

**FDA’S ACCELERATED APPROVAL, EMERGENCY USE  
AUTHORIZATION, AND PRE-APPROVAL ACCESS:  
CONSIDERATIONS FOR USE IN PUBLIC HEALTH EMERGENCIES  
AND BEYOND**

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*The Food and Drug Administration (“FDA”) continues to balance two seemingly competing goals: protecting the public from unsafe treatments and increasing the public’s access to treatments. While tensions between the goals of protection and access have ostensibly skyrocketed since the beginning of the COVID-19 global pandemic, these tensions have, in fact, been long-standing since the initial creation of the Agency. A closer examination of historic events underlying FDA’s regulatory structure, however, illustrates that the goals of safety/regulation and speedy access/individual autonomy are not and need not be considered at opposite sides of a pendulum where policymakers focus on innovative ways to generate and capture data, while also furthering safety and enabling appropriate access.*

*To that end, this Article reviews FDA’s approval process for drugs and biologics and delves into some events that have promoted safety within FDA’s current regulatory structure, along with events that led to the creation of alternative pathways that enable accelerated approval, emergency use authorization, and earlier access to investigational drugs and biologics both through the FDA process and through Right to Try laws, which exist outside of FDA’s purview.*

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*This Article then turns toward the data collection imperative that is inherent in clinical research, particularly in working to end public health emergencies and preparing for future public health emergencies. This Article discusses the consequences and opportunity costs of unfettered access to investigational drugs and emphasizes the need for flexible and accessible clinical trial structures to improve participation and data generation, particularly for people of color and vulnerable populations for whom the pandemic has magnified long-standing health disparities. This Article concludes that (1) FDA's existing alternative pathways should be scrutinized to determine if there are innovative ways to further incentivize the creation of data, as well as capture and optimize the data borne out of these uses; (2) mechanisms to increase knowledge of and access to clinical trials should be implemented to ensure sufficient enrollment that reflects the demographics of the larger patient population; and, (3) the global pandemic should be considered an opportunity to work to strengthen both safety of and access to treatment and promote diversity and inclusivity in all aspects of research, development, and treatment.*

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*“As Americans face health scares, public health has become a subject of household conversation. The public vacillates from apathy to alarm, torn between security and civil liberties.”<sup>1</sup>*

## I. INTRODUCTION

In times of crisis, the U.S. government should work to promote safety and security without a corresponding loss of individual liberties.<sup>2</sup> For example, following the horrific September 11 Attack and the subsequent anthrax attacks, Congress passed the U.S. Patriot Act to improve national security through surveillance and data collection.<sup>3</sup> Although imperfect, the legislative response directed resources to prevent future terrorist attacks by working to enhance public safety and protect individual rights.<sup>4</sup>

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<sup>1</sup> Lawrence O. Gostin, *A Very Long Journey: A Decade’s Quest for Quarantine Regulations*, 94 MILBANK Q. 724, 727 (2016).

<sup>2</sup> *Id.*

<sup>3</sup> See *Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act (USA Patriot Act) of 2001*, Pub. L. No. 107-56, 115 Stat. 271 (2001) [hereinafter “U.S. Patriot Act”].

<sup>4</sup> Ron Wyden et al., *Law and Policy Efforts to Balance Security, Privacy and Civil Liberties in Post-9/11 America*, 17 STAN. L. & POL’Y REV. 331, 331 (2006) (“Those who bear the responsibility to put security first must understand that if civil liberties are not prominent among their concerns, their efforts may diminish the uniquely American freedoms they seek to protect. But in the same way, those who prize and vigorously defend civil liberties must do so with the recognition that a proliferation of security failures and terrorist success would diminish Americans’ true freedom to a degree beyond any law. To ensure the safety and liberty of all Americans, advocates and policymakers must agree to a basic premise: the security of the nation and the protection of individual freedoms are not, and must not be drawn as, mutually exclusive.”).

Similarly, to protect public safety in the investigational drug arena, Congress enacted Project Bioshield of 2004 (“Project Bioshield”), which ultimately paved the way for the Food and Drug Administration (“FDA”) to invoke Emergency Use Authorizations (“EUAs”) for investigational drugs in public health emergencies and other emergency situations.<sup>5</sup> EUAs, as well as corresponding policy movements that support individual autonomy and access to investigational products through alternative pathways and deregulation, have seemingly moved FDA away from its protective regulatory framework.<sup>6</sup> But perhaps the goals of “safety (which tends to emphasize regulation) and speedy access (which values innovation and individual choice) in moving treatments and vaccines from bench to bedside”<sup>7</sup> are not mutually exclusive. In this case, FDA’s north star for strengthening existing alternative pathways—such as accelerated approval, emergency use authorization, and pre-approval access—should focus on innovative ways to generate and capture data, which can further safety and efficacy drugs and vaccines, while also supporting access and future innovation and development.<sup>8</sup> The data generation component,

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<sup>5</sup> *Emergency Use Authorizations*, FDA, <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> [<https://perma.cc/KLG9-QG99>] (last visited Jan. 20, 2022) (explaining that, where the Secretary of Health and Human Services (“HHS”) declares that an emergency use authorization is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions).

<sup>6</sup> See generally Christine Coughlin, Nancy M.P. King & Melissa McKinney, *Regenerative Medicine and the Right to Try*, 18 WAKE FOREST J. BUS. & INTELL. PROP. L. 590 (2018) (discussing the tensions between safety and access).

<sup>7</sup> See Nicolas P. Terry & Christine Coughlin, *A Virtuous Circle: How Health Solidarity Could Prompt Recalibration of Privacy and Improve Data and Research*, 74 OKLA. L. REV. 51, 69 (2021).

<sup>8</sup> As of this writing, there are currently two competing bills in Congress that would affect FDA’s accelerated access pathways. See Nicholas Florco, *Lawmakers Face Off About the Future of the FDA’s Accelerated Approval Pathway*, STAT. (Mar. 17, 2022), <https://www.statnews.com/2022/03/17/future-accelerated-approval-fda-debate/#:~:text=Lawmakers%20face%20off%20about%20the%20future%20of%20the%20FDA's%20accelerated%20approval%20pathway&text=WASHINGTON%20%E2%80%93%20Lawmakers%20are%2>

however, is critical, not only in an ongoing public health emergency but also in order to prepare for future public health emergencies.

Part II of this Article reviews FDA's approval process for drugs and biologics—with a focus on vaccines—from submitting the investigational new drug application (“IND”) to FDA, through the clinical trial process to confirm safety and effectiveness before marketing the product in interstate commerce, to post-market surveillance trials and other safeguards. This Part also briefly reviews the practice of off-label use of medical products, along with the interplay between patent protection and research and development. Part III delves into FDA's history and examines events that underlie FDA's current regulatory structure to enhance safety. Part IV then provides a historical overview of events leading to the creation of alternative pathways that enable accelerated approval, emergency use authorization, or earlier access to investigational drugs and biologics, along with their benefits and potential consequences. Part V reviews the history and use of related legislation—“Right to Try” laws—existing outside of FDA's purview. Part VI follows by examining the data collection imperative, particularly in public health emergencies; discussing the consequences and opportunity costs of rushing access; and emphasizing the need for flexible and accessible clinical trial structures to improve participation and data generation. This Part then takes a deeper dive into the critical nature of long-standing

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of facing, and the center in the debate [https://perma.cc/43TH-6XJ5]. The bill put forward by the Democrats is the Accelerated Approval Integrity Act of 2022, which was introduced by Energy and Commerce Committee Chairman Frank Pallone, Jr. (D-NJ). Press Release, Frank Pallone, Jr., Chairman, House Comm. on Energy & Com. (Mar. 7, 2022), <https://energycommerce.house.gov/newsroom/press-releases/pallone-introduces-bill-to-improve-fda-s-accelerated-approval-program> [https://perma.cc/N72E-XE95]. This bill requires sponsors to complete Phase IV (post market) studies on drugs that receive accelerated approval with a five-year term for drugs to be marketed absent confirmation of clinical benefit or “significant progress to that goal.” *Id.* The Republican bill, the Accelerating Access for Patients Act of 2022, is a counterproposal, which grants FDA authority to use expedited procedures for withdrawal of products but requires FDA to promulgate such procedures. The Accelerating Access for Patients Act of 2022, H.R. 6969, <https://www.congress.gov/bill/117th-congress/house-bill/6996> [https://perma.cc/T6PQ-EWC5]; *see also* The Promising Pathway Act, S. 1644 (reducing FDA's discretion to act upon negative data).

disparities for people of color and vulnerable populations with respect to health-related outcomes generally and COVID-19 related outcomes specifically,<sup>9</sup> along with their underrepresentation in clinical research.<sup>10</sup> This Article concludes that (1) FDA’s existing alternative pathways should be scrutinized to determine if there are innovative ways to further incentivize the creation of data, as well as capture and optimize the data borne out of these uses; (2) mechanisms to increase knowledge of and access to clinical trials should be implemented to ensure sufficient enrollment that also reflects the demographics of the larger population; and, (3) diversity and inclusivity should be promoted in all aspects of research, development, and treatment.

## II. BRIEF OVERVIEW OF FDA APPROVAL PROCESS

While by no means perfect, FDA approval is considered the “gold standard.”<sup>11</sup> FDA asserts its lengthy approval process provides rigorous scientific validity and protects “public health and patients from unknown and unintended consequences by making drugs safer and ultimately requiring more proof of effectiveness.”<sup>12</sup> Although

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<sup>9</sup> *Risk for COVID-19 Infection, Hospitalization, and Death by Race/Ethnicity*, CDC, <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html> [<https://perma.cc/8VVC-KWAX>] (last updated Feb. 1, 2022); see also *Health Equity Considerations & Racial & Ethnic Minority Groups*, CDC, <https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html> [<https://perma.cc/SQG8-BW69>] (last updated July 24, 2020); Gregorio A. Millett et al., *Assessing Differential Impacts of COVID-19 on Black Communities*, 47 *ANNALS EPIDEMIOLOGY* 37, 37–44 (2020).

<sup>10</sup> See L. Ebony Boulware et al., *Combatting Structural Inequities—Diversity, Equity, and Inclusion in Clinical and Translational Research*, *NEW ENG. J. MED.* (Jan. 20, 2022) (internal citations omitted), <https://www.nejm.org/doi/full/10.1056/NEJMp2112233> [<https://perma.cc/DX5J-48KQ>]; see Allan Gaw, *Beyond Consent: The Potential for Atrocity*, 99 *J. ROYAL SOC’Y MED.* 175, 175 (2006).

<sup>11</sup> R. Alta Charo, *Speed Versus Safety in Drug Development*, in *FDA IN THE TWENTY-FIRST CENTURY* 251, 263 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).

<sup>12</sup> Coughlin et al., *supra* note 6, at 597 (internal citations omitted).

the standards for biologics<sup>13</sup> (the category under which vaccines are regulated)<sup>14</sup> and drugs<sup>15</sup> differ, FDA requires “substantial evidence” of effectiveness for both.<sup>16</sup>

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<sup>13</sup> 42 U.S.C. § 262(a); *see also* *Vaccine Testing and the Approval Process*, CDC, <https://www.cdc.gov/vaccines/basics/test-approve.html> [<https://perma.cc/BUV2-3QDZ>] (last visited Feb. 1, 2022) (discussing that FDA’s Center for Biologics Evaluation and Research (“CBER”) regulates vaccine products); *see also* *What Are “Biologics” Questions and Answers*, FDA, <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers> [<https://perma.cc/4DSV-E8WV>] (last visited Feb. 2, 2022) (“Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies . . . . In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized.”). Biologics are regulated not only through the Federal Food, Drug, and Cosmetic Act but also under section 351 of the Public Health Services Act, which provides for further controls over all aspects of the manufacturing process and the ability to immediately suspend a license where a public health danger exists. *See* 42 U.S.C. § 262.

<sup>14</sup> *See Vaccine Development – 101*, FDA <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101> [<https://perma.cc/PBH7-WREA>] (last visited Jan. 20, 2022) (“Vaccines work by mimicking the infectious bacteria or viruses that cause disease. Vaccination stimulates the body’s immune system to build up defenses against the infectious bacteria or virus (organism) without causing the disease. The parts of the infectious organism that the immune system recognizes are foreign to the body and are called antigens. Vaccination exposes the body to these antigens . . . . After vaccination, the immune system is prepared to respond quickly and forcefully when the body encounters the real disease-causing organism.”).

<sup>15</sup> 21 U.S.C. § 355(d). FDA defines a drug as any product “intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease . . . [and that is] intended to affect the structure or any function of the body.” *Id.* § 321(g)(1).

<sup>16</sup> 21 U.S.C. § 355(b)(1) (providing a “safe and effective” standard for drugs); 42 U.S.C. § 262(a)(2)(C)(i)(1) (providing a “safe, pure, and potent” standard for biologics). While FDA also provides oversight and premarket approval or clearance for medical devices, considering the differences and added complexities for medical devices, an analysis of medical device policy is outside the scope of this Article. For an excellent overview of the commonalities in the approval

### A. FDA's Approval Process

From a bird's eye perspective, the approval process is as follows: After developing an investigational drug or vaccine in the laboratory, manufacturers must submit an IND containing initial "preclinical" research from laboratory and animal testing (along with other relevant information) to show that the drug is ready for human trials.<sup>17</sup> FDA conducts a preliminary review to ensure that human research subjects will not incur unreasonable risks.<sup>18</sup>

Vaccines and drugs undergo three phases of clinical testing on human subjects. Phase 1 typically consists of smaller numbers of healthy participants where the researchers focus largely on safety, analyzing the effects of various dosages and side effects.<sup>19</sup> If the Phase 1 clinical trial does not raise unacceptable safety concerns,<sup>20</sup> the process moves to Phase 2, which involves more participants and allows for comparisons to better determine the drug's effectiveness.<sup>21</sup> Phase 3 consists of even larger pools of participants (potentially thousands) to determine safety and efficacy.<sup>22</sup>

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processes between drugs and biologics, along with other valuable insights, see Patricia J. Zettler et al., *Drug and Vaccine Development and Access*, in *COVID-19 POLICY PLAYBOOK: LEGAL RECOMMENDATIONS FOR A SAFER, MORE EQUITABLE FUTURE* (S. Burris et al., eds., 2021).

<sup>17</sup> See Aaron S. Kesselheim et al., *An Overview of Vaccine Development, Approval, And Regulation, With Implications For COVID-19*, 40 *HEALTH AFF.* 25, 26 (2021) (citing Valerie Marshall & Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 *PEDIATRICS* S23–30 (Supp. 1 2011)); see also Coughlin et al., *supra* note 6, at 598; Austin Winniford, *Expanding Access to Investigational Drugs for Treatment Use: A Policy Analysis and Legislative Proposal*, 19 *HEALTH MATRIX* 205, 215 (2009).

<sup>18</sup> *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA, <https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> [<https://perma.cc/G7GF-5C72>] (last updated Nov. 24, 2017).

<sup>19</sup> *Id.*

<sup>20</sup> *See id.*

<sup>21</sup> *See id.*

<sup>22</sup> *See id.*; see also Kesselheim et al., *supra* note 17, at 26 ("Because vaccines are administered to healthy people, there is a low tolerance for adverse events, even rare ones. This requires a larger sample size that would be needed, for example, for a study of a new antibiotic to treat an acute infection.").



After a manufacturer successfully completes the clinical trial process and submits a Biologics License Application (“BLA”)<sup>23</sup> or corresponding New Drug Application (“NDA”),<sup>24</sup> FDA can ask for additional input and recommendations from an advisory committee,<sup>25</sup> such as the Vaccines and Related Biological Products Advisory Committee (“VRBPAC”), before granting (or declining to grant) full approval.<sup>26</sup> Following approval (or “authorization” under an EUA, for vaccines) by FDA, the Centers for Disease Control and Prevention’s (“CDC”) Advisory Committee on Immunization Practices (“ACIP”), which is comprised of independent medical and health experts, reviews the data, holds a hearing, and makes recommendations as to its use.<sup>27</sup>

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<sup>23</sup> 21 C.F.R. § 601.2(a).

<sup>24</sup> 21 C.F.R. § 314.50.

<sup>25</sup> See 21 U.S.C. § 355(n)(1). See also Audrey D. Zhang, Jason L. Schwartz & Joseph S. Ross, *Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008-2015*, 97 MILBANK Q. 796, 804–05 (2019) (examining factors in advisory committee and FDA agency decision-making).

<sup>26</sup> See *Vaccines and Related Biological Products Advisory Committee*, FDA, <https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/vaccines-and-related-biological-products-advisory-committee> [<https://perma.cc/Z7Z5-PY7K>] (last updated Apr. 26, 2019).

<sup>27</sup> See *ACIP Vaccine Recommendations and Guidance*, CDC, <https://www.cdc.gov/vaccines/hcp/acip-recs/index.html> [<https://perma.cc/5QDX-GRLD>] (last updated July 13, 2013) [hereinafter “*ACIP Vaccine Recommendations and Guidance*”]; see *Emergency Preparedness and Vaccine Safety*, CDC, <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/emergencypreparedness/index.html> [<https://perma.cc/4RYM-2D9N>] (last visited Jan. 21, 2022). Other programs, such as CDC’s Clinical Immunization Safety Assessment (“CISA”) Project, CDC’s Vaccine Safety Datalink, and FDA’s Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, and others, also exist. See Kesselheim et al., *supra* note 17, at 27–28. Whenever serious problems are detected through VAERS, or another post-market surveillance program, after a vaccine has been distributed for use, the CDC’s ACIP revises or retracts its recommendation. See *ACIP Vaccine Recommendations and Guidance*. But see Ed Silverman, *Is the FDA Taking Advice from its Expert Panels? A new Analysis Points to Inconsistencies in the Process*, STAT (May 2, 2022), <https://www.statnews.com/pharmalot/2022/05/02/fda-advisory-committee-approvals/> [<https://perma.cc/9J4W-KBU9>]

Developing and guiding a new product (a vaccine or a drug) through market approval can cost millions, even billions, of dollars.<sup>28</sup> Most products fail to complete the process<sup>29</sup> because of costs exceeding expectations, negative clinical outcomes, a lack of safety or efficacy, or a flawed study design.<sup>30</sup> The approval process is risky: For cancer treatments, only 3.4% of applications that make it past preliminary review to Phase 1 clinical trials were approved.<sup>31</sup> The rate for vaccines, at least pre-pandemic, was higher at 33.4%.<sup>32</sup> And, the process takes time: In fact, navigating a vaccine or a drug through the clinical trial process can take years or decades.<sup>33</sup> But the rigorous regulatory burdens—despite the understandable frustrations they may create—are designed to promote health goals;<sup>34</sup> and, most of the time, they succeed. Consider, as an

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(discussing that FDA seems “increasingly disinterested in advice from its hand-picked outside experts” based on a significant decrease in cases where advisory panels have been convened, as well as an increase in cases where, after convening an advisory panel, FDA endorsed a drug that the committee voted against approving).

<sup>28</sup> See Olivier J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018*, 323 JAMA 844, 844 (2020).

<sup>29</sup> See David W. Thomas et al., *Clinical Development Success Rates 2006–2015*, BIOTECHNOLOGY INNOVATION ORG. (2016), <https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf> [<https://perma.cc/EF8T-TJ33>]; see also Chi Heem Wong, Kien Wei Sah & Andrew W. Lo, *Estimation of Clinical Trial Success Rates and Related Parameters*, 20 BIostatistics 273, 277 (2019) (estimating drug development success rates from both aggregated clinical trial success rates and disaggregated estimates across several trial features).

<sup>30</sup> Thomas et al., *supra* note 29.

<sup>31</sup> See *id.*; see generally Joseph A. DiMasi et al., *Development Times and Approval Success Rates for Drugs to Treat Infectious Diseases*, 107 CLINICAL PHARMACOLOGY & THERAPEUTICS 324, 327 (2020) (discussing how to consider data to achieve optimal evaluation metrics for investigational drugs).

<sup>32</sup> See Thomas et al., *supra* note 29.

<sup>33</sup> Dave Roos, *How a New Vaccine was Developed in Record Time in the 1960s*, HISTORY, <https://www.history.com/news/mumps-vaccine-world-war-ii> [<https://perma.cc/G5N6-R5GY>] (last updated Oct. 29, 2021) (explaining that, before the COVID-19 pandemic, the fastest recorded development for a vaccine was four years).

<sup>34</sup> See *infra* notes 54–76 and accompanying text.

example, FDA's initial rejection of tissue plasminogen activator, ("tPA"), a drug used to break up ischemic blood clots. The company retested the drug, whereby data showed that, at a lower dose, the drug was more effective with fewer side effects (and less expensive), the drug received FDA approval.<sup>35</sup>

### *B. The Post-Approval Process*

Following approval, vaccines and drugs continue to be evaluated by FDA through Phase IV trials, which are studies either required by FDA or agreed to by manufacturers that are conducted after a product is marketed.<sup>36</sup> These studies collect data that (1) compare the product with other products on the market; (2) monitor the product's long-term safety and effectiveness; and, (3) determine the product's cost-effectiveness.<sup>37</sup> Phase IV studies are critical to understanding how vaccines and drugs work in real world settings.<sup>38</sup> As a result of these Phase IV studies, data has come to light, which has resulted—albeit, probably not as easily or as quickly as it should

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<sup>35</sup> FRAN HAWTHORNE, *INSIDE THE FDA: THE BUSINESS AND POLITICS BEHIND THE DRUGS WE TAKE AND THE FOOD WE EAT* 49 (2005); *see, e.g.*, Christine Coughlin & Nancy M.P. King, *The Stories We Tell: Narrative, Policymaking and the Right to Try*, 11 WAKE FOREST J.L. & POL'Y 17, 38 (2020) (discussing the events surrounding the initial rejection and subsequent approval of tPA as an example of the difficulty surrounding generating "positive narratives about the role that clinical research plays in improving the public's health").

<sup>36</sup> *Postmarketing Clinical Trials*, FDA (Mar. 29, 2019), <https://www.fda.gov/vaccines-blood-biologics/biologics-post-market-activities/postmarketing-clinical-trials> [<https://perma.cc/Q8Q8-PA5H>] ("The Food and Drug Administration Modernization Act of 1997 (FDAMA) amended the Food, Drug and Cosmetic Act by adding a new section 506B (21 U.S.C. 356b). This section provides additional authority for monitoring the progress of postmarketing studies that drug and biologic applicants have agreed to conduct. Congress enacted this section in response to concerns expressed by [FDA] and the public about the timeliness of completing postmarketing studies and about the need to update drug labeling with information obtained from such studies."). These studies are also referred to as post-marketing studies or post-market surveillance studies. *See* 21 U.S.C. § 356b.

<sup>37</sup> *See* Viraj Suvarna, *Phase IV of Drug Development*, 1 PERSPS. CLINICAL RSCH. 57, 60 (2010).

<sup>38</sup> Kesselheim et al., *supra* note 17, at 27.

have<sup>39</sup>—in removing products, such as Vioxx and Xigris, from the market.<sup>40</sup>

In addition to post-market surveillance studies, FDA has additional oversight mechanisms unique to vaccines,<sup>41</sup> one of which is FDA’s Vaccine Adverse Event Reporting System (“VAERS”).<sup>42</sup> VAERS enables clinicians, manufacturers, and the public to voluntarily report adverse events that occur post-vaccination.<sup>43</sup> This data, in turn, instructs FDA and CDC as to whether further studies may be needed. VAERS is somewhat limited by its voluntary reporting requirements, so its value stems from providing data on correlation rather than causation.<sup>44</sup>

### C. Off-label Use

While FDA approves vaccines and drugs for certain uses, FDA does not regulate the general practice of medicine. Physicians can prescribe FDA-approved drugs in an “off-label” manner—that is, when the drug is not prescribed for the approved dosage amount by FDA, administered in a different way, or when the drug is used to

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<sup>39</sup> *Id.* at 27–28 (citing Steven Woloshin et al., *The Fate of FDA Postapproval Studies*, 377 NEW ENGL. J. MED. 1114, 1114–17 (2017) (“However, analysis of required Phase IV studies across all drugs and biologics have found that they are frequently completed not on time, if at all.”)).

<sup>40</sup> In 2004, Merck & Co. implemented a voluntary worldwide withdrawal of rofecoxib (Vioxx) after a post-market surveillance study indicated that patients taking the drug long-term incurred twice the risk of a heart attack compared with patients receiving a placebo. Paul A. Dieppe et al., *Lessons from the Withdrawal of Rofecoxib*, 329 BMJ 867, 867 (2004). In 2011, Eli Lilly & Co. announced its voluntary worldwide market withdrawal of Xigris [drotrecogin alfa (activated)] after a post-market study showed that the drug failed to provide a survival benefit for patients with severe sepsis and septic shock. Mike Mitka, *Drug for Severe Sepsis is Withdrawn from Market, Fails to Reduce Mortality*, 306 JAMA 2439, 2439 (2011). For an excellent overview of the FDA process and the Emergency Use Authorization pathway, see Jacob S. Sherkow, *Regulatory Sandboxes and the Public Health*, 2022 U. ILL. L. REV. 357, 373 (2022).

<sup>41</sup> See Kesselheim et al., *supra* note 17, at 28.

<sup>42</sup> *Vaccine Adverse Event Reporting System*, HHS, <https://vaers.hhs.gov/> [<https://perma.cc/R29C-TB9K>] (last visited Feb. 11, 2022).

<sup>43</sup> Kesselheim et al., *supra* note 17, at 28.

<sup>44</sup> See *ACIP Vaccine Recommendations and Guidance*, *supra* note 27 and accompanying text.

treat a disease or illness other than for what FDA has approved it.<sup>45</sup> This ability not only provides physicians a mechanism to use their medical training and expertise to treat patients in a manner they deem most beneficial to the patient but also affords physicians a right of individual autonomy with respect to medical treatment decision making:

Off-label use also reflects an ongoing willingness by physicians to explore all possibilities for soothing, if not curing, patients. This behavior has accelerated in recent years, now that Internet access has provided more information than ever before to physicians and patients. Notably, the improved ability to research medications and their uses has prompted a greater sense of activism among some patients to pursue treatments, regardless of approved indications.<sup>46</sup>

The practice of prescribing in an off-label manner is usually safe. The products have undergone rigorous clinical testing, producing data that confirms the drug's risks versus benefits. However, these drugs may still pose a threat, given that they are being used on a case-by-case basis to treat a condition for which the drug was not previously vetted.<sup>47</sup> As also observed during the COVID-19 pandemic, off-label use can lead to problems with access for those who need the medication for its approved purpose. For

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<sup>45</sup> See *Understanding Unapproved Use of Approved Drugs "Off Label"*, FDA, <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label> [https://perma.cc/T7KH-U9PV] (last updated Feb. 5, 2018). FDA can also require a Risk Evaluation and Mitigation Strategy ("REMS") "to help reduce the occurrence or severity of a particular serious adverse event [and] help support a drug's safe use as described in the product's FDA-approved prescribing information" which serves to limit off-label use. *Frequently Asked Questions About REMS*, FDA, <https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems> [https://perma.cc/4YKU-TH7Z] (last updated Jan. 26, 2018). Also, if insurers do not cover treatments because they are being used off-label, that will also serve to limit its use. See Amanda Bowers, *Is There a Better Way to Guide Payers on Off-Label Coverage?*, 5 BIOTECH. HEALTHCARE, 9, 9–10 (2008).

<sup>46</sup> Ed Silverman, *Setting the Bar Higher for Off-Label Use of Biologics*, 8 BIOTECH. HEALTHCARE 14, 14 (2011).

<sup>47</sup> See Zettler et al., *supra* note 16, at 143 ("In response, some states (and the District of Columbia) used their authority to regulate medical practice to limit off-label prescribing or dispensing of drugs for Covid-19 and communicated the lack of evidence demonstrating their effectiveness for Covid-19.").

instance, after a study revealed that the dexamethasone (a steroid) reduced the death rate by roughly one-third among seriously ill patients on ventilators,<sup>48</sup> off-label use of the drug increased and resulted in a shortage due to hoarding.<sup>49</sup> In addition, widespread off-label use may deprive the medical community of a comprehensive understanding of how a given drug reacts to a novel disease or illness physicians are attempting to treat, limiting the effectiveness and the speed with which that information can be utilized going forward.<sup>50</sup>

#### D. FDA's Approval Process and Patents

All in all, FDA's approval process for drugs and vaccines operates in tandem with the U.S. patent system in order to foster research and innovation.<sup>51</sup> The regulatory structure, which emphasizes safety, works alongside patent and liability protections to provide market exclusivity, enabling developers to recoup

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<sup>48</sup> See Press Release, Univ. of Oxford, *Low-cost Dexamethasone Reduces Death by up to One Third in Hospitalized Patients with Severe Respiratory Complications of COVID-19* (June 16, 2020), [https://www.recoverytrial.net/files/recovery\\_dexamethasone\\_statement\\_160620\\_v2final.pdf](https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf) [<https://perma.cc/56FX-EKV3>]; see also Jamie Ducharme, *A Low-Cost Steroid Shows Promise for Treating SARS-COV-2. But Take the News with a Grain of Salt*, TIME (June 16, 2020, 2:56 PM), <https://time.com/5854416/dexamethasone-covid-19/> [<https://perma.cc/U2GJ-P9BP>].

<sup>49</sup> See Ed Silverman, *Hospitals See Shortages of a Cheap Steroid that One Study Says Helps Sars-Cov-2 Patients*, STAT (June 25, 2020), <https://www.statnews.com/pharmalot/2020/06/25/covid19-coronavirus-dexamethasone-shortages/> [<https://perma.cc/DC8Q-A9L2>]; see also Eli Cahan, *Drug Recently Shown to Reduce Coronavirus Death Risk Could Run Out, Experts Warn*, SCI. MAG. (June 21, 2020, 6:25 PM), <https://www.sciencemag.org/news/2020/06/corticosteroid-drug-recently-shown-reduce-coronavirus-death-risk-could-run-out-experts> [<https://perma.cc/3BB5-CHFV>] (discussing concerns from public health officials on hoarding of dexamethasone).

<sup>50</sup> See generally Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Governmental Oversight*, 37 J.L. MED. & ETHICS 476 (2009) (examining the risks and benefits of the current regulatory framework for off-label prescriptions).

<sup>51</sup> Coughlin et. al, *supra* note 6, at 597; see generally Rebecca Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007) (providing an excellent discussion of the relationship between patents, FDA drug regulation, and biopharmaceutical innovation).

research and development costs and make a profit for shareholders.<sup>52</sup> Manufacturers are also afforded liability protections regarding vaccines and other products developed in response to public health emergencies.<sup>53</sup> These features encourage future research and development of innovative treatments, which, in theory, will help future patients.

### III. HISTORICAL EVENTS IN ENHANCING SAFETY

FDA works to balance the seemingly competing goals of protecting the public from unsafe treatments with increasing access to investigational treatments to support individual autonomy. Finding the appropriate balance, however, is understandably difficult, particularly given these seemingly conflicting goals. Critics argue that FDA is overly bureaucratic, stifles innovation and development, and delays access to products that may help treat patients who may not have the luxury of time;<sup>54</sup> others believe FDA tries to employ a “thoughtful, savvy, and swift introduction of new medicines through the review process.”<sup>55</sup>

History provides a helpful lens to analyze past problems in order to identify present patterns that otherwise might have been

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<sup>52</sup> Coughlin et. al, *supra* note 6, at 597 (citing Eisenberg, *supra* note 51, at 361).

<sup>53</sup> Under the Public Readiness and Emergency Preparedness (“PREP”) Act of 2005, Pub. L. 109-148, 119 Stat. 2818 (2005), manufacturers were granted immunity from liability except in cases of willful misconduct. The U.S. Health and Human Services Secretary may issue a separate PREP Act declaration where “a disease or other health condition or threat to health constitutes a public health emergency. . .or there is a credible risk. . . .” 42 U.S.C. § 247d-6d. The PREP Act also established the Countermeasures Injury Compensation System which, with some limitations, will compensate individual who die or suffer serious physical injury because of an emergency medical countermeasure. 42 U.S.C. § 247d-6d(a)(2)(B); *see* CONG. RSCH. SERV., LSB10443, THE PREP ACT AND COVID 19: LIMITING LIABILITY FOR MEDICAL COUNTERMEASURES 2 (2020).

<sup>54</sup> Benjamin N. Rome & Jerry Avorn, *Drug Evaluation During the Covid-19 Pandemic*, 382 NEW ENG. J. MED. 2282, 2283 (2020).

<sup>55</sup> Peter J. Pitts, *Too Fast or Too Slow: Is FDA Moving at the Right Speed?*, HEALTH AFFS. (Mar. 19, 2021), <https://www.healthaffairs.org/doi/10.1377/forefront.20210317.69490/full/> [<https://perma.cc/9AJ5-SE9X>].

invisible.<sup>56</sup> This, in turn, may shed light on how to overcome barriers that have hindered progress. Below are brief historical descriptions of events that have strengthened FDA's safety and/or efficacy requirements with respect to investigational vaccines and drugs.<sup>57</sup>

At the turn of the twentieth century, children diagnosed with diphtheria were often treated with an antitoxin produced by inoculating horses with small amounts of diphtheria that would produce an immune response.<sup>58</sup> The horses then were bled periodically to extract the serum.<sup>59</sup>

In St. Louis, Missouri, a retired milk wagon horse named Jim was responsible for producing the antitoxin.<sup>60</sup> Although initially serving his purpose, Jim eventually had to be euthanized after contracting tetanus.<sup>61</sup> The St. Louis Health Department claimed that the tainted batch of blood extracted from Jim during the time he showed signs of tetanus was neither distributed nor used. Tragically, however, a mislabeled batch was used, and thirteen children died due to Jim's tetanus-contaminated antiserum.<sup>62</sup> In response,

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<sup>56</sup> Dep't of History, *Why Study History?*, U. WIS., <https://history.wisc.edu/undergraduate-program/history-careers/why-history/> [<https://perma.cc/TJD5-4T4A>] (last visited Jan. 18, 2022).

<sup>57</sup> See Coughlin et al., *supra* note 6, at 596–615 (discussing portions of this historical overview); see HAWTHORNE, *supra* note 35, at 21–33.

<sup>58</sup> Mallory Warner, *How Horses Helped Cure Diphtheria*, NAT'L MUSEUM OF AM. HIST. (Aug. 13, 2013), <https://americanhistory.si.edu/blog/2013/08/how-horses-helped-cure-diphtheria.html> [<https://perma.cc/88TC-JZMQ>] (discussing how, in 1890, scientists learned that children suffering from diphtheria could be potentially cured with exposure to small doses of anti-toxin, which could be developed from the blood serum of horses).

<sup>59</sup> Charles Richter & John Emrich, *Hero Horses in the Fight Against Disease*, AM. ASSOC. OF IMMUNOLOGISTS (Oct. 2021), <https://www.aai.org/About/History/History-Articles-Keep-for-Hierarchy/Hero-Horses-in-the-Fight-Against-Disease> [<https://perma.cc/TE97-HW8S>].

<sup>60</sup> *Id.*

<sup>61</sup> *Id.*

<sup>62</sup> *Id.*; see *Milestones in U.S. Food and Drug Law*, FDA, <https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law> [<https://perma.cc/9NQH-62MP>] (last visited Jan. 18, 2022) [hereinafter *Milestones in U.S. Food and Drug Law*]; *The Road to the Biotech Revolution—Highlights of the 100 Years of Biologics Regulation*, FDA, <https://www.fda.gov/about-fda/fda-history/history-biologics-regulation> [<https://perma.cc/KP4L-RJQW>] (last visited Jan. 18, 2022).



Congress passed the Biologics Control Act of 1902, which provided for government regulation of vaccine production.<sup>63</sup>

A few years later, Congress passed the Pure Food and Drug Act of 1906, which prohibited the marketing and sale of misbranded and adulterated foods, drinks, and drugs in interstate commerce.<sup>64</sup> This legislation was also promulgated in response to social and political pressure after various publications revealed unsanitary conditions and food-handling practices in meat-packing plants.<sup>65</sup>

Congress likewise enacted the 1938 Food, Drug, and Cosmetic Act in response to social outrage after a drug company sold a liquid antibacterial elixir that contained a poisonous raspberry flavoring, killing nearly one-hundred people, including thirty-seven children.<sup>66</sup> This Legislation marked the beginning of modern drug regulation by requiring that manufacturers show a drug is safe before marketing the drug.<sup>67</sup>

In another tragic event in 1955, more than 260 people contracted polio from batches of a vaccine that contained the live virus because the virus was not properly inactivated.<sup>68</sup> An investigation in what

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<sup>63</sup> Biologics Control Act of 1902, Pub. L. No. 57-244, 32 Stat. 728 (1902).

<sup>64</sup> Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906) (repealed 1938) (laying the foundation for what would become the statute that established the Food and Drug Administration).

<sup>65</sup> See Andrew Glass, *Pure Food and Drug Act Passes June 23, 1906*, POLITICO (June 23, 2014, 12:02 AM), <https://www.politico.com/story/2014/06/fda-theodore-roosevelt-108164> [<https://perma.cc/B7Y3-LB9Y>].

<sup>66</sup> Coughlin & King, *supra* note 35, at 21–33.

<sup>67</sup> See Federal Food, Drug and Cosmetic Act of 1938, ch. 675, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. § 301 et seq. (2018)). This Legislation contained provisions “[e]xtending control to cosmetics and therapeutic devices; [r]equiring new drugs to be shown safe before marketing-starting a new system of drug regulation; [e]liminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases; [p]roviding that safe tolerances be set for unavoidable poisonous substances; authorizing standards of identity, quality, and fill-of-container for foods; [a]uthorizing factory inspections; and [a]ding the remedy of court injunctions to the previous penalties of seizures and prosecutions.” *Milestones in U.S. Food and Drug Law*, *supra* note 62.

<sup>68</sup> *Historical Vaccines Safety Concerns*, CDC, <https://www.cdc.gov/vaccine-safety/concerns/concerns-history.html> [<https://perma.cc/QL5L-G5XK>] (last visited Jan. 18, 2022); Michael E. Ruane, *The Tainted Polio Vaccine that Sickened*

became known as “the Cutter Incident” revealed a systemic “lack of experience and expertise at Cutter Laboratories that had gone undetected by inspectors [of the Laboratory of Biologics Control].”<sup>69</sup> This tragedy led to the creation of the Division of Biologics Standards, initially an independent entity within the National Institutes of Health (“NIH”) but ultimately came under the ambit of FDA. Later, the Division was renamed the Center for Biologics Evaluation and Research, which today controls the federal oversight of vaccines.<sup>70</sup>

Less than a decade later, news reports emerged regarding the significant pressure FDA pharmacologist and physician Frances Oldham Kelsey had received to approve Thalidomide, a drug marketed in western Europe to alleviate morning sickness during pregnancy that had been linked to severe birth defects.<sup>71</sup> The public outcry spurred Congress to pass the Kefauver-Harris Drug Amendment of 1962, establishing a more rigorous clinical trial

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*and Fatally Paralyzed Children in 1955*, WASH. POST (Apr. 14, 2020), <https://www.washingtonpost.com/history/2020/04/14/cutter-polio-vaccine-paralyzed-children-coronavirus/> [<https://perma.cc/6MWN-KD4D>].

<sup>69</sup> See PAUL OFFIT, *THE CUTTER INCIDENT: HOW AMERICA’S FIRST POLIO VACCINE LED TO A GROWING VACCINE CRISIS* 727 (YALE U. PRESS, 2005); see also Michael Fitzpatrick, *Review: The Cutter Incident: How America’s First Polio Vaccine Led to a Growing Vaccine Crises*, 99 J. ROYAL SOC. MED. 156, 156 (2006) (explaining that, according to Offit, the threat of litigation can harm innovation, particularly with respect to vaccine development).

<sup>70</sup> See Fitzpatrick, *supra* note 69, at 156. A subsequent court order requiring Cutter Industries to compensate those harmed by its vaccine “opened the floodgates to a wave of litigation. As a result, ‘vaccines were among the first medical products almost eliminated by lawsuits. Indeed, the National Vaccine Injury Compensation Program was introduced in 1986 to protect vaccine manufacturers from litigation on a scale that threatened the continuing production of vaccines.’” See *id.*; see also *The History of Vaccines*, COLL. PHYSICIANS PHILA., <https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation> [<https://perma.cc/27HH-GLQL>] (last visited Jan. 21, 2022) (providing a helpful timeline of milestones in vaccine history); see *Vaccine Development-101*, *supra* note 14 and accompanying text.

<sup>71</sup> See Robert D. McFadden, *Frances Oldham Kelsey, Who Saved U.S. Babies from Thalidomide, Dies at 101*, N.Y. TIMES (Aug. 7, 2015), <https://www.nytimes.com/2015/08/08/science/frances-oldham-kelsey-fda-doctor-who-exposed-danger-of-thalidomide-dies-at-101.html> [<https://perma.cc/Z84V-EMZX>]; see *Milestones in U.S. Food and Drug Law*, *supra* note 62.

process and mandating manufacturers to submit evidence of both safety and efficacy.<sup>72</sup>

In 1976, CDC identified a new strain of influenza genetically similar to the 1918 “Spanish Flu.” After reported pressure by then President Gerald Ford (who was running for reelection), as well as the discovery of an unfortunate memorandum written by an FDA official that read in relevant part, “[t]he Administration can tolerate unnecessary health expenditures better than unnecessary deaths and illness,” the federal government rapidly deployed a national vaccination program.<sup>73</sup>

Vaccine manufacturers, however, demanded that the government indemnify them for any potential claims, leading unsurprisingly to the public perception: “‘There’s something wrong with [the] vaccine.’ This public misperception, warranted or not, ensured that every coincidental health event that occurred in the wake of the swine flu shot [was] scrutinized and attributed to the vaccine.”<sup>74</sup> The swine flu pandemic never emerged, but reports linking the vaccine with Guillain-Barré syndrome (an immune system disorder) did receive significant publicity.<sup>75</sup> This public health failure was dubbed the “swine flu snafu” and was attributed to inappropriate political influence guiding public health decision-making, highlighting the critical nature of obtaining support for public health mandates through effective public messaging.<sup>76</sup>

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<sup>72</sup> Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 780 (2019); see Charo, *supra* note 11, at 252–53 (providing discussion on the effect of the Thalidomide tragedy on clinical trials and regulations).

<sup>73</sup> David J. Sencer & J. Donald Millar, *Reflections on the 1976 Swine Flu Vaccination Programs*, 12 EMERGING INFECTIOUS DISEASES 29, 30 (2006).

<sup>74</sup> *Id.* at 31.

<sup>75</sup> Christopher Klein, *When the U.S. Tried to Fast Track a Flu Vaccine*, HISTORY (Sept. 20, 2020), <https://www.history.com/news/swine-flu-rush-vaccine-election-year-1976> [<https://perma.cc/F8UA-J6ZK>].

<sup>76</sup> *Id.*; see also Jeffrey Young, *The Presidential Public Health Failure History Forgot*, HUFFINGTON POST (Apr. 29, 2020), [https://www.huffpost.com/entry/ford-swine-flu-vaccination\\_n\\_5ea831f2c5b6ab20b1532511](https://www.huffpost.com/entry/ford-swine-flu-vaccination_n_5ea831f2c5b6ab20b1532511) [<https://perma.cc/6AS3-X78V>]; see also Jonathan Iwry, *FDA Emergency Use Authorization from 9/11 to Covid 19: Historical Lessons and Ethical Challenges*, 76 FOOD & DRUG L.J., at 337, 343 (2021) (providing an excellent in-depth examination of the

In response to these (and other) events, FDA enhanced its regulatory structure in favor of safety and created some liability protections for manufacturers.<sup>77</sup> But, despite the long-standing public outcry that occurred in response to the tragic events discussed above, FDA's approval framework was, and still is, criticized for doing more harm than good.<sup>78</sup> This tension incentivized FDA to provide patients with accelerated approval (or authorization) of, or pre-approval access to, potentially promising vaccines and drugs.<sup>79</sup>

#### IV. ALTERNATIVE FDA PATHWAYS

In the 1980s and early 1990s, AIDS patients and their advocates became vocal critics of FDA. These critics argued that the Agency was focused on satisfying obscure standards of safety and efficacy for the sake of unknown future patients rather than on helping currently dying patients with potentially lifesaving drugs during a large-scale public health crisis.<sup>80</sup> Dr. Anthony Fauci—the same scientist serving as Chief Medical Advisor to President Biden—was instrumental in proposing frameworks that would enable experimental medications to be administered for treatment purposes while the drugs were still being studied in clinical trials.<sup>81</sup>

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history of FDA's use of EUAs, as well as ethical and legal considerations for their use during the COVID-19 pandemic).

<sup>77</sup> Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 780 (2019) (codified as amended in scattered sections of 21 U.S.C).

<sup>78</sup> Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America's Drug Constitution*, 42 AM. J.L. & MED. 687, 700–01 (2016).

<sup>79</sup> See generally LEWIS A. GROSSMAN, CHOOSE YOUR OWN MEDICINE: FREEDOM OF THERAPEUTIC CHOICE IN AMERICA (2021) (discussing the social, historical, and political underpinnings of this tension).

<sup>80</sup> Grossman, *supra* note 78 at 15–17.

<sup>81</sup> Philip J. Hilts, *FDA, in Big Shift, Will Permit Use of Experimental Aids Drug*, N.Y. TIMES (Sept. 29, 1989), <https://www.nytimes.com/1989/09/29/us/fda-in-big-shift-will-permit-use-of-experimental-aids-drug.html> [<https://perma.cc/Q4JX-Y8AH>]; see also Suzanne White Junod, *FDA and Clinical Drugs: A Short History*, FDA, <https://www.fda.gov/media/110437/download> [<https://perma.cc/X3L3-3T2B>] (last visited Feb. 2, 2022) (“One lesson learned from the AIDS epidemic . . . is the scientific utility of surrogate endpoints in certain circumstances. . . . Surrogate endpoints measure outcomes that are not clinically valuable by themselves (lowered cholesterol, blood pressure, elevated t-cell

### A. Accelerated Approval

The AIDS crisis, as well as its corresponding patient advocacy movement, called for FDA, *inter alia*, to expedite its approval process.<sup>82</sup> In 1992, FDA began its Accelerated Approval Program to shorten the amount of time required to gain approval of certain medical products for serious conditions with little or no alternative treatment options by allowing submission of real world evidence<sup>83</sup> and earlier surrogate endpoints<sup>84</sup> to satisfy FDA's safety and efficacy standards.<sup>85</sup>

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counts), but are thought to correspond with improved medical outcomes (decreased heart disease or stroke, fewer opportunistic infections for AIDS patients).”).

<sup>82</sup> See Marie-Amélie George, *The Fight Against AIDS Has Shaped How Potential SARS-COV-2 Drugs Will Reach Patients*, WASH. POST (Apr. 29, 2020, 6:00 AM), <https://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302/> [https://perma.cc/8SHR-AAXL]; Douglas Crimp, *Before Occupy: How AIDS Activists Seized Control of the FDA in 1988*, ATLANTIC (Dec. 6, 2011), <https://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302/> [https://perma.cc/7XBU-YXSC].

<sup>83</sup> Real world evidence is defined as “clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of [real world data].” *Real World Evidence*, FDA, <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence> [https://perma.cc/2MZD-3YNB]32SK-2U67] (last visited Feb. 3, 2022); *see also* 21st Century Cures Act, Pub. L. No. 114-225 (2016) (providing, *inter alia*, additional focus on the use of real-world evidence and real-world data to support regulatory decision making). Whereas real world data “are...data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources,” including electronic health records, claims and billing activities, product and disease registries, patient-generated data, data from mobile devices, and other related sources. *Id.*

<sup>84</sup> *Accelerated Approval Program*, FDA, <https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program> [https://perma.cc/6278-UX9E] (last visited Jan. 17, 2022) (“A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.”).

<sup>85</sup> *See Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, FDA, <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/>

Accelerated approval designation allows FDA to approve high-priority drugs for use by affording more flexibility in the data, as described above.<sup>86</sup> After receiving accelerated approval, manufacturers instead rely on post-market surveillance studies for the purposes of establishing safety and efficacy in real world conditions.<sup>87</sup> If the Phase IV study does confirm a clinical benefit, FDA will grant traditional approval; if, however, later trials fail to confirm a clinical benefit, the drug can be removed from the market.<sup>88</sup>

For instance, in 2001, FDA granted accelerated approval for imatinib meysylate (Gleevac) for certain patients suffering from a type of chronic leukemia. Follow up studies showed a 90.88% survival rate after two years of treatment, which enabled the drug to obtain full approval in 2003.<sup>89</sup> On the other hand, in 2016 FDA conditionally approved eteplirsen (Exondys 51) for Duchenne

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fast-track-breakthrough-therapy-accelerated-approval-priority-review [https://perma.cc/H7XJ-PYAH] (last visited Jan. 18, 2022). Other designations that do not provide for market authorization but may provide for a quicker review or possibly tax credits and exclusivity include: (1) Fast Track: a program designed to promote a quicker review process for drugs that treat “a serious or life-threatening disease or condition” when that drug would fill “unmet medical needs”; (2) Breakthrough Therapy: program designed to promote a quicker review process for drugs that treat “a serious or life-threatening disease or condition” when that drug could be a “substantial improvement over available therapies”; and, (3) Priority Review: designed to ensure that FDA takes action on the application within six months. *Id.*

<sup>86</sup> Holly Fernandez Lynch & Christopher T. Robertson, *Challenges in Confirming Drug Effectiveness after Early Approval*, 374 SCI. 1205, 1205 (Dec. 3, 2021).

<sup>87</sup> *Id.* at 1205.

<sup>88</sup> *Id.* But see Melody Petersen, *Science Hasn't Shown These Medications Work. They're Being Sold Anyway*, L.A. TIMES (Mar. 3, 2022), [https://www-latimes-com.cdn.ampproject.org/c/s/www.latimes.com/business/story/2022-03-03/fda-accelerated-approval?\\_amp=true](https://www.latimes.com.cdn.ampproject.org/c/s/www.latimes.com/business/story/2022-03-03/fda-accelerated-approval?_amp=true) [https://perma.cc/Z28Q-HT3V] (“Although the FDA has the power to remove these drugs when studies later show the medicines don’t work, that move has been rare.”). See generally Erica M. Cox et al, *Regulatory Affairs 101: Introduction to Expedited Regulatory Pathways*, 13 CLIN. TRANS. SCI. 451, 455 (2020).

<sup>89</sup> Anna Kaltenboeck et al., *Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Certainty, Access, Innovation, and Costs*, INST. FOR CLINICAL & ECON. REV. 4, 4 (2021).

Muscular Dystrophy, despite debate regarding whether the drug demonstrated a likelihood of clinical benefit. Confirmatory evidence, which could lead to full approval, is not expected until 2026.<sup>90</sup> The controversy surrounding Exondys 51 is one of many situations that led public health law scholars to question whether the data collection requirement for accelerated approvals is sufficiently robust and timely.<sup>91</sup> Congress, moreover, has been focusing on reforming the accelerated access with competing bills, such as the Accelerated Approval Integrity Act of 2022 proposed by Democrats,<sup>92</sup> and the Accelerating Access for Patients Act of 2022, the Republican members' counter-proposal.<sup>93</sup> The Accelerated Approval Integrity Act would, *inter alia*, provide for new expedited procedures to remove drugs approved via this pathway where clinical benefit is not timely confirmed through post-market studies and would impose a five-year time limit for allowing products to stay on the market without confirming benefits.<sup>94</sup> The Republican counter-proposal, seen as more favorable to pharmaceuticals, also grants FDA authority to use expedited procedures for the withdrawal of products but requires FDA to promulgate such procedures.<sup>95</sup> While at the time of this writing it is unclear whether

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<sup>90</sup> *Id.*; See also Lynch & Robertson, *supra* note 86, at 1205 (reviewing factors affecting post-market approval studies and offering ideas for reform).

<sup>91</sup> Professors Holly Fernandez Lynch and Christopher Robertson also recently noted that, “more than 1 in 10 accelerated approvals predating 2016 still haven’t produced evidence to support transition either to traditional approval or withdrawal.” Holly Fernandez Lynch & Christopher T. Robertson, *A New Alzheimer’s Drug Shows Shy the FDA’s Speedy Approval Access Process Is Broken*, WASH. POST (Jan. 10, 2022), <https://www.washingtonpost.com/outlook/2022/01/10/fda-drug-approval-accelerated-alzheimer/> [<https://perma.cc/J3YX-VF6Q>]. However, as Lynch and Robertson describe in *Challenges*: “[F]or the threat of withdrawal to be meaningful, required confirmatory evidence would also have to be truly confirmatory, generated through trials with appropriate randomization, blinding, and controls, measuring meaningful health outcomes. Unfortunately, even if enacted, the PPA would not meet this standard, instead proposing reliance on “real world evidence (RWE) and registries.” Lynch & Robertson, *supra* note 86, at 1206.

<sup>92</sup> H.R. 6963, 117th Cong. (2022); see *supra* note 8.

<sup>93</sup> *Id.*

<sup>94</sup> *Id.*

<sup>95</sup> *Id.*

either bill will pass, the fact that both political parties are focused on FDA's accelerated approval pathway suggests that some type of legislative reform will likely occur.<sup>96</sup>

### *B. Emergency Use Authorization*

As discussed above, following the September 11 and anthrax attacks, Congress provided FDA the ability to issue an EUA, whereby investigational medical products can be made available to patients before undergoing the rigorous premarket approval process. Allowing authorization for marketing, rather than approval, furthers the goal of incentivizing rapid “development of new technologies directed to the crisis at hand.”<sup>97</sup>

Under the EUA framework, FDA will authorize a medical product for use in interstate commerce if, based on the “totality of scientific evidence,” FDA has a “reasonable” belief that (1) the product “may be effective”; (2) the known and potential benefits of authorization outweigh the known and potential risks; and, (3) no formally approved alternatives are available.<sup>98</sup>

To trigger an EUA, the Secretary of Health and Human Services (“HHS”) must declare that, based on current circumstances, a

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<sup>96</sup> Brittany Cafero & Taber Rueter, *Competing Bills Propose Amendments to FDA's Accelerated Approval Program*, REEDSMITH (Mar. 18, 2022), <https://www.healthindustrywashingtonwatch.com/2022/03/articles/legislative-developments/competing-bills-propose-amendments-to-fdas-accelerated-approval-program/> [<https://perma.cc/6XTM-V2DH>].

<sup>97</sup> Sherkow, *supra* note 40, at 361; see Jonathan Iwry, *From 9/11 to Covid-19: A Brief History of FDA Emergency Use Authorization*, HARV. L. BILL OF HEALTH (Jan. 28, 2021), <https://blog.petrieflom.law.harvard.edu/2021/01/28/fda-emergency-use-authorization-history/> [<https://perma.cc/UP4A-2T7S>].

<sup>98</sup> Sherkow, *supra* note 40, at 374.



domestic,<sup>99</sup> military,<sup>100</sup> or public health emergency<sup>101</sup> exists, justifying that medical countermeasures be authorized into interstate commerce, or a material threat to the health and security of U.S. citizens living abroad.<sup>102</sup> With respect to the COVID-19 pandemic, HHS Secretary Azar declared a public health emergency on January 31, 2020 and followed up with a declaration that the COVID-19 pandemic justified authorization of EUAs on February 4, 2020.<sup>103</sup>

EUAs may also be issued for unapproved uses of already-approved products.<sup>104</sup> While medical providers have the authority to prescribe and dispense FDA-approved products for off-label uses,<sup>105</sup> an EUA allows the federal government to utilize the Strategic National Stockpile (“SNS”) to store and collect medical products to be distributed across the country.<sup>106</sup> Additionally, an EUA can reduce some regulations for certain medical products, including eliminating the informed consent and Institutional Review Board’s (known as “IRB”) approval requirements if the emergency is in effect.<sup>107</sup>

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<sup>99</sup> 21 U.S.C. § 360bbb–3(b)(1)(A) (stating that the Secretary of Homeland Security can determine that “a domestic emergency or a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents . . .”).

<sup>100</sup> 21 U.S.C. § 360bbb–3(b)(1)(B) (stating that the Secretary of Defense can determine that a military emergency, or a significant potential for a military emergency exists that involves “a heightened risk to United States military forces” of attack with a CBRN or other agent(s)).

<sup>101</sup> 21 U.S.C. § 360bbb–3(b)(1)(C) (stating that the Secretary of HHS can determine “there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents”).

<sup>102</sup> 21 U.S.C. § 360bbb–3(b)(1)(D).

<sup>103</sup> *Determination That a Public Health Emergency Exists*, HHS (Jan. 31, 2020), <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx> [<https://perma.cc/GYS4-XHWW>]; 85 F. Reg. 7316 (Feb. 7, 2020).

<sup>104</sup> 21 U.S.C. § 360bbb–3(c)(2) (2020).

<sup>105</sup> See Zettler et al., *supra* note 16, at 164.

<sup>106</sup> *Id.* at 143.

<sup>107</sup> CLARE STROUD ET AL., MEDICAL COUNTERMEASURES DISPENSING: EMERGENCY USE AUTHORIZATION AND THE POSTAL MODEL, WORKSHOP SUMMARY 29 (2010).

FDA's ability to authorize medical countermeasures under an EUA terminates when the HHS Secretary determines that the emergency has ceased to exist or when there is a change in the approval status of the product.<sup>108</sup> Along the way, FDA may revoke an EUA if new adverse evidence comes to light. This circumstance occurred early in the COVID-19 pandemic with hydroxychloroquine,<sup>109</sup> which FDA revoked seventy-eight days after issuance when data showed the drug could cause cardiac issues<sup>110</sup> and was neither an effective treatment nor a post-exposure prophylactic.<sup>111</sup>

In June 2020, due in part to the lack of public confidence surrounding vaccines using mRNA technologies, FDA provided guidance that addressed concerns raised by those who skeptically considered mRNA as a new and unproven technology. FDA declared that, in order to receive authorization, these mRNA vaccines would need to achieve at least a 50% reduction in COVID-19 disease, with confidence intervals that excluded less than a 30%

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<sup>108</sup> 21 U.S.C. § 360bbb-3(a)-(g) (2020).

<sup>109</sup> See Matthew Herper, *FDA Warns Against Widespread Use of Hydroxychloroquine, Drug Touted by Trump*, STAT (Apr. 24, 2020), <https://www.statnews.com/2020/04/24/fda-warns-against-widespread-use-of-hydroxy-chloroquine-drug-touted-by-trump> [<https://perma.cc/S6A8-2T2G>].

<sup>110</sup> Press Release, FDA, *FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine* (June 15, 2020), <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and> [<https://perma.cc/J6ER-D85>].

<sup>111</sup> David R. Boulware et al., *A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Sars-Cov-2*, 383 NEW ENG. J. MED. 517, 522 (2020); see *FDA Cautions Against Use of Hydroxychloroquine or Chloroquine for COVID-19 Outside of the Hospital Setting or a Clinical Trial Due to Risk of Heart Rhythm Problems*, FDA, <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or> [<https://perma.cc/3C9C-T8P>] (last updated July 1, 2020). In the meantime, however, after listening to one of the daily presidential COVID-19 briefings, an Arizona man tragically died after attempting to prevent infection by ingesting an aquarium cleaner that contained chloroquine phosphate, a related chemical compound that is used to treat fish for parasites. Kimberly Hickok, *Husband and Wife Poison Themselves Trying to Self-medicate with Chloroquine*, LIVE SCI. (Mar. 24, 2020), <https://www.livescience.com/coronavirus-chloroquine-self-medication-kills-man.html> [<https://perma.cc/4242-MX8M>].

reduction,<sup>112</sup> which has come to be a high standard referred to as an EUA-plus.<sup>113</sup> The EUA-plus standard applies only to vaccines; other authorized products, such as AstraZeneca's COVID-19 preventative therapeutic, Evusheld (used for high-risk immunocompromised patients who may not be able to mount a sufficient immune response to vaccines), are subject to the lower "may be effective" standard.<sup>114</sup>

EUAs, along with other federal programs, such as Operation Warp Speed,<sup>115</sup> the Accelerating COVID-19 Therapeutic

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<sup>112</sup> *Development and Licensure of Vaccines to Prevent COVID-19* U.S. Food & Drug Admin., FDA (June 2020), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19> [<https://perma.cc/NPB2-9FXR>]; Sarah Oweremohle, *Marks: Prepare for "EUA-Plus" for Covid Vaccines*, POLITICO (Sept. 11, 2020, 12:06 PM), <https://www.politico.com/newsletters/prescription-pulse/2020/09/11/marks-prepare-for-eua-plus-for-covid-vaccines-790343> [<https://perma.cc/8U3Y-VG5U>].

<sup>113</sup> Pfizer-BioNTech, Moderna, and Johnson & Johnson, three of the leading vaccine manufacturers, provided data that exceeded even the EUA-plus guidance before seeking authorization. Helen Branswell, *Comparing the Covid-19 Vaccines Developed by Pfizer, Moderna, and Johnson & Johnson*, STAT. (Feb. 2, 2022), <https://www.statnews.com/2021/02/02/comparing-the-covid-19-vaccines-developed-by-pfizer-moderna-and-johnson-johnson/> [<https://perma.cc/ZV66-JUT2>].

<sup>114</sup> This fact is not saying that Evusheld or other COVID-19-related therapeutics authorized for use under an EUA are less safe or effective but, instead, is simply an example that shows the EUA-plus standard provided to vaccines exists in a separate category than other COVID-19 therapeutics.

<sup>115</sup> U.S. GOV'T ACCOUNTABILITY OFF., GAO-21-319, OPERATION WARP SPEED, GAO, <https://www.gao.gov/products/gao-21-319> [<https://perma.cc/PD22-BJ36>] (last visited Jan. 21, 2022) (describing a partnership between the HHS and the Department of Defense ("DOD") aimed to help accelerate the development of a COVID-19 vaccine by selecting promising vaccine candidates that use different mechanisms to stimulate an immune response, starting large-scale manufacturing during clinical trials); see Holly Fernandez Lynch, et al., *Helpful Lessons and Cautionary Tales: How Should Covid-19 Drug Development and Access Inform Approaches to Non-Pandemic Diseases*, 21 AM. J. BIOETHICS 4, 5 (2021) [hereinafter *Helpful Lessons*] ("OWS was designed to accelerate the development and distribution of safe and effective COVID-19 vaccines, therapeutics, and diagnostics through: (1) betting on several horses; (2) collaboration and coordination to reduce bureaucratic, logistical, and manufacturing hurdles; and (3) massive funding to the tune of more than \$18 billion on vaccines and \$8 billion on therapeutics.").

Interventions and Vaccines (“ACTIV”),<sup>116</sup> and the Coronavirus Treatment Acceleration Program<sup>117</sup> have incentivized development and saved countless lives. In fact, EUAs have been so successful that some patients and advocates now question whether the EUA standard should be applied to drugs and treatments for other serious diseases,<sup>118</sup> such as neurodegenerative diseases, as well as certain cancers and genetic conditions.<sup>119</sup>

But the EUA process is by no means a perfect tool—either for a pandemic or for other devastating diseases and conditions.<sup>120</sup> EUAs have no definitive time frame, which raises concerns that EUAs could be authorized long-term or indefinitely. While FDA can impose reporting requirements and restrictions on products authorized pursuant to an EUA, long-term authorization can present incentive problems for manufacturers.<sup>121</sup> There is also concern that

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<sup>116</sup> *Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)*, NIH, <https://www.nih.gov/research-training/medical-research-initiatives/activ> [<https://perma.cc/E9PQ-UCBZ>] (last visited Feb. 14, 2022); see *Helpful Lessons*, *supra* note 115, at 6.

<sup>117</sup> *Coronavirus Treatment Acceleration Program (CTAP)*, FDA, <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap> [<https://perma.cc/392E-CXBA>] (last visited Jan. 21, 2022); see also *Helpful Lessons*, *supra* note 115, at 6 (explaining that CTAP launched “as an emergency effort to streamline its review and advice process so that treatment studies could begin as quickly as possible”).

<sup>118</sup> See *Helpful Lessons*, *supra* note 115, at 4 (“[T]his ‘all hands-on deck’ effort against Covid-19 . . . [has] left other patient communities inspired by what is possible—and frustrated that their concerns have been comparatively neglected. Those with serious unmet treatment needs are now asking important questions: . . . Why isn’t Emergency Use Authorization an option for our conditions?”).

<sup>119</sup> *Id.* at 4 (“Although the full extent and success of the . . . response to Covid-19 are unlikely to be feasible in other disease areas, stronger collaboration between government and industry, efforts toward unified priority-setting for product development and trial enrollment, and attention to enabling preapproval access to promising investigational products without undermining the ability to answer key questions about safety and effectiveness all have the potential for successful translation beyond Covid-19.”).

<sup>120</sup> See Zettler et al., *supra* note 16 at 144 (“EUAs are a form of pre-approval access, and . . . products issued EUAs are not necessarily safe or effective countermeasures for COVID-19. Misunderstandings about what an EUA signifies could drive inappropriate policy decisions or undermine public trust in FDA decisions when products issued EUAs prove ineffective or unsafe.”).

<sup>121</sup> See Christine Coughlin & Ana Iltis, *Defining Emergency*, (forthcoming).

some manufacturers will submit either lower quality or a lower quantity of data due to the relaxed regulatory bar for authorization—the “may be effective” standard rather than the “gold standard” of “substantial evidence of effectiveness” for approval.<sup>122</sup> Further, EUAs do not require a patient to be unable to participate in clinical trials. Patients can access treatments through an EUA, such as for a vaccine, rather than risk receiving a placebo in the clinical trial; accordingly, this effect may act as a disincentive for research and development.<sup>123</sup>

### C. Expanded Access

Another reform stemming from the AIDS crisis is FDA’s formal creation of the “expanded access” pathway to enable patients with a serious or life-threatening disease and who are not eligible to participate in clinical trials, to receive experimental medications before market approval or authorization.<sup>124</sup> Today, access to experimental treatments before market approval under one of the three expanded access categories (individual patients,<sup>125</sup> intermediate-size patient populations,<sup>126</sup> and widespread treatment use involving a treatment protocol or treatment IND<sup>127</sup>) is afforded to patients who “have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.”<sup>128</sup> In addition, FDA must determine that the potential benefits outweigh the potential risks of the treatment<sup>129</sup> and that the request will not interfere with clinical trials.<sup>130</sup> The most commonly used expanded access pathway is an individual patient pathway, through which 99% of requests for access to investigational drugs

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<sup>122</sup> *Id.*

<sup>123</sup> See Zettler et al., *supra* note 16, at 143.

<sup>124</sup> See Coughlin & King, *supra* note 35, at 24–26; see also George, *supra* note 82.

<sup>125</sup> 21 C.F.R. § 312.310 (2022).

<sup>126</sup> *Id.* § 312.315.

<sup>127</sup> *Id.* § 312.320.

<sup>128</sup> *Id.* § 312.305(a)(1).

<sup>129</sup> *Id.* § 312.305(a)(2).

<sup>130</sup> *Id.* § 312.305(a)(3).

pursuant to the pathway are approved, usually provided within a matter of hours or days.<sup>131</sup>

In the context of vaccines, expanded access has been successfully employed in previous public health emergencies. For instance, during a meningitis outbreak at Princeton University, FDA allowed use of the meningococcal group B vaccine (“Bexsero”), which had been approved in Europe and Australia, under an IND application through its expanded access program.<sup>132</sup> The vaccination campaign was successful, and no student in the vaccinated cohort contracted meningitis.<sup>133</sup> Bexsero received full FDA approval in 2015.<sup>134</sup>

However, in a public health emergency, “[b]road application of [expanded access] programs can create even more missed scientific opportunities, as participants, drugs, money and data are shunted away from standard clinical trials to less formalized crises-driven [emergency use authorization] programs.”<sup>135</sup> This scenario and subsequent effect occurred with investigational convalescent plasma treatment, which uses antibodies derived from previously recovered COVID-19 patients. Patients were able to receive the treatment under expanded access due to a limited number of clinical

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<sup>131</sup> See *Expanded Access: Information for Patients*, FDA, <https://www.fda.gov/news-events/expanded-access/expanded-access-information-patients> [<https://perma.cc/Q7HZ-ZPEK>] (last updated May 20, 2019); Coughlin et al., *supra* note 6, at 607.

<sup>132</sup> Lucy A. McNamara et al., *First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak*, 135 *PEDIATRICS* 798, 798–99, 804 (2015) (concluding “[t]he outbreak investigation and highly successful vaccination campaign. . . can serve as a model for how to approach similar outbreaks in the future”).

<sup>133</sup> *Id.* at 801.

<sup>134</sup> *Bexsero*, FDA, <https://www.fda.gov/vaccines-blood-biologics/vaccines/bexsero> [<https://perma.cc/4YQF-PXL4>] (last updated Jan. 7, 2022).

<sup>135</sup> Ori Rosenberg & Dov Greenbaum, *Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs*, 20 *AM. J. BIOETHICS*, 89, 89 (2020).

testing sites, and then under an EUA, which does not compel clinical trial participation.<sup>136</sup>

## V. RIGHT TO TRY LEGISLATION

Right to Try laws, which exist outside of FDA's authority, highlight the understandable frustration and lack of control patients and their advocates feel when conventional approved treatments are unavailable, and the possibility of an experimental, yet unapproved, treatment exists but is not accessible. Right to Try legislation, which exists both at the federal level and within forty-one states, allows terminally ill individuals the right to ask a manufacturer for access to a drug that has successfully completed Phase 1 testing.<sup>137</sup> This legislation has its historical roots in the untimely death of college student Abigail Burroughs, who was diagnosed in 2000 with head and neck cancer and was unsuccessful in seeking experimental treatments.<sup>138</sup>

After Abigail's death, her father founded the Abigail Alliance for Better Access to Developmental Drugs (the "Alliance"), an organization dedicated to reducing the barriers to access of non-FDA approved drugs for terminally ill patients who have exhausted

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<sup>136</sup> *Helpful Lessons*, *supra* note 115, at 12–14 (“[I]t is critical to avoid making Expanded Access so expansive that these programs interfere with the capacity to run trials necessary for high quality evidence production.”); see Sue Sutter, *Convalescent Plasma EUA ‘Could Have Been Done Better’ but Not a ‘Total Catastrophe—FDA’s Marks*, PINK SHEETS (Feb. 11, 2022), <https://pink.pharmaintelligence.informa.com/PS145579/Convalescent-Plasma-EUA-Could-Have-Been-Done-Better-But-Not-A-Total-Catastrophe--FDAs-Marks> [<https://perma.cc/6HTG-LYQV>] (“[Director of the Center for Biologics Evaluation and Research (“CBER”)] Peter Marks’ main regret is that the FDA did not have a better handle on the product quality attributes needed to maximize convalescent plasma’s potential benefit when the EUA was granted.”).

<sup>137</sup> Coughlin et al., *supra* note 6, at 616; *Right to Try*, FDA, <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try> [<https://perma.cc/UK52-8AGX>] (last updated Jan. 14, 2020).

<sup>138</sup> See Abigail All. for Better Access to Dev. Drugs v. Von Eschenbach, 445 F.3d 470, 473 (D.C. Cir. 2006); Sam Adriance, *Fighting for the “Right To Try” Unapproved Drugs: Law as Persuasion*, 124 YALE L.J. F. 148, 150 (2014).

all other alternatives.<sup>139</sup> The Alliance initially filed a lawsuit against FDA, which proved to be largely unsuccessful.<sup>140</sup> However, the lawsuit and threat of future legal action motivated larger drug manufacturers to create their own expanded access programs.<sup>141</sup> In 2012, Cancer Treatment Centers of America, a for-profit hospital chain, partnered with the Goldwater Institute, a libertarian think tank that supported limiting FDA's regulatory power<sup>142</sup> and coined the phrase "right to try."<sup>143</sup>

On May 30, 2018, then-President Trump signed into law the "Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew

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<sup>139</sup> Adriance, *supra* note 138, at 150; *see also* Winniford, *supra* note 17, at 208–09. This suit was not the first challenge to FDA's policies regarding the terminally ill's access to experimental drugs. *See Rutherford v. United States*, 442 U.S. 544, 556 (1979) (upholding FDA's action in blocking approval for the marketing of Laetril—a cancer treatment used outside the U.S., comprised of apricot pit extract and almonds—and concluding that a right for terminally ill individuals to access unproven therapies did not exist in this circumstance).

<sup>140</sup> *Abigail All.*, 445 F.3d at 471–72. For an excellent and in-depth discussion of this case and its effect, *see generally* 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, L. & ETHICS 135 (2010).

<sup>141</sup> Vanessa Fuhrmans, *Under Pressure, Drug Firms Bow to 'Compassionate Use'*, WALL ST. J. (Dec. 5, 2002, 12:13 AM), <http://www.wsj.com/articles/SB1039029132132913913> [<https://perma.cc/PD9X-FVGZ>].

<sup>142</sup> For background on the Goldwater Institute, *see* Marc Lacey, *A Watchdog for Conservative Ideals*, N.Y. TIMES (Dec. 25, 2011), <https://nyti.ms/ruPGcp> [<https://perma.cc/EF2V-XFE6>]. *See also* *Federal Right to Try: Questions and Answers*, RIGHT TO TRY, <http://righttotry.org/rtt-faq/> [<https://perma.cc/227E-44LY>].

<sup>143</sup> CHRISTINA CORIERI, EVERYONE DESERVES THE RIGHT TO TRY: EMPOWERING THE TERMINALLY ILL TO TAKE CONTROL OF THEIR TREATMENT 1–3 (Goldwater Inst. Ed., 2014), [https://goldwaterinstitute.org/wp-content/uploads/cms\\_page\\_media/2015/1/28/Right%20To%20Try.pdf](https://goldwaterinstitute.org/wp-content/uploads/cms_page_media/2015/1/28/Right%20To%20Try.pdf) [<https://perma.cc/AVF2-RKZY>]; *see also* Erin Mershon, *How the 'Right-to-Try' Movement Muscled Its Way into Washington*, STAT (Mar. 7, 2018), <https://www.statnews.com/2018/03/07/right-to-try-movement-washington/> [<https://perma.cc/9GRE-5BKX>] (detailing the history of the right to try movement); *see generally* Jose Miola & Bernadette Richards, *Would We Be Right to Try "Right to Try,"* 31 HEALTH MATRIX 107 (2021) (comparing U.S. Right to Try laws with the UK model and concluding that the laws do not represent a significant change in treatment access to investigational drugs).



Bellina Right to Try Act of 2017,” which allows patients to ask manufacturers for access to investigational products in situations where the patient: (1) has a terminal disease; (2) has exhausted all FDA-available options including clinical trials; (3) consults with a physician who recommends the experimental drug; and, (4) provides informed consent in writing to use the experimental drug, which must have completed Phase 1 testing.<sup>144</sup> At that time, Senator Ron Johnson, who introduced the first iteration of the Trickett Wendler Right to Try Act of 2016,<sup>145</sup> wrote a letter to Commissioner Scott Gottlieb, then-Head of FDA, clarifying that his intent behind the legislation was to “diminish the power of the FDA over people’s lives.”<sup>146</sup>

Right to Try laws, like FDA’s expanded access program, are pathways of compassion. But, Right to Try laws are less flexible than expanded access because, under Right to Try laws, products must have completed Phase 1 studies.<sup>147</sup> Whereas expanded access, because it is under FDA’s purview, provides more flexibility and may even allow patients to receive a medical treatment earlier in the process (such as, first in humans) than Right to Try.<sup>148</sup> Right to Try

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<sup>144</sup> See *infra* note 148 and accompanying text.

<sup>145</sup> See S. 2912, 114th Cong. (2016).

<sup>146</sup> See U.S. S. Comm. on Homeland Sec. and Gov’t Aff., *Johnson to FDA: Agency Should Comply with Right to Try Laws*, <https://www.hsgac.senate.gov/media/majority-media/johnson-to-fda-agency-should-comply-with-right-to-try-law> [<https://perma.cc/5PRK-8JJZ>] (May 31, 2018).

<sup>147</sup> “Right to Try” is really a misnomer since it is only the right to ask the manufacturer for permission to access the drug. Right to Try laws do not compel physicians to assist patients or manufacturers to provide access. See Coughlin et al., *supra* note 6, at 616.

<sup>148</sup> See Nicholas Florko, *When ‘Right to Try’ Isn’t Enough: Congress Wants a Single ALS Patient to Get a Therapy Never Tested in Humans*, STAT (May 31, 2019), <https://www.statnews.com/2019/05/31/when-right-to-try-isnt-enough/> [<https://perma.cc/F7SM-PM8A>] (discussing the story of Jaci Hermstad, then a 25-year-old suffering from ALS who was able to go through FDA to be the first human subject for an experimental form of ALS treatment); see also Janet Woodcock & Peter Marks, *Drug Regulation in the Era of Individualized Therapies*, 381 NEW. ENG. J. MED. 1678, 1679 (2019) (“[N]ew drug-discovery paradigm also raises many ethical and social issues. Patients and their families, of necessity, function more like project collaborators than traditional trial participants . . .”).

laws may have helped to “raise[] [patient] awareness that non-trial access [is] possible, thus galvanizing patients and their doctors to request it.”<sup>149</sup>

Earlier in the COVID-19 pandemic, former President Trump remarked: “What we’re talking about today is beyond Right to Try. Right to Try has been, by the way, a tremendous success. People are living now that had no chance of living . . . .”<sup>150</sup> These statements, in turn, led to speculation that Right to Try laws may be used as a way for patients to access experimental COVID-19 therapies. The Utah legislature did pass a “right to try” bill to shield physicians from liability and expand the “right to try” to allow patients to access experimental COVID-19 drugs.<sup>151</sup> In addition, NRx Pharmaceuticals recently announced it was making ZYESAMI, a vasoactive intestinal peptide, available to patients for whom Remdesivir or other treatments are ineffective and who are not able to participate in NIH trials.<sup>152</sup> However, there has not been a rush of patients

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<sup>149</sup> Alison Bateman-House, “*Right to Try*” Is Law, Now What?: Part I, HEALTH AFF. (Oct. 25, 2018), <https://www.healthaffairs.org/doi/10.1377/forefront.20181024.111856/full/> [<https://perma.cc/Y2PP-M7MX>]. Consider also, however, the Orphan Drug Act of 1983, which helped to provide a more formal pathway and created tax incentives for companies to invest in treatments for rare diseases. Nevertheless, the right to try framework finds a footing in the potential treatment of rare diseases, and some private businesses may see an opportunity to operate in a space with less rigorous government regulations. See Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049; see also *Developing Products for Rare Diseases & Conditions*, FDA, <https://www.fda.gov/industry/developing-products-rare-diseases-conditions> [<https://perma.cc/U3CZ-CTBN>] (Dec. 20, 2018).

<sup>150</sup> *Remarks by President Trump, Vice President Pence, and Members of the Coronavirus Task Force in Press Briefing*, TRUMP WHITE HOUSE ARCHIVES (Mar. 19, 2020, 11:31 AM), <https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-briefing-6/> [<https://perma.cc/L2CM-5J9M>].

<sup>151</sup> See S.B. 3002, 63d Leg., 3d Spec. Sess. (Utah 2020).

<sup>152</sup> Decker Westenburg & Marina McNairy, *Utah Legislature Approves ‘Right to Try’ COVID-19 Experimental Drugs*, DAILY UNIVERSE (Apr. 17, 2020) <https://universe.byu.edu/2020/04/17/utah-legislature-wraps-up-day-two-of-special-session/> [<https://perma.cc/5HM6-5ELQ>]; NRX Pharmaceuticals Announces Expansion of Zyesami (Aviptadil) US Expanded Access and Right to Try Programs for Patients with COVID-19 Respiratory Failure Who Have

attempting to obtain access to investigational drugs through the Right to Try pathway.<sup>153</sup>

## VI. PUBLIC TRUST AND THE DATA GENERATION IMPERATIVE

Regardless of one's ideological stance on the merits of FDA, the reality is that the public benefits from FDA's regulatory structures,<sup>154</sup> whatever imperfections those structures may hold. As the review of historic milestones above illustrates, public health is necessarily political. The history reflected above, as seen most dramatically with events like the 1976 "swine flu snafu," however, reiterates the need to conduct and communicate data-driven decisions in an apolitical manner. These actions are not only a matter of responsible science but are also necessary for public trust,<sup>155</sup> as well as for future research and development.

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*Exhausted All Approved Treatments*, BIOSPACE (Jan. 18, 2022), <https://www.biospace.com/article/releases/nrx-pharmaceuticals-announces-expansion-of-zyesami-aviptadil-us-expanded-access-and-right-to-try-programs-for-patients-with-covid-19-respiratory-failure-who-have-exhausted-all-approved-treatments/> [<https://perma.cc/L6FF-BVDV>].

<sup>153</sup> Jennifer Byrne, *Right to Try: A 'Well-Intentioned' but 'Misguided' Law*, HEALIO: HEMONC TODAY (Mar. 10, 2020), <https://www.healio.com/news/hematology-oncology/20200303/right-to-try-a-wellintentioned-but-misguided-law> [<https://perma.cc/VKQ8-VYUJ>]; see also CONG. RES. SERV., R45414, EXPANDED ACCESS AND RIGHT TO TRY: ACCESS TO INVESTIGATIONAL DRUGS 15-16 (2021), <https://crsreports.congress.gov/product/pdf/R/R45414> [<https://perma.cc/JNW4-FK8Y>] (discussing unknowns that exist with Right to Try laws including whether more patients have received access, whether more manufacturers are granting access, and what FDA's role should be in implementing requirements as the law's purpose was to remove FDA from the equation).

<sup>154</sup> Article II, Section 2 of the U.S. Constitution provides for a Cabinet to advise the President. U.S. Const. art. II, § 2. The Cabinet consists of the Vice President, the Attorney General, as well as the Secretary (or Head of) each of the fifteen Cabinet-level Departments, including the Secretary of HHS. These Cabinet-level appointments are political in nature. FDA, along with its sister organization, CDC, are agencies within HHS.

<sup>155</sup> See Zettler et al., *supra* note 16, at 144 (discussing that, in November 2020, FDA made a commitment "to proactively make public its reviews of data and information supporting decisions to issue, revise, or revoke drug and biological product EUAs," further noting that "[s]uch transparency can help the public

*A. Data Collection in Public Health Emergencies*

As history illustrates, where individual autonomy and access to medical treatments through alternative pathways are weighted too heavily, the public health community may lose out on opportunities to help mitigate current or future public health emergencies or other devastating diseases and conditions. Consider, for instance, the 2014 Ebola crisis. While large numbers of patients were given a range of different medications, therapies that could ultimately provide collective treatment were not realized due to a lack of data generation.<sup>156</sup> As one scholar noted, “virtually all studies were single-group interventions without concurrent controls, which led to no definitive conclusion related to efficacy or safety. . . . This tragedy of not discovering new therapies during an outbreak cannot be repeated.”<sup>157</sup>

Understanding and learning lessons from history will ensure this mistake is not repeated with the COVID-19 pandemic or in future public health emergencies. While treating desperately ill individuals is, of course, critical, alternative pathways should be used in a manner to seek collective treatments through data generation.<sup>158</sup> Indeed, it is only through a focus on data collection—even where investigational drugs and vaccines are being used for treatment

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understand the agency’s reasoning and what is known about the safety and effectiveness of COVID-19 countermeasures, as well as encourage public trust in agency decision-making”).

<sup>156</sup> Andre C. Kalil, *Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics*, 323 J. AM. MED. ASS’N 1897, 1897 (2020).

<sup>157</sup> *Id.*

<sup>158</sup> See Kalil, *supra* note 156, at 1897–98.

purposes<sup>159</sup>—that both safety and access can be optimized.<sup>160</sup> Where data collection is prioritized, these data form patterns that offer new conclusions, which are critical for public health emergencies both now and in the future.<sup>161</sup>

Emphasizing the importance of data generation is not to say that accelerated approval, emergency use, and pre-approval pathways are unnecessary or should be limited in any way. To the contrary, access to investigational drugs, particularly for terminally ill patients or in a public health emergency, is critical. The three existing alternative regulatory pathways are not only valuable and effective but also promote individual autonomy. These procedures can and should be available while continuously being studied and strengthened,<sup>162</sup> so that, through the generation of quality data, safety

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<sup>159</sup> For an excellent discussion on the need to focus on both access and data generation, along with specific recommendations for reform to both the accelerated approval and expanded access pathways, see Holly Fernandez Lynch & Alison Bateman-House, *Facilitating Both Evidence and Access: Improving FDA's Accelerated Approval & Expanded Access Pathways*, 48 J.L., MED. & ETHICS, 365, 369 (2020) (“What is clear . . . is that with appropriate safeguards for both desperate patients and data generation, the risks and benefits of trying an unapproved drug can sometimes be reasonable for a patient or group of patients, especially as a product proceeds through clinical development and promising evidence begins to accumulate.”).

<sup>160</sup> For a comprehensive discussion on considerations regarding safety and speed, see generally Charo, *supra* note 11, at 252–56.

<sup>161</sup> While too early to make predictions, a possible example of how responsible science can foster innovation and technology is FDA’s “EUA-plus” for mRNA vaccines and the recent FDA approval of those vaccines based on news that an experimental mRNA HIV vaccine shows some promise in pre-clinical studies. See *Experimental mRNA HIV Vaccine Shows Promise in Animals*, NAT’L INSTS. OF HEALTH (Jan. 11, 2022), <https://www.nih.gov/news-events/nih-research-matters/experimental-mrna-hiv-vaccine-shows-promise-animals> [<https://perma.cc/LF4L-NGTG>] (discussing that “[f]irst two FDA-approved COVID-19 vaccines have been extremely successful and helped launch the technology. But researchers have been studying mRNA technology for other uses for decades. Researchers are now investigating whether mRNA can be used to create vaccines that protect against other viruses”).

<sup>162</sup> See *Helpful Lessons*, *supra* note 115, at 9 (discussing the use of adaptive trial designs in achieving the dual goals of safety and access and noting that “encouraging broader use of adaptive trial designs and platform trials that test multiple interventions against a single control group can also speed progress and

regulations can co-exist—even flourish—with affording patients access and individual choice.<sup>163</sup>

For instance, the drug Remdesivir, developed by biopharmaceutical company Gilead Sciences (“Gilead”) over a ten-year period, was first used to treat hepatitis C in 2009 and resurfaced during the Ebola outbreak in 2014.<sup>164</sup> In early February 2020, the first doses of Remdesivir for experimental treatment were given to sick COVID-19 patients under expanded access; Gilead simultaneously formalized an agreement to conduct clinical trials of

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provide clear answers to research questions”). *See generally* Kaltenboeck et al., *supra* note 89; *Developing Therapeutics During the Coronavirus Pandemic and Future Public Health Emergencies*, INFECTIOUS DISEASES SOC’Y OF AM. (Feb. 3, 2021), [https://www.idsociety.org/globalassets/idsa/optimizing-euas-and-clinical-trial-design-brief\\_final.pdf](https://www.idsociety.org/globalassets/idsa/optimizing-euas-and-clinical-trial-design-brief_final.pdf) [<https://perma.cc/9KMX-AVKZ>].

<sup>163</sup> A potential example of this balancing is Aduhelm for treatment of early-stage Alzheimer’s, another devastating and heartbreaking disease. In addition to significant clinical and media backlash due to the lack of positive data about clinical benefit, as well as an advisory committee recommendation against allowing the drug to be marketed, the Centers for Medicare and Medicaid Services (“CMS”) released a proposed National Coverage decision memorandum stating that Medicare would only cover Aduhelm if the patient is enrolled in randomized, controlled trials. *See CMS Proposes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Jan. 11, 2022), <https://www.cms.gov/newsroom/press-releases/cms-proposes-medicare-coverage-policy-mono-clonal-antibodies-directed-against-amyloid-treatment> [<https://perma.cc/A4X8-GLFM>]; Zachary Brennan, *Updated: CMS to Restrict Coverage of Biogen’s Controversial Alzheimer’s Drug to Only Clinical Trials*, ENDPOINTS NEWS (Jan. 11, 2022), <https://endpts.com/cms-to-restrict-coverage-of-biogens-controversial-alzheimers-drug-to-only-clinical-trials/> [<https://perma.cc/6ABS-LKBZ>]. *But see* Alison Bateman House (@ABatemanHouse), TWITTER (Feb. 4, 2022, 12:23 PM), <https://twitter.com/ABatemanHouse/status/1489650840545763337> [<https://perma.cc/25G7-7FMS>] (noting that “CMS paying for a drug that’s both 1) FED approved for an unmet need & 2) subject to lots of ?s re that approval only when used in the context of a #clinicaltrial is the PERFECT way to balance the twin demands of access and evidence generation”).

<sup>164</sup> Bret Stephens, *The Story of Remdesivir*, N.Y. TIMES: OPINION (Apr. 17, 2020), <https://www.nytimes.com/2020/04/17/opinion/remdesivir-coronavirus.html> [<https://perma.cc/ZG9E-582D>].

the drug.<sup>165</sup> By mid-March 2020, Gilead enrolled thousands of patients in studies and released an open letter about a network of “active sites” being developed for expanded access to the drug.<sup>166</sup> After positive results regarding efficacy were formally announced, FDA issued an EUA authorizing use for hospitalized patients with severe disease as a result of COVID-19.<sup>167</sup> Subsequently, Remdesivir received full FDA approval for both hospitalized patients<sup>168</sup> and, more recently, for non-hospitalized patients who are at high risk for COVID-19 disease progression.<sup>169</sup> Remdesivir’s path to full approval—the path that both the Pfizer/BioNTech and Moderna vaccines followed and completed—confirms the ability to use alternative pathways to generate data and ultimately obtain full FDA approval.

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<sup>165</sup> Joseph Walker, *Gilead Sciences Offers Experimental Drug for Coronavirus Treatments, Testing*, WALL ST. J. (Jan. 31, 2020, 8:33 PM), <https://www.wsj.com/articles/gilead-sciences-offers-experimental-drug-for-coronavirus-treatments-testing-11580511519> [<https://perma.cc/4TDZ-XZCJ>].

<sup>166</sup> Daniel O’Day, *An Open Letter from Our Chairman and CEO*, STORIES@GILEAD (Mar. 28, 2020), <https://stories.gilead.com/articles/an-open-letter-from-our-chairman-and-ceo> [<https://perma.cc/N6SW-Z7AR>].

<sup>167</sup> *Gilead Announces Results from Phase 3 Trial of Investigational Antiviral Remdesivir in Patients with Severe Covid-19*, GILEAD (Apr. 29, 2020), <https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-Sars-Cov-2> [<https://perma.cc/XP9W-QXUL>]; *Coronavirus (Covid-19) Update: FDA Issues Emergency Use Authorization for Potential Covid-19 Treatment*, FDA (May 1, 2020), <https://www.fda.gov/news-events/press-announcements/coronavirus-Sars-Cov-2-update-fda-issues-emergency-use-authorization-potential-Sars-Cov-2-treatment> [<https://perma.cc/8AZ5-37PL>].

<sup>168</sup> *FDA Approves First Treatment for Covid-19*, FDA (Oct. 22, 2020), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19m> [<https://perma.cc/WC28-5CPX>].

<sup>169</sup> *FDA Approves Veklury® (Remdesivir) for the Treatment of Non-Hospitalized Patients at High Risk for COVID-19 Disease Progression*, GILEAD (Jan. 21, 2021), [https://www.gilead.com/news-and-press/press-releases/2022/1/fda-approves-veklury-remdesivir-for-the-treatment-of-nonhospitalized-patients-at-high-risk-for-covid19-disease-progression#:~:text=\(Nasdaq%3A%20GILD\)%20today%20announced,to%20severe%20COVID%2D19%2C%20including](https://www.gilead.com/news-and-press/press-room/press-releases/2022/1/fda-approves-veklury-remdesivir-for-the-treatment-of-nonhospitalized-patients-at-high-risk-for-covid19-disease-progression#:~:text=(Nasdaq%3A%20GILD)%20today%20announced,to%20severe%20COVID%2D19%2C%20including) [<https://perma.cc/G5BB-6LNZ>].

But, to lead to valid conclusions that enable scientific advancement, data must be of a sufficient quantity and quality. This, in turn, leads to the need to ensure that there is sufficient knowledge of and access to clinical trials.

### *B. Overcoming Barriers in Clinical Trial Participation*

To gather the data needed to establish safety and efficacy and to seek future treatments, a sufficient number of research subjects need to participate.<sup>170</sup> However, there are well-known barriers to clinical trial participation.<sup>171</sup> Some potential research subjects are not aware that clinical trials exist. Others may not satisfy the strict eligibility requirements<sup>172</sup> but may be eligible for access to treatment under the expanded access program or through Right to Try laws.<sup>173</sup>

The COVID-19 pandemic has spurred some technological innovation not only in the area of telehealth for treatment<sup>174</sup> but also

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<sup>170</sup> See, e.g., Gina Kolata, *For Scientists Racing to Cure Alzheimer's, The Math is Getting Ugly*, N.Y. TIMES (July 23, 2018), <https://www.nytimes.com/2018/07/23/health/alzheimers-treatments-trials.html> [<https://perma.cc/CF2K-26MH>]; *FDA Approves First COVID-19 Vaccine*, FDA (Aug. 23 2020), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine> [<https://perma.cc/GP5H-7ZAL>]; *Coronavirus (COVID-19) Update: FDA Takes Key Action by Approving Second COVID-19 Vaccine*, FDA (Jan. 31, 2021), <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine> [<https://perma.cc/5FHD-AV98>].

<sup>171</sup> See generally Joseph M. Unger et al., *Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation*, 111 J. NAT'L CANCER INST. 245 (2019) (examining the prevalence and resulting need to address structural barriers to clinical trial participation for cancer patients).

<sup>172</sup> See Nancy M.P. King & Jacob Perrin, *Ethical Issues in Stem Cell Research and Therapy*, 5 STEM CELL RSCH. & THERAPY 1, 2 (2014); see also Coughlin et al., *supra* note 6, at 601 (citing Mark Greener, *Drug Safety on Trial*, 6 EMBO REPS. 202, 203 (2005)) (“While such eligibility requirements may seem unreasonable at first, these restrictions help generate scientifically sound data while protecting subjects because they limit the complications that can arise from drug interactions, comorbidity, and advanced disease complexity.”).

<sup>173</sup> See *supra* notes 124–153 and accompanying text.

<sup>174</sup> See generally Adam Binder et al., *Treating Hematologic Malignancies During a Pandemic: Utilizing Telehealth & Digital Technology to Optimize Care*,



for research and development—increasing clinical trial participation by allowing researchers to follow patients through telehealth conferences as opposed to onsite testing.<sup>175</sup> Clinical trial participation, however, may still involve travel, additional medical tests and clinical appointments, and even hospitalization.<sup>176</sup> Additionally, some potential subjects do not want to risk being placed in the placebo arm of the clinical trial, when they can assuredly obtain their sought after treatment through an alternative path, such as an EUA.<sup>177</sup> Combined together, these and other factors can limit research subject participation and, in turn, the data generation needed to ensure safety and efficacy for future innovation. Thus, continuing to work on ways to improve knowledge about clinical trials; using technology and other innovation to make it easier for subjects to participate; implementing adaptive clinical trial designs;<sup>178</sup> and, increasing transparency with respect to the risks and benefits of the experimental treatment,<sup>179</sup> are essential components of data generation. Subsequently, this data creates generalizable knowledge

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10 FRONTIERS IN ONCOLOGY (June 26, 2020) (examining patient-centered models of care during the COVID-19 pandemic).

<sup>175</sup> See HHS ET AL., FDA GUIDANCE ON CONDUCT OF CLINICAL TRIALS OF MEDICAL PRODUCTS DURING COVID-19 PUBLIC HEALTH EMERGENCY: GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND INSTITUTIONAL REVIEW BOARDS (2020).

<sup>176</sup> See Rebecca Dresser, *The “Right to Try” Investigational Drugs: Science and Stories in the Access Debate*, 93 TEX. L. REV. 1631, 1635 (2016); see Coughlin et al., *supra* note 6, at 601.

<sup>177</sup> See Zettler et al., *supra* note 16, at 143.

<sup>178</sup> See Kalil, *supra* note 156, at 1898.

<sup>179</sup> A primary problem here is the therapeutic misconception. See Gail E. Henderson et al., *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, 11 PLOS MED. 1735, 1736 (2007) (“Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial.”). A secondary problem, which is no less important, is that people tend to believe that what is new and experimental in a clinical trial may be superior; thus, the ideals underlying clinical equipoise should be broadly communicated to and understood by participants. See Spencer Phillips Hey & Robert Truog, *The Question of Clinical Equipoise and the Patient’s Best Interest*, AMA J. ETHICS 1108, 1109, 1113-14 (Dec. 2015).

that will help future patients, just as today's patients benefit from the knowledge gained from past patients.<sup>180</sup>

*C. Tragic Consequences and Opportunity Costs*

This Article previously reviewed the catastrophic consequences surrounding the use of Thalidomide and improperly inactivated polio vaccines. History is replete with other examples where regulators relied on less robust data to the detriment of public health.<sup>181</sup>

This reliance, of course, has had direct and sometimes tragic consequences for patients who are harmed by taking an unsafe vaccine or drug. However, there are also additional opportunity costs: What do these patients lose by *not* taking the (potentially) more effective vaccine or drug?

A classic example of this dilemma occurred in the early 1990s when high-dose chemotherapy, followed by autologous bone marrow transplantation (a treatment commonly abbreviated to "HDCT-ABMT"), was used to treat metastatic breast cancer.<sup>182</sup> Anecdotal evidence showed that patients were obtaining better results with HDCT-ABMT than with lower dose chemotherapy.<sup>183</sup> Although clinical trials were being conducted to confirm if HDCT-ABMT's benefit over lower dose chemotherapy, physicians prescribed HDCT-ABMT outside of clinical trials, which limited clinical trial enrollment and participation.<sup>184</sup> After enough women finally enrolled in the clinical trials, the data showed that the low dose chemotherapy was not only more effective but had fewer side effects than HDCT-ABMT.<sup>185</sup> In the meantime, many women were not only treated with a less safe and ineffective regimen but also lost the opportunity to receive the safer and more effective treatment.<sup>186</sup>

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<sup>180</sup> See Lynch & Bateman-House, *supra* note 159, at 369.

<sup>181</sup> See *supra* notes 58–76 and accompanying text.

<sup>182</sup> Coughlin & King, *supra* note 35, at 48 n.172 (internal citations omitted).

<sup>183</sup> *Id.*

<sup>184</sup> *Id.*

<sup>185</sup> *Id.*

<sup>186</sup> See Byrne, *supra* note 153 (quoting Professor Holly Fernandez Lynch as follows: "Many patients, especially those who are desperately ill, will think, 'I'll

The FDA approval process, and even its alternative pathways, are designed to limit tragic consequences and opportunity costs. Experimental treatments may ultimately be safe and effective treatments; however, they are not always the superior treatment option and may, in fact, be unsafe or ineffective.<sup>187</sup> Making this determination and creating generalizable knowledge for the future is the point of research, as thoughtfully described below by Professors Lynch and Bateman-House:

The reality is that one function of requiring FDA approval prior to marketing is to restrict whether and how patients can access investigational drugs so that rigorous clinical testing becomes possible. The options available to current patients are limited in part for the benefit of future patients, while current patients benefit from contributions to clinical advancement made by patients who came before them.<sup>188</sup>

Safe and effective clinical advancement is the goal, particularly in public health emergencies. But, to make meaningful progress, society and science must identify and fix the gross inequities that exist for people of color and other vulnerable communities in every aspect of the research and treatment process. This initiative is not only a moral and ethical imperative but, “[a]s a matter of public health, nobody is safe unless everybody is safe.”<sup>189</sup>

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try anything . . . But, they still have something to lose. They could take a medication that could make them die faster or in a worse way. There also is the concern that if a patient is continuing to try everything under the sun, they might be losing valuable time with their families, or they might be missing out on palliative options.”).

<sup>187</sup> See, e.g., Michael M. Malinowski, *Throwing Dirt on Doctor Frankenstein’s Grave: Access to Experimental Treatment at the End of Life*, 65 HASTINGS L.J. 615, 616–19 (2014) (describing the painful outcome of a patient’s decision to turn for a second time to unproven, experimental treatments).

<sup>188</sup> Lynch & Bateman-House, *supra* note 159, at 369.

<sup>189</sup> Mark Rothstein & Christine Coughlin, *Undocumented Immigrants and the Covid-19 Vaccination*, HASTINGS CTR. BIOETHICS FORUM (Mar. 8, 2021), <https://www.thehastingscenter.org/undocumented-immigrants-and-covid-19-vaccination/> [<https://perma.cc/H2FB-EMM8>]; see also *Helpful Lessons*, *supra* note 115, at 7 (“[T]he privileged among us certainly bear an ethical obligation to care about and respond to issues that inhibit the flourishing of others, even if they are unlikely to affect us personally. Yet the reality is that the perceived immediacy of the personal threat and associated self-interest—as well as the fear and urgency that came with an entirely novel pathogen—have distinguished COVID-19 from most other diseases in terms of calls for societal response.”).

*D. Breaking the Cycle: Enhancing Diversity, Equity, and Inclusion in all Aspects of Research and Treatment*

Most critically, there is a deep distrust of clinical research due to the many past abuses that have occurred in the name of medical research, especially within Black and Brown communities.<sup>190</sup> Communities of color have suffered a disproportionate burden of COVID-19-related disease and outcomes<sup>191</sup> and are disproportionately afflicted with many of the underlying comorbidities that present the most risk.<sup>192</sup> In addition to disparities in treatment, disparities also exist in the lack of data supporting safety and efficacy for members of racial and ethnic minorities.<sup>193</sup> Indeed, with respect to Remdesivir, Black, Latinx, and Native American individuals were far less likely to participate in the clinical trials.<sup>194</sup> After analyzing data from the trials, scholars noted that, it is “alarming that long-standing racial health disparities have been extended to COVID-19 clinical trials when racial and ethnic

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<sup>190</sup> The documentation of such abuses is replete within the literature as more abuses continue to be uncovered. *See, e.g.,* Zachery Brennan, *J&J Regrets Paying for Study that Injected Incarcerated Black Men with Asbestos*, ENDPOINTS (Mar. 7, 2022), <https://endpts.com/jj-regrets-paying-for-study-that-injected-incarcerated-black-men-with-asbestos-report/> [<https://perma.cc/GP9L-X7AD>] (discussing Johnson & Johnson’s role in “newly unsealed court documents [that] reveal that Johnson & Johnson paid for a study that injected 10 incarcerated Black men with asbestos, as part of the company’s early talcum powder trials”).

<sup>191</sup> Monica Webb Hooper et al., *Covid-19 and Racial/Ethnic Disparities*, 323 JAMA 2466–67 (2020); *see, e.g.,* Akilah Johnson, *Black Adult Hospitalizations Reached a Pandemic High During the Omicron Wave CDC Study Finds*, WASH POST (Mar. 18, 2022), <https://www.washingtonpost.com/health/2022/03/18/black-hospitalizations-omicron-cdc/> [<https://perma.cc/7Q2L-ZQ8Y>] (“In January [2022], the CDC found, hospitalization rates for Black patients reached the highest level for any racial or ethnic group since the dawn of the pandemic.”).

<sup>192</sup> *See supra* notes 8–10 and accompanying text; *see Coronavirus Disease 2019 Case Surveillance—United States, May 22–May 30*, CDC (June 19, 2020), <https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?ftag=MSFd61514f> [<https://perma.cc/WP44-9QWX>].

<sup>193</sup> Daniel B. Chastain et al., *Race Disproportionality in Covid Clinical Trials*, 383 NEW ENG. J. MED. e59(1), e59(1)–(2) (2020), <https://www.nejm.org/doi/pdf/10.1056/NEJMp2021971?articleTools=true> [<https://perma.cc/D35B-M5QY>].

<sup>194</sup> *Id.*

minority groups have so much to gain from this research, including the opportunity to receive lifesaving treatment.”<sup>195</sup>

This problem is, of course, not new. Individuals in these demographic groups have historically been underrepresented in clinical trials, as clinical trial enrollees lack diversity: Only 4% to 5% of participants in trials of drugs submitted for approval by FDA between 1997 and 2014 were from groups historically underrepresented in medicine.<sup>196</sup> Thus, the data borne from these trials do not accurately represent the populations. This lack of representation may lead individuals in these groups to receive treatments and other medical interventions that are inherently less effective for members of their certain populations.<sup>197</sup> This ineffective result leads to even further distrust, which then cycles into worse health outcomes.

While there are initiatives<sup>198</sup> and guidance<sup>199</sup> to combat this problem, breaking (or even disrupting) the cycle will require long-term commitments and an expansive and multi-tiered approach to not only create more opportunities for participation (such as

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<sup>195</sup> *Id.* at e59(2).

<sup>196</sup> Boulware et al., *supra* note 10, at 201 (citing T.C. Knepper & H.L. McLeod, *When Will Clinical Trials Finally Reflect Diversity?* NATURE 2018; 557:157-159). *But see* Jill Fisher, *Hidden Racial Disparities in FDA-Required Research*, REGUL. REV. (Apr. 12, 2022), <https://www.theregreview.org/2022/04/12/fisher-hidden-racial-disparities-fda-required-research/> (“Although people of color are not explicitly targeted for recruitment to Phase I trials, profound racial inequities influence which health people are most willing to put their bodies on the line for the modest income offered. By maintaining a deeply racialized social system, the United States creates a market of health individuals for Phase I trials.”).

<sup>197</sup> Ashwarya Sharma & Latha Palanlappan, *Improving Diversity in Medical Research*, NATURE REV. DISEASE PRIMERS 74 (2021); *see* Chastain et al., *supra* note 193, at e59(2).

<sup>198</sup> *See, e.g., National Institutes of Health, Increasing Participant Diversity, Inclusion, and Engagement in HEAL Research*, NIH (Dec. 14, 2021), <https://heal.nih.gov/research/cross-cutting-research/participant-diversity-inclusion-engagement> [<https://perma.cc/7X84-YWVG>].

<sup>199</sup> *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry*, FDA (Nov. 2020), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial> [<https://perma.cc/75FW-KDSW>].

ensuring trial sites exist in underserved communities) but to also eliminate barriers to access, so that more individuals from underrepresented populations run the trials and are involved in every aspect of research. Research protocols should be examined to be inclusive in every aspect of their design. However, racism is deeply embedded in every societal structure; thus, no long-term change will be possible without creating long-term engagement, relationships, and partnerships between all the diverse stakeholders and affected communities.<sup>200</sup>

## VII. CONCLUSION

This Article began with a quote from Professor Lawrence Gostin: “As Americans face health scares, public health has become a subject of household conversation. The public vacillates from apathy to alarm, torn between security and civil liberties.”<sup>201</sup> This fluctuation has played out time and time again.

The United States is understandably desperate for treatments for COVID-19, as well as for many other diseases and conditions. Although having hope is important to overcome severe illness and disease,<sup>202</sup> without a sufficient quantity of data that is grounded in science, hope ranks up there with the effectiveness of “thoughts and prayers” in preventing shootings in schools.

The current COVID-19 pandemic will either cease to exist or, more likely, turn toward endemicity. To move forward, rather than creating new pathways, all aspects of FDA’s existing alternative

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<sup>200</sup> For an excellent discussion on the role of bioethics concerning structural racism, see Larry Churchill et al., *The Future of Bioethics*, 50 HASTINGS CTR. REP. 54, 54–56 (May 2020).

<sup>201</sup> Lawrence O. Gostin, *A Very Long Journey: A Decade’s Quest for Quarantine Regulations*, 94(4) MILLBANK Q. 724, 726 (Dec. 2016).

<sup>202</sup> See Byrne, *supra* note 153 (quoting Professor Gregg Gonsalves: “It’s very hard to push back against hope and fear with facts and evidence.”); see also Tamara J. Patterson, *The Cost of Hope at the End of Life: An Analysis of State Right to Try Statutes*, 105 KY. L. J. 685, 705 (2017) (discussing the need for providers to have difficult conversations with terminally ill patients about their treatment goals as a way to avoid false hope).

pathways should be scrutinized to determine if there are innovative ways to further incentivize the creation of data, as well as capture and optimize the data borne out of these uses. In addition, mechanisms to increase knowledge of and access to clinical trials must be prioritized so that enough participants are enrolled, and the participants reflect the demographics of the larger patient population. Lessons from past mistakes should inform and ensure that data-driven decisions are communicated to the public in an effective and apolitical manner. History will judge this generation even more harshly if this opportunity is not taken to strengthen both safety of and access to treatments and narrow or eliminate ethically impermissible health disparities.