretary would maintain a list of covered

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251. Authorized by the Public Readiness and Emergency Preparedness Act of 2005, Pub. L. No. 109-148, Division C, § 2, the Countermeasures Injury Compensation Program compensates individuals for serious physical injury or death arising out of use of certain covered countermeasures, including measures against viruses with pandemic potential, such as Zika, Marburg, Ebola, and smallpox, and other health threats. *See Covered Countermeasures*, HEALTH RES. & SERVS. ADMIN. (Sept. 2023), https://www.hrsa.gov/cicp/covered-countermeasures [perma.cc/6SEJ-C3NH]. The Act gives immunity to "covered person[s]" for losses "caused by, arising out of, relating to, or resulting from" administration or use of covered countermeasures, including losses causally connected to testing, manufacture, distribution, and administration of the countermeasure. 42 U.S.C. § 247d-6d(a)(1), (a)(2)(B).

HRSA is also the administrator of the Black Lung Clinics Program, which provides care and counseling to current and former coal miners who often suffer from serious and life-threatening respiratory ailments as a result of occupational exposure to coal dust during mining. *See* HEALTH RES. & SERVS. ADMIN., BLACK LUNG CLINICS PROGRAM: 2017-2020 COHORT SNAPSHOT 2–4, https://www.hrsa.gov/sites/default/files/hrsa/rural-health/blcp-2017-2020-cohort-snapshot.pdf [perma.cc/DB7D-YVX7]. The federal black lung benefits program, administered by the Department of Labor, has had a decidedly less favorable track record of awarding benefits to claimants than the Vaccine Injury Compensation Program. For a discussion of the history and evolution of the black lung benefits program, including challenges involved in its implementation and subsequent appeals, see Pete S. Michaels, *The Constitutional Conundrum of Black Lung Appeals: Two Proposed Solutions*, 23 U. MICH. J.L. REFORM 27, 29–34 (1989); Allen R. Prunty & Mark E. Solomons, *Federal Black Lung Update*, 92 W. VA. L. REV. 849, 850–61, 878–80 (1990); Brian C. Murchison, *Due Process, Black Lung, and the Shaping of Administrative Justice*, 54 ADMIN. L. REV. 1025, 1027–32, 1045–94 (2002).

therapies, which would include all therapies for which an indication approved under accelerated approval was withdrawn since the inception of the accelerated approval pathway. As additional indications are withdrawn, whether at the request of the drug manufacturer or at the agency's behest, these therapies would be added to the list of covered therapies. Grounds for an indication's withdrawal would not affect eligibility for compensation; that is, as long as an indication originally approved under the pathway is withdrawn, recipients of the therapy *for that indication* would become part of the class of individuals eligible for recovery.

If a patient received a covered therapy for an indication not approved under accelerated approval, however, she would not be eligible for compensation, even if another one of the therapy's indications would qualify a recipient for recovery. For example, recipients of durvalumab for the treatment of urothelial cancer, an indication approved under accelerated approval and later withdrawn, would be eligible to petition for recovery; however, those who were prescribed durvalumab for the treatment of stage III non-small cell lung cancer and extensive-stage small-cell lung cancer, neither of which was approved under the accelerated approval pathway,[252] could not petition for recovery under the program.

What a petitioner must show to receive compensation under the program would vary depending on whether the petitioner suffers a table or non-table injury. First, a petitioner could demonstrate that she suffered a table injury, which would trigger a presumption of causation and would enable a claimant to become eligible for remedies such as past and future unreimbursable medical expenses, lost wages, pain and suffering, and death benefits.[253] Pain and suffering may include

252. *See Imfinzi (durvalumab) Prescribing Information*, *supra* note 115.

253. The routes to compensation—a presumption of causation for a table injury versus an option to prove causation for a non-table injury—would be analogous to the Vaccine Injury Compensation Program. *See* Cook & Evans, *supra* note 224, at S75; Ellen Clayton Wright & Gerald B. Hickson, *Compensation Under the National Childhood Vaccine Injury Act*, 116 J. PEDIATRICS 508, 510 (1990). The federal government has established various other compensation programs that obviate the need to prove causation in order to recover. Notably, the Radiation Exposure Compensation Act, Pub. L. No. 101-426, 104 Stat. 920 (1990) (codified at 42 U.S.C. § 2210 note), permitted recovery for certain cancers and other diseases among individuals exposed to ionizing radiation during testing of nuclear weapons or during uranium mining, milling, or transportation of uranium ore. Claimants must show at least one year of uranium-related employment (or a certain level of radiation exposure), participation in nuclear testing, or physical presence in an affected area during certain time periods, along with documentation of a compensable condition. *Id.* §§ 2210 note 4(a)(2), 5(a). Qualifying individuals are eligible for a one-time lump sum payment. *Id.* §§ 2210 note 4(a)(2)(C), 5(a)(1); 28 C.F.R. § 79.75. Since the establishment of the program, more than 42,000 claims have been awarded. *Awards to Date 06/10/2025*, U.S. DEP'T OF JUST. CIVIL DIV. (June 10, 2025), https://www.justice.gov/civil/awards-date-06102025 [perma.cc/P2CX-GJ9R].

Another notable example of a presumption of causation among members of a certain class who experienced a specific health injury is the presumption granted to HIV-infected recipients of blood clotting factor, and their spouses or children if HIV-infected, that the viral infection was causally associated with administration of clotting factor. Enactment of the Ricky Ray Hemophilia Relief Fund Act of 1998, Pub. L. No. 105-369, 112 Stat. 3368 (codified at 42 U.S.C. 300cc-22 note), established a trust fund to finance one-time compassionate payments to HIV-infected individuals, primarily hemophiliacs as well as infected spouses and children, who received transfusions of a clotting factor at a time when HIV transmission via the blood supply had not yet been identified. The terminal disease suffered as a result of medical treatment intended to heal rather than harm made compassionate payments to hemophiliacs and their loved ones especially exigent and compelling. Personal injury and financial toxicity suffered by cancer patients and others with serious or life-threatening conditions as a result of inefficacious and later-withdrawn accelerated therapies furnish a similarly compelling case for compensation.

compensation for intangible harm, such as emotional distress and dignitary harm resulting from consumption of an ineffective treatment for a serious or life-threatening condition.[254] Table injuries would be derived from a drug's label at the time of accelerated approval, with periodic adjustments to the list of table injuries as changes are made to drug labels. Second, a petitioner suffering a non-table injury could submit a claim, with the burden of proving by a preponderance of the evidence that the accelerated product caused her injury. Thresholds for more serious injury, such as a requirement that the injury result in hospitalization, surgery, or medical expenses exceeding a prescribed amount,[255] could limit the number of claims and preserve trust funds for the most severely injured.[256]

Recipients of covered therapies would have a three-year statute of limitations from the date of withdrawal of an indication in which to submit a claim for recovery. At the time an indication is withdrawn, the manufacturer must notify public and private payers, who in turn would be responsible for contacting beneficiaries prescribed the therapy.

3. Liability Protections

Manufacturers of accelerated products would enjoy immunity from tort liability for harm resulting from known risks of an accelerated therapy for which the drug label offers a warning. This immunity would not result in an unfair gain to manufacturers because, even in its absence, lawsuits for harms caused by accelerated products are rare due to the cross-section of conditions that accelerated products tend to treat—serious, life-threatening conditions with a heavy cancer predominance. The relevant patient populations that tend to take therapies approved under the pathway are unattractive clients for personal injury or product liability attorneys working on a contingent fee basis; the advanced age and comorbid conditions of the typical cancer patient,[257] for example, complicate the task of establishing causation and lower the likelihood that plaintiffs will prevail. Although often quite ill at baseline, patients taking accelerated therapies nonetheless may suffer discrete injuries traceable to the therapy itself, many of which have established risk profiles at the time accelerated approval is granted.[258] The compensation program proposed here would allow recipients of withdrawn therapies to enjoy a

254. For an insightful exploration of intangible harm in the clinical research context and how the law may better recognize those intangible forms of harm, see Saver, *supra* note 143.

255. The Vaccine Injury Compensation Program has a similar, though not identical, requirement. *See* 42 U.S.C. § 300aa-11(c)(1)(D); *Who Can File a Petition*, HEALTH RES. & SERVS. ADMIN. (Feb. 2025), https://www.hrsa.gov/vaccine-compensation/eligible [perma.cc/V583-WLAN] (noted under the heading "Severity Requirements").

256. For a discussion of injury thresholds involved in other no-fault systems, see Studdert & Brennan, *supra* note 250, at 232.

257. *See Age and Cancer Risk*, NAT'L CANCER INST. (Mar. 5, 2021), https://www.cancer.gov/about-cancer/causes-prevention/risk/age [perma.cc/YCW3-4TGC] (citing "advancing age" as the "most important risk factor for cancer overall" but also noting that the average age at diagnosis varies by cancer type and certain cancers tend to occur more commonly in younger populations); Helen Fowler, Aurelien Belot, Libby Ellis, Camille Maringe, Miguel Angel Luque-Fernandez, Edmund Njeru Njagi, Neal Navani, Diana Sarfati & Bernard Rachet, *Comorbidity Prevalence Among Cancer Patients: A Population-Based Cohort Study of Four Cancers*, 20 BMC CANCER 1, 3 (2020).

258. *See supra* note 67 and 84.

more assured and rapid path to recovery after injury, bypassing the need for protracted litigation.[259]

The program would possess other limitations and features resembling those of the Vaccine Injury Compensation Program, including a monetary cap on death benefits and pain and suffering;[260] unavailability of punitive damages as a remedy under the program and in a subsequent civil action, except in the event of fraud, intentional misconduct, criminal or illegal activity, and perhaps gross negligence; and the potential to receive an award of attorneys' fees irrespective of an award of compensation. As with many other federal compensation programs, benefits would be secondary to those of any other public or private third-party payor.[261]

There would, however, be a few notable differences. The proposal here advocates making the compensation program the exclusive remedy for table injuries, which mirror on-label risks; manufacturers would also receive the benefit of a presumption of adequacy of warning for on-label risks. However, petitioners would be free to reject an award of compensation and pursue tort remedies for injuries resulting from risks of which they were not warned. Effectively, the program would preempt design defect claims *and* failure to warn claims against drug manufacturers for on-label risks but would leave unaltered the ability to pursue traditional tort remedies for injuries resulting from risks for which no warning was provided.

Also central to the program would be a mandate for drug manufacturers to develop a set of informational materials warning patients—in a manner easy to understand—of the specific risks of the drug, the nature of accelerated approval, the basis on which accelerated approval was granted, and the existence of the

259. Those individuals who suffer a non-table injury would still bear the burden of proving causation and so would face the challenge of showing by a preponderance of the evidence that the drug, and not an underlying condition, caused the harm suffered. Because children who receive vaccines are most often healthy at the time of administration, it may be easier to identify injuries resulting from vaccines than injuries resulting from accelerated therapies. For a related discussion (in the context of no-fault for medical injury) of the difficulty of "disentangling the financial consequences of iatrogenic injury from the underlying illness," see PAUL WEILER, MEDICAL MALPRACTICE ON TRIAL 140 (1991). Professor Weiler observes a "significant difference" between worker's compensation and no-fault for medical injury, namely that "[u]nlike the employee who goes to work or the driver who gets into a car, the patient who enters a hospital is already suffering from an underlying illness, which may itself be capable of producing the disabling losses in question." *Id.* Admittedly, the nexus between injury and administration of an accelerated therapy may be difficult to establish concretely in some cases, making the proposal suggested here more challenging to implement. *See* COPLAND & HOWARD, *supra* note 250, at 14 (acknowledging the same for a no-fault proposal to compensate unforeseen adverse effects of drugs and devices, and remarking that "[i]solating a drug's impact from other confounding factors is difficult").

260. A standard $250,000 death benefit is common among federal compensation programs. For example, the Public Safety Officers' Benefits Program provides for a $250,000 death benefit for certain state and federal law enforcement officers, firefighters, and others killed in the line of duty. 34 U.S.C. § 10281(a). This benefit is subject to annual adjustments based on the Consumer Price Index for All Urban Consumers (CPI-U). *Id.* § 10281(h). The distribution scheme of the Public Safety Officers' Benefits Program with respect to recipients of death benefits could provide a model for the program proposed here (i.e., benefits to the surviving spouse and/or child, to the child or children in equal shares if there is no surviving spouse, to the individual designated to receive benefits if there is no surviving spouse or children, or to the recipient of the most recently executed life insurance program, etc.), *id.* § 10281(a), or a death benefit could be paid to the estate of the deceased, as in the Vaccine Injury Compensation Program, *see* 42 U.S.C. § 300aa-15(a)(2).

261. *See, e.g.*, 42 U.S.C. § 239c(b); *id.* § 239d(c)(1).

compensation program. Such information would go beyond what is currently present on drug labels regarding accelerated approval and would be geared toward patients, not providers. Healthcare providers would be obligated to present patients with the informational materials at the time of prescription; failure to do so would constitute negligence. The aim of this requirement is to ameliorate the informational deficits surrounding accelerated approval and help achieve informed treatment decision-making. Although this Article has argued that patients with serious and life-threatening conditions tend to misperceive risks associated with treatment and that the scientific and regulatory intricacies of accelerated approval limit the usefulness of additional disclosure, the program would be remiss not to mandate a more concerted effort to achieve informed treatment decisions.[262]

4. Establishment of an Accelerated Approval Trust Fund

Awards of compensation would be paid from a trust fund analogous to that used to fund the Vaccine Injury Compensation Program and financed by a combination of prescription drug user fees and a tax calculated based on the product revenue of the withdrawn therapy. An excise tax on all drugs approved under accelerated approval is another means (in the view of the author, a less favorable means) to finance the fund. A revenue-based tax, levied only on withdrawn products, would account for a drug's price and sales volume while avoiding a broad-based tax on all accelerated products that could disincentive use of the accelerated approval pathway.

5. Incentives under the Program

Although the primary intent of the program is to provide redress for harms resulting from accelerated approval, a secondary goal is to achieve a more efficient level of risk in the utilization of the accelerated approval pathway. Because the tax, like the list of covered therapies, will be determined post hoc (that is, after a drug initially approved under accelerated approval gets withdrawn), drug manufacturers have an incentive to seek accelerated approval only when they have confidence that confirmatory trials will indeed verify the benefits predicted by changes to a surrogate or intermediate clinical endpoint. When clinical trials verify benefit and a drug receives a traditional approval, the compensation program does not become operative, and no tax is levied. However, when a manufacturer chooses not to complete confirmatory trials and instead voluntarily withdraws an accelerated product, or when withdrawal occurs after confirmatory trials fail to verify predicted benefits, a manufacturer becomes subject to the tax, and patients who have received the therapy for a withdrawn indication become eligible to petition for recovery. In this manner, the compensation program imposes a form of enterprise liability on drug manufacturers who choose not to undertake confirmatory trials or whose drugs do not live up to their promise under accelerated approval, thereby

262. Adjuncts to required disclosures such as comprehension performance standards could improve the effectiveness of disclosure. For a discussion of comprehension performance standards and how those standards can be crafted, see Lauren E. Willis, *Performance-Based Consumer Law*, 82 U. CHI. L. REV. 1309, 1311–13, 1335–41, 1355–57 (2015) (identifying as an intended effect of comprehension performance standards "to bring products into alignment with consumer expectations" but noting the "ultimate benefit . . . is increased consumer decisional autonomy," *id.* at 1341).

incentivizing companies to learn from past mistakes and take greater care in the use of the pathway and the fulfillment of postapproval obligations.[263] The linking of the tax to withdrawal of an accelerated product places a thumb on the scale in favor of more careful use of the accelerated approval pathway by drug manufacturers.

A potential criticism of this proposal is that it may cause drug manufacturers to raise prices, passing along to consumers the costs of contribution to the Trust Fund. Of course, a drug no longer on the market cannot be subject to a price increase; however, many therapies remain on the market for other FDA-approved uses after an indication approved under accelerated approval gets withdrawn, and in theory, drug manufacturers could increase prices of those therapies (or other therapies in their portfolio) to offset contributions to the Trust Fund. Price increases are unlikely for two reasons: First, drug manufacturers will achieve savings under the program in the form of liability protection related to on-label risks, for which the compensation program would become the sole and exclusive remedy. Second, the program may encourage broader use of accelerated therapies in the first instance, offsetting a manufacturer's later contributions if a drug gets withdrawn.

In light of the trade-offs involved in early access to new drugs, one scholar has argued in favor of "measures to slow the uptake of . . . new drugs and new indications for which uncertainties are the greatest,"[264] such as narrowly drawn on-label indications and restrictions to off-label prescribing and direct-to-consumer advertising.[265] But these sorts of curtailments to drug access in the early years after a product's approval risk depriving patients of the advantages that expedited programs were designed to confer. Rather than place additional limits on who can access a drug approved under accelerated approval, an ex post compensation scheme of the kind proposed here would encourage broader use of all accelerated products by relieving patients of the risk of uncompensated injuries. In so doing, it may, in fact, increase the uptake and utilization of drugs approved under the pathway, thereby offsetting costs of the compensation program and enabling more patients to benefit from expedited access.[266]

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263. *Cf.* Weiler, *supra* note 250, at 941. Some may argue that it is worth differentiating withdrawals due to a manufacturer's failure to *complete* a confirmatory trial (whether due to business reasons, insufficient accrual of patients to the trial, or other considerations) and withdrawals after *completed* confirmatory trials fail to confirm predicted benefits. Noncompliance with confirmatory trial requirements may, in some instances, be faultier than completed but negative trials (indeed, the latter may entail no negligence on the part of the manufacturer but merely an inaccurate prediction of benefit by the FDA) and so may warrant greater liability in order to exert a deterrent effect on manufacturers tempted to shirk postapproval trial duties. To disincentive such behavior, a higher tax rate could be applied when a manufacturer does not see confirmatory trials through to completion and lacks a valid reason for doing so.

264. R. Alta Charo, *Speed Versus Safety in Drug Development*, *in* FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 251, 263 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).

265. *See id.* at 256.

266. The Smallpox Emergency Personnel Protection Act of 2003, Pub. L. No. 108-20, 117 Stat. 638 (codified as amended at 42 U.S.C. § 239 *et seq.*), applied a similar rationale: compensation for injury was intended to increase the number of immunized civilian health workers under the Bush Administration's smallpox vaccination program. *See* SUSAN THAUL, CONG. RSCH. SERV., RL31960, SMALLPOX VACCINE INJURY COMPENSATION 1–2 (2003).

Some might ask why increased utilization would occur when this Article has highlighted that consumers of drugs approved under the pathway are currently unaware of accelerated approval and its clinical and risk implications. Notwithstanding patients' current lack of awareness, patients and

Finally, because on-label risks would give rise to compensable table injuries, one might be concerned that manufacturers would be less forthcoming about what risks are included in drug labels. Under the proposed program, manufacturers would enjoy immunity from large and uncertain jury verdicts for failure to warn of on-label risks; therefore, they would have an incentive to disclose risks known at the time of accelerated approval and make rapid updates to drug labels as new knowledge arises about a product's risks.

6. Other Considerations

A potential response to the proposal for an administrative compensation scheme is the following: Why not simply improve the process of informed consent around accelerated approval, such that manufacturers and the FDA can rest with greater assurance on the proposition that patients have assumed the risk of accelerated products? In other settings involving serious drug safety risks, such as FDA-mandated Risk Evaluation and Mitigation Strategies (REMS), the FDA commonly requires patient and prescriber agreements prior to a therapy's administration.[267] Something similar could be instituted for drugs approved via an expedited pathway. In the clinical trial context, where earlier stage therapies are genuinely experimental, there is a heavy reliance on informed consent—albeit imperfect—to protect clinical trial participants.

Singular reliance on informed consent, however, leaves the problem of unremedied harm and the issue of distributive justice in the accelerated approval context untouched. It must be remembered that accelerated therapies are *on the mass market*, not administered under controlled conditions to a limited few with their specific consent and regular follow-up (as are drugs in an investigational setting). And for the reasons discussed previously, too many fissures exist along the path to informed consent down which the process may tumble: even curable deficits in provider knowledge around accelerated approval cannot overcome patients' unlikely comprehension of the intricacies of the pathway and its relevance for their therapeutic decision. This proposal deliberately mandates creation and dissemination of informational materials—in this case, materials about accelerated approval, the existence of the compensation program, and a therapy's risks. Therefore, the proposal presented here does not dispense with informed consent but rather acknowledges the limitations of informed consent and its inability to make whole injured patients. On this point, however, a useful addition to patient-facing informational materials could be a risk assessment or risk score for each accelerated therapy—that is, a measure of a therapy's likelihood of verification of clinical benefit. The FDA is in a good position to develop and report such a score, which could become an important tool for physicians in the informed consent process.

Alternatively, some might argue, why stop an administrative compensation scheme at the point of withdrawn accelerated approval drugs? Why not extend no-

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providers may more readily opt for therapies approved under the pathway once informed of the possibility of compensation for on-label risks and out-of-pocket drug spending should a therapy be withdrawn.

267. *See, e.g.*, *Patient Agreement Form, Mifepristone Tablets, 200 mg*, U.S. FOOD & DRUG ADMIN. (Jan. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_Patient_Agreement_Form.pdf [perma.cc/L282-PZWY].

fault compensation to harms from all drugs or all drugs that prove inefficacious to the consumer? Many other nations have adopted no-fault compensation for pharmaceutical products, including Japan, Germany, Norway, and Sweden, among others.[268] Such a broad and sweeping change to the system of drug products liability in the United States could go a long way toward a more equitable framework for redressing harms of drug and biological products, and by reducing litigation risk, could also produce greater certainty and predictability for drug companies. However, because no drug is entirely safe, the feasibility and administrability of such a system must be questioned. Accelerated approval spawns an important subset of drug and biological products for treatment of cancer and other serious and life-threatening conditions. The unique uncertainties associated with these products, in addition to known toxicities, high prices, and a low likelihood that consumers can successfully avail themselves of the tort system, make the implementation of a no-fault scheme a logical outgrowth of the Vaccine Injury Compensation Program and a moral imperative.

CONCLUSION

The accelerated approval pathway embodies a fundamental compromise intended to benefit patients with serious and life-threatening illnesses: drugs come to market more quickly based on predictions of clinical benefit, and manufacturers must verify and confirm clinical benefit postmarketing. The pathway anticipates an ongoing interchange between drug manufacturers and the agency, and the pathway's effectiveness depends on prompt action when trials fail to verify clinical benefit. Withdrawal of some fraction of accelerated products is an anticipated byproduct of the pathway. Forgotten in the compromise, however, are the very patients that accelerated approval was designed to benefit. Although it is true that many individuals enjoy longer lives and diminished symptoms of disease from earlier drug access, some individuals incur costs and suffer harm without countervailing benefits. This Article makes the case that an administrative compensation program providing recompense for harms of later-withdrawn accelerated products is the missing piece in the puzzle of expedited access.

268. *See, e.g.*, Cecilia Bakker & Nicholaas Honig, *Addressing Pharmaceutical Injuries: The US Landscape*, 103 CLINICAL PHARMACOLOGY & THERAPEUTICS 384, 384 (2018).