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## Early Access to Unapproved Medicines in the United States and France

Erika Lietzan & Isabelle Moine-Dupuis\*

### Abstract:

In 2018, President Trump signed a federal “right to try” law, claiming that it would give desperately ill patients earlier access to unapproved medicines, by allowing the patient, doctor, and drug company to arrange for access without federal oversight. Critics of the law argued that it would not meaningfully increase access to experimental medicines, because federal oversight was not the obstacle in the first place. And they were correct. U.S. law already permitted companies to provide terminally ill patients with early access to unapproved medicines. The problem was instead that companies did not take advantage of this option. This Article offers new insights into U.S. law on early access, as well as the new right-to-try law, by offering a comparative perspective using French law. We explore the historical, legal, and cultural differences between France and the United States that may explain differences in their early access systems and why the right-to-try law emerged in one country but not the other. The differing approaches reflect in part differing reactions to arguments grounded in personal autonomy and patients’ rights, when held up against utilitarian arguments for premarket approval and traditions of medical paternalism. Using the French experience, this Article also considers the possibility that the key to increasing use of expanded access in the United States might be financial: making it worthwhile for companies, by allowing them to profit from sales, and making the medicines and associated healthcare services free for patients through insurance coverage.

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## INTRODUCTION

In spring 2014, a first-grader with cancer became a poster child for the growing “right to try” movement in the United States. When Josh Hardy was nine months old, doctors diagnosed him with a malignant, highly aggressive, and rare form of kidney cancer.<sup>1</sup> After successful treatment, he faced recurrences in 2008 and again in 2009, before being declared “cancer-free for two years” in May 2013.<sup>2</sup> But in the fall of 2013, doctors diagnosed him with myelodysplastic syndrome, bone marrow failure stemming from years of chemotherapy and radiation treatments.<sup>3</sup> Josh received a bone marrow transplant in early 2014, but weakening of his immune system led to a life-threatening adenovirus infection.<sup>4</sup> After receiving the standard of care for this infection—cidofovir—led to kidney failure, Josh was out of options. There were no other approved drugs to treat the infection.

Josh’s physicians at St. Jude Children’s Hospital in Tennessee turned to an unapproved drug, brincidofovir, made by Chimerix Inc., a small company based in North Carolina.<sup>5</sup> The company was in the middle of a phase 3 clinical trial—the last trial needed for regulatory approval—but they were studying the use of this drug in preventing cytomegalovirus (CMV) reactivation in adult stem cell transplant recipients, a different indication.<sup>6</sup> The company had also just released promising results from a small study using brincidofovir to treat early adenovirus infections in stem cell transplant patients.<sup>7</sup> Without a doubt, the federal government would have permitted Chimerix to provide Josh the drug on a “compassionate use” basis under its “expanded access” regulations.<sup>8</sup> Under these regulations, the U.S. Food and Drug Administration (FDA) permits a company to provide an unapproved drug to a patient with a serious or life-threatening condition who is *not* enrolled in its clinical trials, if certain conditions are met. The company must be willing to provide the drug, however, and it has to ask FDA for permission before proceeding. Chimerix turned the doctors and family down, however, saying

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1. Kenneth I. Moch, *Ethical crossroads: expanded access, patient advocacy, and the #SaveJosh social media campaign*, 1 MED. ACCESS @ POINT OF CARE e119 (2017), <https://journals.sagepub.com/doi/pdf/10.5301/maapoc.0000019> [<https://perma.cc/34KB-MREY>]. Moch was Chief Executive Officer of Chimerix during the events described in the article.

2. Elena Gerasimov, *Saved Josh: The Gears of a Successful Patient Advocacy Campaign*, KIDS v. CANCER 1–2 (Mar. 9, 2016), <https://www.kidsvcancer.org/wp-content/uploads/2016/01/Hardy-Case-Study-final-March-9-2016.pdf> [<https://perma.cc/C4D2-UQTY>].

3. *Id.*; Moch, *supra* note 1, at e122.

4. Moch, *supra* note 1, at e122.

5. Gerasimov, *supra* note 2, at 3.

6. Moch, *supra* note 1, at e121.

7. Moch, *supra* note 1, at e121. Statistical significance had not been achieved, but the study showed numerical benefit in virologic response, treatment failures, and mortality.

8. *See infra* Section 2. Commitment to the Gatekeeping Model.

that it wanted to focus on enrolling patients in the ongoing CMV trial to complete the research needed for approval.<sup>9</sup> The family turned to social media, which led to a barrage of phone calls and emails to the company from the public and from state and federal legislators, media headlines such as “Company denies drug to dying child,” and death threats against family members of the company’s Chief Executive Officer.<sup>10</sup>

Facing this onslaught, Chimerix worked with FDA to design and launch a twenty-patient study of the drug for the treatment of adenovirus infections in immunocompromised patients, in which Josh would be the first enrolled patient.<sup>11</sup> On March 12, 2014, he received his first dose.<sup>12</sup> Nineteen days later the virus was undetectable, and ten days later Josh left the hospital.<sup>13</sup> This opened the floodgates. Three days after announcing the trial, the company received six more requests for the drug, and within six months the company had enrolled eighty patients in its twenty-patient study.<sup>14</sup> Although the drug eliminated Josh’s viral infection, his cancer eventually returned, and he died in September 2016.<sup>15</sup>

The story made national news, and for the next few years it played a role in a larger public debate about the rights of dying patients to try experimental medicines to save their own lives and the proper role of the federal government—if any—in limiting those rights. Just one month before the Josh Hardy firestorm hit social media, the Goldwater Institute published a paper arguing that every state should enact a “right to try” measure, which it had drafted, to “allow terminal

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9. Gerasimov, *supra* note 2, at 2–3.

10. Moch, *supra* note 1, at e125; see Elizabeth Cohen, *Company Denies Drug to Dying Child*, CNN HEALTH (Mar. 11, 2014), <https://www.cnn.com/2014/03/10/health/cohen-josh/index.html> [<https://perma.cc/CSB4-86DW>].

11. Moch, *supra* note 1, at e125. Because the drug was unapproved and the company had decided against providing expanded access, a formal clinical trial designed to support approval of the drug for Josh’s condition was the only legal mechanism by which Josh could receive the drug.

12. *Id.*

13. *Id.*; David Kroll, *Josh Hardy Going Home After Getting Chimerix Anti-Viral Drug*, FORBES (Jul. 17, 2014), <https://www.forbes.com/sites/davidkroll/2014/07/17/josh-hardy-going-home-after-getting-chimerix-anti-viral-drug> [<https://perma.cc/A48J-KR82>].

14. Moch, *supra* note 1, at e126. Although the drug eventually failed its phase 3 trial in CMV, Chimerix is still studying the drug’s antiviral activity. See Press Release, Chimerix, Chimerix Presents Results from Post-hoc Analysis of Phase 3 Study (Feb. 22, 2019), <https://ir.chimerix.com/news-releases/news-release-details/chimerix-presents-results-post-hoc-analysis-phase-3-study> [<https://perma.cc/42LU-WV63>]; Jessica Merrill, *Chimerix Sees Options For Brincidofovir Despite Disappointing CMV Data*, PINK SHEET (Feb. 22, 2016), <https://pink.pharmaintelligence.informa.com/PS079135/Chimerix-Sees-Options-For-Brincidofovir-Despite-Disappointing-CMV-Data>.

15. Cathy Dyson, “*Now He is Healed*”; *Mourning the Death of 10-Year-Old Josh Hardy*, FREDERICKSBURG FREELANCE STAR (Sept. 22, 2016), [https://www.fredericksburg.com/news/local/now-he-is-healed-mourning-the-death-of-10-year-old-josh-hardy/article\\_3da24a7a-ee8b-5c74-89a8-f58adeb0ff31.html](https://www.fredericksburg.com/news/local/now-he-is-healed-mourning-the-death-of-10-year-old-josh-hardy/article_3da24a7a-ee8b-5c74-89a8-f58adeb0ff31.html) [<https://perma.cc/862X-PL22>].

patients access to investigational drugs that have completed basic safety testing.”<sup>16</sup> This was not a new idea: U.S. policymakers and courts had heard similar arguments for decades.<sup>17</sup> But the arguments gained traction this time, and after more than two-thirds of the states enacted right-to-try laws, the federal government followed suit.<sup>18</sup> Under the federal right-to-try law, a patient, doctor, and drug company can proceed to treatment with an unapproved medicine *without* seeking permission first from the federal government. Expanded access, in contrast, requires FDA’s permission.

But the problem for Josh was not federal law in the first place. His problem was that Chimerix refused to provide brincidofovir on a compassionate basis outside of a conventional clinical trial. And Chimerix was not an outlier. Drug companies often decline to provide experimental medicines to dying patients who do not qualify for ongoing trials.<sup>19</sup> The federal right-to-try law addressed a few reasons companies may decline requests—specifically, concerns about liability exposure and concerns that adverse events will affect the medicine’s approval or labeling—but seemingly as an afterthought. It was not a fully fleshed-out attempt to improve access to investigational drugs so much as an attempt to cut FDA out of the process. And because FDA was not the problem in the first place, there remains a serious question whether the law will have any effect on access to experimental medicines.

Many scholars have explored the ethical arguments for providing early access to unapproved medicines on a compassionate basis.<sup>20</sup> There is also a rich body of

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16. Christina Corieri, *Everyone Deserves the Right to Try: Empowering the Terminally Ill to Take Control of Their Treatment*, GOLDWATER INSTITUTE 1 (Feb. 11, 2014), [https://goldwaterinstitute.org/wp-content/uploads/cms\\_page\\_media/2015/1/29/Right%20To%20Try.pdf](https://goldwaterinstitute.org/wp-content/uploads/cms_page_media/2015/1/29/Right%20To%20Try.pdf) [<https://perma.cc/XW4Y-SA9H>].

17. See *infra* Section 0.

18. See Jacqueline Howard, *What you need to know about right-to-try legislation*, CNN HEALTH (May 29, 2018), <https://www.cnn.com/2018/03/22/health/federal-right-to-try-explainer/index.html> [<https://perma.cc/LH9Y-KM8F>] (noting that thirty-eight states had passed right-to-try laws).

19. Gail A. Van Norman, *Expanding Patient Access to Investigational Drugs: Single Patient Investigational New Drug and the “Right to Try”*, 3 JACC: BASIC TO TRANSLATIONAL SCI. 280, 287 (2018) (“Although companies have developed internal pathways by which individual patients can achieve access to investigational drugs, the majority of such requests are denied.”); Lewis A. Grossman, *FDA and the Rise of the Empowered Consumer*, 66 ADMIN. L. REV. 627, 632 (2014) (“The pharmaceutical industry has never been enthusiastic about expanded access programs for unapproved, investigational therapies.”).

20. E.g., Eline Bunnik, Nikkie Aarts & Suzanne van de Vathorst, *The Changing Landscape of Expanded Access to Investigational Drugs for Patients with Unmet Medical Needs: Ethical Implications*, 10 J. PHARMACY POL’Y & PRAC., Feb. 21, 2017, at 1; Eline Bunnik, Nikkie Aarts & Suzanne van de Vathorst, *Little to Lose and No Other Options: Ethical Issues in Efforts to Facilitate Expanded Access to Investigational Drugs*, 122 HEALTH POL’Y 977 (2018); Arthur Caplan, *Is It Sound Public Policy to Let the Terminally Ill Access Experimental Medical Innovations?*, 7 AM. J. BIOETHICS, Jun. 1, 2007, at 1; Arthur Caplan & Kenneth Moch, *Rescue Me: The Challenge of*

legal and public policy literature on these issues and on the history of expanded access in the United States.<sup>21</sup> This Article offers fresh insights on early access schemes, by providing a comparative perspective using French law. Both the United States and France use a regulatory gatekeeper for new medicines, requiring premarket approval based on testing data. Both legal systems have evolved in the last half century to permit access before approval in some cases: under “expanded access” in the United States and “temporary authorization for use” (ATU) in France. Functionally, the early access schemes are similar, preserving a gatekeeping mechanism and respecting the basic premises and goals of the new medicine preapproval paradigm. But the schemes differ in their genesis and specifics, and they operate within fundamentally different healthcare finance systems. We explore the historical, legal, and cultural differences between the two countries that may explain these differences. These same differences help explain why the right-to-try law—which rejects the basic premises and goals of the preapproval paradigm—emerged in the United States but is unlikely to emerge in France.

This Article makes two claims. First, the differences between the two countries’ approaches to early access and right-to-try reflect in part differing reactions to arguments grounded in personal autonomy and patients’ rights, when held up against utilitarian arguments for premarket approval and traditions of medical paternalism. New drug approval schemes are utilitarian, using the barrier

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*Compassionate Use in the Social Media Era*, HEALTH AFFAIRS BLOG, Aug. 27, 2014, <https://www.healthaffairs.org/doi/10.1377/hblog20140827.041027/full/> [https://perma.cc/RDR3-L5ES]; Daniele Carrieri, Fedro A. Peccatori & Giovanni Boniolo, *The Ethical Plausibility of the “Right to Try” Laws*, 122 CRITICAL REV. ONCOLOGY/HEMATOLOGY 64, 66 (2018); Audrey Chapman, *Proposal for Patient Obligations for Access to Unapproved Interventions: Both Too Much and Not Enough*, 14 AM. J. BIOETHICS, Oct. 17, 2014, at 25; Kasper Raus, *An Analysis of Common Ethical Justifications for Compassionate Use Programs for Experimental Drugs*, 17 BMC MED. ETHICS, Oct. 18, 2016, at 1; Udo Schüklenk & Christopher Lowry, *Terminal illness and access to phase 1 experimental agents, surgeries, and devices: reviewing the ethical arguments*, 89 BRITISH MED. BULL. 7, 9 (2009); Mary Jean Walker, Wendy A. Rogers & Vikki Entwistle, *Ethical Justifications for Access to Unapproved Medical Interventions: An Argument for (Limited) Patient Obligations*, 14 AM. J. BIOETHICS, Oct. 17, 2014, at 3, 4.

21. E.g., Rebecca Dresser, *The “Right to Try” Investigational Drugs: Science and Stories in the Access Debate*, 93 TEX. L. REV. 1631 (2015); Elizabeth Weeks Leonard, *The Public’s Right to Health: When Patient Rights Threaten the Commons*, 86 WASH. U. L. REV. 1335, 1343–44 (2009); Michael J. Malinowski, *Throwing Dirt on Doctor Frankenstein’s Grave: Access to Experimental Treatments at the End of Life*, 65 HASTINGS L. J. 615 (2014); Seema Shah & Patricia Zettler, *From a Constitutional Right to a Policy of Exceptions: Abigail Alliance and the Future of Access to Experimental Therapy*, 10 YALE J. HEALTH POL’Y LAW & ETHICS 136, 178–79 (2010); Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs*, 120 HARV. L. REV. 1813 (2007); Patricia J. Zettler, *The Implications of Post-Phase 1 and Off-Label Treatment Use of Experimental Drugs: How Expansive Should Expanded Access Be?*, 18 KAN. J.L. & PUB. POL’Y 135 (2009); Patricia J. Zettler & Henry T. Greely, *The Strange Allure of State “Right-to-Try” Laws*, 174 JAMA INTERNAL MED. 1885 (2014).

to entry as leverage to force the production of robust scientific data to support new medicines. They are also paternalistic, because the approval decision in any particular case requires judgment calls about the value and significance of specific benefits, which stray well beyond the science and trump whatever judgment call a particular patient might have made. Both countries enacted early access schemes in response to arguments from patient groups newly empowered in the AIDS era, who were seeking greater control over their own medical care and the right to accept the risk of using unproven medicines when facing death. Arguments grounded in autonomy principles and rights-based jurisprudence have had more salience in the United States than in France, however, driving some differences between expanded access and ATUs. And right-to-try laws found traction in the United States due to a seeming alliance between patients making arguments grounded in autonomy and rights-based jurisprudence and groups advocating for reduction in the size and power of the federal government.

Second, the right-to-try law is unlikely to increase access to unapproved medicines, and we use the French experience to hypothesize changes to the U.S. expanded access scheme that *would* increase access. Most importantly, we consider the possibility that the key to increasing use of expanded access in the United States might be financial: making it worthwhile for companies to supply unapproved medicines, by allowing them to profit from sales, and making the medicines and associated healthcare services free for patients through insurance coverage. The French minimize the fiscal impact of these choices by also imposing price controls, however, and it is unclear whether U.S. policymakers and the public would accept the full French approach. Adopting a partial solution, such as permitting profit but not mandating insurance coverage, or vice versa, may be ineffective, raise new issues, or both.

This Article proceeds as follows. Section I explains the basic approach to medicine regulation in both countries—premarket review of scientific data by an expert agency—and how the modern premarket review model differs from an earlier model of postmarket enforcement power. It also explains the tradeoff inherent in premarket approval paradigms—that requiring data delays patient access to potential treatments—and discusses the paternalism and utilitarianism in the premarket review model.

Section II explains how shifts in thinking about the relationship between individual and government on matters of health led to refinement of the French and U.S. gatekeeping frameworks with laws that permit access to medicines before approval. It explains how these arrangements responded to autonomy and patient rights arguments but are broadly consistent with the approach and goals of the new drug approval paradigm. Further, it explains how the differences between the two schemes reflect broader sociocultural and legal differences tied to the weight given to autonomy and patients' rights arguments and views on medical paternalism.



Section III describes the U.S. right-to-try law, comparing it to expanded access, and exploring the social and cultural differences between the countries that made this law possible in the United States.

Section IV addresses steps that U.S. policymakers may need to take to increase use while preserving, rather than sidestepping, the basic regulatory framework in place for new medicines. It borrows heavily from the successful French early access scheme in exploring the possibility that the impediments are mainly financial, though it also considers other changes that might be needed.

### I. THE NEW MEDICINE GATEKEEPING MODEL

In both the United States and France, a new medicine must be approved as safe and effective by a regulator—FDA and the Agency for Medicines and Health Product Safety (ANSM), respectively—before it can be placed on the market for use by patients.<sup>22</sup>

#### *A. The Premarket Approval Requirement*

The premarket approval requirement reflects two basic assumptions: first, that society has a profound interest in the generation of high-quality evidence about the effectiveness and safety of new medicines, and second, that the evidentiary standard should serve as a barrier to entry, enforced by an agency composed of scientific experts.<sup>23</sup> These assumptions come from hard lessons in history. Congress enacted the basic statute requiring premarket safety review of drugs in

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22. There are two pathways to market for an innovative new medicine in the United States: approval of a new drug application submitted under § 355(b)(1) of the Federal Food, Drug, and Cosmetic Act, or, if the drug is biological, a biologics license application submitted under section 351(a) of the Public Health Service Act. 21 U.S.C. § 355(b)(1) (2018); 42 U.S.C. § 262(a) (2018). There are four pathways to market in France: (1) approval by the French National Agency for Medicines and Health Product Safety (ANSM) under Article L.5121-8 of the French Public Health Code; (2) for certain types of medicine, centralized approval by the European Commission following review by the European Medicines Agency; (3) simultaneous approval for France and other individual EU Member States (chosen by the company) under a decentralized procedure, in which one country takes the lead in review of the application; and (4) approval through “mutual recognition,” in which a company asks France to respect the decision of another EU Member State that has approved the medicine. *See* CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. L.5121-8 (Fr.); Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, 2004 O.J. (L 136) 1, 5–6, 33 (EC) [hereinafter Regulation 726/2004]; Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, 2001 O.J. (L 331) 67 (EC) [hereinafter Directive 2001/83]; EUR. COMM’N, *THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION* vol. 2A, ch. 1, § 3.2 (2019).

23. *See* Erika Lietzan, *Access Before Evidence and the Price of FDA’s New Drug Authorities*, 53 U. RICH. L. REV. 1243, 1293–95 (2019).

1938 on the heels of a tragedy in which an inadequately tested sulfanilamide preparation killed more than one hundred people, including many children.<sup>24</sup> Without a premarket review requirement, FDA was left to pursue the company after the fact for misbranding the drug.<sup>25</sup> Changes to the statute in 1962 converted the premarket review requirement into a premarket approval requirement with a robust effectiveness standard, following a tragedy in which more than 10,000 children in forty-six countries were born with severe deformities after their mothers used thalidomide during pregnancy.<sup>26</sup>

The new approach shifted the burden of proof to companies seeking to market medicines. This ensures the production of high-quality data to support use and prescribing decisions.<sup>27</sup> It also gives the regulator—the gatekeeper—more power. The ability to grant or withhold permission to enter the market provides powerful leverage during the research process. And enforcement of the premarket approval requirement is far more efficient than any regime that places the burden on the government to begin proceedings and prove there is something wrong after a medicine enters the market.<sup>28</sup>

In both countries, proof of safety and effectiveness takes the form of data from laboratory and animal testing as well as human (“clinical”) trials.<sup>29</sup> Developing these data is an iterative process. After trials in relevant animals show that a new

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24. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938); DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 85–92 (2010).

25. U.S. Dep’t. of Agric., Letter from the Secretary of Agriculture Transmitting in Response to Senate Resolution No. 194 a Report on Elixir Sulfanilamide-Massengill, S. Doc. No. 75-124 at 1, 9 (“[T]he only basis of action under the Food and Drugs Act against the interstate distribution of the ‘elixir’ was the allegation that the word implies an alcoholic solution, whereas the product was a diethylene glycol solution . . . [and] [t]o protect the public from drugs which, like the ‘elixir’ are dangerous because of their inherent toxicity, it is the Department’s recommendation that legislation be enacted to provide . . . [l]icense control of new drugs.”).

26. CARPENTER, *supra* note 24, at 213–97.

27. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOM. & TECH. L. REV. 345, 370–71 (2007); Amy Kapczynski, *Dangerous Times: The FDA’s Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357 *passim* (2018).

28. See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1797 (1996).

29. See 21 U.S.C. § 355(d) (2018) (standard for approval of a new drug in the United States); 42 U.S.C. § 262(a) (2018); 21 C.F.R. § 601 (2020) (standard for approval for a biological product in the United States); CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. L.5121-9 (Fr.) (grounds for denying approval of a medicine in France); *id.* art. L.5121-20 (indicating that more detailed rules, including those governing trials, will be set forth in decrees). A company does not repeat the process for each country in which it seeks approval. Although some regulators may require trials that others do not—such as trials in a local population—companies are usually able to use the same pivotal safety and effectiveness data. The actual applications will be different, reflecting each regulator’s content and format requirements, including with respect to the types of analysis performed and the types of detailed reports written.

drug is safe to begin testing in humans, the applicant begins with small safety tests and moves gradually to larger and larger trials.<sup>30</sup> Phase 1 trials entail the initial introduction of the investigational medicine in humans and focus on questions of absorption, distribution, metabolism, excretion, and side effects of increasing dose.<sup>31</sup> These trials sometimes also generate early evidence of effectiveness, if the subjects are patients rather than healthy volunteers.<sup>32</sup> Phase 2 trials assess the effectiveness of the medicine in patients, as well as common short-term side effects and risks.<sup>33</sup> The pivotal trials providing statistically robust proof of effectiveness—phase 3 trials—often involve thousands of patients and clinical trial sites around the world.<sup>34</sup>

The three-phase approach dates to the 1960s and is somewhat obsolete.<sup>35</sup> Today, there are few hard-and-fast rules about clinical trial design. A company's premarket clinical development program will usually include trials that can be classified as phase 1, phase 2, or phase 3. But some companies start with a "phase 0" trial to examine administration of a micro-dose to a very small group of volunteers, and companies often run trials that combine elements of phase 1 and phase 2, or phase 2 and phase 3.<sup>36</sup> Regardless of the design of the overall research program, the goal is the same. Regulators look for randomized, controlled, double-blinded, prospective, interventional trials, which are the gold standard for approval of a new medicine.<sup>37</sup> If these trials are large enough, they can support a conclusion that the tested drug is effective, meaning that it causes the therapeutic benefit measured.<sup>38</sup>

30. See Lietzan, *Access Before Evidence*, *supra* note 23, at 1246–47.

31. *E.g.*, 21 C.F.R. § 312.21(a) (2020).

32. *E.g.*, *id.* Most phase 1 trials use healthy volunteers, but phase 1 trials of oncology drugs and other drugs with narrow therapeutic indices that are intended for life-threatening conditions are often conducted in patients. The decision whether to recruit healthy volunteers or patients is made on a case-by-case basis, considering a variety of factors relating to the safety of the trial participants and the quality of the data being generated. *E.g.*, Jie Shen et al., *Design and Conduct Considerations for First-in-Human Trials*, 12 *CLINICAL & TRANSLATIONAL SCI.* 6 (2019).

33. *E.g.*, 21 C.F.R. § 312.21(b) (2020).

34. *E.g.*, 21 C.F.R. § 312.21(c) (2020).

35. New Drugs for Investigational Use: Proposed Exemptions, 27 *Fed. Reg.* 7,990, 7,990–91 (Aug. 10, 1962).

36. *E.g.*, FDA, GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND REVIEWERS: EXPLORATORY IND STUDIES (Jan. 2006), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exploratory-ind-studies> [<https://perma.cc/NVS4-43BG>].

37. Vinay Prasad & Vance W. Berger, *Hard-Wired Bias: How Even Double-Blind Randomized Controlled Trials Can Be Skewed from the Start*, 90 *MAYO CLINIC PROC.* 1171, 1171 (2015) (“Well-designed, adequately-powered randomized controlled trials . . . are rightfully considered the highest form of evidence on which to base treatment and diagnostic decisions, minimizing potential biases, particularly confounding, that plague nonrandomized evidence.”).

38. Thomas R. Frieden, *Evidence for Health Decision Making — Beyond Randomized Controlled Trials*, 377 *NEW ENG. J. MED.* 465, 465 (2017); *see also* FDA, GUIDANCE FOR INDUSTRY: E9 STATISTICAL PRINCIPLES FOR CLINICAL TRIALS 1, 10–12 (Sept. 1998),

Whether the data support a finding of effectiveness, and whether the applicant has conducted all reasonably applicable safety testing, are scientific judgments. The new medicine frameworks in France and the United States appropriately give these calls to expert agencies composed of scientists. By assigning the job of application review to agencies staffed by scientists, the frameworks ensure that the data supporting each new medicine face at least one formal structured assessment grounded in science.<sup>39</sup>

### *B. Paternalism and Utilitarianism in the Premarket Model*

No medicine is, however, perfectly safe or always effective in the patients for whom it is labeled. Patients are heterogeneous, and clinical responses vary.<sup>40</sup> Side effects are inevitable; medicines are biologically active, and the relationship between a patient's body and a chemical product can be complex.<sup>41</sup> As a result, when approving a new medicine for the market, the most a regulator can ask for is proof that a medicine's benefits outweigh its risks.<sup>42</sup>

It is, however, impossible to be certain about this.<sup>43</sup> No premarket research and development program can generate complete information about a medicine's clinical profile.<sup>44</sup> In clinical trials the experimental medicine is administered under tightly controlled conditions, to ensure that the resulting data can be interpreted. In

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<https://www.fda.gov/media/71336/download> [<https://perma.cc/4F73-86D8>].

39. See Robert M. Temple, *Commentary on "The Architecture of Government Regulation of Medical Products,"* 82 VA. L. REV. 1877, 1898 (1996) ("[A]part from contributing independent review, the existence of the regulator helps maintain the safety assessment enterprise, as public standards, applicable to all parties, assure a level playing field and discourage excessive corner-cutting.").

40. E.g., Richard L. Kravitz, Naihua Duan & Joel Braslow, *Evidence-Based Medicine, Heterogeneity of Treatment Effects, and the Trouble with Averages*, 82 MILLBANK Q. 661, 699 (2004) ("Even if the treatment is delivered uniformly, the outcomes will still vary because, as noted earlier, individual patients differ according to their preexisting risk without treatment, responsiveness to treatment, vulnerability to side effects, and health state preferences or utilities."); see also Anup Malani, Oliver Bembom & Mark van der Laan, *Accounting for Heterogeneous Treatment Effects in the FDA Approval Process*, 67 FOOD & DRUG L. J. 23, 24 (2012) ("It is common for drugs to have different effects in different patients, a phenomenon statisticians call 'heterogeneity in treatment effects.'").

41. See FDA, STRUCTURED APPROACH TO BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING 1, 1 (Feb. 2013) (recognizing that "all drugs have some ability to cause adverse effects").

42. E.g., FDA, BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING: DRAFT PDUFA VI IMPLEMENTATION PLAN (FY 2018-2022), 1, 3 (2018) ("Simply put, for a drug to be approved for marketing, FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients.").

43. See generally Lietzan, *Access Before Evidence*, *supra* note 23, at 1297–98.

44. FDA, STRUCTURED APPROACH, *supra* note 41, at 9 ("Although drug regulatory decisions are informed by an extensive body of evidence on the safety and efficacy of a proposed product, in many cases, FDA must draw conclusions from imperfect data.").

the real world, patients may have other diseases and conditions, are more biologically heterogeneous, and may take other medicines.<sup>45</sup> Also, premarket testing involves administration of the experimental medicine to fewer people and for less time than would happen in the real world.<sup>46</sup> As a result of these and other limitations, the risks and benefits of a new medicine may turn out to be different than suggested by premarket testing. Some adverse reactions could be more frequent or more severe than expected. Some may have been too rare to emerge in clinical trials, and some might emerge only after long-term use.<sup>47</sup> The medicine may be less effective or ineffective in patient groups that were not included in the trials.<sup>48</sup>

Approval really means only that the data gathered so far show that the medicine's benefits outweigh its risks.<sup>49</sup> There is, therefore, a tradeoff at the heart of any premarket approval paradigm. On the one hand, although it is impossible to eliminate all uncertainty about a proposed new medicine, more testing will generally provide more certainty. On the other hand, additional testing delays the regulatory decision, and thus market entry. If the regulator still approves the medicine at the end, the additional testing delayed access to a medicine with a positive benefit-risk ratio. Patients who could have benefitted from the medicine had to wait. And if the medicine treated a serious or life-threatening disease, some patients may have missed the opportunity to use the medicine.<sup>50</sup>

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45. *E.g., id.* at 9 (noting that trials are designed to show the benefit of a medicine compared with a control and that some patients may be “excluded to improve the ability to detect a benefit that can be attributed to the drug”). *See generally* Kravitz, *supra* note 40.

46. Frieden, *supra* note 38, at 465 (noting various limitations of randomized controlled trials, including that they have limited duration and sample size).

47. *E.g.,* Comm. on the Assessment of the U.S. Drug Safety Sys., The Inst. of Med., The Future of Drug Safety: Promoting and Protecting the Health of the Public 1, 106 (Alina Baciu, Kathleen Stratton & Sheila P. Burke, eds. 2007) (“Safety information can emerge from clinical trials, but rare events may not surface at all; if they do, it is at a rate so low that one cannot distinguish a drug-caused event from one expected by chance (background incidence).”).

48. *E.g.,* Kravitz, *supra* note 40, at 667 (“By convenience, [randomized controlled trials] are usually characterized by narrow inclusion criteria and recruitment. Under these conditions, the heterogeneity of treatment effects may be dramatically underestimated, and even assiduous investigators can be misled into thinking that their results are more generalizable than they actually are.”).

49. *See generally* Lietzan, *Access Before Evidence*, *supra* note 23, at 1297–98. FDA takes a “population” approach to assessing benefit-risk, meaning that it focuses on the entire patient population for whom the medicine will be labeled. *See* Mark Van Der Laan, Anup Malani & Oliver Van Der Benbom, *Improving the FDA Approval Process* (John M. Olin Law & Econ., Working Paper No. 580 (2d Series), Public Law and Legal Theory, Working Paper No. 367, 2011). Approval therefore includes the possibility of an undesirable outcome, and negative benefit-risk balance, for any particular individual in the population.

50. *See* Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, *Innovation in the pharmaceutical industry: new estimates of R&D costs*, 47 J. HEALTH ECON. 20, 23 (2016) (reporting average time from synthesis to human testing of 31.2 months and an average time from start of

How much information is enough for a decision on the risk-benefit profile of a new medicine depends on the relative weight given to two goals: (1) earlier release of new medicines to patients and (2) reduction of uncertainty about the effects of those medicines. Scholars, doctors, patients, regulators, and policymakers may disagree about the tradeoff here.<sup>51</sup> A patient facing death may care more about the cost of delay and less about the risk that a drug is unsafe or ineffective.<sup>52</sup> And the benefit-risk assessment for any particular medicine reflects value judgments that stray well beyond science—such as how *much* a particular side effect matters and how *much* extending life for a month matters. As FDA says, these decisions occur “at the intersection of law, science, medicine, policy, and judgment.”<sup>53</sup>

As a result, the modern medicine approval paradigm is partly paternalistic.<sup>54</sup> A medicine may not be sold for use by a patient—even if the benefits exceed the

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clinical testing to approval of 96.8 months).

51. For example, there is debate about whether regulators set the evidentiary bar too *low* for approval of drugs intended to treat cancer. Regulators often approve these drugs on the basis of trials using surrogate measurements—such as tumor shrinkage or progression-free survival—because these measurements are easier and quicker to measure than the true endpoint of interest, overall survival. Some argue that the association between surrogate outcomes and clinically meaningful outcomes is weak and that FDA should wait for robust clinical outcomes data, rather than approving new medicines on the basis of small increases in questionable surrogate measurements. *E.g.*, Robert Kemp & Vinay Prasad, *Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused?*, 15 BMC MED., Jul. 21, 2017, at 1; Vinay Prasad et al., *The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-Analyses*, 175 JAMA INTERNAL MED. 1389 (2015).

52. See Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 GEO. L.J. 559, 579 (2008) (noting that the risk of approving drugs that turn out not to be safe and effective may be less concerning to patients facing imminent death, because delay could be catastrophic); Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL’Y 295, 298 (2000) (“Terminally ill patients lacking effective conventional treatments confront a risk-benefit determination very different from that of the general public. Such patients have far greater incentives than the larger public to gather their own information and to take risks.”); Christina Sandefur, *Safeguarding the Right to Try*, 49 ARIZ. ST. L. J. 513, 536 (2017) (arguing that “the FDA system presumes that the public should not have access to medicine until federal officials certify it as both safe and effective to their satisfaction” but “dying patients face a different risk/benefit calculus than other people”).

53. FDA, STRUCTURED APPROACH, *supra* note 41, at 2.

54. See Richard Epstein, *Regulatory Paternalism in the Market for Drugs: Lessons from Vioxx and Celebrex*, 5 YALE J. HEALTH POL’Y & ETHICS 741, 758 (2005) (“The implicit paternalism of allowing FDA supremacy assumes that a distant bureaucracy, which has its own institutional biases, will be a better guardian of all potential users than the people themselves. It is often said that the ability to take risks and bear their consequences is one of the marks of a self-reliant population.”); Michael D. Greenberg, *Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval*, 13 ALB. L. J. SCI. & TECH. 663, 671–76 (2003) (discussing and critiquing the “regulatory paternalism” of the drug approval process); Marie-Louise Lamau, *Le recours au principe d’autonomie en éthique clinique*, 234 REVUE D’ÉTHIQUE ET DE THÉOLOGIE MORALE 63 (2005) (discussing medical paternalism in France).

risks from the perspective of the patient, and even if avoiding delay is more important to the patient than knowing more about the drug—until a regulator agrees to permit it, based on its own assessment of benefits and risks. The approval paradigm is also utilitarian, because it focuses on maximizing overall welfare.<sup>55</sup> The decision to require premarket approval based on evidence that may take a decade to generate focuses on the needs of the population as a whole.<sup>56</sup> It places the need for high quality evidence over the preferences of individual patients, who may want access to potentially beneficial medicines before that evidence has been generated. Policymakers have decided that the public as a whole is better off if market entry is denied until robust evidence has been produced. The use of controls in premarket clinical trials similarly places the needs of the study—quality data for the benefit of future patients—above the needs of any particular patient enrolled in the study.<sup>57</sup>

## II. EARLY ACCESS MECHANISMS WITHIN THE GATEKEEPING FRAMEWORK

Over the last half century, policymakers in France and the United States have refined the regulatory gatekeeping model as the broader relationship between the individual and state on matters of personal health has evolved. As a practical matter, a patient today has access to more personal health information than a patient fifty years ago, as well as more information about diseases and potential medical interventions. As a matter of political economy, a patient today has more influence over laws and public policy relating to his health. And as a legal matter, a patient today has more decision-making authority over personal health matters, which can constrain others in the healthcare system—for example, when courts have recognized “rights” that the government must respect. These developments are intertwined and linked by a thread: elevation of individual agency and autonomy in matters of personal health.<sup>58</sup> Empowerment of the patient has collided with the paternalism and utilitarianism of the gatekeeping model, leading to the

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55. Utilitarian theory is most associated with the writings of Jeremy Bentham. JEREMY BENTHAM, *AN INTRODUCTION TO THE THE PRINCIPLES OF MORALS AND LEGISLATION* (J.H. Burns & H.L.A Hart eds., Clarendon Press 1996) (1823). This approach would be considered “rule” utilitarian, in the sense that it assumes this rule can produce better results (more overall well-being) than any other approach. A different, also utilitarian, approach would say that greater overall well-being will be achieved if every individual maximizes his or her own utility.

56. Walker, *supra* note 20, at 4 (“Regulation of new medical interventions draw on population-focused rather than individual approaches to ethics—taking account of the potential for harm of unrestricted access . . . and of the opportunity costs should ineffective interventions be approved.”).

57. Schüklenk & Lowry, *supra* note 20, at 9 (quoting Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases during the AIDS epidemic, that the randomized controlled trial “routinely asks physicians to sacrifice the interests of their particular patients for the sake of the study”).

58. See generally Grossman, *Empowered Consumer*, *supra* note 19 (making this argument).

refinement of gatekeeping frameworks at the heart of this Article: creation of mechanisms giving patients access to medicines *before* approval.<sup>59</sup>

#### A. *Evolution in the Relationship between Individual and State*

Patients have access to more information today. In 1954, only sixty-five percent of U.S. households owned a television set; today, more than three quarters of households own a desktop or laptop computer, and seventy-seven percent have a broadband Internet subscription.<sup>60</sup> Patients can use the Internet to access information about diseases, approved medicines, other types of interventions, ongoing research, and ongoing clinical trials.<sup>61</sup> Significant advances in medicine have also occurred over the same half century, meaning that the information available is deeper and richer. Improvements in diagnostic technology have reshaped our understanding of the human body in both healthy and pathological states, enhancing our understanding of disease and making possible new areas of pharmacological intervention.<sup>62</sup> Profound advances in genetics, virology, and immunology have transformed the field of microbiology. And the biotechnology revolution has worked hand in hand with improved imaging capability and an explosion in computing capability to revolutionize our understanding of human disease and our therapeutic options, making possible, for example, molecular engineering.<sup>63</sup> Patients today know more because information technology has

59. Others have recounted the U.S. history in detail. *E.g.*, Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America's Drug Constitution*, 42 AM. J. L. & MED. 687 (2016); Zettler, *Implications*, *supra* note 21. To our knowledge, no one has considered the parallels in French history.

60. *U.S. Census Bureau History: Public Broadcasting*, U.S. CENSUS BUREAU (Oct. 2015), [https://www.census.gov/history/www/homepage\\_archive/2015/october\\_2015.html](https://www.census.gov/history/www/homepage_archive/2015/october_2015.html) [https://perma.cc/R53L-9LHW]; CAMILLE RYAN & JAMIE M. LEWIS, U.S. CENSUS BUREAU, COMPUTERS AND INTERNET USE IN THE UNITED STATES: 2015 (2017), <https://www.census.gov/content/dam/Census/library/publications/2017/acs/acs-37.pdf> [https://perma.cc/GQQ3-5YK4].

61. The reality of access varies. Some patients own multiple computers and handheld devices, for example, while others may need to walk to a public library on days they do not work. Some information—such as reports in peer-reviewed medical and scientific journals—resides behind a paywall, limiting its access to patients with resources or access through an employer. Some patients and caregivers have ample time for research, others much less. Some patients have the training to understand scientific and statistical literature, while others do not.

62. Electron microscopy evolved from permitting rudimentary diagnosis of kidney disease and tumors in the 1960s to identifying a wide range of subtle cellular changes characteristic of diseases. Ronald E. Gordon, *Electron Microscopy: A Brief History and Review of Current Clinical Application*, in 1180 HISTOPATHOLOGY 119 (Christina E. Day ed., 2014). Since the earliest nuclear magnetic resonance images of humans were published in the 1970s, the field has undergone dramatic change—with improvements in hardware (such as the introduction of superconducting magnets and the invention of phased array radiofrequency coils) as well as the development of a variety of rapid imaging and contrast enhanced cardiac imaging. Robert R. Edelman, *The History of MR Imaging as Seen through the Pages of Radiology*, 273 RADIOLOGY S181 (2014).

63. See generally Ronald Evens & Kenneth Kaitin, *The Evolution of Biotechnology and Its*



improved *and* because there is more information.<sup>64</sup>

The changing information landscape coincided with a rights revolution that began in the 1960s.<sup>65</sup> The rights revolution included a series of rights-affirming judicial decisions ranging over a wide field relating to medicine and health—for example, limiting the grounds on which the government may involuntarily commit an adult,<sup>66</sup> recognizing the rights of prisoners to avoid the unwanted administration of antipsychotic drugs,<sup>67</sup> assuming a right to refuse lifesaving hydration and nutrition,<sup>68</sup> and identifying several health-related prerogatives related to contraception and abortion within a “right to privacy.”<sup>69</sup> In the late 1970s, a group of terminally ill cancer patients persuaded a federal court that the right to privacy included a right to purchase an unapproved new drug, amygdalin, from sellers in other countries.<sup>70</sup> These decisions embraced autonomy principles, finding that the

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*Impact on Health Care*, 34 HEALTH AFF. 210 (2015).

64. See Grossman, *Empowered Consumer*, *supra* note 19, at 639 (citing changes in the “health information environment” contributing to patient empowerment); JAY KATZ, *THE SILENT WORLD OF DOCTOR AND PATIENT* (1984) (explaining how information politics fueled movement for patient autonomy and reform in the doctor-patient relationship). Also, an increase in the prevalence of chronic disease may be prompting patients to take advantage of the information explosion and insist on more collaborative long-term relationships with their doctors. See JANINE BARBOT, *LES MALADES EN MOUVEMENT: LA MEDECINE ET LA SCIENCE A L’EPREUVE DU SIDA* (2002); SEBASTIEN DALGALARRONDO, *SIDA: LA COURSE AUX MOLECULES* (2004).

65. The rights revolution included legislative changes as well as the judicial decisions noted in text. Max N. Helveston, *Judicial Deregulation of Consumer Markets*, 36 CARDOZO L. REV. 1739, 1745 (2015) (“Large legislative expansions of consumers’ rights occurred in the 1960s and early 1970s, which saw the enactment of statutes like the Consumer Product Safety Act, the Consumer Credit Protection Act, and state consumer protection acts.”).

66. *O’Connor v. Donaldson*, 422 U.S. 563, 576 (1975) (“[A] State cannot constitutionally confine without more a nondangerous individual who is capable of surviving safely in freedom by himself or with the help of willing and responsible family members or friends.”).

67. *Washington v. Harper*, 494 U.S. 210, 229 (1990) (“The forcible injection of medication into a nonconsenting person’s body represents a substantial interference with that person’s liberty.”).

68. *Cruzan v. Dir., Mo. Dep’t. of Health*, 497 U.S. 261, 281 (1990) (“It cannot be disputed that the Due Process Clause protects an interest in life as well as an interest in refusing life-sustaining medical treatment.”).

69. *E.g.*, *Griswold v. Connecticut*, 381 U.S. 479 (1965) (finding that Connecticut law prohibiting the use of contraceptives was unconstitutional); *Roe v. Wade*, 410 U.S. 113, 153 (1973) (“This right of privacy, whether it be founded in the Fourteenth Amendment’s concept of personal liberty and restrictions upon state action, as we feel it is, or, as the District Court determined, in the Ninth Amendment’s reservation of rights to the people, is broad enough to encompass a woman’s decision whether or not to terminate her pregnancy.”).

70. The resulting injunction did not survive appeal, however, and the Tenth Circuit disagreed with the trial court’s view of the privacy cases. FDA had asserted that Laetrile (amygdalin) required premarket approval, which meant that the plaintiffs could not receive shipments of the compound from sources outside the United States. In 1977, a federal district court ruled that Laetrile qualified for a statutory exemption from the approval requirement. It also ruled in the alternative that FDA’s decision—“denying the right to use a nontoxic substance in connection with one’s own personal health-care”—had infringed the constitutional “right of privacy.” *Rutherford v. United States*, 438 F.

patient should make the healthcare decisions relating to his or her own body.<sup>71</sup>

A series of free speech rulings affirmed the right of consumers to receive information,<sup>72</sup> many related to the availability and cost of medical treatments.<sup>73</sup> During these same decades, FDA's policies governing the communication of information about medicines to patients evolved. For example, in the 1970s the agency permitted companies to advertise their prices directly to consumers.<sup>74</sup> In the 1980s it allowed direct-to-consumer (DTC) advertising disclosing the uses of prescription drugs.<sup>75</sup> And in the 1990s it issued guidance paving the way for DTC broadcast advertising.<sup>76</sup> These developments made it possible for patients to

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Supp. 1287 (W.D. Okla. 1977). After the Supreme Court reversed the statutory ruling, *United States v. Rutherford*, 442 U.S. 544 (1979), the Tenth Circuit declined to consider the constitutional argument, writing that the privacy cases protect "the decision by the patient whether to have a treatment or not," but that "his selection of a particular treatment, or at least a medication, is within the area of governmental interest in protecting public health." *Rutherford v. United States*, 616 F.2d 455, 457 (10th Cir. 1980).

71. Grossman, *Empowered Consumer*, *supra* note 19, at 637 ("One important aspect of the rights revolution that blossomed in the 1970s was the notion of 'patients' rights.'"). Although the patients' rights movement came of age in the 1970s, the notion that patients' rights play a role in law is much older. *E.g.*, *Schloendorff v. Soc'y of N.Y. Hosp.*, 105 N.E. 92, 93 (N.Y. 1914) ("[E]very human being of adult years and sound mind has a right to determine what shall be done with his own body . . .").

72. *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 756 (1976) (holding that protection of speech is afforded "to the communication, to its source and to its recipients both").

73. *E.g.*, *Bigelow v. Virginia*, 421 U.S. 809 (1975) (reversing conviction of Virginia newspaper editor for printing an advertisement from an organization in New York that would help women locate clinics and hospitals in New York for low-cost abortions); *Va. State Bd. of Pharmacy*, 425 U.S. at 748 (1976) (holding that state bans on advertising prescription drug prices violated the First and Fourteenth Amendments); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (finding that federal law that prohibited advertising and promotion of compounded medicines violated the First Amendment); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998) (holding that FDA's restrictions on use of textbooks and journal reprints to promote unapproved uses of approved drugs violated the First Amendment), *vacated sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) (vacating on mootness grounds because government changed its interpretation of the statutory provisions); *United States v. Caronia*, 703 F.3d 149, 168 (2d Cir. 2012) (construing the misbranding provisions of the drug statute as "not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs," in order to avoid construction that "would unconstitutionally restrict free speech"); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015) (finding manufacturer likely to succeed on the merits of claim that the threat of enforcement action chilled it from sharing information with doctors about an unapproved use of its drug).

74. *Reminder Labeling and Reminder Advertisements for Prescription Drugs*, 40 Fed. Reg. 58,794 (Dec. 18, 1975).

75. *Direct-to-Consumer Advertising of Prescription Drugs; Withdrawal of Moratorium*, 50 Fed. Reg. 36,677 (Sept. 9, 1985). FDA had not banned this advertising, but companies had generally refrained. After two advertisements ran in 1983, FDA called for a moratorium to consider the rules that should apply. It withdrew the moratorium in 1985.

76. *Guidance for Industry on Consumer-Directed Broadcast Advertisements; Availability*, 64

assume a greater role in decisions about their own care, though some believe that DTC advertising needs greater oversight.<sup>77</sup> The agency now requires that some prescription drugs have labeling for patients, in addition to the usual labeling for prescribers.<sup>78</sup> A district court rejected the argument that patient labeling for estrogen interfered with the practice of medicine,<sup>79</sup> reflecting a cultural shift away from medical paternalism.<sup>80</sup>

Similar changes affected the relationships of patients in France to their healthcare providers and to the state, but these changes came later in time and were more limited in scope. Patient groups in France grew more empowered, especially during the AIDS crisis of the 1990s.<sup>81</sup> A rights revolution, embracing patients' rights, occurred in France as it did in the United States. But because France is a civil law country, not a common law country, the rights revolution has mainly taken the form of statutory changes. In 2002, a Patients' Rights Law profoundly changed the relationship between a patient and his or her doctor, laying out the patient's rights and the doctor's responsibilities, and reforming malpractice

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Fed. Reg. 43,197 (Aug. 9, 1999). These advertisements were already legal, but it had been unclear how to comply with the agency's advertising regulations in the new medium. The guidance explained how, effectively making the advertisements possible.

77. See Grossman, *Empowered Consumer*, *supra* note 19, at 657–62 (discussing emergence of direct-to-consumer advertising in connection with patients becoming active participants in their own treatment decisions); U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-03-177, *PRESCRIPTION DRUGS: FDA OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING HAS LIMITATIONS* 1, 16 (2002) (“[A]bout 8.5 million consumers received a prescription after viewing a DTC advertisement and asking their physician for the drug in 2000.”); Bo Wang & Aaron S. Kesselheim, *The Role of Direct-to-Consumer Pharmaceutical Advertising in Patient Consumerism*, 15 *AMA J. OF ETHICS* 960, 960 (2013) (arguing that “the lack of firm regulatory guidelines governing” direct-to-consumer advertising “may lead to suboptimal treatment decisions and health and economic outcomes”). The information revolution has also facilitated the spread of *misinformation* about medicine and disease. Erin Connolly, *Cleaning Up “Fake News” in Health Care*, *MEDICAL BAG* (Nov. 21, 2018), <https://www.medicalbag.com/home/more/ethics/cleaning-up-fake-news-in-health-care> [<https://perma.cc/7TJY-7A8E>].

78. Grossman, *Empowered Consumer*, *supra* note 19, at 652–57 (discussing patient labeling requirements introduced in the 1970s).

79. *Pharm. Mfrs. Ass'n v. Food & Drug Admin.*, 484 F. Supp. 1179 (D. Del. 1980), *aff'd per curiam*, 634 F.2d 106 (3d Cir. 1980); see also Grossman, *Empowered Consumer*, *supra* note 19, at 653–54.

80. See generally DAVID J. ROTHMAN, *STRANGERS AT THE BEDSIDE: A HISTORY OF HOW LAW AND BIOETHICS TRANSFORMED MEDICAL DECISION MAKING* (1991) (discussing transformation in the practice of medicine in the United States due in part to the redefinition of the role of the physician and the rejection of paternalism).

81. Paul Véron & François Vialla, *De quelques difficultés entourant l'action de groupe en matière de santé*, 127 *REVUE LAMY DROIT DES AFFAIRES* 45 (2017); Philippe Amiel, *Les associations de patients et la recherche clinique académique et industrielle*, 199 *BULLETIN DE L'ACADEMIE NATIONALE DE MÉDECINE* 589 (2015) (discussing the growth of the patients' rights movement in France especially in the 2000s).

liability for doctors.<sup>82</sup> While the seminal U.S. litigation relating to the right to refuse lifesaving hydration and nutrition concluded in 1990,<sup>83</sup> France did not enact legislation governing palliative care and giving individuals the *choice* to refuse life support measures until 2005.<sup>84</sup> And the French courts grappled with the issue only last year, when a patient injured in a motorcycle accident received life support for years without brain activity.<sup>85</sup> Finally, although patients in France today have more information, a greater sense of autonomy, and a more egalitarian relationship with their doctors than did their counterparts fifty years ago, they have less comparatively than patients in the United States today.<sup>86</sup>

### B. Access to Investigational Medicines through a Gatekeeper

In both countries, the shifting relationship between patients and the state put pressure on the gatekeeping model for new medicines.<sup>87</sup> Policymakers responded

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82. Loi 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé, JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE [J.O.] [OFFICIAL GAZETTE OF FRANCE], Mar. 5, 2002, p. 4118. See generally Florence G'Sell-Macrez, *Medical Malpractice and Compensation in France, Part I: The French Rules of Medical Liability since the Patients' Rights Law of March 4, 2002*, 86 CHI.-KENT L. REV. 1093 (2011). Historically, the relationship between a patient and private physician was governed by contract (and liability under the contract was governed by the Civil Code), while the relationship between a patient and physician in a public hospital was governed by "administrative" (public) law. Cf. GÉRARD MÉMETEAU, TRAITÉ DE LA RESPONSABILITÉ MÉDICALE (1996); René Savatier, *La responsabilité médicale en France (aspects de droit privé)*, 28 REVUE INTERNATIONALE DE DROIT COMPARÉ 493 (1976). But the 2002 law created a new unified scheme for medical malpractice liability. See G'Sell-Macrez, *supra*. French prosecutors had also sometimes brought criminal charges against healthcare professionals in the past. For example, they took action in the 1850s after physicians investigating the contagiousness of secondary syphilis had "inoculated" a non-syphilitic ten-year-old boy with pus taken from a patient suffering from secondary syphilis. See Alex Dracoby, *Ethics and Experimentation on Human Subjects in Mid-Nineteenth-Century France: The Story of the 1859 Syphilis Experiments*, 77 BULL. HIST. MED. 332, 360–61 (2003) (describing the trial of Antoine Gailleton and Joseph-Frédéric Guyenot).

83. See *Cruzan v. Dir., Mo. Dep't. of Health*, 497 U.S. 261, 281 (1990).

84. Loi 2005-370 du 22 avril 2005 relative aux droits des malades et à la fin due vie, J.O., Apr. 23, 2002, p. 7089; see Antoine Baumann et al., *Ethics review: End-of-life legislation—the French model*, 13 CRITICAL CARE 204 (2009) (explaining that the new law "authorizes the withholding or withdrawal of treatments when they appear 'useless, disproportionate or having no other effect than solely the artificial preservation of life'").

85. See Aurelien Breeden, *French Court Clears Way to End Life Support for Man in Vegetative State*, N.Y. TIMES, June 28, 2019, <https://www.nytimes.com/2019/06/28/world/europe/france-vincent-lambert-life-support.html> [https://perma.cc/8NCG-T2HF]; see also Aline Cheynet de Beaupré, *Entre la vie et la mort : juger la fin de vie*, 3 LES CAHIERS DE LA JUSTICE 413 (2017) (discussing recent changes to the 2005 law); Paul Véron & François Vialla, *Arrêt des traitements : deux premières applications de la loi du 2 février 2016*, 5 L'ACTUALITE JURIDIQUE. DROIT ADMINISTRATIF 301 (2017) (discussing early application of this law).

86. See *infra* Section 0.

87. Anna B. Laakman, *Customized Medicine and the Limits of Federal Regulatory Power*, 19 VAND. J. ENT. & TECH. L. 285, 321–22 (2016) ("The rise of an increasingly influential patient

in part with mechanisms allowing patients access to new medicines *before* approval for the commercial market.<sup>88</sup>

### 1. Emergence of Early Access Mechanisms

Early access mechanisms emerged during the worst years of the AIDS crisis and responded to the fact that better informed and newly empowered patients were willing to take greater risks in exchange for earlier access to new medicines. In the United States, however, policymaking discussions also included proponents of deregulation—groups who opposed gatekeeping altogether, on philosophical grounds.

Even before the AIDS crisis, FDA had permitted seriously ill patients access to experimental drugs.<sup>89</sup> The agency proposed formalizing early access in 1983, two years after the first major news coverage of AIDS.<sup>90</sup> FDA called the mechanism a “treatment IND.”<sup>91</sup> Recent scholarship has argued persuasively that

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empowerment movement has forced the FDA to significantly revise its review and approval processes.”).

88. Policymakers also responded with mechanisms that moved the market entry decision earlier in time. A few examples follow. The French “fast track” program reduces the timeline for regulatory approval of clinical trials for certain important medicines. ANSM, CLINICAL TRIALS ON MEDICINAL PRODUCTS SUBMITTED TO THE ANSM AS PART OF THE FAST TRACK PROCEDURE, Oct. 10, 2018, [https://www.an-sm.sante.fr/var/an-sm\\_site/storage/original/application/42df327468624f1ce1862ef562c1cc30.pdf](https://www.ansm.sante.fr/var/an-sm_site/storage/original/application/42df327468624f1ce1862ef562c1cc30.pdf) [<https://perma.cc/DJU6-GS7A>]. U.S. law permits accelerated approval of a medicine intended for treatment of serious or life-threatening illness, based on data that do not *show* clinical benefit but rather *predict* it. 21 C.F.R. § 314.500 (2020). European law permits a one-year renewable “conditional marketing authorization”—before comprehensive clinical data have been generated—for certain medicines intended to treat a seriously debilitating or life-threatening disease. Regulation 726/2004, *supra* note 22, at 10; Commission Regulation No. 507/2006 of 29 March 2006 on the Conditional Marketing Authorisation for Medicinal Products for Human use Falling Within the Scope of Regulation (EC) No. 726/2004 of the European Parliament and of the Council, 2006 O.J. (L 92) 6, 8 (EC). *See generally* Jorge Martinabo et al., *Early Market Access of Cancer Drugs in the EU*, 27 ANNALS ONCOLOGY 96 (2016) (describing conditional marketing authorization, authorization under exceptional circumstances, and accelerated assessment in Europe). French law similarly provides for conditional approval of medicines. CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. R.5121-36-1 (Fr.).

89. *See generally* Grossman, *AIDS Activists*, *supra* note 59, at 699–700 (describing single patent exceptions, compassionate use INDs, open label INDs, and the “Group C” program under which the National Cancer Institute furnished investigational cancer drugs to physicians before their approval); *see also* Greenberg, *AIDS*, *supra* note 52, at 316 (describing compassionate use INDs before the AIDS crisis); Zettler, *Implications*, *supra* note 21, at 150 (describing the Group C program).

90. Lawrence K. Altman, *Rare Cancer Seen in 41 Homosexuals*, N.Y. TIMES, July 3, 1981, <https://www.nytimes.com/1981/07/03/us/rare-cancer-seen-in-41-homosexuals.html> [<https://perma.cc/8XF9-WKHE>]; *see* Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720 (June 9, 1983).

91. When a company requests permission to perform clinical trials, it submits an investigational new drug application, or “IND.” Calling the mechanism a “treatment IND” signaled

the proposal was an attempt to partially dismantle the premarket gatekeeping mechanism, advanced by conservatives and libertarians in positions of influence during the Reagan Administration.<sup>92</sup> At one point FDA even proposed shifting the burden to the agency to reject requests for access.<sup>93</sup> The AIDS crisis exploded on the heels of this proposal, however, and many AIDS advocates who sought early access nevertheless supported the basic premarket approval paradigm, rejecting any hint of a lower standard of proof for drugs intended to treat AIDS.<sup>94</sup> With their influence, the final rule was more moderate.<sup>95</sup>

In subsequent years, critics complained that FDA's approach to providing early access lacked clear criteria and submission requirements, leading to inconsistent policies, inequitable access, and preferential access for some categories of patients.<sup>96</sup> Policymakers and courts also continued to hear arguments for early access that combined patient empowerment rhetoric with arguments from rights-based jurisprudence. In 2003, for instance, Abigail Alliance—a public interest group named after a young woman who died of cancer after being denied access to an experimental medicine—asked FDA to permit the commercial sale of drugs after phase 1 trials, contingent on continued progress toward approval.<sup>97</sup> It

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that although the medicine was experimental, the purpose of the use was treatment rather than experimentation.

92. Grossman, *AIDS Activists*, *supra* note 59, at 701.

93. *Id.* at 702–04. FDA also proposed allowing companies to charge for the drugs. *See* Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 8,850 (Mar. 19, 1987) (permitting companies to charge for investigational medicines but allowing FDA to withdraw permission for sale if the price was “manifestly unfair”).

94. Grossman, *AIDS Activists*, *supra* note 59, at 706 (arguing that accelerated approval on the basis of surrogate, rather than clinical, endpoints was controversial within the AIDS community, because it seemed to embrace a lower standard of proof for commercial distribution); *id.* at 714 (pointing out that AIDS activists focused on “bodily freedom” and used the rhetoric of “choice” rather than unrestricted experimentalism). In addition to influencing the development of accelerated approval, AIDS activists played a role in the development of a “parallel track” early access mechanism specific to HIV/AIDS drugs. *Id.* at 718–26; Zettler, *Implications*, *supra* note 21, at 149–50. The parallel track program was meant to enable AIDS patients to enroll in uncontrolled parallel studies, once promising new AIDS drugs began enrollment for Phase 2 trials. *See* Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and Other HIV-Related Disease, 57 Fed. Reg. 13,250 (Apr. 15, 1992). It has not been used much; as of 2005, only one drug (stavudine) had been made available through parallel track. Zettler, *Implications*, *supra* note 21, at 150.

95. Grossman, *AIDS Activists*, *supra* note 59, at 693. *See* Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19,466 (May 22, 1987).

96. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,149 (Dec. 14, 2006) (noting the criticisms). For example, some argued that physicians in academic medical centers tended to be more aware of FDA's early access policies and procedures and that patients treated outside of these centers were therefore unlikely to have access. *Id.*

97. Zettler, *Implications*, *supra* note 21, at 154. By then Congress had also enacted provisions broadly describing expanded access to investigational drugs for treatment use. Food and Drug

then turned to the courts, arguing that the U.S. Constitution provides a right of access to experimental drugs and asking the court to enjoin FDA from preventing the sale of investigational drugs to terminally ill patients.<sup>98</sup> Although Abigail Alliance lost its case,<sup>99</sup> FDA revised its regulations to clarify its early access scheme and improve access, and the resulting “expanded access” regulations remain in place today.<sup>100</sup>

The French history is different, reflecting pressure from patient groups during the AIDS crisis, but no broader movement to eliminate the gatekeeper. There was no legislative basis for access to unapproved medicines before 1992.<sup>101</sup> Patients who had enrolled in clinical trials could sometimes continue treatment while the marketing application was pending, but other patients could not access the unapproved medicine.<sup>102</sup> As in the United States, during the early years of the AIDS crisis patient groups pressed for changes that would allow them medicines still in trials.<sup>103</sup> In 1990, two years after enactment of the first comprehensive French law governing clinical trials,<sup>104</sup> the government decreed that a company

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Administration Modernization Act of 1997, Pub. L. No. 105-115, § 402 (1997) (adding section 561 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb). And it had directed the National Institutes of Health to establish a publicly accessible registry listing ongoing clinical trials of drugs for serious or life-threatening diseases and conditions. *Id.* § 113 (codified at 42 U.S.C. § 282(j)).

98. Zettler, *Implications*, *supra* note 21, at 154–55. Private litigation to force companies to provide access has mostly failed, no matter the legal theory. Shah & Zettler, *supra* note 21, at 152–63 (providing an overview of efforts to obtain access through litigation and noting only one successful contractual claim, which was grounded in an express promise, in *Dahl v. HEM Pharmaceuticals Corp.*, 7 F.3d 1399 (9th Cir. 1993)); *cf.* William M. Janssen, *A “Duty” to Continue Selling Medicines*, 40 AM. J. L. & MED. 330 (2014) (reviewing and dismissing theories for a legal duty to continue selling a medicine once that medicine has been made available, such as a common law duty to initiate a rescue or continue a rescue once initiated). Nor do U.S. or European regulators have any basis to order companies to provide early access. *E.g.*, Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75,150 (“under its existing authority, FDA cannot compel a drug manufacturer to provide access to investigational drugs for treatment use”).

99. *Abigail All. for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007).

100. Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. 40,872 (Aug. 13, 2009) (codified at 21 C.F.R. pt. 312, subpart I).

101. Quiterie de Launet, Agnès Brouard & Christian Doreau, *Les autorisations temporaires d’utilisation (ATU): 50 ans d’histoire de l’évolution de la réglementation des médicaments en France*, 341 REVUE D’HISTOIRE DE LA PHARMACIE 47, 49 (2004).

102. *Id.*

103. *Id.* Groups like Act Up Paris mobilized to gather and share information about the disease and potential treatments, and eventually prominent patient advocates secured seats at the table with government researchers. DIDIER LESTRADE, *ACT UP: UNE HISTOIRE* (2000).

104. Loi 88-1138 du 20 décembre 1988, dite loi Huriet, relative à la protection des personnes qui se prêtent à des recherches biomédicales, J.O., Dec. 22, 1988, p. 16025. The *Loi Huriet* provided a legal framework for clinical trials in France, including the ethical principles of informed consent that apply, and it thus addressed the reluctance of French regulators to authorize trials as well as the liability concerns of doctors and companies—reluctance and concerns that trace their legacy to the Nuremberg Charter after World War II. *See* Anne Laude, *La réforme de la loi sur les recherches*

could in some cases sell investigational medicines to patients unable to enroll in trials.<sup>105</sup> Legislation enacted in 1992 added a new section to the Public Health Code, largely tracking the decree.<sup>106</sup> Further reflection on the AIDS crisis led to later proposals for mechanisms that would allow wider and faster access to unapproved medicines.<sup>107</sup> The resulting law, passed in May 1996, amended the Public Health Code and created the “temporary authorization for use” (ATU) framework in place today.<sup>108</sup>

## 2. Commitment to the Gatekeeping Model

In both countries, early access requires the approval of a regulator. This reflects the basic innovation of twentieth century medicines law and the realization that the public’s interest is best served when scientific and public health authorities have gatekeeping power instead of only the lesser power to take enforcement action after the fact.<sup>109</sup> The standards are similar, reflecting the common themes and origins of the two medicine approval systems. Expanded access in the United States requires a showing that (1) the patient has a serious or immediately life-threatening disease or condition for which there is no comparable or satisfactory alternative therapy; (2) the potential benefit for the patient(s) justifies the potential risks,<sup>110</sup> and the potential risks are not unreasonable in the context of the disease

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*biomédicales*, 2009 RECUEIL DALLOZ 1150.

105. Décret 90-872 du 27 septembre 1990 portant application de la loi Huriot, J.O., Sept. 29, 1990, p. 11862, 11868.

106. Loi 92-1279 du 8 décembre 1992, modifiant le livre V du code de la santé publique et relative à la pharmacie et au médicament, J.O., Dec. 11, 1992, p. 16888, 16891 (adding § L.601-2 to the Public Health Code).

107. de Launet, *supra* note 101, at 51.

108. Loi 96-452 du 28 mai 1996, portant diverses mesures d’ordre sanitaire, sociale et statutaire, J.O., July 6, 1996, p. 7912, 7913. The provisions now appear in Article L.5121-12 of the Public Health Code.

109. Both countries grant most requests, but each denies some. See Jonathan P. Jarow et al., *Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period*, 50 THERAPEUTIC INNOVATION & REG. SCI. 705 (2016) (indicating that FDA rejected roughly thirty-two requests for expanded access between 2005 and 2014). The fact that a regulator generally approves applications for early access does not mean the gatekeeping function is meaningless. First, the approval may follow back-and-forth about appropriate dosing and regimen, among other things. Steve Usdin, *FDA to Facilitate Access to Unapproved Drugs*, BIOCENTURY (Dec. 14, 2018), <https://www.biocentury.com/article/299854/how-fda-plans-to-help-patients-get-expanded-access-to-unapproved-drugs> [<https://perma.cc/2TU7-QCJU>]. Second, marketing applications are also generally approved, and few would argue the preapproval authority is meaningless. Gatekeeping is powerful because it shifts the burden of proof to the party seeking to make a medicine available, it ensures the standard is met before the medicine is made available, and it makes enforcement easier for the government. See *supra* Section 0.

110. When weighing the benefits and risks, FDA will consider the rationale for the intended use of the drug, the criteria for patient selection, pharmacology and toxicology information showing the drug is reasonable safe at the dose intended, and the clinical procedures, laboratory tests, and



being treated; and (3) providing the drug will not interfere with clinical trials that could support marketing approval.<sup>111</sup> In France, the ANSM provides temporary authorization for use, for a limited time and subject to renewal, if (1) the medicine is intended to treat a rare or serious condition, (2) there is no suitable alternative, and (3) there is a presumption of safety and effectiveness.<sup>112</sup> In both countries these general criteria apply to every request for early access, and additional standards must be satisfied depending on whether access will be provided to an individual or a group of patients.

Both countries permit early access for individual patients. In the United States, the general criteria for expanded access must be satisfied, *and* (1) the treating doctor must determine that the probable risk to the patient from the drug is not greater than the probable risk from the disease, and (2) FDA must determine that the patient cannot obtain the drug any other way (for instance, by enrolling in a clinical trial).<sup>113</sup> The agency ordinarily looks for completed phase I trials at doses similar to those proposed for the patient, together with preliminary evidence suggesting effectiveness.<sup>114</sup> In some cases, however, FDA will permit a single patient access based on preclinical (animal) data or even mechanism of action.<sup>115</sup> In France, the ANSM will issue a “nominative” ATU at the request of a doctor, if the basic criteria for ATUs are met, *and* (1) the patient cannot participate in clinical trials, and (2) the benefits to the patient are expected to outweigh the risks.<sup>116</sup> Generally the ANSM requires that there be a submitted or pending application for marketing approval, or at least an ongoing clinical trial in France, but it may make exceptions.<sup>117</sup> Both agencies approve these single-patient requests rapidly: often

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monitoring planned. 21 C.F.R. § 312.305 (2020).

111. 21 C.F.R. § 312.305(a) (2020).

112. *Autorisations temporaires d'utilisation*, ANSM, [https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Qu-est-ce-qu-une-autorisation-temporaire-d-utilisation/\(offset\)/1](https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Qu-est-ce-qu-une-autorisation-temporaire-d-utilisation/(offset)/1) [<https://perma.cc/EGW9-YFUC>]; see generally CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. L.5121-12 (setting rules governing use for therapeutic purposes of medicines without marketing authorization in France); ANSM, NOTICE TO APPLICANTS FOR MARKETING FOR TEMPORARY AUTHORISATION FOR USE (ATU) (July 2015) (hereinafter ATU NOTICE); see also Directive 2001/83, *supra* note 22, at 74 (“A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.”).

113. 21 C.F.R. § 312.310(a) (2020).

114. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,151 (Dec. 14, 2006).

115. *Id.*

116. ATU NOTICE, *supra* note 112, at § 1.1.

117. *Id.* at § 1.1. Indeed, the ANSM may grant access to an unapproved medicine in a desperate case even if the company is not performing clinical trials to support approval. CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. L.5121-12, § III.A.5.

within hours and at most within a few days.<sup>118</sup>

Widespread use in the United States requires a “treatment IND” or “treatment protocol.”<sup>119</sup> The ordinary standards for expanded access apply. If the medicine is intended to treat a serious disease or condition, FDA will look for data from phase 3 trials showing safety and effectiveness, but in some cases it will accept compelling data from phase 2 trials.<sup>120</sup> If the medicine is intended to treat an immediately life-threatening disease, FDA will consider whether “the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury.”<sup>121</sup> This will “ordinarily consist of clinical data from phase 3 or phase 2 trials,” but it could comprise “more preliminary clinical evidence.”<sup>122</sup> Widespread use in France requires a “cohort ATU” proposed by the company developing the drug.<sup>123</sup> The general standards for ATUs apply. Unlike FDA, though, the ANSM also expects the medicine to be the subject of a pending or imminent marketing application.<sup>124</sup> (In this regard, the cohort ATU differs from a nominative ATU, which may be issued earlier in the life of an investigational medicine and can last for years.) This means that “early access” via the cohort ATU in France may not be as *early* in a particular medicine’s research and development timeline as “early access” via treatment INDs in the United States. The industry reports that new medicines become available through the ATU mechanism in France roughly 210 days earlier than they otherwise would become available.<sup>125</sup> The cohort ATU also contains much of the same information as a full-blown marketing application, including

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118. E.g., Lesley R. Navin, *DDI Webinar Series: An Overview of FDA’s Expanded Access Process and the New Individual Patient Expanded Access Application*, FDA 40, <https://www.fda.gov/media/98959/download> [<https://perma.cc/BT59-9TWM>]; ATU NOTICE, *supra* note 112, at § 5.2.

119. 21 C.F.R. § 312.320 (2020). Use will fall under a treatment IND if it is organized by an entity separate from the drug company (which will need the company’s cooperation). Otherwise use falls under a treatment protocol that the company adds to its file at FDA.

120. 21 C.F.R. § 312.320(a)(3) (2020).

121. *Id.*

122. *Id.*

123. *See generally* CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. L.5121-12 (setting rules governing use for therapeutic purposes of medicines without marketing authorization in France); ATU NOTICE, *supra* note 112; Regulation 726/2004, *supra* note 22, at art. 83.

124. A company submits its cohort ATU application when it submits its marketing application or, in some cases, before the marketing application (provided that it files the marketing application within a fixed period of time). ATU NOTICE, *supra* note 112, at § 6.1; *see also* Regulation 726/2004, *supra* note 22, at art. 83.

125. LES ENTREPRISES DU MÉDICAMENT, CHANTIER 3: L’ÉVALUATION ET L’EFFICACITÉ ADMINISTRATIVE POUR UN ACCÈS À L’INNOVATION PLUS RAPIDE (May 10, 2019), <https://www.leem.org/chantier-3-levaluation-et-lefficacite-administrative-pour-un-acces-linnovation-plus-rapide> [<https://perma.cc/2CQN-WGDC>].

draft labeling for the final product and the analytical, preclinical, and clinical data that will ultimately support approval.<sup>126</sup>

Unlike the ANSM, FDA will also permit expanded access for an “intermediate-size” population.<sup>127</sup> The agency explains that this may be necessary if patients cannot participate in ongoing trials—because they do not meet enrollment criteria, because enrollment has ended, or even because the trial site is not geographically accessible.<sup>128</sup> The regulations also describe use of this arrangement when a drug is not under development at all—for instance, because the disease is so rare that the sponsor cannot recruit trial subjects.<sup>129</sup> For intermediate-size groups to enjoy early access, the ordinary standards for expanded access must be met. In addition, there must be (1) enough evidence of safety to justify a clinical trial at the same dose and duration in the same number of people, and (2) preliminary clinical evidence of effectiveness, or of a plausible pharmacologic effect, sufficient to make expanded access use a reasonable therapeutic option for the patients.<sup>130</sup> French law has no equivalent scheme.

These early access mechanisms resonate with the shifting relationship between the individual and the state. Arguments for early access grounded in autonomy principles tended to reason that individuals should have access to medicines of their choosing provided that they are fully aware of the risks and choosing freely.<sup>131</sup> Rights-based jurisprudential arguments similarly focused on the notion that individual rights should rarely be subordinated to the interests of the larger society.<sup>132</sup> Various scholars have pointed out, however, that limiting early access to patients with serious or life-threatening conditions is hard to square with these rationales.<sup>133</sup> After all, if the autonomy principle applies, it surely justifies early access for all patients and not simply the dying.<sup>134</sup> Moreover, some

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126. ATU NOTICE, *supra* note 112, at § 6.1.

127. 21 C.F.R. § 312.315 (2020).

128. 21 C.F.R. § 312.315(a)(2) (2020).

129. 21 C.F.R. § 312.315(a)(1) (2020). Unlike U.S. law, though, French law permits use of the ATU for medicines that treat not only serious diseases but rare diseases. ATU NOTICE, *supra* note 112, at § 1.1.

130. 21 C.F.R. § 312.315(b) (2020).

131. See Schüklenk & Lowry, *supra* note 20, at 10 (discussing this argument).

132. Manik Chahal, *Off-trial Access to Experimental Cancer Agents for the Terminally Ill: Balancing the Needs of Individuals and Society*, 36 J. MED. ETHICS 367, 368 (2010) (“Though risk is evident, according to rights-based theory, competent terminal patients should have the right to choose for themselves what risks they are willing to take, and what actions make life worth living for them.”)

133. *E.g.*, Raus, *supra* note 20, at 1, 7 (identifying and responding to autonomy rationale).

134. Leonard, *supra* note 21, at 1352 (arguing that if expanded access is grounded in an autonomy rationale there is no basis for distinguishing between terminally ill patients and other patients); see also Caplan, *Sound Public Policy*, *supra* note 20, at 2 (arguing that the ethical case for access does not single out the terminally ill as a class deserving of special standing). And, of course, it can be difficult to reach consensus about what exactly constitutes a life-threatening or terminal condition. Caplan, *Sound Public Policy*, *supra* note 20, at 2 (noting that there is no societal consensus

point out that the autonomy rationale may be hard to square with the imposition of any gatekeeping mechanism at all.<sup>135</sup> These are fair points, and indeed some who argue from the autonomy rationale would eliminate the gatekeeper altogether.<sup>136</sup> That the expanded access and ATU schemes do not align perfectly with the autonomy rationale suggests that policymakers considered other principles. The next two subsections explain how the early access schemes in France and the United States reflect additional competing principles.

### 3. *Rigorous Assessment of Informed Consent and Medical Paternalism*

In bioethics, informed consent is consent to a medical intervention, freely given, based on a complete understanding of the intervention, its risks and benefits, and available alternatives.<sup>137</sup> Some argue that uncertainty during premarket testing means that consent is inherently less informed than it would be later.<sup>138</sup> Those arguing from the autonomy principle may respond that a patient can consent to uncertainty as much as to risk. A more compelling concern might be that the very patients for whom early access is considered—those with serious or life-threatening illnesses—may be less likely to give truly informed consent.<sup>139</sup> These patients may be easily swayed by family members who want them to keep fighting, for example, and they may not be emotionally or intellectually prepared to

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on the criteria for classification of a patient as terminally ill and that physicians are “notoriously poor” at predicting the probability of death).

135. Cf. Caplan, *Sound Public Policy*, *supra* note 20, at 2 (arguing that the ethical case for access does not explain why patients should have to wait for phase 1 trial results); Leonard, *supra* note 21, at 1379 (arguing that if a patient’s right to control what he puts in his body is the paramount consideration, there is no basis for requiring any clinical trials or even the prescription requirement).

136. E.g., Epstein, *Erosion*, *supra* note 52, at 574 (“Citizens, as autonomous individuals, should be free to make these decisions for themselves.”); see also Richard A. Epstein, *Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1 (2009) (suggesting elimination of FDA’s gatekeeping role altogether, on autonomy grounds).

137. See Andrea A. Conti, *From informed consent to informed dissent in health care: historical evolution in the twentieth century*, 88 ACTA BIOMEDICA 201 (2017) (describing the principle of informed consent); Joan H. Krause, *Reconceptualizing Informed Consent in an Era of Health Care Cost Containment*, 85 IOWA L. REV. 261, 267–72 (1999) (providing brief overview of the principle and history of informed consent).

138. Carrieri, Peccatori & Boniolo, *supra* note 20, at 68 (noting argument that there is insufficient information for informed consent). Indeed, some would argue that the uncertainty makes rational decision-making impossible; see also Schüklenk & Lowry, *supra* note 20, at 14 (noting this argument).

139. Schüklenk & Lowry, *supra* note 20, at 12 (noting argument that the dying are unable to make fully autonomous choices); see also Jonathan J. Darrow et al., *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279, 284 (2015) (noting that “most patients do not have the training or experience to evaluate the combined pharmacologic, clinical, and statistical information on experimental therapies that is available to them” and that “[r]isk comprehension among the general public is low, is not strongly correlated with self-perceived ability to understand risk, and may be more impaired in sicker patients”).

understand the risks and benefits.<sup>140</sup> Some literature suggests that these patients are prone to therapeutic optimism—an excess of optimism about an intervention’s potential benefits and a tendency to dismiss the potential for harm.<sup>141</sup> Those arguing from the autonomy principle respond that our regulatory framework views patients with serious, life-threatening, even terminal illnesses as competent to enroll in phase 1 and phase 2 clinical trials.<sup>142</sup> This is true even though these subjects often suffer from therapeutic misconception—the mistaken belief that the trial’s purpose is to treat their disease.<sup>143</sup>

Both early access schemes take informed consent seriously. In the United States, the treating doctor is considered an “investigator” (just like an investigator in a normal clinical trial), which triggers the duty to ensure review by an institutional review board (ethics committee), focused on the protection of human subjects.<sup>144</sup> FDA’s informed consent regulations also apply, requiring that the doctor ensure that the patient understands the drug is investigational and that there may be uncertainty about its safety and effectiveness.<sup>145</sup> In France, the treating

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140. See Malinowski, *supra* note 21, at 645 (arguing that the terminally ill should be considered a “vulnerable group” for informed consent purposes).

141. See Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 979; Raus, *supra* note 20, at 7.

142. See John A. Robertson, *Controversial Medical Treatment and the Right to Health Care*, 6 HAST. CTR. REP. 15, 17 (2006) (suggesting these same patients should be able to consent to administration of the same medicines “in a nonresearch setting under a physician’s supervision”).

143. Caplan, *Sound Public Policy*, *supra* note 20, at 2 (“Some patients enrolled in Phase One safety studies believe themselves to be involved in therapeutic experimentation. And almost nothing that any one can do by way of informed consent can disabuse them of this hope.”); Monica H. Schaeffer et al., *The Impact of Disease Severity on the Informed Consent Process in Clinical Research*, 100 AM. J. MED. 261 (1996) (finding that severely ill patients enrolling in phase 1 trials retain the least information from informed consent documents). In other words, these patients believe that investigators focus on the goal of treating them, rather than on strict compliance with the protocol and trial design elements intended to maximize the usefulness and quality of the resulting data. Pat McConville, *Presuming Patient Autonomy in the Face of Therapeutic Misconception*, 31 BIOETHICS 711, 712 (2017); Zettler, *Implications*, *supra* note 21, at 169 (“Even when patients are told they are participating in a research study that is not intended to benefit them personally in any way, patients tend to exhibit a robust therapeutic misconception.”). See also Carrieri, *supra* note 20, at 68 (noting arguments against right-to-try laws given “ethical concern of therapeutic misconception”).

144. 21 C.F.R. § 312.305(c) (2020). This review is meant to ensure that the rights and welfare of human subjects are protected, including by determining that informed consent is obtained in accordance with and to the extent required by federal requirements. FDA, GUIDANCE FOR INDUSTRY: EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE — QUESTIONS AND ANSWERS 1, 5 (Oct. 2017), <https://www.fda.gov/media/85675/download> [<https://perma.cc/6FVZ-MPN6>] (hereinafter EXPANDED ACCESS GUIDANCE). FDA has detailed regulations governing institutional review boards, including their organization, their functions and manner of operation, and the records and reports they must keep. See 21 C.F.R. pt. 56 (2020).

145. FDA, EXPANDED ACCESS GUIDANCE, *supra* note 144, at 6. These detailed regulations cover general requirements for informed consent, exceptions from these requirements, the elements of informed consent, and documentation of informed consent. 21 C.F.R. §§ 50.20-50.27 (2020).

doctor must similarly confirm that the patient has provided informed consent.<sup>146</sup> And although both legal systems envision consent involving the patient *or*, if appropriate, the patient's legally authorized representative, French law *also* allows every patient to designate a trusted person (“*personne de confiance*”) to help with medical decisions.<sup>147</sup>

Although both early access schemes assume that seriously ill and dying patients can make informed decisions about risk and benefit, they are paternalistic in the sense that the regulator plays a direct role in treatment decisions for individual patients.<sup>148</sup> When an individual patient seeks early access in the United States, FDA considers *that* patient's disease, medical history, and prior treatments.<sup>149</sup> It compares the benefits and risks for that patient, and it could in theory reach a different decision than the doctor and patient.<sup>150</sup> The French regulator similarly considers the benefits and risks for individual patients who seek early access. FDA and the ANSM have a more paternalistic role with respect to early access arrangements than with respect to medicines approved for the market. When regulators approve a new medicine, they make the benefit-risk call focusing on the entire intended patient population, and individual treatment decisions are left to doctors.<sup>151</sup> But they oversee individual treatment decisions in early access arrangements.

#### 4. *Prioritizing the Generation of Evidence and Progress Toward Approval*

Early access schemes could interfere with the utilitarian goal of the premarket approval requirement: the generation of high-quality evidence to support market entry and prescribing decisions.<sup>152</sup> A company providing early access spends

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146. ATU NOTICE, *supra* note 112, at § 5.5 (nominative ATU); *id.* at § 6.4 (cohort ATU).

147. CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. L.1111-6; *see also* HAUTE AUTORITÉ DE SANTÉ, LA PERSONNE DE CONFIANCE (Apr. 2016), [https://www.has-sante.fr/upload/docs/application/pdf/2016-03/da\\_personne\\_confiance\\_v9.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2016-03/da_personne_confiance_v9.pdf) [<https://perma.cc/LV39-897Q>].

148. Dresser, *supra* note 21, at 1641–43; Benjamin P. Falit & Cary P. Gross, *Access to Experimental Drugs for Terminally Ill Patients*, 300 JAMA 2793, 2793 (2008) (“Minimization of harm to terminally ill patients is a primary goal of governmentally imposed restrictions on access.”).

149. 21 C.F.R. § 312.305(b)(2)(iii) (2020).

150. In practice, this rarely happens. *See supra* note 109.

151. A doctor may prescribe an approved medicine for any use, including a use for which the medicine is *not* approved. Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972) (“[T]he physician may, as part of the practice of medicine, lawfully . . . vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.”); CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. R.4127-8 (Fr.) (providing that, within the limits of current scientific knowledge, a doctor is free to prescribe the medicine that he considers most appropriate under the circumstances).

152. *See* Caplan & Moch, *Rescue Me*, *supra* note 20 (“In the case of many experimental therapies, there is a clear and growing moral dilemma which society will ultimately need to address:

resources that could instead support ongoing clinical trials and a marketing application. Smaller companies may find it financially prohibitive to supply patients seeking early access while also supplying and funding clinical trials, particularly if the manufacturing process is complex or the raw materials expensive.<sup>153</sup> Diverting resources could slow a medicine's progress to approval and thus delay access for other patients. If the patient seeking early access suffers from a different disease, diverting resources may delay treatment of patients with a disease that the medicine is more likely to treat safely and effectively.<sup>154</sup>

Early access programs may also siphon patients away from trials, interfering with enrollment.<sup>155</sup> This will happen if patients eligible for the trial are also allowed

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Do attempts to help individuals in immediate need place at risk the pursuit of evidence-based regulatory approval that will make a product available as quickly as possible to the largest number of affected and soon-to-be affected individuals?").

153. Tim K. Mackey & Virginia J. Schoenfeld, *Going "Social" to Access Experimental and Potentially Life-Saving Treatment: An Assessment of the Policy and Online Patient Advocacy Environment for Patient Access*, 14 BMB MED. 17, 20 (2016) (noting that "[l]ogistics for investigational drug availability are also challenging, since these drugs are typically manufactured in small lot sizes that can be impacted by manufacturing complications and/or limited availability of active pharmaceutical ingredient/raw materials"); Jerry Menikoff, *Beyond Abigail Alliance: The Reality Behind the Right to Get Experimental Drugs*, 56 KAN. L. REV. 1045, 1063 (2008); Michael Cipriano, *Gottlieb's "Right to Try" Sentiment: Law Fails to Address Difficulties Faced by Drugmakers*, PINK SHEET (Jul. 30, 2018), <https://pink.pharmaintelligence.informa.com/PS123596/Gottliebs-Right-To-Try-Sentiment-Law-Fails-To-Address-Difficulties-Faced-By-Drugmakers> (noting that then-Commissioner Gottlieb pointed out repeatedly that the problem with right-to-try was that companies would not make their drugs available and that with cell-based therapies in particular the "cost of goods isn't trivial"); Kristina Fiore, *Desperate Families Pursue "N-of-1" Trials for Ultra-Rare Diseases*, MEDPAGE TODAY (Aug. 21, 2019), <https://www.medpagetoday.com/special-reports/exclusives/81725> [<https://perma.cc/VH3R-FGXS>] (noting that one small company providing early access to a gene therapy product in 2019 reported a total cost, for four infusions to a single patient, of "hundreds of thousands of dollars").

154. The drug could work in both diseases, to be sure. Abigail Burroughs, for whom the "Abigail Alliance" organization is named, suffered from head and neck cancer and sought (unsuccessfully) access to Erbitux (cetuximab), which was being tested for colon cancer. Complaint at 6–7, Abigail All. for Better Access to Developmental Drugs v. McClellan, Case No. 1:03cv01601, 2004 WL 3777340 (D.D.C. 2004). And today the medicine is approved for both. Still, even if the medicine will work in patients seeking expanded access for a different disease, diverting resources for those patients may slow access for future patients with the first disease the company chose to study.

155. Whether an early access program will discourage participation in ongoing clinical trials may depend on the drug, the disease it is meant to treat, alternative treatments in the market, and the design of the trial. Thousands of patients participated in controlled clinical trials of the lipid-lowering statins, after their approval, to assess their effect on cardiovascular mortality and morbidity, even though these patients faced potential randomization to a potentially inferior alternative therapy. Amicus Brief for Economists John E. Calfee et al. at 14, Abigail All. for Better Access to Developmental Drugs v. Von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007). But low enrollment in the trials of Zidovudine (azidothymidine) in the 1980s suggests that the risk of under-enrollment may be meaningful if the trials are placebo-controlled, particularly if the disease is serious and otherwise untreatable. Leonard, *supra* note 21, at 1361 (noting that patients who were HIV-positive but who did not yet have AIDS would not enroll in clinical trials of AZT in the later 1980s because they were

early access, as they may want to avoid the risk of being randomized to the control group.<sup>156</sup> Interfering with enrollment could slow—or even prevent—the medicine’s progress to market. This will delay or prevent access for future patients, unless those patients also proceed through early access—at which point the premarket approval requirement would become a sham. Slowing the trials not only delays approval for future patients, but also delays the production of robust evidence on which to base treatment decisions.<sup>157</sup> Doctors and patients relying on expanded success during the delay base these decisions on poorer quality evidence.<sup>158</sup>

The French and U.S. schemes address these concerns in three ways, although they differ in the specifics.

First, neither regulator permits early access unless the arrangement will not threaten the completion of trials designed to support approval of the medicine. FDA requires that in all cases of expanded access the agency first find that the proposed use “will not interfere with the initiation, conduct, or completion of clinical trials that could support . . . approval.”<sup>159</sup> An ATU in France may not interfere with the trials that would provide “essential, accurate answers” to questions about the medicine’s benefit-risk ratio.<sup>160</sup>

Second, they partially restrict access to the programs. Limiting an early access program to patients ineligible for clinical trials prevents the program from cannibalizing the pool of potential trial participants. But views on this vary. On the one hand, some suggest equity supports providing early access programs to trial-

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otherwise able to obtain AZT and feared placebo in the trial).

156. Although officials at FDA prefer a placebo control where ethically permissible, in the case of a serious illness patients in a control arm will receive available treatment as a control. Generally controlled trials are viewed as ethical if there is equipoise, meaning genuine uncertainty regarding the comparative therapeutic merits of each arm. Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 *NEW ENG. J. MED.* 141 (1987). Patients may nevertheless decline to enroll due to concerns about receiving an active control rather than the experimental medicine. Menikoff, *supra* note 153, at 1063 (2008) (noting concerns about early access programs affecting enrollment because patients fear randomization); Leonard, *supra* note 21, at 1361.

157. Vinay Prasad & Vance Berger, *Hard-Wired Bias: How Even Double-Blind Randomized Controlled Trials Can Be Skewed from the Start*, 90 *MAYO CLINIC PROC.* 1171, 1171 (2015) (“Well-designed, adequately powered randomized controlled trials . . . are rightfully considered the highest form of evidence on which to base treatment and diagnostic decisions, minimizing potential biases, particularly confounding, that plague nonrandomized of evidence.”).

158. Consider the example of high-dose chemotherapy followed by autologous bone marrow transplant, which was under investigation for treatment of breast cancer. Patients had access to the treatment while the trial was underway, not because of an early access program but because FDA had already approved the chemotherapy agent for another use. This led to low enrollment in the trials, which delayed the eventual finding that the procedure offered no benefit over less risky alternatives. Shah & Zettler, *supra* note 21, at 178–79; *see also* Dresser, *supra* note 21, at 1650.

159. 21 C.F.R. § 312.305(a)(3) (2020).

160. ATU NOTICE, *supra* note 112, at § 1.1.



*ineligible* patients, because these patients are denied access to trials through no fault of their own.<sup>161</sup> Some add that, essentially for utilitarian reasons, regulators must deny early access to patients who could enroll in clinical trials.<sup>162</sup> On the other hand, some have argued that controlled trials are inherently coercive and thus ethical only if trial-eligible patients may obtain access outside the trials.<sup>163</sup> And sometimes requiring that patients be ineligible for trials is a sham, because eligible patients can render themselves ineligible.<sup>164</sup> This second, more expansive view, that early access should be open to all, has not prevailed, perhaps because it risks compromising a medicine's progress to market. Some have also pointed out that opening early access schemes to all patients can raise equity issues if patients with greater resources choose early access to avoid the risks of randomization.<sup>165</sup> Both regulators limit single-patient access to trial-ineligible patients. In the United States, single patients are eligible for early access only if they cannot obtain the drugs in clinical trials.<sup>166</sup> The ANSM will issue an ATU for a single patient only if that patient cannot participate in a clinical trial.<sup>167</sup> For intermediate-size patient groups, FDA will also entertain arguments that the patients are theoretically trial-eligible but *unable* to enroll (for instance, because of geographic proximity to trial sites and lack of resources, over which they have little control).<sup>168</sup> Widespread early access in both countries is available for patients with the disease that the company is studying in controlled trials for marketing approval.<sup>169</sup>

Third, the regulators mitigate the effect of early access on progress to approval by limiting these arrangements to drugs that are nearly finished with premarket research and development. French law embraces this solution more than U.S. law does. The ANSM will not approve a cohort ATU unless the medicine is the subject of a pending or imminent marketing application.<sup>170</sup> In contrast, widespread use under a treatment IND or treatment protocol in the United States usually requires ongoing or completed controlled clinical trials, but can be based on more

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161. Raus, *supra* note 20, at 3 (describing the argument).

162. *E.g.*, Falit & Gross, *supra* note 148, at 2794 (arguing that “authorities must deny access to experimental drugs for patients who are eligible for clinical trials” and “individuals should be adequately deterred from gaming the system by, for instance, initiating therapy with an alternative compound that renders them ineligible for a study”).

163. Schüklenk & Lowry, *supra* note 20, at 20 (noting argument).

164. Walker, *supra* note 20, at 11.

165. *Cf.*, Schüklenk & Lowry, *supra* note 20, at 8 (noting argument that it is coercive to require the terminally ill to risk randomization for the sake of future patients).

166. 21 C.F.R. § 312.310(a)(2) (2020).

167. ATU NOTICE, *supra* note 112, at § 1.1.

168. 21 C.F.R. § 312.515(a) (2020); *see* Carrieri, Peccatori & Boniolo, *supra* note 20, at 66 (suggesting an ethical argument for access in this situation).

169. 21 CFR 312.320(a)(1)(i) (2020); ATU NOTICE, *supra* note 112, at § 6.1.

170. Regulation 726/2004, *supra* note 22, at art. 83.

preliminary data in appropriate situations.<sup>171</sup> For individuals, both regulators will permit access well before phase 3 trials, and FDA will do so even based only on animal testing.<sup>172</sup> And, again, in the United States, an “intermediate-size” group can benefit from early access even if the medicine is not being developed at all.<sup>173</sup> This is impossible in France.

Limiting early access schemes to patients who are ineligible for trials, or to drugs that are nearing premarket approval, is hard to square with autonomy arguments. These limitations reflect instead the influence of utilitarian arguments that the public’s interest in the development of high-quality evidence for proposed new medicines outweighs any individual interests in earlier access.<sup>174</sup> The U.S. expanded access scheme is less limited in these respects than the French ATU scheme, perhaps reflecting greater policymaking deference to autonomy arguments. In the end, though, FDA will still refuse access if it will interfere with trials that could support approval.

Some suggest that the effect of early access on the public’s interest can be partially mitigated by the collection of evidence from early access arrangements, which can inform the regulator’s understanding of the medicine, for the benefit of other patients. Although views vary on the ethics of using data from early access for research,<sup>175</sup> both schemes require the collection and submission of data. When an individual patient receives expanded access in the United States, either the treating doctor or the company must send FDA a written summary of the results.<sup>176</sup>

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171. 21 C.F.R. § 312.320(a)(1) (2020); 21 C.F.R. § 312.320(a)(2) (2020).

172. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,151. For example, in 2019 a 25-year-old woman from Iowa received an experimental antisense oligonucleotide (ASO) targeted at the gene mutation responsible for her rare form of amyotrophic lateral sclerosis (ALS). The company developing the ASO had completed *in vitro* and animal testing, but no trials in humans. Fiore, *supra* note 153; Stella Daskalakis, *Jaci Hermsstad Receives Seventh ASO Infusion as her Mother Honors Her in New York*, KTIV.COM (Oct. 23, 2019), <https://ktiv.com/2019/10/23/jaci-hermsstad-receives-seventh-aso-infusion-as-her-mother-honors-her-in-new-york/> [<https://perma.cc/NA7M-QFAA>].

173. 21 C.F.R. § 312.315(a)(1) (2020). It is unclear whether expanded access has ever been provided on this basis. Expanded access is also available if the drug is approved but no longer marketed, or if the drug contains the same active moiety as an approved but unavailable drug. *Id.* at (a)(3).

174. Leonard, *supra* note 21, at 1343–44; Carrieri, Peccatori & Boniolo, *supra* note 20, at 68 (noting that early access has “direct negative implications for [randomized clinical trials] and general public health interests”). Permitting earlier access for the subset of the population with serious conditions, as both regulators do, also arguably increases overall utility, because this group has a different risk-benefit tradeoff than does the population at large.

175. Walker, *supra* note 20, at 11–12 (reasoning that early access programs might be ethical if they contribute to our understanding of the experimental medicines in question); *but see* Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 981 (noting disagreement about whether it is morally acceptable to collect research data within expanded access programs).

176. 21 C.F.R. § 312.310(c)(2) (2020).

Adverse events must be reported to the agency,<sup>177</sup> and the safety data must be included in any marketing application submitted.<sup>178</sup> Safety data from expanded access could even support the approval decision.<sup>179</sup> The effectiveness data from expanded access, however, are lower in quality than effectiveness data from randomized controlled trials, and they might not support—let alone justify—a finding of effectiveness under the U.S. drug statute.<sup>180</sup> In France, patient monitoring and data collection under an ATU are governed by a protocol for therapeutic use and information collection, drawn up by the company and the ANSM.<sup>181</sup> The company also has adverse event reporting obligations.<sup>182</sup> And with a cohort ATU, the ANSM receives information about the characteristics of the patients, the effectiveness of the medicine, and adverse events resulting from its use.<sup>183</sup> The company must analyze the medicine’s benefit-risk ratio in light of this information.<sup>184</sup>

### III. THE RIGHT-TO-TRY ALTERNATIVE IN THE UNITED STATES

Expanded access in the United States and ATU in France are broadly consistent with the approach and goals of the new medicine approval paradigm. They similarly assume that a scientific agency should serve as the gatekeeper—here, deciding whether a particular patient (or group of patients) may access a

177. 21 C.F.R. § 312.305(c)(4) (2020).

178. 21 C.F.R. § 314.50(d)(5)(iv) (2020) (requiring that an application include a “description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic”).

179. Approval of Epidiolex (cannabidiol) in 2018 was supported in part by safety data from nearly 700 patients who received the product through expanded access. Sean M. O’Connor & Erika Lietzan, *The Surprising Reach of FDA Regulation of Cannabis, Even After Descheduling*, 68 AM. U. L. REV. 823, 917–18 (2018). See also Kate Rawson, *Expanded Access Data Can Support Approval Decisions*, *FDA Says*, PINK SHEET (Nov. 21, 2018), <https://pink.pharmaintelligence.informa.com/PS124296/Expanded-Access-Data-Can-Support-Approval-Decisions-US-FDA-Says> (citing other examples).

180. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40,900, 40,905 (Aug. 13, 2009) (“Because expanded access programs are typically uncontrolled exposure (with limited data collection), it is very unlikely that an expanded access IND would yield effectiveness information that would be useful to FDA in considering a drug’s effectiveness.”); Jan Borysowski, Hans-Jörg Ehni & Andrzej Górski, *Ethics Review in Compassionate Use*, 15 BMC MED., Jul. 24, 2017, at 3 (“Indeed, the value of data collected during the conduct of compassionate use is limited, especially compared to that of randomized controlled trials, the contemporary gold standard of drug efficacy and safety studies”).

181. CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. R.5121-70; ATU NOTICE, *supra* note 112, at § 1.1.

182. ATU NOTICE, *supra* note 112, at § 7.2.2.1, CODE DE LA SANTÉ PUBLIQUE [PUBLIC HEALTH CODE] art. R.5121-166.

183. ATU NOTICE, *supra* note 112, at § 6.2.

184. *Id.* at § 6.9.

medicine. And their design reflects the premise that the paramount goal of a medicine regulatory system remains the generation of high-quality evidence to support a scientific decision on approval for the market. In 2018, the U.S. Congress passed a law taking a fundamentally different approach.<sup>185</sup> The right-to-try law permits access to unapproved medicines without the prior involvement of FDA, rejecting the premarket review mechanism that has characterized new medicines frameworks since the mid-twentieth century in favor of limited *post hoc* enforcement power.

### *A. Elimination of the Gatekeeper*

Congress added a new section to the U.S. drug statute, exempting certain drugs provided to certain patients from the gatekeeping provisions of that statute and from FDA's regulations implementing those provisions. The patient must be diagnosed with a life-threatening disease or condition—generally meaning the likelihood of death is high unless the course of disease is interrupted.<sup>186</sup> (In contrast, expanded access is available when the disease is “serious or immediately life-threatening,” which is broader, because “serious” diseases are included.<sup>187</sup>) The patient must have exhausted approved treatment options and must be unable to participate in a clinical trial involving the drug.<sup>188</sup> The drug itself must be the subject of a pending marketing application or a clinical trial intended to form the primary basis of a claim of effectiveness in an application, and it must have completed phase 1 trials.<sup>189</sup> (In contrast, FDA can authorize expanded access at any time during premarket trials, including phase 1 trials, or even earlier.<sup>190</sup>) If all these criteria are met, the drug may be provided to the patient.

The federal government does not play a role in determining whether these conditions are met. Neither the company nor the doctor seeks permission from FDA.<sup>191</sup> If anyone (apart from the company) plays a gatekeeping role, it is state-licensed doctors. However, FDA must have already given permission for the phase 1 trials, and this limits the pool of permitted compounds to those that the government has deemed safe enough to test in humans. But a patient exercising

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185. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act, Pub. L. No. 115-176, 132 Stat. 1372 (2018) (largely codified at 21 U.S.C. § 360bbb-0a).

186. 21 U.S.C. § 360bbb-0a(a)(1)(A) (2018) (referring to the definition of “life threatening” that appears in 21 C.F.R. § 312.81)). A disease is also life-threatening if it has a potentially fatal outcome and the endpoint for preapproval clinical trials is (or in this case, would be) overall survival. 21 C.F.R. § 312.81(a)(2) (2020).

187. *See supra* Section 0. A disease is considered serious if it is associated with morbidity that has a substantial impact on day-to-day functioning. 21 C.F.R. § 312.300(b) (2020).

188. 21 U.S.C. § 360bbb-0a(a)(1)(B) (2018).

189. 21 U.S.C. § 360bbb-0a(a)(2) (2018).

190. *See supra* Section 0.

191. 21 U.S.C. § 360bbb-0a(b) (2018) (exempting eligible drugs from 21 C.F.R. pt. 312).

the “right to try” does not need to ask the government’s permission. Instead, before the drug can be provided to the patient, a physician in good standing with the appropriate licensing board must determine that the patient has exhausted approved treatment options and cannot participate in a clinical trial. (In contrast, in expanded access situations, FDA makes this determination.<sup>192</sup>) The right-to-try law specifies no actor to enforce the other two threshold eligibility requirements—that the patient’s disease is life-threatening, and that the patient provided informed consent. (In contrast, in expanded access, FDA determines whether the patient’s disease qualifies, holds the investigator responsible for securing informed consent, and requires ethics committee review.<sup>193</sup>)

FDA’s role here is, at best, after the fact. The agency would have to learn of the procedure in the first instance and then, believing that the patient had not provided informed consent or did not suffer from a life-threatening disease, claim that the patient had not been eligible for right-to-try access. If either is true, the drug was *not* exempt from FDA’s gatekeeping authorities, and FDA could take enforcement action. (It would charge the company with introduction of a new drug into interstate commerce without an approved marketing application or effective IND.<sup>194</sup>) But the agency will not learn about right-to-try treatments until the company’s annual summary of right-to-try uses, and the statute does not require those summaries to identify investigators or patients.<sup>195</sup> Even if the agency knew each patient’s identity, it is not clear how FDA could conclude that a patient did not provide informed consent, because the law also says that FDA’s regulations on the protection of human subjects, including the informed consent requirements, do not apply.<sup>196</sup> Presumably FDA would have to find that the relevant state law standard was met, but a court would not defer to its interpretation of that state law. So, these limitations may turn out to be a sham.<sup>197</sup>

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192. 21 C.F.R. § 312.305(a)(1) (2020) (“FDA must determine that . . . there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition”).

193. *E.g.*, 21 C.F.R. § 312.305(a)(1) (2020) (“FDA must determine that the patient or patients to be treated have a serious or immediately life-threatening disease or condition . . .”); 21 C.F.R. § 312.305(c)(4) (2020) (holding the investigator responsible for ensuring informed consent).

194. 21 U.S.C. § 355(a) (2018).

195. FDA plans to issue regulations implementing the annual summary requirement. Michael Cipriano, *Expanded Access Program Improving, But Sponsor Concerns Linger*, PINK SHEET (Sept. 10, 2019), <https://pink.pharmaintelligence.informa.com/PS140818/Expanded-Access-Program-Improving-But-Sponsor-Concerns-Linger>; *OMB Reviewing FDA Proposal for Right to Try Reporting Requirements*, FDA WEEK (Apr. 3, 2020).

196. FDA’s regulations requiring institutional review board (ethics committee) review also do not apply. 21 U.S.C. § 360bbb-0a(b) (2018).

197. To be fair, state law will usually impose its own informed consent obligation on treating doctors. And it may require that access proceed through the same kind of ethics review as FDA would have required. *See* Jeannie Baumann, *Experimental Drug Requests Rising Faster Than Previously Thought*, BLOOMBERG LAW (Nov. 18, 2019), <https://news.bloomberglaw.com/pharma-and-life-sciences/experimental-drug-requests-rising-faster-than-previously-thought> (noting California law

The right-to-try law also strips FDA of its ability to impose conditions on access.<sup>198</sup> For example, in ordinary expanded access situations, the sponsor of the trial (usually the drug company) must notify FDA of any serious and unexpected adverse reaction within 15 days.<sup>199</sup> It also notifies investigators working with the drug. These rules do not apply to drugs made available under right-to-try. The right-to-try law does require each company's annual summary to identify "any known serious adverse events,"<sup>200</sup> but FDA's detailed adverse event rules do not apply,<sup>201</sup> and agency officials believe the data in these annual summaries will be of low quality.<sup>202</sup> FDA's rules relating to maintaining control of the investigational medicine also do not apply,<sup>203</sup> nor do its recordkeeping rules.<sup>204</sup> And the agency has no power to call a halt to the process when patients are subject to unreasonable risk of injury or when the doctors lack the training and experience necessary to administer the drug.<sup>205</sup>

Only three FDA regulations relating to investigational medicines still apply: a regulation governing labeling,<sup>206</sup> a regulation prohibiting promotion,<sup>207</sup> and the regulation limiting how much the company can charge (only the direct costs of making the medicine available).<sup>208</sup> And the agency will have to enforce these rules

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requires that an institutional review board review each access request).

198. 21 U.S.C. § 360bbb-0a(b) (2018) (exempting eligible drugs from sections 502(f), 503(b)(4), 505(a), and 505(i) of the Federal Food, Drug, and Cosmetic Act as well as section 351(a) of the Public Health Service Act, and parts 50, 56, and 312 of title 21 of the Code of Federal Regulations).

199. 21 C.F.R. § 312.32(c) (2020).

200. 21 U.S.C. § 360bbb-0a(d)(1) (2018).

201. *See* 21 C.F.R. § 312.32 (2020) (ordinary adverse event reporting framework, which does not apply).

202. Derrick Gingery, *Unlicensed Stem Cell Clinics are 'Surrogate' for Right to Try, US FDA's Marks Says*, PINK SHEET (Nov. 21, 2018), <https://pink.pharmaintelligence.informa.com/PS124294/Unlicensed-Stem-Cell-Clinics-Are-Surrogate-For-Right-To-Try-US-FDAs-Marks-Says>.

203. *Compare* 21 C.F.R. § 312.61 (2020) ("The investigator shall not supply the investigational drug to any person not authorized under this part to receive it."), *with* 21 U.S.C. § 360bbb-0a(b) (2018).

204. *Compare* 21 C.F.R. § 312.62(a) (2020) ("An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug"), *with* 21 U.S.C. § 360bbb-0a(b) (2018).

205. *Compare* 21 C.F.R. § 312.42(b)(1) (2020), *with* 21 U.S.C. § 360bbb-0a(b) (2018).

206. 21 C.F.R. § 312.6 (2020). This requires that (1) the package label state the drug is limited to investigational use, and (2) the label and labeling not bear any false or misleading statement and not represent that the drug is safe and effective for the purpose for which it is being investigated.

207. 21 C.F.R. § 312.7 (2020). This prohibits (1) representing in a promotional context that the drug is safe and effective for the purpose for which it is being investigated, (2) commercial distribution of the drug, and (3) "unduly" prolonging the investigation after generating sufficient data to support approval.

208. 21 C.F.R. § 312.8(d)(1) (2020). There is confusion on this point. *E.g.*, Adam Feuerstein,

after the fact, when it receives the company's annual summary.

The drug industry did not support the law.<sup>209</sup> The law subverts an eighty-year-old approach to medicine regulation, and its underpinnings may be deeply uncomfortable for the scientific and regulatory personnel at larger companies that operate within, understand, and agree with the basic approach to medicines regulation in this country.<sup>210</sup> Representatives of the Goldwater Institute insist that the scheme is being used,<sup>211</sup> but speakers at a recent conference could identify only one company using the “right to try.”<sup>212</sup> Many companies have said they will

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*Here comes the right-to-try profiteers: The FDA is powerless to stop them*, STAT NEWS (June 20, 2018), <https://www.statnews.com/2018/06/20/right-to-try-opportunism> [<https://perma.cc/8NH2-TUDK>] (stating that medicines can be sold “at a profit” and quoting one CEO who was considering charging \$300,000 per treatment).

209. See Stephen Barlas, “*Right-To-Try*” Legislation Moving Through Congress, But Drug Companies and Some Patient Groups Want Changes, 42 PHARMACY & THERAPEUTICS 739, 739 (2017) (“The Biotechnology Innovation Organization (BIO), the trade group that represents many smaller biopharmaceutical companies, especially those involved in biologics, also opposes the bill.”); *id.* at 741 (“Research pharmaceutical companies are not enthusiastic about the bill.”); *Early Access Programs: Points to Consider*, BIO 2–4 (Apr. 16, 2010), <https://www.bio.org/sites/default/files/legacy/bioorg/docs/files/20100416.pdf> [<https://perma.cc/4PVJ-LCQY>] (“A patient’s right to treatment based on his or her autonomous decision-making ability does not supersede a company’s ethical responsibility to develop and market safe and effective products as fast as possible . . . . In some circumstances, . . . by allowing early access, the company risks market approval of the product. Thus, the question often confronting companies is whether to put an entire project at risk – and therefore jeopardize availability of a drug for a larger patient population – in order to provide early access to a product for an individual or small group of patients.”)

210. Criticism of the state right-to-try laws and the federal proposal was robust. Rebecca Dresser, “*Right to Try*” Laws: The Gap between Experts and Advocates, 45 HASTINGS CTR. REP. 9, 9 (2015) (“Scientists and policy experts are virtually unanimous in criticizing right to try laws.”); Christopher Morrison, *Critics Say “Right to Try” Wrong for Patients*, 36 NATURE BIOTECHNOLOGY 294, 294 (2018) (noting the opposition of “a diverse group” of critics including “many patient advocacy groups, the biotech industry, and FDA officials”).

211. Michael Cipriano, *Right to Try Conversation Should be Redirected Toward Reimbursement of Unapproved Drugs, Experts Say*, PINK SHEET (Jan. 29, 2019), <https://pink.pharmaintelligence.informa.com/PS124659/Right-To-Try-Conversation-Should-Be-Redirected-Toward-Reimbursement-Of-Unapproved-Drugs-Experts-Say> (quoting Goldwater representative that companies are using it).

212. Sue Sutter, *Expanded Access Advocates Seek Reimbursement Mandate, Manufacturer Incentives from Congress*, PINK SHEET (Feb. 11, 2020), <https://pink.pharmaintelligence.informa.com/PS141654/Expanded-Access-Advocates-Seek-Reimbursement-Mandate-Manufacturer-Incentives-From-Congress> (noting that “Epi-topoietic Research Corporation has approved 10 requests for access to Gliovac (ERC1671), a cell-based immunotherapy for glioblastoma multiforma and gliosarcoma,” under a right-to-try program). See also *ERC-USA Initiates Therapy Under Right to Try Law with First Patient in California Using Investigational Compound ERC1671 for Treatment of Glioblastoma*, GLOBENEWSWIRE (Jan. 8, 2019), <https://www.globenewswire.com/news-release/2019/01/08/1682156/0/en/ERC-USA-Initiates-Therapy-Under-Right-to-Try-Law-With-First-Patient-In-California-Using-Investigational-Compound-ERC1671-for-Treatment-of-Glioblastoma.html> [<https://perma.cc/U8ZF-ND4F>]

continue to provide experimental medicines under traditional expanded access programs or simply focus on seeking approval.<sup>213</sup>

*B. Explaining the Enactment of Right-to-Try in the United States*

The right-to-try mechanism differs conceptually from the early access mechanisms in the United States and France. The early access mechanisms assume that generating high-quality phase 3 data and securing regulatory approval remain paramount goals, and thus retained the regulator's gatekeeping role. Proponents of the right-to-try law explicitly rejected this utilitarianism, saying that "the most troubling argument in favor of the FDA's veto power is that the agency is always mindful of the effect expanded access may have on the clinical-trial process."<sup>214</sup> Its legislative sponsors openly explained that the law was meant to reduce FDA's power and, instead, empower patients to choose potentially life-saving therapies.<sup>215</sup> These arguments suggest that enactment of the right-to-try law in the United States can be explained by three things.

First, the United States has a robust history and tradition of valuing personal autonomy, including autonomy in personal medical decisions. Proponents of the "right to try" invoked this tradition, putting forward arguments that found their roots in the writing of John Stuart Mill and Gerald Dworkin—that the state may interfere with the choices of an autonomous individual only to prevent harm to others.<sup>216</sup> The individual, they argued, has a moral right—perhaps a constitutional right, some argued<sup>217</sup>—to try to save his or her own life. Further, the state cannot

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213. Derrick Gingery, *Unlicensed Stem Cell Clinics*, *supra* note 202 (noting that Johnson & Johnson has declined to use right-to-try and that Brainstorm Cell Therapeutics, developing Nurown for ALS, announced in June 2018 that it would use right-to-try and then changed its mind); Sue Sutter, *Why The Right-to-Try Law is Not Right for Some Biotech Companies*, PINK SHEET (June 13, 2018), <https://pink.pharmaintelligence.informa.com/PS123274/Why-The-RightToTry-Law-Is-Not-Right-For-Some-Biotech-Companies> (noting that Alnylam and Sarepta said they would not use it because they are focusing on approval).

214. Corieri, *supra* note 16, at 16.

215. Letter from Sen. Ron Johnson, Chairman, Senate Committee on Homeland Security and Governmental Affairs, to Scott Gottlieb, Comm'r, FDA (May 31, 2018), <https://www.hsgac.senate.gov/media/majority-media/johnson-to-fda-agency-should-comply-with-right-to-try-law> [<https://perma.cc/Q3T8-BVJ9>] ("[T]his legislation is fundamentally about empowering patients to make decisions in cooperation with their doctors and the developers of potentially life-saving therapies . . . [and it] intends to diminish the FDA's power over people's lives, not increase it.").

216. Corieri, *supra* note 16, at 21–22; *see also* Bruce J. Winick, *On Autonomy: Legal and Psychological Perspectives*, 37 VILL. L. REV. 1705, 1712 (1992) (discussing John Stuart Mill's "harm principle," that "the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others" in the context of various healthcare decisions); *see generally* JESSICA FLANIGAN, PHARMACEUTICAL FREEDOM: WHY PATIENTS HAVE A RIGHT TO SELF-MEDICATE (2017).

217. *E.g.*, Volokh, *supra* note 21, at 1829–30; Corieri, *supra* note 16, at 21.



“reasonably demand” to decide what risks an informed and competent individual may take when facing death.<sup>218</sup> Respect for personal autonomy means leaving this decision to the patient. In the United States, the strong consumer empowerment movement and a political-legal commitment to the unencumbered flow of information acclimated patients to a high degree of involvement in their healthcare decisions. This aligns with the U.S. emphasis on personal autonomy and provided fertile ground for the right-to-try movement.<sup>219</sup>

Second, many in the United States favor a reduced role for government, especially the federal regulatory apparatus. Two strands of thinking are at play here. To begin with, the federalist system of governance generally reserves to the states matters relating to medicine and health.<sup>220</sup> This leads to skepticism about, and hostility towards, a federal agency intervening when a state-regulated doctor decides the best course forward for a patient. The state right-to-try laws trace their lineage to laws enacted forty years ago, when patients—frustrated with FDA’s failure to approve Laetrile for the treatment of cancer—persuaded the states to legalize its sale within their borders.<sup>221</sup> There is also a robust deregulatory movement in the United States only tangentially related, if at all, to state’s rights. Thirty years ago during the AIDS crisis, some were prepared to repeal the effectiveness standard or even eliminate FDA’s gatekeeping role altogether.<sup>222</sup> Patient groups were divided over the ultimate objective: some merely sought early access but embraced the goal of full approval under the approval standard, while others focused on, as one scholar recently put it, getting “drugs into bodies.”<sup>223</sup> In the 1990s, the latter groups found common cause with deregulatory forces. The same thing happened with the right-to-try initiative, the origins of which lie with the Goldwater Institute, a conservative and libertarian public policy think tank in Arizona. This organization drafted a model right-to-try law in February 2014, which it then distributed to the states.<sup>224</sup> A majority of states passed right-to-try laws in the years that followed.<sup>225</sup> The proliferation of state laws snubbing the

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218. Schüklenk & Lowry, *supra* note 20, at 11 (describing the argument).

219. The law passed with a “sense of the senate” provision stating that the law “expands the scope of individual liberty and agency among patients.” Pub. L. No. 115-176 § 3, 132 Stat. 1372 (2018).

220. Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L. J. 845 (2018).

221. Grossman, *AIDS Activists*, *supra* note 59, at 693.

222. *Id.* at 712.

223. *Id.* at 706.

224. Zettler & Greely, *Strange Allure*, *supra* note 21, at 1885.

225. The state laws varied somewhat in their details. Most state laws authorized doctors to prescribe—and companies to provide and charge for—investigational medicines that had completed phase 1 trials. Some also provided the doctor and company with protection from liability arising from the injury. *E.g.*, 2015 OR. LAWS ch. 819 (codified at OR. REV. STAT. § 127.990 (2019)). Despite these state laws, federal law continued to prohibit the shipment of unapproved medicines across state lines to patients. 21 U.S.C. § 355(a) (2018). Some supported the federal right-to-try legislation for this

federal government eventually provided the catalyst for the federal law.<sup>226</sup> Enactment of the right-to-try law thus reflects an alignment between patients' rights groups and deregulatory libertarians, the seeds of which had been planted during the Reagan Administration. Like AIDS advocates in the 1990s who were presented with proposals to dismantle FDA, patients eventually realized that the right-to-try proposal was not in their interests; it was mainly an attack on FDA regulatory power and was not designed—or, as explained in the next Section, likely—to increase their access to unapproved drugs.<sup>227</sup> But by then it was too late.

Third, healthcare delivery in the United States is colored by widespread fear, and even denial, of mortality. Popular culture venerates youthfulness and vigor, while respectful representations of the elderly and dying are virtually absent.<sup>228</sup> Patients and their caregivers are slow to discuss palliative care and slower still to seek hospice.<sup>229</sup> Physicians are often reluctant to begin end-of-life care discussions with their patients.<sup>230</sup> Discussions of terminal illness are cast in metaphors of war, and death itself characterized as “loss” of a “battle”—creating a sense of failure in

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reason: to give effect to the clear policy preference of the states. *E.g.*, Ellen A. Black, *State “Right to Try” Acts: A Good Start, but a Federal Act is Necessary*, 45 SW. L. REV. 719, 755 (2016) (arguing that “a federal right to try act, such as the Right to Try Act of 2015, is necessary to enable the implementation of state right to try acts”).

226. This pattern is not uncommon. *See* Diane R. H. Winters, *The Benefits of Regulatory Friction in Shaping Policy*, 71 FOOD & DRUG L. J. 228 (2016) (discussing other examples).

227. Carrieri, Peccatori & Boniolo, *supra* note 20, at 67 (noting that “[right to try] laws appear to be a largely symbolic attack to the governmental authority of the FDA, masked by libertarian ethos of conferring more rights to patients”); Barlas, *supra* note 209, at 741 (noting that the bill was “presented as a boon to terminally ill individuals” but was in fact “opposed by so many groups representing them”).

228. Kirk Combe & Kenneth Schmader, *Naturalized Myths of Aging: Reading Popular Culture*, 4 J. AGING & IDENTITY 79 (1999) (concluding that “the majority of Americans have generally negative attitudes towards elders and the aging process,” and that the “ageism” that “permeates our culture” is in large part due to popular culture’s impact on common opinion); *see, e.g.*, Stacy L. Smith, Marc Choueiti & Katherine Pieper, *Over Sixty, Underestimated: A Look at Aging on the Silver Screen in Best Picture Nominated Films*, USC ANNENBERG SCH. FOR COMM’N & JOURNALISM (Feb. 2017), [https://www.annenberg.usc.edu/sites/default/files/Over\\_Sixty\\_Underestimated\\_Report\\_2\\_14\\_17\\_Final.pdf](https://www.annenberg.usc.edu/sites/default/files/Over_Sixty_Underestimated_Report_2_14_17_Final.pdf) [<https://perma.cc/U77K-G5XD>] (finding that seniors are “scarce” in films and finding a prevalence of negative verbal and nonverbal references to age).

229. *E.g.*, Lisa Jane Brighton & Katherine Bristowe, *Communication in Palliative Care: Talking about the End of Life, Before the End of Life*, 92 POSTGRADUATE MED. J. 466 (2016); Aline Sarradon-Eck et al., *Understanding the Barriers to Introducing Early Palliative Care for Patients with Advanced Cancer: A Qualitative Study*, 22 J. PALL. MED. 508 (2019).

230. Kay Manning, *Doctors Slow to Have End-of-Life Conversations*, CHI. TRIB. (Dec. 6, 2016), <https://www.chicagotribune.com/lifestyles/health/sc-end-of-life-health-1207-20161205-story.html> [<https://perma.cc/V5ZM-QXDX9>]; Barbara Feder Ostrov, *Most Doctors Unsure How to Discuss End-of-Life Care, Survey Says*, KAISER HEALTH NEWS (Apr. 14, 2016), <https://khn.org/news/most-doctors-unsure-how-to-discuss-end-of-life-care-survey-says> [<https://perma.cc/S2AL-B7EB>]; Mieke Visser, Luke Deliens & Dirk Houttekier, *Physician-Related Barriers to Communication and Patient- and Family-Centered Decision-Making Towards the End of Life in Intensive Care: A Systemic Review*, 18 CRITICAL CARE 604 (2014).

death and a corresponding sense of obligation to fight.<sup>231</sup> This fuels not only an immense body of research focusing on longevity, but also a powerful technological imperative—to save life at any cost, to exhaust all possibilities that medical science has to offer.<sup>232</sup> This aligns with a powerful norm in the United States: the duty to seek to rescue.<sup>233</sup> Together, these factors create fertile ground for a law that appears to give more options to the desperately ill.

In contrast, two aspects of the French legal and cultural landscape make the “right to try” an unlikely fit.

First, the French healthcare system remains paternalistic. The law only recently recognized the patient’s right to information about his or her own health.<sup>234</sup> Patients have less access to information about medical products than in the United States and fewer options to purchase medical products without the involvement of a healthcare professional. There is no direct-to-consumer advertising of prescription drugs in France.<sup>235</sup> Under the “monopole officinal,” only authorized pharmacies may sell medicines. No medicines are sold over the counter in the sense that they are sold in the United States—freely at a gas station or in a grocery store, without the involvement of a pharmacist.<sup>236</sup> And although each country has responded to drug safety tragedies by giving its medicines regulator more power, the French response—to crises from the Stalinon affair in

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231. *E.g.*, Carrieri, Peccatori & Boniolo, *supra* note 20, at 68 (noting U.S. “social norms and expectations of maintaining a ‘fighting spirit’”).

232. *E.g.*, Malinowski, *supra* note 21, at 632 (noting the “compulsion to exhaust all medical science resources”).

233. Caplan & Moch, *Rescue Me*, *supra* note 20.

234. *See supra* note 82 (discussing the 2002 Patients’ Rights Law).

235. Only the United States and New Zealand permit direct-to-consumer advertising of prescription drugs that includes a description of the uses of the products. C. Lee Ventola, *Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic*, 36 PHARMACY & THERAPEUTICS 669 (2011).

236. *But see* AUTORITÉ DE LA CONCURRENCE, AVIS N° 19-A-08 DU 4 AVRIL 2019 RELATIF AUX SECTEURS DE LA DISTRIBUTION DU MÉDICAMENT EN VILLE ET DE LA BIOLOGIE MÉDICALE PRIVÉE 204–206 (Apr. 4, 2019), <https://www.autoritedelaconcurrence.fr/sites/default/files/2019-05/19a08.pdf> [<https://perma.cc/4D9G-EY2K>] (discussing reorganization of the pharmacy monopoly and recommending that certain health products be allowed for sale outside pharmacies); *French Health Minister Opposed to Selling Over-the-Counter Drugs in Supermarkets*, THE LOCAL (Apr. 5, 2019), <https://www.thelocal.fr/20190405/french-health-minister-opposed-to-selling-over-the-counter-drugs-in-supermarkets> [<https://perma.cc/KUP7-3R9C>] (noting that French antitrust authority wants to liberalize the monopole officinal and has recommended permitting sale of certain medicines, such as ibuprofen, at supermarkets).

the 1950s<sup>237</sup> to the recent Mediator scandal<sup>238</sup>—has also included greater responsibilities for and elevation of the role of *pharmacists* through the lifecycle of drugs, from manufacture through delivery to patients.<sup>239</sup> Although there has been a modest patient empowerment movement in France, medical paternalism—and with it a passive attitude of deference to doctors and pharmacists—still tends to trump patient autonomy arguments in French culture and law.

Second, French culture and law remain deeply committed to the notion of equality—in this context, equality of access, treatment, and outcome—tracing its roots to the principles of political equality that fueled the Revolution of 1789 and ideals of socioeconomic equality that took root in 1792 (which drove, for example, the abolition of the entire tax system of the Old Regime).<sup>240</sup> This special tradition has played a powerful role in French politics and culture ever since. It counsels against laws and policies that might lead to differing results depending on socioeconomic status, including solutions that allow a patient's initiative and personal connections to provide treatment options others lack.<sup>241</sup> It also tends to lead to pro-regulatory sentiment, because regulation can serve the end of ensuring equality in treatment. Patients have a less aggressive sense of empowerment in France, and those who might want access for themselves without ANSM's involvement are less likely to find powerful allies interested in reducing the role

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237. In this crisis, an anti-infective drug caused nearly 100 deaths and led to reexamination of the French system for drug safety monitoring. See generally Christian Bonah & Jean-Paul Gaudillière, *Faute, accident ou risque iatrogène? La régulation des événements indésirables du médicament à l'aune des affaires Stalino et Distilbène*, 3 REVUE FRANÇAISE DES AFFAIRES SOCIALES 123 (2007) (describing the Stalino affair and subsequent changes in French drug regulation).

238. Mediator (benfluorex) reached the market in 1976 as an adjunctive therapy for hyperlipidemia and diabetes with obesity. It was a fenfluramine, and the class was eventually associated with serious cardiovascular risks and generally withdrawn from the market, but Mediator remained on the market in Europe until 2009. The company marketing the drug, Servier, had argued that benfluorex was pharmacologically different from fenfluramine and dexfenfluramine. By 2009, French doctors had prescribed the drug off label for obesity for decades. Some believe the drug had caused as many as 2,000 deaths before its withdrawal, and an exhaustive report from the French Inspection Générale des Affaires Sociales (IGAS) blamed not only the company but also the regulator, the medical and scientific communities, and the regulatory framework. Asher Mullard, *Mediator Scandal Rocks French Medical Community*, 377 THE LANCET 890 (2011).

239. Mathieu Guerriaud, *Pharmacien responsable, une exception française au service de la sécurité de la sécurité du médicament*, in Mathieu Guerriaud, Clotilde Jourdain-Fortier & Isabelle Moine-Dupuis, LE DROIT DES AFFAIRES PHARMACEUTIQUES, VERS LA CARACTÉRISATION D'UNE LEX PHARMACEUTICA (LexisNexis, forthcoming).

240. See Christian Morrison & Wayne Snyder, *The Income Inequality of France in Historical Perspective*, 4 EUR. REV. ECON. HIST. 59, 70–76 (2000) (discussing changes in 1792 and trends towards greater income equality over time).

241. Changes made to French law in 2002 illustrate this. As noted *supra* note 82, historically, the liability of a private physician was governed by the Civil Code, while the liability of a physician in a public hospital was governed by public law. But under the Patients' Rights Law of 2002, all health liability issues are now governed by the Public Health Code, which ensures that patients are treated equally under the law.

of the regulatory state.

#### IV. INCREASING USE OF EXPANDED ACCESS IN THE UNITED STATES

Supporters of the right-to-try law said that it addressed two impediments to use of expanded access in the United States: (1) a burdensome regulatory framework that either precluded, or at least discouraged, expanded access arrangements, and (2) the failure of companies to participate in expanded access.<sup>242</sup> But the regulatory framework was not the problem. The new law does not permit access to any more drugs than FDA's expanded access regulations already do, and in some important respects it is narrower. Moreover, the agency rarely refuses requests for expanded access.<sup>243</sup> In addition, as discussed below, the modest changes made to address company reluctance were probably insufficient. The right-to-try law is unlikely to increase use of unapproved medicines.<sup>244</sup> If policymakers want to increase use of the expanded access regime, they will need to address the actual impediments to its use. This requires thinking about reasons companies do not provide access, reasons patients do not request expanded access, and reasons prescribers refuse to participate in access arrangements.

##### *A. Addressing Barriers to Company Participation in Expanded Access*

The primary problem has been that drug companies decline to provide requested drugs. Supporters of the right-to-try law tried to address this. To begin with, some companies may be concerned about products liability exposure arising out of adverse events during expanded access.<sup>245</sup> Under the right-to-try law, a company faces no liability arising out of any act or omission with respect to medicine provided to patients.<sup>246</sup> And some companies may be concerned adverse

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242. See generally Corieri, *supra* note 16.

243. See *supra* note 109; see also U.S. Gov't Accountability Office, GAO-18-157T, Testimony Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives: FDA's Expanded Access Program 1, 2 (Oct. 3, 2017) (“[O]f the nearly 5,800 expanded access requests that were submitted to FDA from fiscal year 2012 through 2015, FDA allowed 99 percent to proceed.”).

244. E.g., 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) (arguing that “the bill would probably have minimal effects . . . because it targets alleged barriers to early access that aren't actually rate-limiting”); Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357, 2375–76 (2018) (“The law's provisions mainly target the FDA, despite the fact that the Agency has not been the main barrier to access. It will therefore likely do little to help patients.”).

245. Shah & Zettler, *supra* note 21, at 182–83 (discussing company concerns about liability); see also Zettler, *Implications*, *supra* note 21, at 170 (suggesting “sponsors may face traditional tort liability if adverse events occur”).

246. Pub. L. No. 115-176, § 2(b)(1), 132 Stat. 1372 (2018) (not codified).

outcomes will affect the medicine's labeling or approval, or even trigger an order to stop ongoing trials.<sup>247</sup> The right-to-try law limits FDA's use of the data arising out of the patient's use of the medicine: the agency cannot use a clinical outcome from use under the right-to-try law to delay approval of the medicine unless the sponsor requests that use or the agency finds that using the clinical outcome is critical to determining the medicine's safety.<sup>248</sup> The exception is essential from a public health perspective, but it also effectively nullifies the provision; if FDA needs to use the data, it can and will. Still, concerns about regulatory outcomes and liability exposure probably do not fully explain the reluctance of companies to participate in expanded access. Recent scholarship suggests that concerns about adverse regulatory outcomes and liability exposure are not well-founded.<sup>249</sup> It is likely that at least the larger and more sophisticated companies knew this.

The real impediment to company participation in expanded access in the United States might be financial: there is a hypothetical risk of liability and no real financial upside to participation.<sup>250</sup> Experimental drugs are not covered by private payers or government insurance programs.<sup>251</sup> The patient must bear the cost of the

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247. *E.g.*, Menikoff, *supra* note 153, at 1061–62 (noting that FDA officials report companies with concerns that unexpected toxicity in a patient receiving early access will lead to a clinical hold).

248. 21 U.S.C. § 360bbb-0a(c)(1) (2018).

249. One study published in 2017 considered regulatory actions taken by FDA on 261 molecular entities from 2010 through 2016, finding “no instance in which expanded access . . . lead to a negative regulatory action for drug approval” and only one instance in which a safety event had “what might be interpreted as a negative effect on product labeling.” Jonathan P. Jarow & Richard Moscicki, *Impact of Expanded Access on FDA Regulatory Action and Product Labeling*, 51 THERAPEUTIC INNOVATION & REG. SCI. 787 (2017); *see also* Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 980 (“In practice, serious adverse events in expanded access programs have rarely led to regulatory problems . . . in the USA: over a 10-year period, only 2 out of 1000 (recent) expanded access programs according to FDA.”). FDA has also reassured companies that adverse events will “be viewed through the proper lens” and that the notion that adverse events could hold up approval is “urban lore.” Kate Rawson, *Expanded Access Data Can Support Approval Decisions, FDA Says*, PINK SHEET (Nov. 21, 2018), <https://pink.pharmaintelligence.informa.com/PS124296/Expanded-Access-Data-Can-Support-Approval-Decisions-US-FDA-Says>. Another study of programs over a 10-year period found only two instances in which FDA called a temporary halt to ongoing trials after an event involving a patient who had received early access, out of 11,000 early access arrangements. Van Norman, *supra* note 19, at 289; *see also* Amy McKee et al., *How Often Are Drugs Made Available Under the Food and Drug Administration's Expanded Access Process Approved?*, 57 J. CLINICAL PHARMACOLOGY S136 (2017) (reviewing all individual early access requests to FDA's drug center for Fiscal Year 2010 to Fiscal Year 2014 and reporting no apparent product liability cases arising out of the use).

250. Grossman, *Empowered Consumer*, *supra* note 19, at 672 (suggesting that treatment INDs are rare in part because of the risk of liability exposure without any prospect for profit).

251. Sutter, *Expanded Access Advocates Seek Reimbursement*, *supra* note 212 (“Insurers generally will not pay for the cost of investigational drugs or for ancillary services unless they represent standard of care, numerous speakers said.”); Zettler, *Implications*, *supra* note 21, at 168 (“Private health insurance, Medicare, and Medicaid have not paid for treatment access to investigational drugs in the past and probably will not pay for such access in the future. Even if

experimental medicine, unless the company does. And companies are limited in what they may charge: FDA allows a company to recover only direct costs, meaning the cost per unit to manufacture the drug (raw materials, labor, supplies and equipment that are not reusable) and the direct costs to ship and handle the drug.<sup>252</sup> But disclosing direct costs at the preapproval stage could distort the public's understanding of the true cost of bringing the medicine to market.<sup>253</sup> The direct cost of manufacturing a particular unit of medicine—the tablets taken or the solution prepared and injected—is in many respects a meaningless number, trivial compared to the fully capitalized cost of more than a decade of premarket research and development, including any other drugs that failed in premarket trials along the way. Making the drug available at direct cost before approval can make it difficult to charge a price after approval that reflects *all* the cost of bringing the medicine to market.<sup>254</sup> Increasing use of expanded access in the United States may mean addressing these financial issues.

This hypothesis finds support in the French experience. The French approach to financing early access is exactly the opposite of the U.S. approach, and some evidence suggests the French ATU program is more heavily used than the U.S. expanded access program. To begin with, French law permits drug companies to profit from ATU arrangements. Pricing is “free”—meaning that the company may profit from the sale and, indeed, the medicine is technically not subject to the price

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patients are only being charged for the cost of the drugs, that cost could be unaffordable for many low-income persons.”).

252. 21 C.F.R. § 312.8(d)(1) (2020); Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. 40,872, 40,875 (Aug. 13, 2009). Allowing recovery of costs was intended to address industry “reluctance” to participate in expanded access. Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. at 40,905. If a company is providing expanded access to an intermediate-size or large patient population, it may also recover the costs of monitoring the expanded access protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access arrangement. 21 C.F.R. § 312.8(d)(2) (2020). A company may not charge for indirect costs, such as expenditures for physical plant and equipment used to make large quantities of the drug; research and development costs; or administrative, labor, or other costs that would be incurred anyway. Charging for Investigational Drugs Under an Investigational New Drug Application, 74 Fed. Reg. at 40,896.

253. See Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 980 (suggesting that in the United States, companies preferring not to disclose direct costs may choose to provide for free or not at all).

254. Sutter, *Expanded Access Advocates Seek Reimbursement*, *supra* note 212 (quoting CEO of a third-party sponsor of large group expanded access programs, that “no company wants” to reveal its “internal cost structure, which you have to do in any cost recovery,” and “then come to market three years later and have Bernie Sanders tell everybody, ‘Hey, here’s another pharma company boosting up their prices.’”); *cf.* Lietzan, *Access Before Evidence*, *supra* note 30, at 1271–72 (noting public outrage when a drug made available inexpensively to patients for a time becomes much more expensive after the marketing authorization process is complete).

controls that would apply after approval (if it were covered by public insurance).<sup>255</sup> Although companies could choose to provide the drugs for free, many avail themselves of the opportunity to charge. We know this in part because the French system ended up changing its charging rules a few years ago to control spiraling costs.<sup>256</sup> Today, a company cannot deviate substantially from the price that will be set after the medicine's approval.<sup>257</sup> But it may charge its *ordinary* price for the medicine, and the ability to profit could make the ATU attractive to companies, turning it into the equivalent of early market entry.<sup>258</sup>

Even if U.S. policymakers did not allow drug companies to profit from expanded access, they might still need to address the financial impediments that patients face.<sup>259</sup> Even though investigational medicines are provided free or at cost, senior FDA officials report that patients face barriers because of costs unrelated to the medicine itself, such as laboratory work and infusion services.<sup>260</sup> In contrast, nearly everyone in France is covered by statutory national health insurance, and an unapproved medicine provided to a patient under an ATU is covered by this

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255. For a general overview of pharmaceutical price controls in France, see Marc A. Rodwin, *What Can the United States Learn from Pharmaceutical Spending Controls in France?*, THE COMMONWEALTH FUND (Nov. 11, 2019), <https://www.commonwealthfund.org/publications/issue-briefs/2019/nov/what-can-united-states-learn-drug-spending-controls-france>. Broadly speaking, pricing of covered products is negotiated with the French Economic Committee for Health Products (CEPS) based in part on the outcome of a health technology assessment regarding the medical benefit to be derived from the drug (as compared to previous products). See generally Martin Koehring, *Value-Based Healthcare in France: A Slow Adoption of Cost-Effectiveness Criteria*, THE ECONOMIST INTELLIGENCE UNIT (Dec. 8, 2015), <https://eiuperspectives.economist.com/healthcare/value-based-healthcare-france-slow-adoption-cost-effectiveness-criteria>.

256. See *infra* Section 0. The authors consulted with two individuals who advise companies providing medicines through ATUs in France. One reported that most of his clients provide the medicine free of charge, but the other reported the opposite, that most of her clients charge for the medicine.

257. See *infra* Section 0.

258. See, e.g., Nathan Kennell, *Insights into Utilization of French Compassionate Use Programs (ATU)*, LINKEDIN PULSE (Apr. 11, 2018), <https://www.linkedin.com/pulse/insights-utilization-french-compassionate-use-programs-nathan-kennell> [<https://perma.cc/AEF2-RY54>] (using two case studies to describe how the ATU process “presents an avenue to obtain early market access” and concluding that “effective ATU utilization may lead to earlier, more extensive patient access, which increases clinical utilization and improves the perceived value of therapy”).

259. For similar reasons, some argue that the right-to-try law is unlikely to improve access so long as payers will not reimburse for the drugs. E.g., Christine Coughlin, Nancy King, & Melissa McKinney, *Regenerative Medicine and the Right to Try*, 18 WAKE FOREST J. BUS. & INTELL. PROP. L. 590, 618 (2018) (“[R]ight to try legislation does not compel insurance providers to cover the cost of expanded access to experimental products” and “does nothing to address the reality [that] public and private payers reasonably question the cost-effectiveness of payment for unproven interventions.”); see also Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 979 (arguing that very little is done in the United States to make investigational drugs available and accessible and citing, as one explanation, the fact that they are usually not reimbursed).

260. Sutter, *Expanded Access Advocates Seek Reimbursement*, *supra* note 212 (noting that patients sometimes resort to GoFundMe to raise money for expanded access).



insurance.<sup>261</sup> The French early access program is said to be one of the most attractive (to patients) in Europe *because* of this reimbursement.<sup>262</sup>

Many patients use the French early access scheme. The ANSM reports tens of thousands of patients receiving early access through the ATU mechanism every year. In 2017, for instance, more than 8,000 patients received medicine through cohort ATUs, and another 16,000 received medicines through named patient ATUs.<sup>263</sup> Comparable statistics are not readily available for the United States, but the drug center at FDA receives around 1,000 requests for expanded access every year, most for single patients, and it grants over 99 percent.<sup>264</sup> One report found that in a recent four-year period, only 4 percent of granted requests pertained to intermediate or large groups.<sup>265</sup> FDA apparently does not keep track of the number of patients treated under these requests,<sup>266</sup> so it is impossible to know whether fewer patients receive access under treatment INDs in the United States than under cohort ATUs in France. But many more patients enjoy access to experimental medicines under the nominative (single patient) ATU in France than receive expanded access on an individual patient basis in the United States.

The early access schemes of France and the United States are different, but not different enough to explain this disparity. Something else is going on. One rational explanation would be that more companies participate when they can profit and that more patients participate when insurance covers the medicine and associated care. But there could be additional contributing factors. One might be

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261. Cipriano, *Conversation*, *supra* note 211. Most countries in Europe do not reimburse experimental medicines. See Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 980 (noting that France and Turkey have reimbursement systems in place; that in other countries the financial burden falls on the hospital, the hospital pharmacy, or the patient; and that Dutch hospitals have policies precluding patients from paying at all which means that if the insurer will not cover the medicine the hospital will not provide it).

262. See Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20, at 980.

263. ANSM, SUMMARY ACTIVITY REPORT 2017, 1, 9, [https://www.ansm.sante.fr/var/ansm\\_site/storage/original/application/f5c61007e0b47de16a3c07354eb6f6d6.pdf](https://www.ansm.sante.fr/var/ansm_site/storage/original/application/f5c61007e0b47de16a3c07354eb6f6d6.pdf) [<https://perma.cc/L4WY-7C48>]. Reports in earlier years were similar. See ANSM, 2014 ANNUAL REPORT, 1, 9, [https://ansm.sante.fr/var/ansm\\_site/storage/original/application/ee4fa2afa64ec300a551d912ff7c0559.pdf](https://ansm.sante.fr/var/ansm_site/storage/original/application/ee4fa2afa64ec300a551d912ff7c0559.pdf) [<https://perma.cc/5DWH-52B4>] (reporting that 12,111 patients received medicines via cohort ATUs and 12,822 patients via nominative ATUs); see also Martinalbo, *supra* note 88, at 103 (noting in 2016 that French ATU scheme had managed over 130 cohorts since 1994). The schemes do differ in scope: the French ATU scheme permits access to drugs for rare diseases in addition to drugs for serious diseases. See *supra* note 129. But because the diseases are rare, these ATUs probably do not explain the large disparity in utilization rates.

264. Jarow, *Expanded Access*, *supra* note 109, at 707; see also Grossman, *AIDS Activists*, *supra* note 59, at 739 (noting that treatment INDs remain rare).

265. U.S. Gov't Accountability Office, GAO-17-564, *Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used* 1, 18 (Jul. 11, 2017).

266. *Id.* at 18.

that new medicine approval in France lags behind new medicine approval in the United States.<sup>267</sup> Once a company is allowed to sell its new medicine in one country (the United States), perhaps it is more likely to agree to expanded access in the other (France). That said, the discrepancy between the United States and France seems to relate to access for single patients, rather than access under treatment INDs in the United States and cohort ATUs in France. If the explanation were attributable to FDA approving new medicines before the ANSM approves them, one might expect the approval lag to manifest mainly in cohort ATUs rather than nominative, single-patient arrangements. In any case, a review of nominative ATUs from 2018 shows that the ANSM provides access in many cases *before* approval in the United States.<sup>268</sup> Finally, even if there are more explanations for the willingness of companies to participate in France, this brings only one party to the table. French *patients* can participate because of robust health insurance covering both the medicine and the medical services—a benefit that U.S. patients lack.

### *B. Addressing the Financial Structure of Expanded Access*

The healthcare finance system in the United States is complex, and assessing a financial solution to the expanded access problem is beyond the scope of this Article. But a few cautionary points are worth making. The French solution has many parts that work together. A partial solution in the United States—free pricing without reimbursement, or reimbursement without free pricing, or free pricing without either price controls or insurance—may not work and could introduce new problems.

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267. E.g., Nigel S.B. Rawson, *Canadian, European and United States New Drug Approval Times Now Relatively Similar*, 96 REG. TOXICOLOGY & PHARMACOLOGY 121, 121 (2018) (examining 460 drugs approved by Health Canada, FDA, or the EMA between 2002 and 2016 and finding that the median EMA approval time was 371 days, while the median FDA approval time was 304 days); Robera Joppi et al., *Food and Drug Administration vs. European Medicines Agency: Review Times and Clinical Evidence on Novel Drugs at the Time of Approval*, 86 BRITISH J. CLINICAL PHARMACOLOGY 170, 172 (2019) (finding that the median review time for the 66 drugs approved by FDA and the EMA in 2015-2017 was longer at the EMA by a median of 121.5 days).

268. While some medicines provided to individual French patients (such as brigatinib) were already available in the United States, others (such as erdafitinib and alpelisib) would not be approved by FDA until the following year. For a list of current nominative ATUs, see *Référentiel des ATU nominatives*, ANSM, [https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Referentiel-des-ATU-nominatives/\(offset\)/3](https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Referentiel-des-ATU-nominatives/(offset)/3) [<https://perma.cc/F2PV-FWKE>]. For a list of past nominative ATUs, see *Liste des spécialités autorisées dans le cadre d'ATU nominatives*, ANSM, [http://dev4-afssaps-marche2017.integra.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-nominative-Liste-des-specialites-autorisees/\(offset\)/3](http://dev4-afssaps-marche2017.integra.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-nominative-Liste-des-specialites-autorisees/(offset)/3) [<https://perma.cc/YT2U-JHSV>]. For a list of current cohort ATUs, see *Liste des ATU de cohorte en cours*, ANSM, [https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-de-cohorte-en-cours/\(offset\)/5](https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-de-cohorte-en-cours/(offset)/5) [<https://perma.cc/27DX-7QWU>].

To begin with, free pricing by itself may exacerbate disparities in access to experimental medicines.<sup>269</sup> Even when companies provide their experimental medicines for free or at cost, there are concerns about allocation. The Josh Hardy story reveals one issue: companies may respond more to patients who are vocal and who use social media and political pressure in their campaigns.<sup>270</sup> The other issue is ancillary costs. Even if a company provides its experimental medicine for free, the costs of the associated medical care—physician fees, the costs of services such as monitoring, the cost of travel and lodging, and opportunity costs for caregivers who accompany the patient—may limit treatment to patients with more resources. Even though companies may charge freely in France, the French ATU scheme is structured to avoid disparities; the ANSM pushes out information about medicines available through the mechanism,<sup>271</sup> patients receive the medicines for free, and the associated medical care is also covered by national health insurance. If U.S. policymakers permitted companies to price freely during expanded access and did not somehow mandate insurance coverage and address other financial barriers, disparities in access could become profound and would be viewed by many as morally unacceptable.

Permitting free pricing and somehow covering the cost for patients might eliminate the inequities in allocation and increase the number of patients enjoying early access. But it would require thinking about moral hazard. Classical economic theory tells us that a consumer compares the benefit he expects with the marginal

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269. Darrow et al., *supra* note 139, at 284 (arguing that early access programs “can also raise concerns about equity” because insurers may not step in when the company declines to shoulder the cost, leading some to argue “that expanded access generally favors the rich or well-connected over the poor”); Schüklenk & Lowry, *supra* note 20, at 16 (citing concern, from a “justice” perspective, that cost difference might mean the burden of clinical trial participation falls “disproportionately on members of economically disadvantaged groups”). *Cf.* Carrieri, Peccatori & Boniolo, *supra* note 20, at 67 (arguing that the “right to try” law could reinforce preexisting financial inequalities because the wealthy are more likely to have access to experimental medicines).

270. Caplan & Moch, *Rescue Me*, *supra* note 20 (“Should an experimental product be made available to an individual patient who is more vocal, more sophisticated in the use of media, more knowledgeable about the system, more adept at electronic searches?”). That said, although sophisticated use of media and technology to pressure companies appears to be on the rise, it remains unclear whether these strategies actually work. Mackey & Schoenfeld, *supra* note 153, at 22–23 (offering “high-profile case studies” in which the patient had “a multimedia strategy in place that was well-articulated, professionally executed (including various multimedia assets), and included coordinated message propagation across multiple popular online platforms . . . in addition to personal websites” but noting that “achieving robust public engagement and media coverage did not appear to associate with better chances of accessing experimental treatment”).

271. Unlike FDA, the ANSM maintains a list of medicines that can be prescribed via a nominative ATU if certain criteria are satisfied (and in all other cases, the doctor may simply apply for a nominative ATU as previously described). *See supra* note 268.

cost to him.<sup>272</sup> In health care, this generally leads to over-consumption,<sup>273</sup> and particularly at the end of life, this effect could be even more pronounced.<sup>274</sup> Terminally ill patients and their caregivers tend to place a high value on extending life even for a few months, higher than they would if asked earlier in the patient's life.<sup>275</sup> And for an insured patient in the United States, the marginal financial costs typically comprise his insurance premium and any co-payments and deductible involved. A third-party payer covers the full financial cost of the medicine and associated healthcare services, passing the cost to others (taxpayers in the case of public insurance, other policy holders in the case of private insurance).

Providing reimbursement, within the context of a national health insurance system that also covers the cost of associated health care, eliminates most disparities in access—a goal of the French legal system that generally takes priority even in the face of arguments about personal autonomy. The persistent paternalism of the French healthcare system may help reduce the insurance effect, thereby reducing moral hazard. In contrast, U.S. society emphasizes patients' rights, worships the technological imperative, and prizes fighting terminal illness over palliative care and a good death, so mandatory insurance coverage for experimental medicines could trigger high utilization rates—including the kinds of last-ditch efforts that family members, caregivers, treating doctors, and even the patients themselves may in retrospect wish they had not tried.<sup>276</sup>

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272. See generally Russell Korobkin, Comparative Effectiveness Research as Choice Architecture: The Behavioral Law and Economics Solution to the Health Care Cost Crisis, 112 MICH. L. REV. 523, 529–31 (2014).

273. *Id.* at 529; see also Paul T. Menzel, The Value of Life at the End of Life: A Critical Assessment of Hope and Other Factors, 39 J. L. MED. & ETHICS 215, 220 (2011) (“Because of the ‘insurance effect’ . . . what is actually spent is not a good indication of value.”); see also Sidney A. Shapiro & Joseph P. Tomain, REGULATORY LAW AND POLICY: CASES AND MATERIALS 52 (“Expense accounts, insurance, and medical benefits have the effect of encouraging consumers to spend more than they would if the expenses were paid directly (internalized) by the consumer . . . . The economic difficulty with a moral hazard is that costs can be inflated over what they otherwise would be if someone else were not paying.”). There is a large body of empirical literature exploring the impact of health insurance on spending, which is beyond the scope of this Article. See Liran Einav & Amy Finkelstein, Moral Hazard in Health Insurance: What We Know and How We Know It, 16 J. EUR. ECON. ASS'N 957 (2018) (describing the literature).

274. Menzel, *supra* note 273, at 221 (“Insured patients, and often their providers as well, have an incentive to use every bit of care that has even the slimmest, pie-in-the sky prospect of benefit, regardless of its cost. People see themselves as having paid their insurance ‘dues’ already, and their future premiums will not increase by more than micro-pennies because of *their one current use of marginal care.*”).

275. *Id.* at 217 (explaining the apparently high value of life extension, including the fact that six months of additional life is perceived as higher value by a person with a shorter remaining lifespan, both because the six additional months represent a greater proportion of his remaining life and because the gain from the extension is more temporally proximate).

276. For a compelling personal account of experimental treatments that, in retrospect from a family member's perspective, were the wrong choice, see Malinowski, *supra* note 21.

Moral hazard, though, also leads directly to the problem of cost. New medicines can be expensive while companies recover their investment in research and development and while their competitors are legally prohibited from making copies. Free pricing for experimental medicines, combined with mandatory insurance, could impose significant costs on the U.S. healthcare system. The French learned this the hard way. A review of all medicines available through ATU that received marketing authorization between January 1, 2005, and June 30, 2010, found that a 12% premium on average was paid to companies while a medicine was on this status.<sup>277</sup> They now manage the fiscal impact of early access by requiring the company to reimburse the government in some cases—including when the amount paid by the government exceeds a certain threshold and when the price imposed after approval is lower than the free price during early access.<sup>278</sup> Responses from industry have not been positive. Many companies have criticized the scheme, citing its administrative complexity and the business uncertainties in free pricing that will be second-guessed later.<sup>279</sup> In the United States, price controls for medicines remain a controversial issue.

Finally, even if companies were allowed to charge normal prices, some might not participate in expanded access. Companies decline to participate for various reasons. Liability protection for companies and doctors within the expanded access framework is important. In addition, some companies will want to focus on enrolling patients in ongoing trials in order to complete the research needed for approval. Others might always decline to provide access, as a matter of policy, thinking that this the best way to avoid a complicated public relations challenge.<sup>280</sup>

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277. Albane Degrossat-Théas et al., *Temporary Authorization for Use: Does the French Patient Access Programme for Unlicensed Medicines Impact Market Access After Formal Licensing?*, 31 PHARMACOECONOMICS 335, 335 (2013); Eveline Van Keymeulen & Laëtitia Bénard, *New Requirements for Temporary Authorisations for Use in France*, ALLEN & OVERY LIFE SCIENCES HUB (June 6, 2017), <https://www.aolifescienceshub.com/new-requirements-temporary-authorisations-use-france> [<https://perma.cc/AL2W-KVC9>].

278. Loi 2016-1827 du 23 décembre 2016 de financement de la sécurité sociale pour 2017, J.O., Dec. 24, 2016, no. 1. *See generally Autorisations temporaires d'utilisation (ATU)*, MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ, <https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisations-temporaires-d-utilisation-atu> [<https://perma.cc/DVF6-RL5T>].

279. *E.g.*, LES ENTREPRISES DU MÉDICAMENT, *supra* note 125 (noting that medicines available through the ATU scheme are reaching only ten percent of the eligible population and arguing that the changes wrought by later financing laws—meaning the complex reimbursement requirements—have made the ATU scheme “very complicated, even ineffective”).

280. Whether public relations considerations lead to providing or declining access will vary. Providing access may be necessary to avoid a public relations nightmare triggered by a sophisticated and media-savvy patient with a compelling story, but providing access only to patients with the knowledge and resources to launch a media campaign may raise ethical issues that trigger a different kind of public scrutiny. Some companies have addressed these issues with external boards that rule on access requests or with lotteries for expanded access. *See* Bunnik, Aarts & van de Vathorst, *Little to Lose*, *supra* note 20 (noting that Johnson & Johnson has established an external board to review

*C. Barriers to Provider and Patient Participation in Expanded Access*

Senior FDA officials have reported that many doctors are unwilling to participate in expanded access because—even if the medicine is provided for free or at cost—their services are not covered by insurance.<sup>281</sup> With little financial upside, doctors may be deterred by the prospect of liability for injuries that may result.<sup>282</sup> The right-to-try law tries to address this risk, relieving them from “liability in a cause of action” arising out of an “alleged act or omission with respect to an eligible investigational drug provided to an eligible patient” unless there was reckless or willful misconduct, gross negligence, or an intentional tort.<sup>283</sup> Although this provides some coverage, it may simply shift the focus of litigation to whether the doctor was reckless or grossly negligent. The drafters also overlooked the relationship between this uncodified liability provision and the codified provision governing patient eligibility in the first instance. If the patient’s informed consent was not provided, the patient was not an “eligible patient” in the first place. This appears to leave open the possibility of both a private tort suit arising out of defective informed consent and proceedings brought by the state’s licensing board. More robust liability protection may be needed to entice doctors to participate in expanded access.<sup>284</sup>

Finally, more targeted legislation might help address inequities caused by knowledge deficits in the United States. Perhaps eligible patients do not ask for early access because they are receiving treatment from physicians unaware of the option.<sup>285</sup> Skepticism in minority communities about medical research—the legacy of significant historical failures in human subject protection—may further contribute to the knowledge deficit and reduce the number who seek access.<sup>286</sup> In a system that provides early access to those who think to request it—but that does

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requests based on “equality, need, and efficacy”). Still others may be concerned about the public relations challenge in the event of an unforeseen adverse event, particularly if the patient has garnered sympathetic media attention.

281. Sutter, *Expanded Access Advocates Seek Reimbursement*, *supra* note 212.

282. Zettler, *Implications*, *supra* note 21, at 170; *see also* Van Norman, *supra* note 19, at 289 (noting that physicians may be reluctant to recommend an experimental medicine on the grounds that they lack enough information make benefit-risk calls).

283. Pub. L. No. 115-176, § 2(b), 132 Stat. 1372 (2018) (not codified).

284. *See* Meghan K. Talbott, *The Implications of Expanding Access to Unapproved Drugs*, 35 J. L. MED. & ETHICS 316, 317–18 (2007) (discussing theories of physician liability such as common law fraud, intentional misrepresentation, battery, and lack of informed consent).

285. *Cf.* Bunnik, Aarts & van de Vathorst, *Changing Landscape*, *supra* note 20, at 10 (suggesting that low uptake is partially the result of knowledge deficits).

286. Allen L. Gifford et al., *Participation in Research and Access to Experimental Treatments by HIV-Infected Patients*, 346 NEW ENG. J. MED. 1373, 1379 (2002) (“[F]ewer than half as many black patients as white patients attempt to obtain experimental HIV medications, suggesting that there is less awareness and a more widespread negative attitude about research in minority communities.”).

not otherwise push out information about the availability of medicines before approval—patients with less education, less access to information, and fewer (or less sophisticated) healthcare providers are less likely to receive early access. The success of relentless social media campaigns and influential public figures in securing a patient expanded access also favors patients with greater knowledge and resources. In contrast, in part because of the long tradition of regulating to avoid disparities and inequities, the French regulator pushes out information about medicines available through the early access mechanism. In France, knowledge deficits may be less of an issue.

#### CONCLUSION

The right-to-try laws were never really about increasing patient access to new medicines. They were about championing individual rights and patient autonomy in matters of medical care, at least at the end of life, and reducing the role of the federal government in such matters. There is room for debate about the merits of a federal gatekeeper in this exceptional situation, though not (in the view of the authors) for serious debate about the merits of our common medicine approval framework. And because the right-to-try law represents a rejection of the basic assumptions of this framework—the need for high-quality evidence to support commercial market entry and prescribing decisions, and the importance of a single scientific regulator assessing the quality of that evidence—it is indefensible on that ground alone. Moreover, as a way of meaningfully expanding access to unapproved medicines, or improving the equity of access among groups with varying socioeconomic statuses and levels of sophistication in medical matters, it is equally indefensible. Patient groups were slow to realize that the fight for right-to-try was not really a fight in their interests, and the proponents of this law must shoulder some of the blame.

There are clear impediments to a fully functional expanded access scheme, and U.S. policymakers might look to the apparent success of the French ATU scheme—reported to be one of the most attractive in Europe, from the patient perspective—for at least some answers. Robust empirical investigation of the French scheme would be helpful. But there is good reason to think that expanded access will not be equitably available in this country so long as patients face significant financial hurdles and healthcare providers need reimbursement for the services they provide. Consistent and proactive dissemination of information about available expanded access programs from a trusted party—as in France—might mitigate some of the knowledge deficit. Allowing the companies to charge freely for their drugs might tip the balance for some companies, but doing so may create many follow-on problems, and the full French solution—nationalized health insurance and, more importantly, price controls—is not politically viable in the

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United States for now. The best short-term solution may be to facilitate financial support and reimbursement under traditional expanded access programs while studying the full French solution in more detail.