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FDA'S ACCELERATED APPROVAL PATHWAY: A RARE DISEASE PERSPECTIVE

History and Opportunities for Reform

A Report Commissioned by NORD[®]

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EXECUTIVE SUMMARY

Accelerated approval is critical to providing access to new, safe, and effective drugs to patients with serious and life-threatening diseases and conditions for which there are no meaningful alternatives. It is a complicated and nuanced pathway with a long and important history, but accelerated approval does not alter US Food and Drug Administration's (FDA) gold standard of substantial evidence of safety and effectiveness. To the contrary, accelerated approval is granted based on FDA's finding that a drug is safe and effective for its intended use—the exact same approval standard as that used for traditional approval. Accelerated approval simply permits FDA to accept a different type of data from traditional drug approval. Traditional approval relies on a direct demonstration of clinical benefit, while accelerated approval relies on surrogate endpoints and intermediate clinical endpoints that can be measured earlier than irreversible morbidity or mortality. Because these endpoints are expected to predict clinical benefit, FDA can make the risk-benefit calculation that an accelerated approval drug's benefits outweigh its risks—just like FDA does for a traditional approval—and then confirm the clinical benefit in postmarketing confirmatory studies conducted after (and as a condition of) the accelerated approval.

Accelerated approval has been used to provide expedited access to patients for hundreds of new drugs, including treatments for HIV/AIDS, cancers, and rare diseases, allowing millions of patients faster access to new drugs and better health outcomes because of accelerated approvals. For rare disease patients specifically, accelerated approval offers a

valuable source of hope. Over 25 million Americans suffer from rare diseases and, of these diseases, more than 90% lack an FDA-approved treatment. By relying on surrogate and intermediate clinical endpoints for approval, sponsors can bring vital drugs to market under shorter timeframes, with less cost, and smaller participant groups than traditional clinical trials, and patients can have earlier access to lifesaving therapies.

Today, nearly thirty years after the introduction of the accelerated approval pathway, some stakeholders argue that accelerated approval is a “lesser” pathway—a lower standard of approval, which, as the paper below sets forth, is untrue. Other stakeholders legitimately argue that FDA has insufficient tools to maximize the utility of accelerated approval and ensure that postmarketing requirements are satisfied. Instead of seeking to remedy these criticisms of the accelerated approval pathway, recent proposals have sought to address drug pricing concerns by altering Medicaid prescription drug rebate requirements for therapies approved through the accelerated approval pathway. However, using accelerated approval as a proxy for high drug costs to payors is misguided. Accelerated approval problems require accelerated approval solutions that account for the importance of this pathway to rare disease patients. They cannot be solved with broad solutions designed to resolve drug pricing challenges that would, ultimately, disincentivize research and development and slow the availability of novel drugs to patients with rare diseases.

Solutions should be designed to reinforce the existing areas where accelerated approval has been successful, and to promote the transparent and accountable use of accelerated approval going forward. There are several options for doing this that focus on the pathway itself, including:

- Improved reporting and FDA engagement post-approval;
- Enhanced accelerated approval drug labeling;
- Utilizing real world evidence to support conversion to full approval and discharge postmarketing study requirements;
- Clear safety labeling change authorities for FDA with respect to accelerated approval drugs; and
- More effective expedited withdrawal procedures.

Done correctly, these tools could preserve the utility of the accelerated approval pathway in speeding safe and effective drugs to patients who need them, maintain crucial incentives for innovation in rare disease areas, all while simultaneously ensuring due diligence and good faith in meeting postmarketing requirements.

Section I of this paper provides a historical background on FDA's traditional drug approval process and the development of the accelerated approval pathway. Section II explains the standards for granting accelerated approval, the postmarketing confirmatory study requirement, and how accelerated approval has been used for rare disease and other drugs. Section III delves into the "dangling" approval problem and FDA's current mechanisms for ensuring that drug sponsors comply with their postmarketing confirmatory study requirements. Section IV analyzes some current proposals being contemplated to fix the accelerated approval pathway and recounts the reasons why drug pricing reforms miss the mark. Last, Section V offers various accelerated approval solutions to increase transparency, accountability, and efficiency, while protecting the pathway's value for rare disease patient populations.

I. HISTORY OF ACCELERATED APPROVAL

Contextualization in Drug Development

The Federal Food, Drug, and Cosmetic Act (“FD&C Act” or “the Act”) was passed in 1938.^{1,2} Catalyzed by the sulfanilamide disaster, which killed more than a hundred people, the Act was a huge milestone. In relevant part, it required that new drugs be shown to be safe prior to marketing. Subsequently, in the early 1950s, the Durham-Humphrey amendments created the category of drugs that we now know as “prescription drugs,” *i.e.*, drugs that cannot be used safely without the supervision of a health care provider and for which a prescription was required for sale.³ And in 1962, this time on the heels of the thalidomide debacle, Congress passed the Kefauver-Harris Drug amendments, and a demonstration of efficacy was required for FDA approval.⁴ For the first time, manufacturers were required to provide “substantial evidence” that their drugs were effective, defined as “adequate and well-controlled investigations, including clinical investigations... on

the basis of which it could fairly and responsibly be concluded... that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”⁵

FDA implemented the efficacy requirement for new drugs moving forward,⁶ promulgating regulations describing the scientific principles of adequate and well-controlled clinical investigations.⁷ In this way, FDA’s “substantial evidence of efficacy” standard—including data from “adequate and well-controlled studies”—was born.⁸ FDA regulations defined “adequate and well-controlled” clinical investigations as permitting “a valid comparison with a control to provide a quantitative assessment of drug effect.”⁹ In practice, this meant studies that typically were blinded,¹⁰ randomized,¹¹ and placebo-controlled,¹² and generated data that enabled a direct assessment of clinical benefit.¹³

1 Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. § 301 *et seq.*); see *Weinberger v. Hyson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612 (1973) (“The 1938 Act, which established a system of premarketing clearance for drugs, prohibited the introduction into commerce of any ‘new drug’ unless a new drug application (NDA) filed with the Food and Drug Administration (FDA) was effective with respect to that drug.”) (citing section 505(a) of the FD&C Act); Lewis A. Grossman, *AIDS Activists, FDA Regulation, and the Amendment of America’s Drug Constitution*, 42 Am. J.L. & Med. 687, 690 (2016).

2 The Public Health Service Act (“PHS Act”) was passed, in relevant part, in 1944 (Pub. L. No. 78-410, 58 Stat. 628 (codified as amended at 42 U.S.C. § 201 *et seq.*)), and in 1972 regulation of biological products was transferred from NIH to FDA. While references throughout this document are made to approvals under the FD&C Act and its standard for “safety and effectiveness,” we intend for purposes of this paper to also include the approval of biological products under section 351 of the PHS Act (42 U.S.C. § 262) and its standard of “safety, purity, and potency.” The term “drugs” as used throughout includes biological products, as defined in section 351(i)(1) of the PHS Act. See 42 U.S.C. § 262(i)(1). And potency has long been interpreted to include effectiveness. See 21 C.F.R. § 600.3(s).

3 See Pub. L. No. 82-215, 65 Stat. 648 (codified as amended at 21 U.S.C. § 353(b)).

4 Pub. L. No. 87-781, § 102, 76 Stat. 780, 781–82.

5 21 U.S.C. § 355(d), as added by the Kefauver-Harris Drug amendments.

6 Simultaneously, implementation of the Kefauver-Harris efficacy requirement necessitated a retrospective examination of some 4,000 drugs for which efficacy had not been required to be established prior to marketing. FDA worked with the National Academy of Sciences-National Research Council (“NAS—NRC”) to evaluate the efficacy of these older drugs and formed the Drug Efficacy Study Implementation (“DESI”). See U.S. Food and Drug Admin., Drug Efficacy Study Implementation (DESI), <https://www.fda.gov/drugs/enforcement-activities-fda/drug-efficacy-study-implementation-desi> (last updated Aug. 28, 2020).

7 See 21 U.S.C. § 355(d); 35 Fed. Reg. 3073, 3073 (Feb. 17, 1970).

8 See 21 U.S.C. § 355(d); 21 C.F.R. §§ 314.126 & 314.50.

9 21 C.F.R. § 314.126(b)(2).

10 *Id.* § 314.126(b)(5).

11 *Id.* § 314.126(b)(4).

12 *Id.* § 314.126(b)(2)(i).

13 *Id.* § 314.126(a) (“The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.”).

More than one adequate and well-controlled investigation was considered necessary to substantiate results from a single trial and minimize external influences (*e.g.*, bias and chance) that could result in a false demonstration of efficacy (*i.e.*, a false positive). Thus, two adequate and well-controlled clinical trials became the standard.¹⁴

Over time, clinical trial methodology became increasingly sophisticated.¹⁵ During the late 1970s, FDA increasingly engaged with stakeholders on trial design, forming and collaborating with external advisory committees, conducting workshops to support clinical guideline development and publishing detailed descriptions of study designs and data expectations for drugs being developed in various therapeutic areas.¹⁶ FDA generally required sponsors to demonstrate effectiveness through a showing of actual clinical benefit, *i.e.*, a direct measure of how a patient feels, functions, or survives.¹⁷ In some circumstances, FDA did accept and approve marketing applications based on data from clinical trials that showed a drug's impact on a

validated surrogate endpoint, *i.e.*, an endpoint that is accepted as a surrogate for clinical benefit, to support "traditional" approval.¹⁸ Prior to the evolution of the pathway for accelerated approval, review of efficacy in a drug application was very much about whether or not the application had shown clinical benefit. Clinical trials were designed with that goal in mind, whether it was achieved through a demonstration of benefit on the clinical outcome or on the surrogate endpoint.¹⁹ This, in turn, informed FDA's ultimate determination of whether the benefits of a drug outweigh the risks of that drug.²⁰

Development of Accelerated Approval Pathway

In the 1980s, the HIV/AIDS epidemic drastically altered the landscape for drug development.²¹ Between the summer of 1981 and the fall of 1982, the Center for Disease Control and Prevention (CDC) received reports of more than 500 AIDS cases; by the fall of 1982, new cases of AIDS were being reported daily and there was an overall case-mortality rate of 41 percent.²² The numbers

14 Subsequently, the FDA Modernization Act ("FDAMA") recognized that evidence from a single adequate and well-controlled clinical investigation, along with confirmatory evidence (obtained prior to or after such investigation), could be sufficient to establish effectiveness. The principles of validating study results to guard against false positives, however, remained. See U.S. Food & Drug Admin., Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products 14 (Dec. 2019) ("Demonstrating Substantial Evidence Guidance"), <https://www.fda.gov/media/133660/download>.

15 See Loutfy Madkour, *Nucleic Acids as Gene Anticancer Drug Delivery Therapy* 314 (Academic Press 2019) ("Everyone came to believe that trials should have a prospectively defined and identified endpoint, a real hypothesis and an actual analytical plan." (quoting Bob Temple)).

16 Suzanne White Junod, *FDA and Clinical Trials: A Short History*, U.S. Food & Drug Admin. (2014), <https://www.fda.gov/media/110437/download>.

17 Demonstrating Substantial Evidence Guidance, *supra* note 14, at 2; U.S. Gov't Accountability Office, GAO-09-866, *New Drug Approval: FDA Needs to Enhance its Oversight of Drugs Approved on the Basis of Surrogate Endpoints* 1 (Sept. 2009) ("GAO New Drug Approval Report"), <https://www.gao.gov/products/gao-09-866>.

18 U.S. Food & Drug Admin., *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* 11 (May 1998) ("Clinical Evidence of Effectiveness Guidance"), <https://www.fda.gov/media/71655/download> (explaining that "it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness," and that a validated surrogate endpoint could thus "support ordinary approval," at the time the accelerated approval pathway was created).

19 See *id.* at 11; GAO *New Drug Approval Report*, *supra* note 17, at 1–2.

20 Demonstrating Substantial Evidence Guidance, *supra* note 14, at 3 ("[A] drug with greater risks may require a greater magnitude and certainty of benefit to support approval").

21 The Centers for Disease Control and Prevention ("CDC") published its first report on HIV/AIDS in 1981. See James W. Curran & Harold W. Jaffe, *AIDS: The Early Years and CDC's Response*, 60 *Morbidity & Mortality Weekly Rep.* 64 (Oct. 7, 2011), available at <https://www.cdc.gov/mmwr/preview/mmwrhtml/su6004a11.htm>.

22 Ctrs. for Disease Control & Prevention, *Current Trends Update on Acquired Immune Deficiency Syndrome (AIDS) – United States*, 31 *Morbidity & Mortality Weekly Rep.* 507 (Sept. 24, 1982), available at [https://www.cdc.gov/mmwr/preview/mmwrhtml/00001163.htm#:~:text=Between%20June%201981%20and,in%20243%20cases%20\(41%25\)](https://www.cdc.gov/mmwr/preview/mmwrhtml/00001163.htm#:~:text=Between%20June%201981%20and,in%20243%20cases%20(41%25)).

of cases, and deaths, increased rapidly during the 1980s.²³

The AIDS epidemic—with its staggeringly high death toll and commensurate urgency around developing treatments—catalyzed a reconsideration of clinical trial requirements. New thinking was necessary for what was and was not essential to the demonstration of efficacy, including how FDA defined “adequate and well-controlled studies.” For example, in 1987, FDA created of a new class of investigational new drug (IND) application, the “treatment IND,” which would permit patients to receive investigational treatments in an unblinded setting without compromising sponsors’ ability to use data collected through such treatment in new drug applications.²⁴ FDA was reluctant to permit completely open clinical trials, however, worrying that it would undermine data collection that could support drug approvals.²⁵

In the late 1980s, the AIDS crisis was worsening and protesters were regularly assembled outside of FDA’s headquarters²⁶ demanding, among other things, that FDA reduce the stringency of the efficacy requirement for new drugs intended to treat incurable, fatal diseases.²⁷ Scientists sought ways to streamline clinical trials for HIV/AIDS drugs and focused on the utility of surrogate

endpoints which, while not direct measures of clinical benefit, were known to demonstrably correlate with improved outcomes.²⁸ For example, improved t-cell count was determined to reliably predict fewer infections in AIDS patients and was accepted as a surrogate endpoint that could be used to demonstrate the efficacy of HIV/AIDS drugs.²⁹ This scientific advancement seemingly resolved the debate about modifying the efficacy requirement: if approval of HIV/AIDS treatments (among others) could be predicated successfully on the use of surrogate endpoints, the “substantial evidence of efficacy” standard did not need to be compromised in order to get treatments to patients at a faster pace.

As consensus grew about the utility of surrogate endpoints in clinical trial design,³⁰ FDA embraced drug approval reform and promulgated regulations formalizing the accelerated approval pathway.³¹ By 1992, FDA issued a final rule that set forth the accelerated approval pathway.³² Under accelerated approval, FDA could expedite the approval of and patient access to drugs that were intended to treat serious and life-threatening diseases and conditions for which there were unmet medical needs. By relying on surrogate endpoints or other intermediate clinical endpoints

23 Ctrs. for Disease Control & Prevention, HIV and AIDS – United States, 1981 - 2000 (June 1, 2001), <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5021a2.htm>.

24 21 C.F.R. §§ 312.34 & 312.35.

25 Junod, *supra* note 16, at 14.

26 See Grossman, *supra* note 1, at 709–10.

27 See *id.*

28 See U.S. Food & Drug Admin., Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment 3 (Nov. 2015), www.fda.gov/files/drugs/published/Human-Immunodeficiency-Virus-1-Infection-Developing-Antiretroviral-Drugs-for-Treatment.pdf.

29 See *id.*

30 Approval of the first statin drug, for example, was predicated on the validated surrogate endpoint of lower cholesterol, which was accepted as a proxy for reduced risk of heart disease. Editorial, *Biomarkers: The Next Generation*, 9 *Nature Reviews: Drug Discovery* 415 (June 2010), <https://www.nature.com/articles/nrd3196.pdf>.

31 FDA also created the fast track, breakthrough therapy, and priority review designations to advance the development and review of new drugs and address unmet needs in the treatment of a serious medical condition. See U.S. Food & Drug Admin., Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics 1 (May 2014) (“Expedited Programs Guidance”), <https://www.fda.gov/media/86377/download>.

32 “21 C.F.R. §§ 314.500 *et seq.* & 601.40 *et seq.*; 57 Fed. Reg. 58942, 58942 (Dec. 11, 1992).

that could be measured earlier than irreversible morbidity, development programs could be faster while still meeting FDA's gold standard for drug review. This would provide patients with faster access to treatments that were otherwise approvable, including that the substantial evidence of efficacy standard had been met.

Approval based on surrogate endpoints was not new.³³ What was new was the idea that approval could rest on surrogate endpoints that were “reasonably likely to predict clinical benefit” but about which there may be lingering uncertainty as to the relationship to actual clinical benefit.³⁴ The accelerated approval pathway reflected that for patients with serious or life-threatening illnesses, where there was an unmet medical need, there may be a different risk-benefit calculation: “the more serious the illness and the greater the effect of the drug on that illness, the greater the acceptable risk from the drug. If products provide meaningful therapeutic benefit over existing treatment for a serious or life-threatening disease, a greater risk may also be acceptable.”³⁵ This was an explicit application of the risk-benefit calculation underlying all drug approvals. Drug review has always involved “weighing whether the benefits of the drug outweigh its risks” and included consideration of uncertainties regarding

benefits and risks.³⁶ Recognizing that reliance on a surrogate endpoint “almost always introduces some uncertainty into the risk/benefit assessment,” an accelerated approval sponsor was thus required to “persuasively support the reasonableness of the proposed surrogate as a predictor and show how the benefits of treatment will outweigh the risks” by conducting a postmarketing confirmatory study.³⁷

Importantly, in promulgating the accelerated approval regulations, FDA considered—and rejected—the idea that accelerated approval was creating a different standard. On this key point, FDA was unequivocal: “[t]he evidence available at the time of approval under this rule *will meet the statutory standard*, in that there must be evidence from adequate and well-controlled studies showing that the drug will have the effect it is represented to have in its labeling.”³⁸ Accelerated approval did not represent a “lower standard,” nor one “inconsistent with section 505(d) of the Act,” but rather an approval based on assessment of a different type of data demonstrating “that the same statutory standard has been met.”³⁹

In 2012, Congress codified the accelerated approval pathway by enacting the Food and Drug Administration Safety and Innovation Act

33 57 Fed. Reg. at 58944.

34 *Id.*

35 New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 13234, 13236 (proposed Apr. 15, 1992) (to be codified at 21 C.F.R. Parts 314 and 601); see Inst. for Clinical & Econ. Rev., Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and their Impact on Uncertainty, Access, Innovation, and Costs 5 (Apr. 26, 2021) (“ICER Report”), <https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway--ICER-White-Paper--April-2021.pdf>; Expedited Programs Guidance, *supra* note 31, at 16.

36 Clinical Evidence of Effectiveness Guidance, *supra* note 18, at 1, 3.

37 57 Fed. Reg. at 58944.

38 *Id.* at 58943–44 (emphasis added).

39 *Id.* at 58944.

(FDASIA),⁴⁰ which amended the FD&C Act.⁴¹ In codifying the accelerated approval pathway, Congress acknowledged the vital role the accelerated approval pathway served for patients with rare diseases and expressed their hope that it would bring life-saving drugs to the market expeditiously.⁴² Congress also affirmed FDA’s conclusion that accelerated approval did not create a different standard for drug approval, stating that accelerated approval “may result in fewer, smaller, or shorter clinical trials... without compromising or altering the high standards of the FDA for the approval of drugs.”⁴³

II. ACCELERATED APPROVAL IN PRACTICE

Standards for Accelerated Approval

The basic premise of accelerated approval is that—for serious and life-threatening diseases or conditions, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments—more uncertainty regarding the clinical benefit of a product might be tolerable. This was true of HIV/AIDS treatments, when exceedingly high mortality rates and lack of any approved therapies

affected the overall risk-benefit calculation, and approval based on surrogate endpoints was entirely appropriate, notwithstanding lingering uncertainty about the predictive value of those endpoints. Approval was predicated on appropriate evidence that the endpoints in question were predictive of (*i.e.*, “reasonably likely” to predict) clinical benefit, and that the risk-benefit calculation therefore warranted approval in those circumstances.

Under either accelerated or traditional approval, though, the standard for approval is the same: whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling based on substantial evidence of effectiveness⁴⁴ As described above, traditional approval is predicated on a demonstration of clinical benefit, such as prolonged life or better quality of life, or an established, validated surrogate endpoint like disease-free survival for oncology drugs.⁴⁵ Like traditional approval, accelerated approval is based, in relevant part, on substantial evidence of efficacy from adequate and well-controlled clinical trials. An accelerated approval sponsor must produce data establishing that the surrogate endpoint or intermediate clinical endpoint is “reasonably likely”⁴⁶ to predict

40 Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112–144, §§ 803, 901(b), 902(a), 126 Stat. 993, 1079, 1083–87 (2012).

41 See 21 U.S.C. § 356(c). In the codified version, Congress made two notable modifications to the Agency’s regulations. First, the original requirement that the new drug provide a meaningful therapeutic benefit to patients over existing treatments was replaced with more the flexible “tak[e] into account . . . the availability or lack of alternative treatments.” Second, Congress specified that accelerated approval “may” be subject to one or both of two requirements: (1) that appropriate post-approval studies be conducted to verify and describe the predicted effect on the surrogate or intermediate clinical endpoint; and (2) pre-dissemination review of promotional materials. *Id.* In practice, these changes have not altered FDA’s practices. See U.S. Food & Drug Admin., *Accelerated Approval Program* (Oct. 26, 2020), <https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program> (“Drug companies are still required to conduct studies to confirm the anticipated clinical benefit.”)

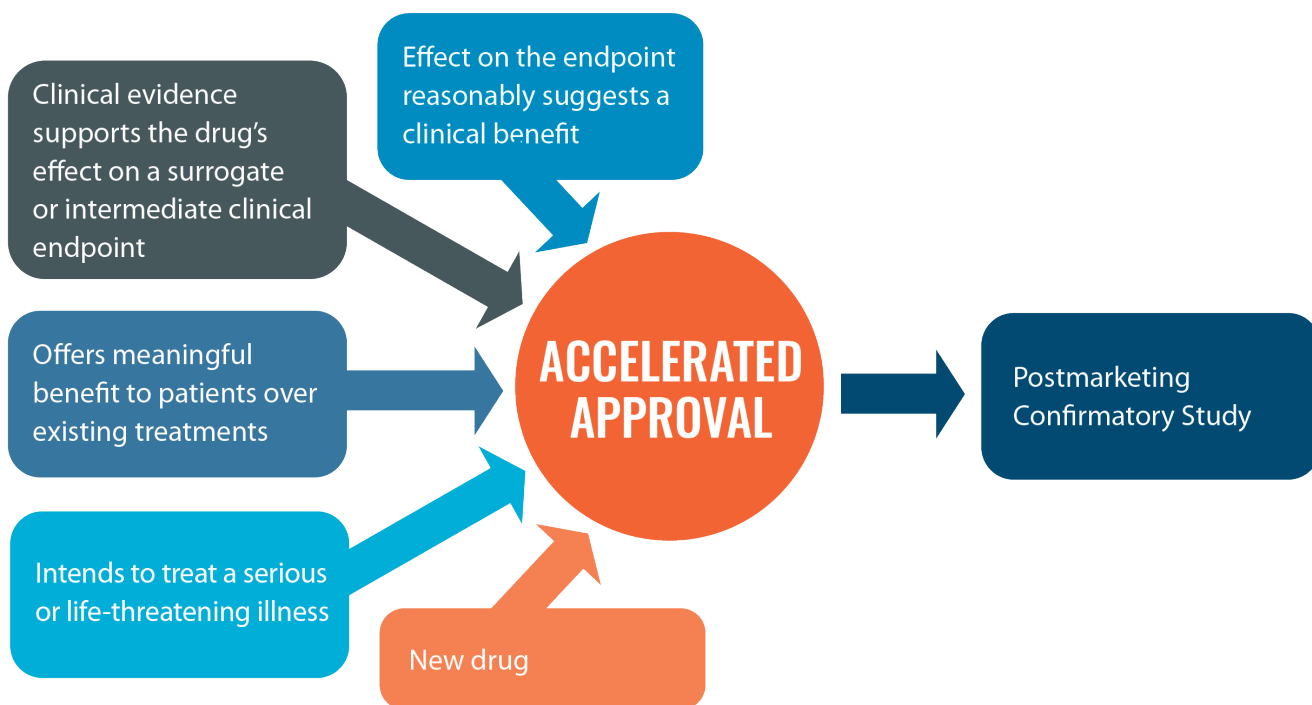
42 See H.R. Rep. 112–495, *35–36 (2012).

43 See 158 Cong. Rec. H3825–01, H3848 (2012).

44 See Expedited Programs Guidance, *supra* note 31, at 19.

45 John R. Johnson et al., *Accelerated Approval of Oncology Products: The Food and Drug Administration Experience*, 103 J. Nat’l Cancer Inst. 636, 637 (Apr. 2011), available at <https://doi.org/10.1093/jnci/djr062>.

46 Whether the proposed endpoint is reasonably likely to predict clinical benefit—and can thus support accelerated approval—is a matter of FDA’s scientific judgment. Factors that may influence the Agency’s judgment are laid out in the Expedited Programs Guidance and discussed in Sec. II.A, *infra*. See Expedited Programs Guidance, *supra* note 31, at 19–23.



a drug's intended clinical benefit,⁴⁷ and agree to conduct a postmarketing confirmatory study or studies to verify and describe the relationship between the endpoint and the anticipated expected clinical benefit.⁴⁸ The difference between the two approval pathways is a question of evidence regarding the predictive ability of an endpoint, *i.e.*, how much direct clinical evidence there is regarding that particular endpoint.

For accelerated approvals, adequate and well-controlled studies will have shown that a drug has

an effect on one of two types of endpoints: (1) a surrogate endpoint⁴⁹ that is “reasonably likely” to predict clinical benefit; or (2) an intermediate clinical endpoint⁵⁰ other than an effect on irreversible morbidity or mortality (IMM) that is “reasonably likely” to predict an effect on IMM or other clinical benefit.⁵¹ In other words, accelerated approval is based on a drug's effect on a surrogate or intermediate clinical endpoint that is “reasonably likely” to impact clinical outcomes. However, the meaning of the approval—that the product is safe and effective for its intended uses—is the same.

47 21 U.S.C. § 356(c); Expedited Programs Guidance, *supra* note 31, at 19–22. FDA takes a comprehensive approach in its evaluation. FDA determines whether a particular endpoint is appropriate by considering all relevant evidence including the pathophysiologic or causal pathways of the disease, the drug's effect on the endpoint, and empirical and clinical evidence that supports a conclusion that the drug is reasonably likely to have an effect on the endpoint. Empirical evidence can include, among other things, epidemiological, pathophysiologic, therapeutic, pharmacologic, or other evidence developed using biomarkers. See Expedited Programs Guidance, *supra* note 31, at 19–22.

48 See 21 U.S.C. § 356(c)(2); 21 C.F.R. §§ 314.510 & 601.41 (1993). Accelerated approval sponsors also are required to obtain preapproval of promotional materials prior to their use in marketing.

49 A “surrogate endpoint” can be a laboratory measurement, radiographic image, or physical sign that is reasonably likely to predict a drug's intended clinical benefit on overall survival (e.g., long-term suppression of HIV viral load in plasma; reduction in tumor size; progression-free survival (PFS) in advanced cancer patients; and sputum culture status and infection relapse rates in patients with pulmonary tuberculosis). Expedited Programs Guidance, *supra* note 31, at 17–19; ICER Report, *supra* note 35, at 12; Kelong Han et al., *Progression-free Survival as a Surrogate Endpoint for Overall Survival in Glioblastoma: A Literature-based Meta-analysis From 91 Trials*, 16 *Neuro-Oncology* 696, 696–97 (2014), available at <https://academic.oup.com/neuro-oncology/article/16/5/696/1192459?login=true>.

50 Intermediate clinical endpoints may include, for example, a short-term, significant decrease in the relapse rate of multiple sclerosis; or a demonstrated delay in delivery of early labor. Expedited Programs Guidance, *supra* note 31, at 18.

51 See 21 U.S.C. § 356(c)(1)(A); 21 C.F.R. §§ 314.500, 314.510, 601.40 & 601.41 (1993); 57 Fed. Reg. at 58958–59.

Not surprisingly, then, the same labeling requirements apply to accelerated approval drugs and traditionally approved drugs. Drugs approved through both pathways include, in the INDICATIONS AND USAGE section, a “succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits.”⁵² One notable difference is that, for accelerated approval drugs, the “succinct description of limitations” typically includes a statement in the INDICATIONS AND USAGE section, as well as in the highlights, that an indication “is approved under accelerated approval based on [a surrogate or intermediate clinical endpoint]” and that “[c]ontinued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).”⁵³ Similar statements are expected in the CLINICAL STUDIES section of accelerated approval drug labeling.⁵⁴ We consider the appropriateness of additional thinking regarding labeling of accelerated approval drug products further in Section V, *infra*.

Expedited Access with Postmarket Confirmation of Benefit

“[M]illions of patients with serious or life-threatening illnesses” have received earlier access to new drugs under the accelerated approval pathway.⁵⁵ For patients and sponsors, accelerated approval

offers substantial advantages. Sponsors often can study surrogate or intermediate clinical endpoints under shorter timeframes, with less cost, and smaller participant groups compared to the clinical trials studying a validated endpoint.⁵⁶ Patients suffering from life-threatening diseases and conditions stand to gain earlier access to novel drugs years before FDA ultimately verifies the drugs’ effect on clinical outcome.⁵⁷ Studies of oncology treatments estimate that the accelerated approval resulted in access to patients 3.4–4.7 years faster on average,⁵⁸ and as much as 12.6 years faster for individual drugs⁵⁹—a meaningful difference when time is crucial to saving patients’ lives or producing better health outcomes.

An essential component of this faster access is the postmarketing confirmation that the surrogate or intermediate clinical endpoint used in an accelerated drug approval is verified to actually be predictive of the anticipated clinical benefit.⁶⁰ FDA will have relied on shorter, smaller clinical trials for the approval,⁶¹ accepting some level of uncertainty that the surrogate or intermediate clinical endpoint will not be confirmed to be predictive of actual clinical benefit.⁶² In order to resolve those uncertainties, FDA then requires sponsors to conduct postmarketing confirmatory studies to verify and describe the drugs’ intended

52 21 C.F.R. § 201.57(c)(2)(i)(B).

53 U.S. Food & Drug Admin., Guidance for Industry: Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway 2–3 (Jan. 2019) (“Accelerated Approval Labeling Guidance”), <https://www.fda.gov/media/119755/download>.

54 *Id.* at 4.

55 GAO New Drug Approval Report, *supra* note 17, at Appx. V, 1.

56 ICER Report, *supra* note 35, at 5.

57 GAO New Drug Approval Report, *supra* note 17, at 8.

58 Julia A. Beaver et al., A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review, 4 JAMA Oncology 849, 851 (2018); Johnson et al., *supra* note 45, at 640.

59 Johnson et al., *supra* note 45, at 642–43.

60 See Expedited Programs Guidance, *supra* note 31, at 16.

61 See *id.*

62 GAO New Drug Approval Report, *supra* note 17, at 9.

effect on the applicable surrogate or intermediate clinical endpoint.⁶³

On first blush, the postmarketing study requirement seems straightforward. The reality, as discussed further in Section III.B, *infra*, is that designing, enrolling, and completing postmarketing studies can be very complex. Confirmatory trials often are already underway or fully enrolled at the time FDA grants accelerated approval.⁶⁴ If they are not already underway, FDA generally will work with the sponsor to develop the study design and the timeline for enrollment, and completion of the study will be a postmarketing requirement for the accelerated approval.⁶⁵ Postmarketing confirmatory studies must be carried out with “due diligence,”⁶⁶ and, as discussed in Section V, *infra*, sponsors are required to report their progress to FDA annually.⁶⁷

Accelerated Approval in Practice: Oncology and Rare Disease

From its origin in the HIV/AIDS crisis, accelerated approval has come to be used in scenarios when the conduct of clinical trials targeting direct clinical benefit can be extremely lengthy. This includes, for example, diseases that have long disease courses,⁶⁸ as well as diseases in which the rare incidence of a clinical event that suggests a clinical benefit necessitates very large clinical trials.⁶⁹ As noted above, as of December 31, 2020, FDA had approved a total of 253 new drugs under the accelerated approval pathway.⁷⁰ From 1992 through roughly 2010, accelerated approval was primarily used to approve drugs indicated for treatment of HIV (39.7% of approvals); cancer (35.6%);⁷¹ and other rare disease treatments and other specialty drugs (24.7%).⁷² Since then, the use of accelerated approval has shifted focus dramatically to focus on oncology drugs. Indeed, approximately 85% of accelerated approvals from 2010 to 2020 were for oncology indications.⁷³ Studying the effects of an oncology drug on validated surrogates can require large, lengthy clinical trials,⁷⁴ but accelerated

63 See 21 U.S.C. § 356(c)(2); 21 C.F.R. §§ 314.510 & 604.41. FDA also mitigates the risks associated with accelerated approval by requiring that the drug prove to be safe and effective based on substantial evidence, the surrogate endpoint is deemed to be reasonably likely to predict clinical benefit, and the withdrawal of drugs that do not demonstrate a clinical benefit under postmarketing confirmatory studies. See GAO New Drug Approval Report, *supra* note 17, at Appx. V, 1.

64 See 21 C.F.R. §§ 314.510 & 601.41; Expedited Programs Guidance, *supra* note 31, at 22.

65 See Expedited Programs Guidance, *supra* note 31, at 22.

66 See 21 U.S.C. § 356(c)(3)(A). FDA defines “due diligence” to mean that the sponsor must promptly conduct trials to verify the intended clinical benefit. See Expedited Programs Guidance, *supra* note 31, at 22.

67 See 21 C.F.R. §§ 314.81(b)(2) & 601.70(a)–(c).

68 See Expedited Programs Guidance, *supra* note 31, at 15.

69 See *id.*

70 *Id.*

71 Emil D. Kakkis et al., *Assessing the Accelerated Approval Pathway for Rare Disease Therapeutics*, 34 *Nature Biotechnology* 380, 380 (2016).

72 U.S. Food & Drug Admin., CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint (Jan. 14, 2021), <https://www.fda.gov/media/88907/download>

73 This estimate was calculated using the Friends of Cancer Research analysis of CBER’s data on drug and accelerated approvals as of June 30, 2020 in conjunction with CBER’s updated data as of December 30, 2020. See Friends of Cancer Res., *Optimizing the Use of Accelerated Approval 3 (2020)* (“FOCR Report”), https://friendsofcancerresearch.org/sites/default/files/2020-11/Optimizing_the_Use_of_Accelerated_Approval-2020.pdf (stating that 84% of accelerated approval drugs from 2010 to 2019 were for oncology indications); *CDER Drug and Biologic Accelerated Approvals*, *supra* note 72 (stating that FDA has granted 253 accelerated approvals as of December 31, 2020, of which 9 were approved after June 30, 2020 and 7 were for oncology drugs); see also Julia A. Beaver & Richard Pazdur, “Dangling” *Accelerated Approvals in Oncology*, 384 *New Eng. J. of Med.* e68(1), 1 (May 2021) (“[A]pproximately 85% of accelerated approvals in the past 10 years have been granted in oncology.”).

74 Syneos Health, *Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations* 5 (May 2016), https://www.syneoshealth.com/sites/default/files/documents/53424_voinv_35_pursuing_accelerated_approval_wp_l006.pdf.

approval enables sponsors to obtain approval earlier than at the point of completion of large, Phase III trials.⁷⁵ Oncology drug approval also can be based on validated surrogate endpoints such as objective response rate, which can support either accelerated approval or traditional approval.⁷⁶

Accelerated approval is also crucial to facilitate the development of drugs indicated to treat rare diseases⁷⁷—some of which are cancers. Over 25 million Americans suffer from rare diseases,⁷⁸ which are particularly likely to be serious and life-threatening diseases with unmet medical needs. Of the 7,000 rare diseases that have been identified, more than 90% of them have no FDA-approved treatment.⁷⁹ As discussed in Section III.B.1, *infra*, many facets of rare diseases make them particularly difficult to study in clinical trials targeting direct clinical benefit. “[D]eveloping drugs for rare disease can be challenging due to specific rare disease characteristics such as small heterogeneous patient populations, long time-frames for disease progression, a poor understanding of disease natural history, and a lack of prior clinical studies.”⁸⁰ This makes accelerated approval a particularly important tool for the development of treatments for rare diseases.⁸¹

III. COMPLIANCE WITH POSTMARKETING STUDIES AND POSTMARKETING AUTHORITIES

The idea of a postmarketing confirmatory study is critical to the viability of accelerated approval. The level of engagement between FDA and sponsors on developing postmarketing study protocols can vary. Sometimes a sponsor will prospectively target accelerated approval and have studies enrolled or enrolling before submitting a marketing application; sometimes FDA and the sponsor will pivot to accelerated approval during the review process. FDA will have agreed to a postmarketing confirmatory study protocol, submitted by the sponsor, at or before granting accelerated approval.⁸² The study protocol specifies the timelines for completing milestones (*e.g.*, participant enrollment, trial completion).⁸³

After approval, an accelerated approval drug will generally fit into one of three categories: (1) conversion to traditional approval; (2) continued marketing under a “dangling” approval; or (3) voluntary or involuntary withdrawal.

75 *Id.* at 5–6.

76 See FOCR Report, *supra* note 73, at 4.

77 A rare disease is one that affects fewer than 200,000 persons in the United States. See 56 Fed. Reg. 3338, 3339 (Jan. 29, 1991); Jennifer Huron, *New Study Investigates the Number of Available Orphan Products, Generics and Biosimilars*, Nat’l Org. for Rare Disorders (Mar. 25, 2021), <https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/>.

78 Huron, *supra* note 77.

79 *Id.*

80 Emil D. Kakkis et al., *Recommendations for the Development of Rare Disease Drugs Using the Accelerated Approval Pathway and for Qualifying Biomarkers as Primary Endpoints*, 10:16 Orphanet J. of Rare Diseases 1, 1 (2015), available at <https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-014-0195-4.pdf>.

81 See CDER Drug and Biologic Accelerated Approvals, *supra* note 72.

82 Expedited Programs Guidance, *supra* note 31, at 22.

83 *Id.*

Conversion to Traditional Approval

When postmarketing studies go according to plan and are conducted with due diligence, accelerated approvals are generally “converted” to “traditional” approvals. This happens when a sponsor completes the postmarketing confirmatory study and submits a final study report that FDA agrees validates the surrogate or intermediate clinical endpoint and verifies clinical benefit, typically through a demonstration of positive therapeutic effect.⁸⁴ As of 2020, FDA had converted roughly half of accelerated approvals (125 of 253) between 1992 and 2016⁸⁵ and about a third (36 out of 106) between 2010 and 2019.⁸⁶ We are mindful, however, that these numbers are still evolving. Many confirmatory studies—even those pursued with due diligence—can take a long time to complete. As discussed further below, for rare diseases in particular, heterogeneous symptoms and lack of natural history (among other things) can extend the amount of time it takes to generate meaningful study results. This is part of the reason the accelerated approval pathway is so important in this context—because it can expedite patient access during these relatively long periods of time.

“Dangling” Approvals: Incomplete or Inconclusive Confirmatory Studies

In some circumstances, required trials do not happen, do not happen with all deliberate speed, are incomplete, or do not confirm benefit.⁸⁷ Unless withdrawal procedures are initiated (see Section III.C, *infra*) products nonetheless can continue to be marketed as accelerated approval drugs.⁸⁸

1. Incomplete Confirmatory Studies

Confirmatory studies are required to verify and describe a drug’s clinical benefit and must be conducted with “due diligence,”⁸⁹ but they are not always completed. Sometimes this is because the studies are effectively not pursued by applicants; other times enrollment may lag, or the studies may otherwise languish.⁹⁰ Incomplete studies may be because the sponsor is not acting in good faith, or because of difficulties enrolling and completing the confirmatory study, including challenges associated with recruiting patients to participate in a study for a drug that is already approved and actively marketed.

Recruitment challenges are particularly common when it comes to rare disease drugs. Small patient populations combined with the heterogeneity of many rare diseases can also result in heterogeneous clinical trial enrollment,⁹¹ which can make it difficult to pinpoint clinical effect. Studying sub-populations (or verifying clinical benefit in sub-populations) can be exceedingly

84 See Accelerated Approval Labeling Guidance, *supra* note 53, at 5; GAO New Drug Approval Report, *supra* note 17, at 13.

85 ICER Report, *supra* note 35, at 10; see Beaver et al., *supra* note 58, at 851.

86 Amy Brown, *FDA Keeps the Faith in Surrogate Endpoints*, Evaluate Vantage (Feb. 18, 2020), <https://www.evaluate.com/node/15544/pdf>.

87 Gardiner Harris, *F.D.A. Backtracks and Returns Drug to Market*, N.Y. Times (Sept. 3, 2010), <https://www.nytimes.com/2010/09/04/health/policy/04fda.html> (“[M]ore than a third of the 90 drugs approved under the program since [it was established in] 1992 never had studies done proving efficacy.”).

88 Beaver & Pazdur, *supra* note 73, at 1.

89 See 21 U.S.C. § 356(c)(3)(A).

90 See GAO New Drug Approval Report, *supra* note 17, at 32–33; ICER Report, *supra* note 35, at 5.

91 See Kakkis, *supra* note 80, at 1; U.S. Food & Drug Admin., *Rare Diseases at FDA*, <https://www.fda.gov/patients/rare-diseases-fda> (last updated Feb. 20, 2020).

difficult.⁹² A lack of available patients to be enrolled in a clinical trial can undermine the sponsor's ability to power the study to reach statistical significance.⁹³ In addition, the clinical manifestations of rare diseases can be extremely diverse,⁹⁴ which makes verifying and describing clinical benefit (or lack of clinical benefit) particularly challenging. Understanding the biological mechanisms and natural history of rare disease is notoriously difficult.⁹⁵ This is largely driven by the small numbers of patients,⁹⁶ which means that not enough patients with a specific disease have been observed and studied for an understanding of how the disease would progress in the absence of treatment. This lack of natural history means that endpoints used for studying rare disease treatments tend to be very different from endpoints studied in, for example, other oncology arenas. Moreover, many rare diseases have long progression times⁹⁷ with slow or inconsistent disease progression—which means that a clinical study to confirm benefit can take many years even if feasible.

Postmarketing confirmatory studies also can raise unique ethical considerations for rare disease drugs. It is complicated, for example, to study a drug has been approved or treatment of a serious or life-threatening condition in studies where some patients will be randomized to a control arm.⁹⁸ In some types of disease areas, like many cancers, postmarketing confirmatory studies can be conducted in a different patient population

than that initially studied. For example, a confirmatory study may be conducted in patients with a less advanced stage of the same cancer type. This can incentivize and boost enrollment for clinical trials in oncology. For rare diseases, an approved treatment is usually the only treatment. With no alternative options, there can be ethical obstacles to enrolling patients in a study with a placebo arm, and even enrolling the necessary number of participants for a single-arm confirmatory study can be very difficult, as prospective clinical trial participants lack incentives to engage in such clinical trials once the drug or another alternative therapy becomes available.⁹⁹ As discussed in Section V.A, more robust and transparent reporting requirements can give sponsors an opportunity to discuss these types of enrollment challenges with FDA, potentially modify study designs as appropriate, and can give stakeholders an opportunity to understand when confirmatory studies encounter difficulties even when conducted with due diligence.

2. Inconclusive Confirmatory Studies

Confirmatory studies completed in good faith with “due diligence” can be inconclusive with respect to the verification of clinical benefit in the precise indication(s) for which a drug was approved under accelerated approval. There are a number of reasons why the anticipated relationship between the accelerated approval endpoint and clinical benefit may not be apparent: the surrogate

92 U.S. Food & Drug Admin., Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases 23 (July 2014), <https://www.fda.gov/media/89051/download>.

93 See Aya Mitani & Sebastien Haneuse, *Small Data Challenges of Studying Rare Diseases*, JAMA Network Open (Mar. 23, 2020), <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2763223>.

94 See U.S. Food & Drug Admin., *Guidance for Industry: Human Gene Therapy for Rare Diseases 2* (Jan. 2020), <https://www.fda.gov/media/113807/download>.

95 See 80 Fed. Reg. 49242, 49242 (Aug. 17, 2015); Kakkis, *supra* note 80, at 1.

96 See 80 Fed. Reg. at 49242.

97 See Kakkis, *supra* note 80, at 1.

98 See FOIC Report, *supra* note 73, at 3.

99 See *id.*, at 7.

endpoint may not actually have the expected causal relationship to clinical outcome; there may also be a disproportionate or subpopulation-driven benefit; or there may be a smaller-than-expected benefit. In any of those circumstances, it can be difficult to verify clinical benefit in the absence of large-scale clinical trials of long duration.¹⁰⁰ There may also be trial design reasons for inconclusive study results.¹⁰¹

When confirmatory study results are inconclusive, there may be insufficient evidence to confirm clinical benefit. The absence of confirmation of clinical benefit can justify withdrawal in some cases. In other cases, there may be a continued expectation that a surrogate or intermediate clinical endpoint is predictive of clinical benefit and additional studies may be warranted. This is particularly true when the unmet medical needs on which accelerated approval was predicated persist. Confirmatory studies can also show unexpected benefits that can be result in expanded indications or can catalyze additional studies to support other label expansions.

Withdrawal

When a confirmatory study results in a negative finding, *i.e.*, confirmation that the endpoint is not predictive of actual clinical benefit, this can be grounds for withdrawal. As of December 31, 2020, 16 drugs that received accelerated approval status had been withdrawn (6.3%).¹⁰² Of these, 10 were for oncology indications.¹⁰³ Even more recently, the Oncologic Drugs Advisory Committee Meeting (ODAC) examined six accelerated approval indications for which confirmatory trials did not, in fact, confirm expected benefits.¹⁰⁴ After reviewing the evidence presented with respect to those indications, the ODAC recommended that two of the six indications be withdrawn.¹⁰⁵ These types of proceedings may become more common, as FDA brings increasing levels of scrutiny to accelerated approvals for which clinical benefit is not confirmed.

Withdrawal may be undertaken on a voluntary or involuntary basis. Either way, the proceedings impose significant time and resource burdens on FDA, which must undertake a detailed scientific analysis of whether withdrawal is appropriate and engage with the applicant in order to determine the best and most feasible course of action. Along the way, multiple issues require consideration, ranging from the status of follow-on products (*e.g.*, generic drugs that reference the drug in question) to continued patient use under expanded access.

¹⁰⁰ 57 Fed. Reg. at 58944.

¹⁰¹ Beaver & Pazdur, *supra* note 73, at e68(3) (in some cases, multiple sponsors' trials have generated "conflicting results").

¹⁰² See CDER Drug and Biologic Accelerated Approvals, *supra* note 72; ICER Report, *supra* note 35, at 10.

¹⁰³ See CDER Drug and Biologic Accelerated Approvals, *supra* note 72; Beaver & Pazdur, *supra* note 73, at 3.

¹⁰⁴ See 86 Fed. Reg. 14125, 14126 (Mar. 12, 2021).

¹⁰⁵ See Kari Oakes, *ODAC Recommends Pulling 2 of 6 Accelerated Approvals*, Regulatory Focus (Apr. 30, 2021), <https://www.raps.org/news-and-articles/news-articles/2021/4/odac-recommends-pulling-2-of-6-accelerated-approva>; see also U.S. Food & Drug Admin., April 27–29, 2021, *Meeting of the Oncologic Drugs Advisory Committee (ODAC) Webcast Information*, <https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-27-29-2021-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04272021-04292021#event-materials> (last visited June 27, 2021).

As discussed further in Section V.F, *infra*, additional focused resources may help FDA implement better systems regarding withdrawals, when necessary, which could revitalize this important tool.

1. Voluntary Withdrawal

Although the Agency has discretion regarding whether to initiate withdrawal proceedings for a drug, typically FDA will ask an applicant to request withdrawal when grounds exist.¹⁰⁶ Even a sponsor's voluntary withdrawal of a drug from sale requires substantial Agency resources, however. FDA must make a finding regarding the reason for the withdrawal, publish a federal register notice of its determination, and address any relevant abbreviated new drug applications (ANDAs)¹⁰⁷ and requests for continued access. FDA may still receive relisting petitions, and if it does, it must make a determination regarding relisting.¹⁰⁸ Between 1992 and 2020, FDA has overseen the voluntary withdrawal of 15 drugs, of which two were indicated for the treatment of rare diseases.¹⁰⁹

2. Involuntary Withdrawal

FDA also has the authority to withdraw an accelerated approval under statutorily enumerated circumstances. Most relevant here is withdrawal on the basis that the confirmatory study either was not conducted "with due diligence",¹¹⁰ or that the confirmatory study "fail[ed] to verify and describe" the endpoint's predicted

effect on IMM or other clinical benefit.¹¹¹ If FDA initiates withdrawal proceedings, it will notify the applicant of FDA's proposal to withdraw approval in a notice of opportunity for hearing (NOOH).¹¹² FDA's goal in issuing an NOOH may be a voluntary withdrawal, but if that does not happen, FDA may then proceed with the withdrawal.

The statutory accelerated approval provision contemplates that FDA may withdraw accelerated approval "using expedited procedures," including an opportunity for an informal hearing, as prescribed in regulations.¹¹³ However, FDA has not promulgated regulations describing an expedited withdrawal proceeding beyond the initial accelerated approval regulations, which predate the statutory provision and provide for a modified Part 15 hearing.¹¹⁴ Thus, the Agency has approached involuntary withdrawals cautiously, hewing to what is provided in those regulations.

Given the lack of clarity around procedures for—and commensurate sizeable resource commitment necessary for—a withdrawal hearing, FDA has exercised this authority only twice since the establishment of the accelerated approval pathway. The first proceeding, in 2011, was to withdraw accelerated approval of an indication after FDA determined that the confirmatory study, although completed with due diligence, had not verified clinical benefit. That proceeding did not suffer from any specific hurdle or

106 21 C.F.R. § 314.150.

107 If there are approved ANDAs to the listed drug, or before approving any future ANDAs, FDA must determine whether the listed drug was withdrawn for safety or effectiveness reasons. *See id.* §§ 314.161(a) & 314.127(a)(1).

108 *Id.* § 314.122(a)–(b). Section 505(w) of the FD&C Act requires the determination to be made "no later than 270 days after the date the petition is submitted." 21 U.S.C. § 355(w).

109 *See CDER Drug and Biologic Accelerated Approvals, supra* note 72.

110 21 U.S.C. § 356(c)(3)(A).

111 *Id.* § 356(c)(3)(B).

112 21 C.F.R. §§ 314.530(b) & 601.43(b).

113 21 U.S.C. § 356(c)(3).

114 21 C.F.R. §§ 314.530(e) & 601.43(e).

complication that slowed it down; to the contrary, the confirmatory study was done diligently, the data submitted and analyzed, and the public proceedings took place without any major obstacles, technically using an “expedited” and less formal hearing process. The withdrawal decision—which removed the indication in question only and kept the drug on the market for its other approved indications—took three years from the time of approval and two years from submission of the confirmatory study results to FDA. The process included multiple submissions to a public docket, a two-day public hearing including presentations by subject matter experts and an advisory committee vote. This burden is often cited as contributing significantly to FDA’s reluctance to engage in withdrawals since.¹¹⁵ FDA did not again initiate withdrawal proceedings for an accelerated approval until 2020, when a postmarketing confirmatory study failed to verify clinical benefit and raised questions concerning the drug’s effectiveness.¹¹⁶ Moreover, FDA’s reticence on this front is widely known, which can limit the Agency’s leverage to push sponsors voluntarily to remove drugs from the market.

Overall, FDA has faced criticism for failing to promulgate regulations that would streamline the withdrawal proceedings.¹¹⁷ FDA has taken the position that it would be “difficult, if not impossible” to promulgate guidance or regulations because expedited withdrawals involve case-by-case assessments that take into consideration the sponsor’s reasons and the consequences of withdrawal (*i.e.*, the adverse impact on patients).¹¹⁸ One of the complicating factors influencing decisions about whether to initiate withdrawal proceedings that is of particular import for patients with rare disease, for example, is whether the drug is the only approved therapeutic drug available for patients with a particular disease.¹¹⁹

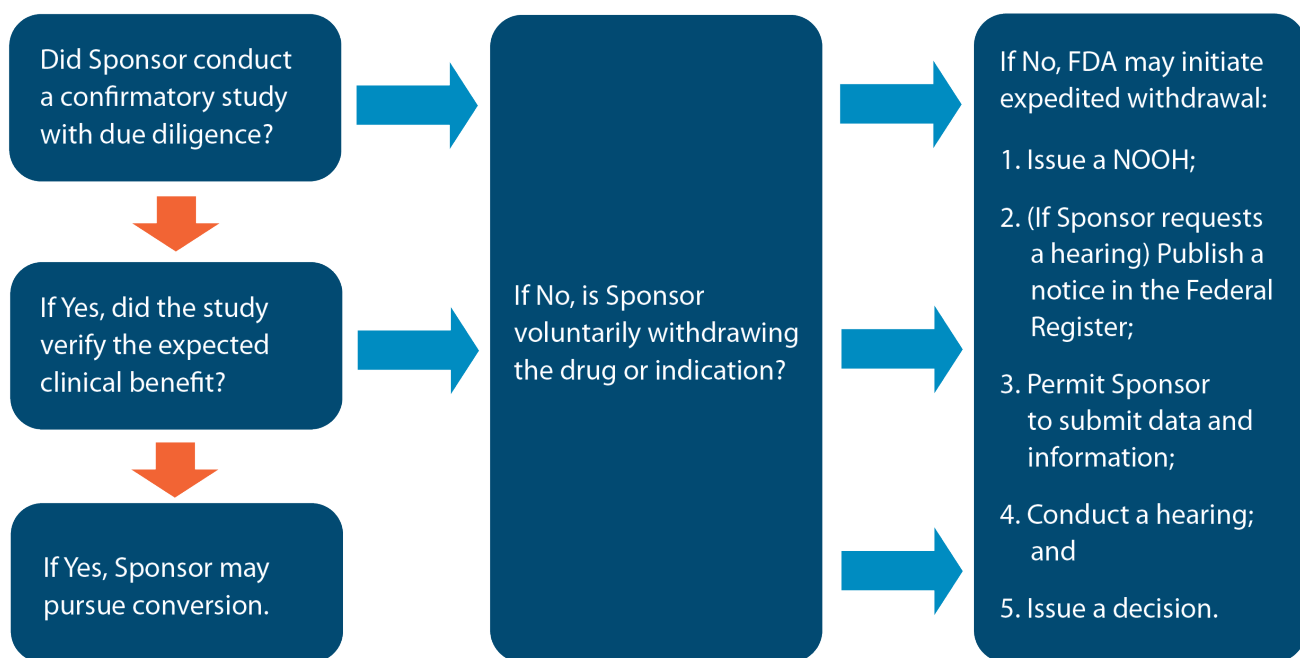
115 See Sue Sutter, *Pink Sheet – Accelerated Approval: US FDA Panel to Reconsider Six Indications for Checkpoint Inhibitors*, Friends of Cancer Res. (Mar. 11, 2021), <https://friendsofcancerresearch.org/news/pink-sheet-accelerated-approval-us-fda-panel-reconsider-six-indications-checkpoint-inhibitors>; *FDA to Consider Taking Back Approvals from Cancer Drugs that Have Failed to Show They Extend or Improve Life*, Associated Press (Apr. 25, 2021), <https://ktla.com/news/nationworld/fda-to-consider-taking-back-approvals-from-cancer-drugs-that-have-failed-to-show-they-extend-or-improve-life/>; see generally U.S. Food & Drug Admin., Docket No. FDA-2010-N-0621, Proposal to Withdraw Approval for the Breast Cancer Indication for AVASTIN (Bevacizumab) (Nov. 18, 2011), <https://www.fda.gov/media/82467/download>.

116 See Letter from Ctr. for Drug Evaluation & Research, U.S. Food & Drug Admin., to AMAG Pharmaceuticals, Inc. (Oct. 5, 2020), https://downloads.regulations.gov/FDA-2020-N-2029-0001/attachment_1.pdf. The request for hearing is pending as of the time of publication of this White Paper. See U.S. Food & Drug Admin., *CDER Perspective on Recently Published Results of EPPPIC Meta-Analysis* (Mar. 26, 2021), <https://www.fda.gov/drugs/drug-safety-and-availability/cder-perspective-recently-published-results-epppic-meta-analysis>.

117 The U.S. Government and Accountability Office recommended that FDA “[c]larify the conditions under which the agency would utilize its authority to expedite the withdrawal of drugs” when the sponsor fails to conduct the required postmarketing confirmatory study with due diligence or the study fails to demonstrate the clinical effectiveness of the drug. GAO New Drug Approval Report, *supra* note 17, at 36.

118 *Id.* at Appx. V, 5–6.

119 *Id.* at Appx. V, 3.



D. Other Enforcement Tools

Commenters generally agree that the threat of withdrawal is an insufficient tool to maximize the utility of accelerated approval and to ensure that postmarketing obligations are met.¹²⁰ Critics of accelerated approval also have been quick to point to problems with the timely completion of postmarketing confirmatory studies and commensurate withdrawal or conversion to full approval.¹²¹ Other than the somewhat blunt instrument of withdrawal, however, FDA lacks effective authority to target dangling approvals, tackle languishing confirmatory studies, revise accelerated approval drug labeling, or require additional studies (after the point of accelerated approval) if needed to refine a drug’s use or if confirmatory studies are inconclusive. For

example, in some cases, the best outcome may not be withdrawal, but a narrowed or modified indication more reflective of true clinical benefit. However, there are legitimate questions about whether FDA has the authority to direct the data generation and/or labeling modifications to effectuate such a change. Additionally, even in cases in which FDA does decide withdrawal of the drug or indication is warranted, FDA is often under enormous pressure from lawmakers and patients not to remove their access to the drug, as demonstrated by previous instances.

120 See U.S. Gov’t Accountability Office, GAO-16-192, *Drug Safety: FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement* 11–12 (Dec. 2015) (“Although FDA is responsible for overseeing postmarket studies and ensuring they are completed in a timely manner, we and others have found that, in the past, FDA has not adequately done so.”).

121 See ICER Report, *supra* note 35, at 28–29; FOIC Report, *supra* note 73, at 7–9; Walid Gellad & Aaron Kesselheim, *Accelerated Approval and Expensive Drugs—A Challenging Combination*, 376 *New Eng. J. Med.* 2001, 2003 (May 25, 2017).

IV. DRUG PRICING CHALLENGES NEED DRUG PRICING SOLUTIONS; TARGETING ACCELERATED APPROVAL IS NOT THE ANSWER

There are several common criticisms of accelerated approval. On the one hand, many believe that FDA does not use the pathway aggressively enough, *i.e.*, that FDA is too reticent to approve drugs through the pathway and requires too much in the way of confirmatory studies. On the other hand, concerns have been raised that there are too many “dangling” accelerated approvals, whether due to lack of due diligence in completing confirmatory studies or inconclusive confirmatory evidence,¹²² and that drugs approved through the accelerated approval pathway are “unproven” or “experimental.”¹²³

More recently, attention has been paid to the high costs of certain accelerated approval drugs to state Medicaid programs and other public or commercial payers, and many ideas for curbing these costs have been proposed.¹²⁴ This focus on high-cost accelerated approval drugs has resulted in proposals for broad brush solutions that attempt to resolve drug pricing challenges through the differential treatment of accelerated approval drugs. For example, the Institute for Clinical and Economic Review (ICER) and the Medicaid and CHIP Payment and Access Commission (MACPAC) both recently advocated for an increase in mandatory federal rebate levels for

accelerated approval drugs until their confirmatory studies are complete and are granted traditional approval.¹²⁵ MACPAC additionally recommended an increase to the additional inflationary rebate on accelerated approval drugs if they do not complete confirmatory studies or covert to traditional approval within a certain number of years.¹²⁶

However, the problems with accelerated approval are separate and apart from drug pricing issues. Drugs that utilize the accelerated approval pathway do often have high list prices; but high list prices are also a concern for many drugs approved through the traditional pathway. Furthermore, manufacturers could account for the mandated higher rebates recommended by ICER and MACPAC for a drug that utilizes the accelerated approval pathway by increasing the overall list price for the drug, possibly resulting in lower Medicaid drug spending but increased drug spending for other public programs or private payers.

The reality is that drug pricing and the accelerated approval pathway are distinct problems that are in need of different, targeted solutions. The solutions for accelerated approval issues should be disaggregated from those for drug pricing issues.

122 See ICER Report, *supra* note 35, at 18–20; Gellad & Kesselheim, *supra* note 121, at 2003; Johnson et al., *supra* note 45, at 643–44; GAO New Drug Approval Report, *supra* note 17, at 14–15, 32–33.

123 Medicaid and CHIP Payment and Access Commission, Transcript, *March 2021 MACPAC Public Meeting* 103 (Mar. 3, 2021), <https://www.macpac.gov/wp-content/uploads/2020/08/MACPAC-March-2021-Meeting-Transcript.pdf>.

124 See Gellad & Kesselheim, *supra* note 121, at 2003.

125 See ICER Report, *supra* note 23, at 30; Chris Park, Medicaid and CHIP Payment and Access Commission, *High-Cost Specialty Drugs: Moving Towards Recommendations 6–7* (Mar. 4, 2021), <https://www.macpac.gov/wp-content/uploads/2021/03/High-Cost-Specialty-Drugs-Moving-Towards-Recommendations.pdf>.

126 See Park, *supra* note 125, at 7.

Accelerated approval problems need accelerated approval solutions, and state Medicaid cost and other drug pricing issues need to be resolved through targeted drug pricing reform solutions. Conflating the two issues can create broader problems in the drug development paradigm and potentially implicate FDA's gold standard for drug review. Given the history of accelerated approval, the way it is used presently, and the hope that it will continue to be a useful tool for expediting therapeutic access to patients with unmet medical needs, it is particularly important that solutions to the previously mentioned challenges associated with the accelerated approval pathway continue to reflect that accelerated approval is a full finding that the drug is safe and effective (and that the benefits of that drug outweigh its risks), and that drug pricing solutions do not undermine the FDA's gold standard for drug review.

Targeting an FDA Approval Pathway for Drug Pricing Reforms Could Undermine the Drug Development Paradigm

Attempting to solve accelerated approval problems using pricing mechanisms could have the unintended effect of creating broader problems for drug review and approval. Accelerated approval drugs are not inherently "riskier" or "lower value" drugs; accelerated approval is not a "partial" or "less than full" approval. As FDA stated in promulgating the accelerated approval regulations, accelerated approval "does not represent either a 'lower standard' or one inconsistent with section 505(d)

of the act, but rather an assessment about whether different types of data show that the same statutory standard has been met."¹²⁷ Indeed, FDA explicitly considered and rejected the idea that accelerated approval was creating a different standard. Rather, FDA explained, "[t]he evidence available at the time of approval under this rule will meet the statutory standard, in that there must be evidence from adequate and well-controlled studies showing that the drug will have the effect it is represented to have in its labeling."¹²⁸

The difference between accelerated approval and traditional approval is actually about the level of existing evidence regarding the predictive ability of the endpoint. When drug effects in a therapeutic area have been studied substantially, as drugs treating heart disease have, for example, there is more evidence from clinical trials to support the predictive value of endpoints. For rare diseases in therapeutic areas with unmet medical needs, there has not been the clinical trial volume necessary to demonstrate the predictive value of the endpoint. Whatever the precise risk-benefit calculation FDA will have made approving a given drug, each approval decision is a finding that the drug has met the standard, including substantial evidence of efficacy.

The drafters of the accelerated approval regulations also considered the question of whether, "because the proposed rule would establish conditions on a drug's approval, third-party payors may decline reimbursement because the so-called approval would have attributes of

127 57 Fed. Reg. at 58944.

128 *Id.* at 58943–44. As FDA noted in the preamble to the final rule, the "effect" in question would be "an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit and labeling will refer to the effect on the surrogate, not to effect on clinical outcome." *Id.* at 58944.

investigational status.”¹²⁹ They concluded that would not happen “because drugs approved under the accelerated approval process meet the statutory standards for safety and effectiveness.”¹³⁰ Thus, they would be “eligible for reimbursement under State Medicaid programs or other third-party plans.”¹³¹

The question of reimbursement for accelerated approval drugs, which are often on the cutting edge and can be extremely expensive, is an important one, but it is not a problem that is unique to or coextensive with accelerated approval. Private insurers generally have the option to determine coverage of specific drugs and they will sometimes deny or otherwise limit coverage of drugs, whether accelerated approval or traditionally approved.¹³² State Medicaid programs, however, are statutorily required to cover virtually all drugs approved by FDA and they have limited wiggle room for imposing cost-saving limitations.¹³³ As a result, some commentators have come to view accelerated approval as “a mandate [to public insurers] to pay high prices for an unproven therapy.”¹³⁴ We suggest that, despite the understandable inclination to “fix” the problem of high costs to public insurers by altering or imposing new conditions on accelerated approval drugs, drug pricing and accelerated approval issues should be considered separately.

A two-tiered paradigm for drug approval could actually exacerbate many of the concerns related to accelerated approval. With respect to both accelerated and traditional approvals, for example, FDA has ambiguous postmarketing authorities regarding new or more tailored information that might warrant narrowing the drug’s indication, and in both cases withdrawal proceedings can be unduly lengthy, cumbersome, and will only be resorted to in the most egregious of cases. In addition, there is no way to draw neat lines between a drug approved through accelerated approval on the basis of a surrogate endpoint and a postmarketing requirement to verify and describe that surrogate endpoint, on the one hand, and a drug approved through “traditional” approval on the basis of an established surrogate endpoint, on the other hand.¹³⁵ This problem is particularly acute for endpoints—like progression-free survival in cancer patients—that are used as the basis for regular approval in some instances and as the basis for accelerated approval in others.¹³⁶ There also may be postmarketing requirements associated with both types of approvals, and those postmarketing requirements may have been made to study any number of issues and for any number of reasons. For example, would a postmarketing registry also be a basis on which to limit reimbursements? What about a postmarketing commitment to collect real-world

129 *Id.* at 58945.

130 *Id.*

131 *Id.*

132 See Gellad & Kesselheim, *supra* note 121, at 2001–02.

133 See generally 42 U.S.C. § 1396r-8. Medicare also requires coverage of drugs that are “reasonable and necessary,” though there is some more room for state maneuvering in Medicare programs. See *id.* § 1395y(a)(1)(A).

134 See Gellad & Kesselheim, *supra* note 121, at 2001–02.

135 Indeed, FDA was approving drugs based on surrogate endpoints prior to accelerated approval. 57 Fed. Reg. at 58944 (“Approval based on surrogate endpoints is not new For example, drugs for hypertension have been approved based on their effects on blood pressure rather than on survival or stroke rate. Similarly, drugs for hypercholesterolemia have been approved based on effects on serum cholesterol rather than on coronary artery disease (angina, heart attacks).”).

136 Johnson et al., *supra* note 45, at 637.

evidence in order to refine labeling? These questions are why it is imperative to remember, in crafting a solution tailored to either problem, that there is only one FDA approval standard across the board.

Maintaining FDA's Gold Standard for Drug Review

Evidence regarding safety and effectiveness can come from a multitude of sources, as can uncertainty about that evidence. For example, there may be uncertainty about whether data generated in precisely controlled clinical trial settings will translate effectively to real-world use in post-market settings, or uncertainty about whether clinical trial data developed in particular patient populations will translate to the broader patient population in which a drug may be indicated. These uncertainties persist regardless of the approval pathway, which itself is often not determined until after an application has been submitted to FDA. It is for good reason that the statutory standard for approval is flexible enough to account for uncertainty:

Reliance on a surrogate endpoint almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known.... Reliance on surrogate markers therefore requires an additional measure of judgment, not only weighing benefit versus risk, as always, but also deciding what the therapeutic benefit is based upon the drug effect on the surrogate.¹³⁷

Ultimately, FDA approval is not an iron-clad promise of safety or effectiveness but a recognition that the applicant has demonstrated that the product is safe and has provided substantial evidence that the product is efficacious. And it means FDA has determined, based on that evidence, the benefits of the drug outweigh the risks. Indeed, as described by FDA, “the effect shown [for accelerated approval] must be such as to outweigh the risks of the treatment under the conditions of use. Therefore, approval under this rule requires that the effect shown be clinically meaningful in the judgment of the agency, and of such importance as to outweigh the risks of treatment.”¹³⁸ For rare serious diseases, and in other areas of unmet medical needs, FDA understands that patients and caregivers may be willing to tolerate a greater level of uncertainty; however, that does not mean that the approval is “less than” a full finding that the statutory standard for approval has been met.

Considering accelerated approval drugs to be a separate tier of “less efficacious” drugs would, essentially, be creating a lower approval standard against which drugs could be developed and still seek FDA approval. This type of dual standard system has the potential to undermine FDA’s gold standard.

¹³⁷ 57 Fed. Reg. at 58944.

¹³⁸ *Id.*

V. ACCELERATED APPROVAL SOLUTIONS TO ACCELERATED APPROVAL PROBLEMS

In contemplating changes to the operation of the accelerated approval pathway, or to drug payment and reimbursement structures, we must be mindful not to jeopardize approval pathways, including accelerated approval, that have successfully led to the innovation and development of new drugs to treat rare diseases. To the contrary, changes, if any, should bolster the areas where accelerated approval has been successful—such as incentivizing drug development in areas of unmet medical need—and should make improvements that will enhance the efficient and transparent use of accelerated approval.

The following discussion offers proposals for accelerated approval solutions to accelerated approval problems. The recommendations proposed would forge an accelerated approval pathway with more nimble enforcement tools and better transparency, while recognizing that accelerated approval is not a lower standard of approval. Accelerated approval provides expedited access to lifesaving drugs for patients who need it the most; we must improve it, not undermine it.

Periodic Review of Progress on Confirmatory Studies

Periodic progress review of confirmatory studies by FDA would help address concerns about transparency and accountability, and it would give FDA regular touchpoints at which to evaluate progress on required postmarketing confirmatory studies. Specifically, accelerated approval sponsors should be required to submit regular reports comparing actual progress to the milestones that the sponsor agreed to at the time of accelerated approval. FDA would then review the reports and provide feedback to the sponsor. For example, FDA could recommend that the sponsor seek to convert the approval to traditional approval, if justified; assess the appropriateness of stated reasons for delay; or consider initiating withdrawal in the event the study is not being pursued with due diligence.

Currently, sponsors with ongoing postmarketing studies for accelerated approvals already provide periodic reports to FDA.¹³⁹ Such sponsors must submit to FDA, among other things, an initial report, and then annual reports, that include information about the progress of the study, including the reasons the sponsor has not met anticipated milestones, if applicable.¹⁴⁰ This obligation continues until FDA determines that the relevant study requirement has been fulfilled, that it is no longer feasible, or that it would not

139 See 21 U.S.C. §§ 356b(a)(1) & 356(c)(2)(A); 21 C.F.R. §§ 314.81(b)(2)(vii) & 601.70(b); U.S. Food & Drug Admin., Guidance for Industry: Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 11–14 (Feb. 2006) (“Reporting Guidance”), <https://www.fda.gov/media/72535/download>.

140 Required information include, in relevant part: (1) the date of the postmarketing study requirement; (2) a description of the postmarketing study requirement; (3) the current status of the postmarketing study requirement—as pending, ongoing, delayed, terminated, or submitted; and (4) an explanation of the status. 21 C.F.R. §§ 314.81(b)(2)(vii)(a) & 601.70(b).

provide useful information.¹⁴¹ FDA publishes limited information, *i.e.*, the sponsor, study status (pending, ongoing, delayed, terminated, or submitted), and reasons, if any, for failure to carry out the study.¹⁴² If a sponsor fails to complete the study by its original or negotiated deadline, FDA will publish a statement on FDA's website stating that the study was not completed and, under certain circumstances, responding to proffered explanations.¹⁴³ This information is included in annual *Federal Register* reports by FDA and in FDA's postmarketing study requirements website.¹⁴⁴ Finally, with respect to accelerated approval postmarketing studies specifically, if a sponsor fails to complete a study by its deadline for reasons not satisfactory to FDA, FDA may require that the sponsor notify prescribers of the failure to complete the study, the questions of clinical benefit, and, as appropriate, any questions of safety that remain unanswered as a result of failure to complete the study.¹⁴⁵

A more robust submission, tailored to accelerated approval postmarketing studies and with a more fulsome role for FDA in terms of reviewing and publishing relevant information, would improve FDA's ability to monitor those studies and respond appropriately to changed circumstances and new data.¹⁴⁶ To facilitate this review, the reports should include a review of ongoing confirmatory studies and subsequent investigational plans, if any; any anticipated challenges with developing,

testing, and marketing; and any changes that may affect the predictive value of the endpoint on which the approval was based. FDA would then be able to regularly consider the continued viability and necessity of the confirmatory study. FDA also could consider—and provide feedback on—questions of study design modification, timeline adjustments, and the continued necessity of the study itself. Or, if early data and real-world use of the drug (including real world evidence from Phase IV studies, discussed further below) could support conversion, FDA could work with the applicant to make that happen. Tailored reporting requirements for accelerated approval drugs, focused on ascertaining the status of confirmatory studies and the diligence with which they are conducted, would give sponsors an additional incentive to complete confirmatory studies. Ensuring FDA review of and feedback on the reports would similarly incentivize sponsors to focus on real world use of their accelerated approval drugs and how scientific advancements may be harnessed to speed confirmation of benefit.

Finally, beyond the basic status information currently published, public availability of summaries of sponsor reports and FDA reviews would provide stakeholders with insight into ongoing progress and problems. A more robust and timely public summary of the report—which includes progress made (or not made) on confirmatory studies and FDA's recommendations for moving forward—would provide enhanced

141 See Reporting Guidance, *supra* note 139, at 9 (citing 21 C.F.R. §§ 314.81(b)(2)(vii) & 601.70(b))

142 21 U.S.C. § 356b(b); Reporting Guidance, *supra* note 139, at 13–14, 16.

143 See 21 U.S.C. § 356b(d).

144 Reporting Guidance, *supra* note 139, at 15; see U.S. Food & Drug Admin., Drug Database, *Postmarket Requirements and Commitments*, <https://www.accessdata.fda.gov/Scripts/cder/pmc/index.cfm> (last updated Apr. 28, 2021).

145 21 U.S.C. § 356b(e).

146 *Cf.* 21 U.S.C. §§ 355-1(a), (g)(2)(A) & (i); 21 C.F.R. § 316.30(b)–(c) (progress reports for orphan-designated drugs); U.S. Food & Drug Admin., Draft Guidance for Industry: REMS Assessment: Planning and Reporting 2–3 (Jan. 2019) (“REMS Guidance”), <https://www.fda.gov/media/119790/download> (discussing REMS Assessment Plans).

accountability and transparency and would incentivize competition of confirmatory studies and conversion of accelerated approval drugs.

Accelerated Approval Labeling

The goals of clarity and transparency would be improved through enhanced labeling for accelerated approval. Through improved accelerated approval drug labeling, clinicians and patients would have ready access to important information and context about the surrogate or intermediate clinical endpoint on which the approval was based, and about ongoing confirmatory studies, as appropriate.

Currently, accelerated approval drug labeling is “in most ways the same” as labeling for traditionally approved drugs.¹⁴⁷ The label must contain “a summary of the essential scientific information needed for the safe and effective use of the drug,” and follow other content and format requirements enumerated in FDA’s labeling regulations.¹⁴⁸ For accelerated approval drugs, this includes, in the “INDICATIONS AND USAGE” section of the Prescribing Information (“USPI”), the indication and a “succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits.”¹⁴⁹

It also includes statements: (1) that the drug

received accelerated approval status; (2) that continued approval is subject to a postmarketing confirmatory study; (3) identifying the endpoint that is under study; (4) disclosing the limitations of that endpoint, if any; and (4) referencing the “Clinical Studies” section for a discussion of available evidence.¹⁵⁰

Enhancing these requirements to add more specific information about the status of confirmatory studies would add clarity and transparency to the USPI. For example, a description of any applicable postmarketing requirements and the timelines for completing them, added to the USPI, would provide stakeholders with ready access to current information regarding the context of the drug’s accelerated approval. It also would provide an incentive for sponsors to complete confirmatory studies and seek conversion of their drugs. And it would enhance monitoring of direct-to-consumer advertising and other promotional materials to ensure appropriate communication about accelerated approvals that is consistent with FDA-approved labeling.¹⁵¹

147 Accelerated Approval Labeling Guidance, *supra* note 53, at 2.

148 See 21 C.F.R. §§ 201.56(a) & 201.57(a). The labeling must include: (1) a highlights limitation statement; (2) the proprietary and established names of the drug, dosage form, route of administration, and controlled substance symbol (if applicable); (3) the initial year that FDA approved the drug; (4) a boxed warning; (5) a list of the sections that have undergone substantive labeling changes; (6) the indications and major limitations of use; (7) the recommended dosage regimens; (8) the strength or potency of the dosage forms; (9) the contraindications; (10) the most clinically significant warnings and precautions; (11) a list of the most frequently occurring adverse reactions; (12) the clinically significant drug interactions; (13) a description of the uses in specific populations; (14) a patient counseling information statement; and (15) the date of the most recent revision of the labeling. *Id.* § 201.57(a).

149 See Accelerated Approval Labeling Guidance, *supra* note 53, at 2–3; *id.* at 3 n.8. When postmarketing confirmatory studies are completed and approval is converted, or when accelerated approval is withdrawn, these labeling statements typically are removed from the USPI through a prior approval supplement. See *id.* at 3.

150 See *id.* at 3–4.

151 According to a study conducted by FDA’s Office of Prescription Drug Promotion (“OPDP”), many direct-to-consumer websites for accelerated approval products did not publish comprehensive information about the accelerated approval drugs and their requirements. 86 Fed. Reg. 31323, 31324–25 (June 11, 2021).

Consideration of RWE for Conversion to Traditional Approval

The 21st Century Cures Act mandated that FDA establish a program to evaluate the potential use of real-world evidence (“RWE”) to help satisfy postmarketing study requirements.¹⁵² FDA should further consider acceptance of real-world evidence from Phase IV studies under accelerated approval and should work to build a formal process for doing so.¹⁵³ If RWE is fit for purpose and otherwise meets regulatory criteria, FDA needs to have a functional mechanism for considering that evidence, along with any clinical data from the confirmatory study, to support conversion of accelerated approval to traditional approval and to discharge postmarketing requirements. FDA could decide whether to convert the drug to traditional approval based on the totality of the evidence, including review of the period reports proposed above, even before a confirmatory study is complete. FDA should be transparent in its consideration of this evidence too, including in published information (discussed in Section V.A, *supra*), whether and the extent to which it has considered RWE in reaching recommendations, and conclusions about next steps regarding confirmatory studies.

As discussed *supra*, there can be difficulties with design, enrollment, and timely completion of postmarketing confirmatory studies for rare disease drugs. Consideration of RWE as part of the evaluation of whether the drug has an effect on the intended clinical benefit would permit FDA to convert accelerated approval drugs to traditional approval, when scientifically appropriate, at an earlier point in time. FDA already utilizes RWE in the postmarket to evaluate safety; we propose that utilization of RWE in the postmarket to evaluate efficacy is appropriate for conversion of accelerated approval of drugs.

Clarification of FDA’s Postmarketing Authorities

Currently, when “new safety information”¹⁵⁴ comes to light, FDA can require safety labeling changes and additional studies to be conducted to identify or assess “serious risks” and signals of “serious risk.”¹⁵⁵ Applicants may be required to make changes to approved labeling¹⁵⁶ following a prescribed process and timetable. These postmarketing authorities should be amended to clarify that they can be applied to update labeling of accelerated approval drugs and to require additional studies related to endpoints used in accelerated approval applications.

Specifically, the FD&C Act should be updated to clarify that the definitions of “serious risk” and “new

152 See 21st Century Cures Act § 3022, 21 U.S.C. § 355g; U.S. Food & Drug Admin., Draft Guidance for Industry: Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics 2 (May 2019), <https://www.fda.gov/media/124795/download>.

153 Real world data (“RWD”) refers to data relating to “patient health status and/or the delivery of health care routinely collected” from sources such as electronic health records, claims and billing activities, product and disease registries, patient-generated data including in home-use settings, and more. U.S. Food & Drug Admin., Framework for FDA’s Real-World Evidence Program 4–5 (Dec. 2018) (“RWE Program Guidance”), <https://www.fda.gov/media/120060/download>. RWE is defined as “clinical evidence about the usage and potential benefits or risks of a medical product.” See *id.* at 4; see also 21 U.S.C. § 355g(b). It is derived from RWD through studies, trials, and analyses thereof. See RWE Program Guidance, *supra* note 153, at 4.

154 See 21 U.S.C. § 355(o)(4)(A); U.S. Food & Drug Admin., Guidance for Industry: Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act 4 (July 2013) (“Safety Labeling Changes Guidance”), <https://www.fda.gov/media/116594/download>.

155 See 21 U.S.C. § 355(o)(3)(4).

156 21 U.S.C. § 355(o)(4); Safety Labeling Changes Guidance, *supra* note 154, at 3.

safety information”¹⁵⁷ include questions related to the predictive value of surrogate and intermediate clinical endpoints used to support accelerated approval—even if facially about efficacy. This would provide FDA with more nimble authorities under which to require and react to postmarketing studies conducted by accelerated approval sponsors. If, for example, a confirmatory study was not conclusive, or if a confirmatory study provided evidence that suggests labeling should be updated (e.g., to a narrower subpopulation), FDA would have clear authority to require labeling changes or additional studies.

Ensuring that these authorities extend to sponsors’ failure to complete postmarketing confirmatory studies with due diligence, negative or inconclusive confirmatory studies, and confirmatory studies that may warrant a change to a drug’s indication, would also have the benefit of removing doubt about the tools available to FDA with respect to the unique concerns of accelerated approval drugs. It would be clear, for example, that FDA can require additional postmarketing studies to further verify and describe benefit,¹⁵⁸ or modify or narrow the indication of an approved drug.¹⁵⁹ FDA would be able obtain additional information and direct the labeling updates that could be necessary once confirmatory studies are conducted. With a range of options broader than just “conversion or withdrawal,” applicants may be incentivized to engage in more rigorous postmarketing studies.

Improving Expedited Withdrawal

Expedited withdrawal procedures should be modernized to facilitate the withdrawal of accelerated approval drugs for which confirmatory studies are negative or for those that are not completed with due diligence.

Accelerated approval was always intended to come with a streamlined way for FDA to withdraw approval if the clinical benefit of the relevant surrogate or intermediate clinical endpoint were not confirmed. When the accelerated approval regulations were first proposed, FDA recognized that “the ability to withdraw approval expeditiously for such drugs is critical. If the agency is not able to withdraw approval rapidly in the event it loses the assurances regarding demonstration of actual clinical benefit... the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the act.”¹⁶⁰ Indeed, Congress contemplated that FDA would issue additional regulations when it codified the accelerated approval pathway: section 506(c)(3) of the FD&C Act provides that the Secretary may expedite the withdrawal of a drug approved under accelerated approval “*as prescribed by the Secretary in regulations* which shall include an opportunity for an informal hearing.”¹⁶¹

157 21 U.S.C. § 355(o)(2); id. § 355-1(b)(3) & (5); Safety Labeling Changes Guidance, *supra* note 154, at 4. “New safety information” currently encompasses information or data derived from clinical trials; adverse event reports; postapproval studies; peer-reviewed biomedical literature; the postmarket risk identification and analysis system under section 505(k); existing information concerning a drug with a REMS requirement; or a REMS assessment. See Safety Labeling Changes Guidance, *supra* note 154, at 3–4.

158 21 U.S.C. § 355(o)(3).

159 *Id.* § 355(o)(4).

160 See 57 Fed. Reg. 13234, 13239 (proposed Apr. 15, 1992).

161 21 U.S.C. § 356(c)(3) (emphasis added).

It is clear that the expedited withdrawal mechanism contemplated in section 506(c) of the FD&C Act is not functioning in the intended, expedited way. Yet FDA has not—and has declined to—clarify the conditions under which it would utilize its expedited withdrawal authority.¹⁶² Consequently, sponsors may continue operating in a gray area and prolong postmarketing confirmatory studies under the belief that FDA will not undertake withdrawal proceedings. Updated expedited withdrawal procedures would provide stakeholders with clear guidance on the bases and processes by which FDA would remove an accelerated approval drug from the market. If those withdrawal processes were truly expedited, it would reduce the resources necessary to contemplate such withdrawal proceedings, make FDA more willing to undertake withdrawal proceedings when justified, and counteract the impression that FDA is unwilling to expend the necessary resources to undertake such proceedings in the face of sponsors who are not honoring their postmarketing confirmatory study requirement.

Increased Funding and Resources for FDA

Expedited withdrawal proceedings and other postmarket actions have long been decried by FDA as overly burdensome, which likely accounts for some of the Agency's reticence in invoking its existing authorities. Many of the ideas proposed herein would require additional, targeted resources at FDA. An increase in federal funding and resources through budgeting and appropriations could provide FDA with the resources necessary to implement some of the reforms contemplated and to exercise its existing authorities when appropriate.

CONCLUSION

The accelerated approval program continues to realize FDA's original vision of expediting the introduction of new drugs intended to treat serious and life-threatening conditions for which there are no meaningful alternatives. Despite its remarkable impact on the health outcomes of patients suffering from rare diseases, FDA needs updated and more effective enforcement tools and resources to ensure that the accelerated approval pathway is operating as intended, including ensuring that drug sponsors comply with postmarketing confirmatory study requirements. Accelerated approval problems require accelerated approval solutions. Our proposed solutions, individually and collectively, would reinforce the areas where accelerated approval has been successful, enhance the areas where accelerated approval could be made more efficient and transparent, and continue to incentivize innovation of new drugs to treat rare diseases.

¹⁶² See GAO New Drug Approval Report, *supra* note 17, at Appx. V, 5–6.

MISSION STATEMENT

NORD, a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 330 patient organization members, is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services.

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