



**STRENGTHENING THE ACCELERATED APPROVAL PATHWAY:  
AN ANALYSIS OF POTENTIAL POLICY REFORMS AND THEIR IMPACT  
ON UNCERTAINTY, ACCESS, INNOVATION, AND COSTS**

April 26, 2021

**Anna Kaltenboeck, MA, MBA**

Program Director and Senior Health Economist, Center for Health Policy and Outcomes  
Memorial Sloan Kettering Cancer Center

**Amanda Mehlman**

Director of Strategic Partnerships  
Institute for Clinical and Economic Review

**Steven D. Pearson, MD, MSc**

President  
Institute for Clinical and Economic Review

## Table of Contents

Introduction .....	4
The Challenge.....	4
Structure of This Paper .....	6
Methods.....	7
Background .....	8
The Accelerated Approval Pathway.....	8
What is Accelerated Approval?.....	8
Why was Accelerated Approval Introduced? .....	9
How Has the Accelerated Approval Pathway Performed Over Time? .....	9
Surrogate Endpoints .....	12
What Are Surrogate Endpoints? .....	12
Which Types of Surrogate Endpoints Are Used for Accelerated Approval?.....	12
How Does the FDA Determine Whether a Candidate Surrogate Endpoint Meets Criteria to be a “Reasonably Likely” Surrogate Endpoint? .....	15
Challenges with Accelerated Approval .....	16
Managing Uncertainty .....	16
Selecting Surrogate Endpoints for Accelerated Approval.....	16
Threshold for Meaningful Change in Surrogate Endpoints .....	17
Uncertainty and the Lack of Randomization .....	17
Delayed and Inadequate Confirmatory Studies.....	18
Inconsistent Regulatory Decisions .....	20
High Costs.....	21
Potential Policy Reforms.....	23
Policies that could be achieved through FDA action .....	24
1. Strengthen the Selection of Surrogate Endpoints .....	24
2. Develop Standardized Accelerated Approval Review Templates.....	25
3. Require Greater Use of Randomized Controlled Trials.....	26
4. Create a New Label Alert and Patient Material for Accelerated Approval Drugs .....	27

5. Increase Enforcement of Requirements to Complete Confirmatory Trials .....	28
6. Create an Annual Renewal Cycle or Sunset Accelerated Approvals Lacking Confirmatory Evidence .....	28
7. Create a Separate “Safety-only” Approval Pathway That Waives Public or Private Insurance Coverage Requirements.....	29
Policies that would require payer and life science industry actions .....	30
8. Increase Mandatory Federal Rebate Levels Until Time of Full Approval.....	30
9. Use Pricing at Marginal Cost to Incentivize Completion of Confirmatory Trials, with Consideration of a Federal Carve-Out .....	31
10. Require Payment Be Based on Outcomes-based Contracts .....	33
Conclusion.....	34
References .....	36
Appendix A: 2021 ICER Policy Summit Attendees .....	41

# Introduction

---

## The Challenge

In 2001, after fewer than three months of review, the Food and Drug Administration (FDA) marked an important moment in the treatment of cancer.<sup>1</sup> That year the FDA granted accelerated approval to imatinib mesylate (Gleevec) for the treatment of patients with chronic myelogenous leukemia who were in blast crisis or had progressed to an advanced stage of disease that was no longer addressable by interferon. The approval was by no means routine at the time. The three trials serving as the basis for the decision were all single-arm studies that evaluated cytogenetic and hematologic response rates – measures that stood in for more traditional primary endpoints, such as overall survival (OS).<sup>2</sup> Offering access so early in a drug’s development was a gamble. Patients and the healthcare system would bear the costs and consequences if the drug didn’t work or proved to have unacceptable side effects. But the possible upside was also enormous. The prognosis at these stages of disease was dire, and patients would otherwise be forced to wait months or years for additional evidence on imatinib to accrue. By 2003, it was clear that the gamble had paid off. The FDA granted full approval on follow-up studies that showed a 90.8% survival rate after two years of treatment.<sup>1</sup> The victory was more than scientific - patients who had received imatinib before its full approval benefitted from the early availability of a treatment that quickly became the standard of care.

But if the success of imatinib stands as one bookend of the experience with the accelerated approval pathway (AAP), the other end might find its exemplar in eteplirsen (Exondys 51). The FDA granted authorization to Sarepta Therapeutics in 2016 to market this treatment as the first for Duchenne Muscular Dystrophy (DMD). The excitement in the patient community was palpable, but the approval came despite sharp and unusually public internal disagreement within the FDA over whether the drug had met the bar for demonstrating reasonable likelihood of clinical benefit. Following its approval, some private payers deemed the evidence inadequate for coverage and balked at paying for eteplirsen, although coverage denials were routinely overturned on appeal. The annual cost of the drug in real-world practice rose to over \$1 million per patient, and the drug quickly became a source of blockbuster revenue for Sarepta.<sup>3</sup> To many, the capstone of this saga has been the drug maker’s failure to follow through on its post-marketing evidence requirement. As part of the accelerated approval of eteplirsen, the FDA required Sarepta to conduct studies to characterize the treatment’s effects by 2018 and to confirm benefits of treatment by 2021.<sup>4</sup> The company launched no studies until late in 2019 and, at the time of this paper, more than four years after eteplirsen’s accelerated approval, no additional evidence of the drug’s efficacy or safety has been made publicly available.<sup>5</sup> The FDA, for its part, has taken no action against Sarepta and, in fact, granted accelerate approvals to its second and third DMD drugs in 2019 and 2021, respectively.<sup>6,7</sup>

Although imatinib showcases the benefits of accelerated approval, and although the APP overall is viewed quite favorably by many stakeholders, eteplirsen serves for others as a cautionary tale. It raises concerns that the direction the AAP has taken recently, if extended into the future, would not support a responsible balance between uncertainty and early access.

How is the AAP structured to find that balance? First, to provide earlier access, it relies on surrogate endpoints. The fundamental assumption of the AAP is that properly selected surrogate endpoints can predict improvement in health outcomes that are clinically relevant and matter to patients. The advantage of surrogate endpoints is that they can be measured over a shorter timeframe in less expensive or smaller studies. The AAP was created to leverage surrogate endpoints while addressing the residual uncertainty about ultimate clinical effects of treatments through confirmatory studies required of the study sponsor after approval. In principle, this approach allows promising new treatments to be approved in a shorter timeline. It also creates an economic incentive for drug makers: companies can commercialize drugs more rapidly, generating sales revenue in parallel with confirmatory trials, rather than waiting for their completion to enter the market. Because faster decisions on less evidence also imply greater uncertainty about safety, the AAP is reserved for conditions with significant medical needs that remain unmet by existing treatment options.

But, as the experience with eteplirsen and other drugs suggests, the mechanism's benefits come with important tradeoffs. One is that the reliance on surrogate endpoints seems to have become more common, even as guidance about the magnitude of change needed to plausibly suggest long-term patient benefit remains largely absent. In addition, the relative uncertainty created by reliance on surrogate endpoints is compounded by the growing use of single-arm studies for regulatory approval, studies whose findings are inherently vulnerable to well-known risks of confounding. Many stakeholders, including patient groups, clinicians, and payers, view these trends combining to produce an erosion in the standards of evidence required for accelerated approval.<sup>8-11</sup> In their judgment, the evidence available at launch seems ever less able to define the appropriate clinical use of new drugs, thereby heightening the risk that patients will receive ineffective or even harmful treatments, and complicating efforts to design prudent insurance coverage criteria.

After the issue of standards of evidence, the eteplirsen decision highlights a second area of concern - that the confirmatory evidence required for conversion of AAP to full approval is often slow to materialize. In some instances, study sponsors fail to conduct or publish required studies at all.<sup>12,13</sup>

And third, magnifying the impact of both these other areas of concern, is the issue of the high prices of drugs launched through the AAP. Drugs coming to market with accelerated approval often arrive with very high price tags, with no apparent discount for the uncertainty surrounding their effectiveness. The general trend towards higher prices for specialty, oncology, and orphan drugs prevails among drugs approved through the AAP. This combination of high prices and uncertainty motivates payers to manage access through eligibility criteria based on the available evidence, only

to be frustrated by the lack of clinical evidence to inform reasonable, evidence-based utilization management policies. Ironically, the resulting access restrictions conflict with the underlying premise of the AAP – to enable earlier access.

These concerns aside, the AAP continues to derive conceptual justification from its underlying goal of providing a more rapid approval pathway for promising treatments when patients lack other options, routine approval requirements would demand additional years of research, and surrogate endpoints appear reasonably likely to predict the desired clinical outcome of treatment. The case for the AAP has also been fortified as drug development science has evolved, and more biomolecular and genetic targets have become available as candidate surrogate endpoints that could be used to speed access to promising treatments.<sup>14</sup>

When viewed broadly across all of the drugs approved through the AAP since its inception, the FDA has stated that it largely considers the pathway to be a success, particularly in oncology, where it points to the relatively small number of approvals that have failed to confirm clinical benefits as a sign of its positive impact.<sup>15</sup> The agency's sense of success is shared by many members of the patient community, who tout the program's ability to deliver access to groundbreaking treatments more rapidly.<sup>16,17</sup> For example, one assessment of oncology treatments concluded that therapies receiving accelerated approval were made available a median of 3.4 years earlier than would be achievable if confirmation of clinical benefit based upon a primary endpoint, such as overall survival, was required.<sup>15</sup>

But other patient groups have expressed concern that the AAP is not serving patients well by allowing drugs with known toxicities but unclear benefits to be introduced.<sup>11</sup> They also worry that the mechanism for ensuring that confirmatory trials are conducted is broken. As the AAP nears the beginning of its fourth decade, the time is ripe to examine whether the balance being struck between uncertainty and access can be improved; whether the cost of drugs approved through the AAP should have some linkage to the state of the evidence base; and whether the incentives or regulatory structures that support the generation of confirmatory evidence need reform.

This paper aims to create a clearer understanding of both the opportunities and the challenges inherent to the AAP. We also present an analysis of potential reform options and their possible consequences as policymakers re-examine how best to strengthen the pathway within the broader landscape of an innovative US health care system.

## **Structure of This Paper**

Evaluating these issues requires a firm understanding of the AAP, including its history and qualifications for use, and the scientific and statistical considerations surrounding surrogate endpoints. This information is presented in the Background section.

We then proceed to examine in greater detail the three major areas of concern: uncertainty arising from the use of surrogate endpoints, the incentive structure for confirmatory trials, and the high costs of drugs granted accelerated approval. Of note, concerns have also been raised by patient advocates, clinical specialty societies, and other stakeholders regarding restrictions on coverage to new drugs approved under the AAP. This is an important issue and merits full consideration. We have addressed in a previous White Paper the ethical goals and design criteria for appropriate cost-sharing and utilization management for drug coverage,<sup>18</sup> and we believe those principles and specific criteria apply to drugs approved under the AAP. We also note that many payers and health plan sponsors believe that the root cause of tighter access restrictions for drugs in recent years is the combination of factors cited above, and that the imbalances and failures of the AAP create market forces that lead to ever greater pressure to restrict access. Whether the AAP has independently contributed to increased access restrictions cannot be determined. However, we will examine policy reforms in the final section of this paper from the perspective that draconian access restrictions should not be the way that the health system seeks to find the balance between uncertainty, cost, and the incentives needed for future innovation.

## Methods

Information to inform this paper was gathered in two ways: a targeted literature review, and interviews with Policy Leadership Forum participants.

The targeted literature review included keyword and hand searches for peer-reviewed and grey literature articles focusing on the US experience with accelerated approval and surrogate endpoints. Additional information was gathered from FDA guidance documents and other materials published by the FDA and NIH in support of the AAP and specific accelerated approvals.

A structured discussion guide was developed using information obtained through this review to gather responses from nine respondents in 30-minute interviews about their views on the advantages and disadvantages of the AAP, as well as the uncertainties that arise from its use.

From this, an inventory of key areas of concern was created, and the ICER research team developed a set of proposed solutions based on the literature review and early stakeholder conversations. The proposed solutions were then presented to four Policy Leadership Forum members to elicit their views about the relative advantages, disadvantages and policy barriers related to these proposed changes to the AAP and its use.

Participants from 29 payer and life science companies met virtually in March 2021 to debate the proposed solutions and provide suggestions for revisions to a draft version of this paper. The participants in this meeting are shown in Appendix A. None of these participants or their organizations should be considered as having approved of any element of this paper.

# Background

---

This section offers further context necessary to understand the AAP, including its history and place among other FDA programs and designations. It also provides an overview of the scientific, statistical, and regulatory considerations that guide the development of surrogate endpoints.

## The Accelerated Approval Pathway

### What is Accelerated Approval?

Accelerated approval is an FDA review pathway meant to expedite marketing authorizations of treatments that would otherwise face prohibitive logistical, feasibility, or cost challenges in demonstrating efficacy and safety. The distinguishing feature of accelerated approval is its reliance on surrogate endpoints, intermediate measures that are considered “reasonably likely” to predict clinical outcomes. Drugs with accelerated approval are subject to postmarketing requirements to confirm their efficacy and safety, as well as other characteristics that present significant uncertainty. Although not formally a feature of the pathway, many of the drugs reviewed in this way also qualify for designations that reduce the review period and increase interactions and meetings with the FDA.<sup>19</sup>

Because surrogate endpoints increase uncertainty about a drug’s effectiveness and safety, the FDA stipulates that accelerated approval is reserved for treatments that:

1. Are for a serious condition, one *“associated with morbidity that has substantial impact on day-to-day functioning.”*
2. Offer a *“meaningful advantage over available therapy”\**, which includes, among other things: there being no other treatment, or there being other treatments but a large remaining portion of patients who have inadequate response to them.
3. Demonstrate *“an effect on an endpoint that is reasonably likely to predict clinical benefit”*<sup>19</sup>

Whether to proceed with AAP is at the discretion and mutual agreement of the study sponsor and the FDA. Sponsors considering the pathway can request to meet with the FDA early in the development process to determine whether the qualifying conditions are met. The FDA can then determine what evidence it requires to grant accelerated approval, and offer this guidance to the sponsor.

---

\* This standard predates the FDA Safety and Innovation Act (FDASIA), which codified the pathway into law in 2012, and did not include a requirement that AAP be reserved for drugs that provide advantages over existing treatments. However, the FDA has continued to promulgate this element of the standard in its guidance.



Upon receiving the results of the pre-approval trials from the study sponsor, the FDA then determines whether to grant accelerated approval or require additional study. This decision is based on a risk-benefit analysis that weighs the potential clinical improvements against the consequences of uncertainty to patients, including potential off-target effects of the drug. If the drug gains accelerated approval, the sponsor is obligated to complete a post-approval confirmatory trial (also known as a phase IV trial), which should already be underway at the time of the approval. When data from a confirmatory trial become available, if the FDA decides that a positive risk-benefit ratio for patients has been confirmed, the FDA can grant full approval. If the evidence is not deemed satisfactory to confirm safety and effectiveness, the FDA can withdraw approval.

## **Why was Accelerated Approval Introduced?**

The AAP was introduced in 1992 as a more flexible alternative to the existing regular FDA review pathway at that time. The requirements for regular review had been established by the 1962 Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act (FD&C).<sup>20</sup> With this law the standard FDA pathway for approval became a phased sequence of clinical trials to determine optimal dosing and then to demonstrate safety and efficacy.

That standard was challenged by patient advocates and other stakeholders in the 1980's, when rising deaths from the HIV/AIDS epidemic outpaced the development and approval of treatments. To many observers the FDA standards were too rigid, producing development timelines inadequate to the challenge of a fast-moving deadly epidemic.<sup>21</sup> These concerns and protests prompted a number of regulatory and legislative changes, and in 1992, as part of this shift in policy, the FDA used its regulatory authority to establish the AAP.

It would be 20 years, however, before the program received further elaboration in statute. In 2012, Congress passed the FDA Safety and Innovation Act (FDASIA), which reinforced the role of the AAP while adding language requiring that surrogate endpoints be “reasonably likely” to predict the desired clinical benefit of treatment.<sup>22</sup> This statute also added the requirement that study sponsors complete confirmatory clinical trials to verify that the drug has the expected effect on the clinical outcome of interest.<sup>19</sup> Under this law the FDA is given the power to withdraw approval of drugs that fail to demonstrate adequate safety and effectiveness through confirmatory trials, but there is no mandatory action required by the FDA to confirm the completion of confirmatory trials or to rescind approval for drugs when confirmatory trials fail to support the safety or effectiveness of the drug.

## **How Has the Accelerated Approval Pathway Performed Over Time?**

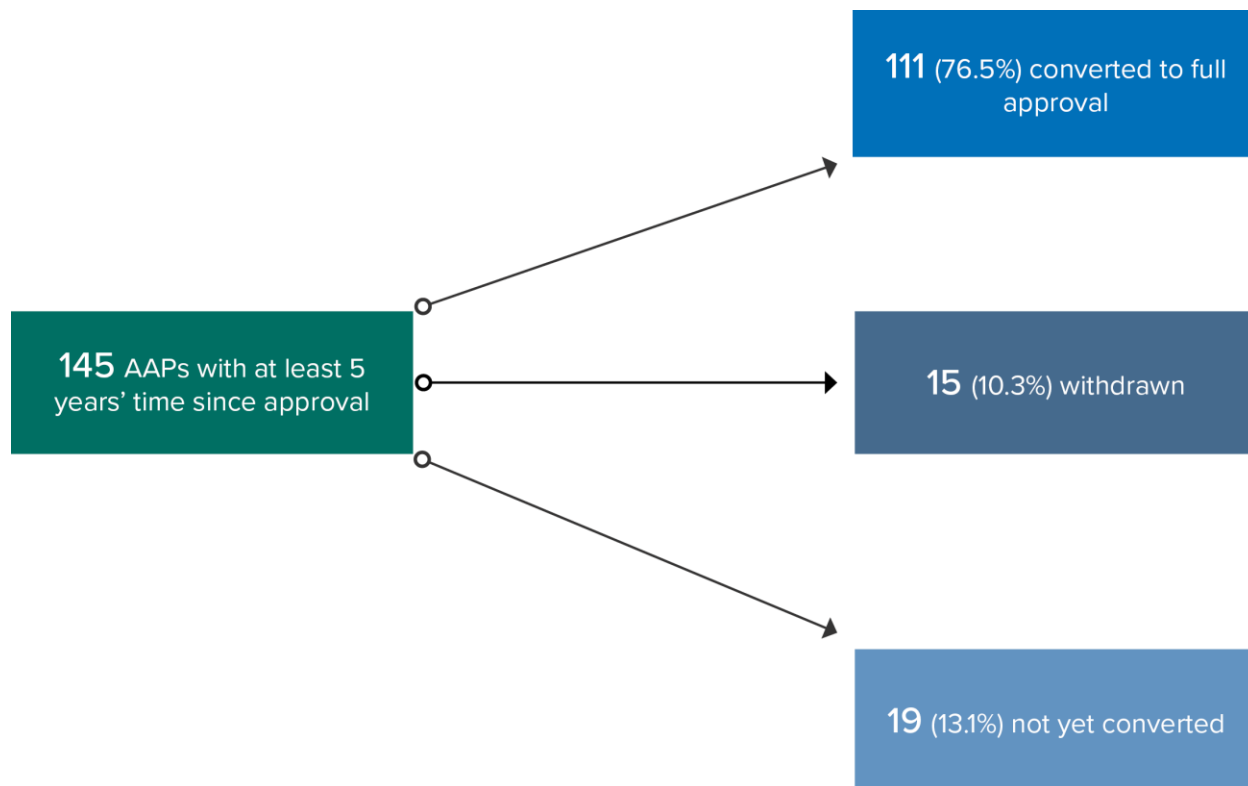
Incorporating elements of the additional language introduced in 2012, the goal of the AAP can be stated as providing faster access to treatments that offer meaningful advantages to patients with serious conditions.

Is it achieving that goal? The FDA largely considers the AAP to be a success, a view shared by many members of the patient community.<sup>15,16,17</sup> One important element in this judgment is the rate of positive conversion to full approval of drugs initially approved through the AAP. Since the introduction of the original accelerated pathway nearly three decades ago, the FDA has granted more than 253 accelerated approvals.<sup>13</sup> Of these, 106 (41.9%) were for orphan indications and 164 (64.8%) for oncology indications. There was also meaningful overlap – 80 (31.6%) of approvals were for oncology indications with orphan status.

In total, 125 (49.4%) of all drugs receiving accelerated approvals have gone on to receive full approval, with a median time to full approval of 3.2 years. Sponsors have withdrawn 16 (6.3%). The remaining 112 (44.3%) drugs have been on the market a median of 1.9 years.

Different conclusions can be drawn from this set of data when using the conversion rate to full approval as a measure of “success.” First, it may be helpful to consider only those drugs for which approximately five years has elapsed since approval, a generous time span during which confirmatory trials could be expected to have been completed. When looking only at the 145 AAP approvals that predate 2016, 111 (76.5%) have converted to full approval, and 15 (10.3%) have been withdrawn (see Figure 1 below). The remaining 19 (13.1%) drugs have been on the market a median of 9.5 years without having evidence allowing them to move to full approval.

**Figure 1. Resolution of accelerated approvals, 1992-2016**



Many argue that a view of the success of the AAP is reinforced by the relatively small number of drugs that have been withdrawn following confirmatory trials. Some rate of failure of drugs receiving accelerated approval should be expected, and thus many stakeholders believe that the balance of the number of drugs moving to full approval versus those withdrawn provides further evidence that the AAP is working as intended. Prominent examples of drugs that have had unfavorable confirmatory trials include bevacizumab for the treatment of breast cancer, gefitinib for patients with non-small cell lung cancer, and olaratumab for patients with soft tissue sarcoma.<sup>23</sup>

However, others find reason for concern in the same approval conversion data. Some raise concerns that the FDA's standard for moving from accelerated to full approval is too generous. The National Breast Cancer Coalition, for example, argues that the agency fails to require convincing evidence of patient benefit in its decisions to grant full approval.<sup>11</sup> Confirmatory trials have often been slow to materialize, and even when results emerge, they are viewed by many as frustratingly ambiguous due to the lack of blinding and randomization. In a landscape analysis surveying 25 years of experience with cancer drugs in the AAP, FDA authors described reviews resulting in 93 accelerated approvals for cancer treatments between 1992-2017. Of these, only 55% had completed confirmatory trials with results that were deemed to verify the benefits on which approval had initially been granted.<sup>15</sup>

Similar findings have emerged from other evaluations of progress from accelerated to full approval, particularly for oncology drugs approved on the basis of progression free survival without evidence of improvement in overall survival. A 2019 Wall Street Journal investigation of confirmatory trial completion showed that among cancer drugs that had received approval between 2015 and 2018 through the AAP, 88% had yet to offer evidence of improvement in overall survival at the time of the article. For those approved even earlier, between 2011-2014, the number without confirmatory evidence of an effect on mortality was still 44%.<sup>24</sup> And yet many of these drugs did receive full approval from the FDA, often solely on the basis of confirmation of PFS benefit or on the basis of PFS benefit demonstrated in an expanded indication.<sup>25</sup>

The FDA has also been criticized for allowing drugs approved through the AAP to remain on the market despite later results from confirmatory trials showing no effect on the primary clinical outcome. For example, the FDA allowed bevacizumab to retain its indication for the treatment of metastatic glioblastoma despite confirmatory evidence showing considerable side effects and no effect on overall survival.<sup>26</sup>

Ultimately, evaluation of the data on the conversion of accelerated approvals to full approvals over the history of the AAP cannot produce a consensus on whether it is working well for patients and the health system. It is not unexpected that different stakeholders, and different individuals among stakeholders, would find different lessons on whether the AAP should be changed to better address the tensions between early access, uncertainty about risks and benefits to patients, costs, and impact on innovation.

## Surrogate Endpoints

From its birth, accelerated approval has relied upon the basic assumption that promising drugs offering important potential benefits to patients can be evaluated on the basis of changes in surrogate endpoints that are “reasonably” likely to predict clinical outcomes that matter to patients. A deeper understanding of the background on how these endpoints are identified and agreed for use with the AAP is therefore important in weighing potential policy reforms to the pathway.

### What Are Surrogate Endpoints?

Traditionally, clinical trials of medical products assess the clinical outcomes experienced by patients. The measures designed to capture this information are referred to as **endpoints**. Clinical endpoints are considered the standard for assessing efficacy of treatment because they allow direct observation of how “*an individual feels, functions, or survives*”.<sup>27</sup> However, clinical trials can be designed around a substitute measure that is considered predictive of clinical outcomes resulting from treatment, known as a **surrogate endpoint**.<sup>28</sup> The aim of using a surrogate endpoint in lieu of a clinical endpoint is to retain adequate ability to detect relative benefits of treatment without the length of time and expense of a trial based on clinical endpoints that usually take far longer to occur. In addition, trials using surrogate endpoints can be helpful in avoiding the analytic problems that arise when patients who are assigned to the placebo arm in a randomized trial have progression in their illness and “cross over” to the active treatment.<sup>29</sup> Shorter trials using surrogate endpoints that are well-designed can produce data less confounded by these events, making it easier to estimate the relative benefits of the investigational agent.

### Which Types of Surrogate Endpoints Are Used for Accelerated Approval?

The FDA accepts surrogate endpoints for clinical studies of pharmaceutical products in several instances. Approval decisions through the traditional review pathway can be based on a **validated surrogate endpoint**, if one is available. The FDA can deem a surrogate endpoint to be validated if it is “*supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit*”.<sup>30</sup> Examples of validated surrogate endpoints include reductions in HbA1c to predict improvements in long-term complications of Type 2 Diabetes Mellitus, and virologic suppression of HIV as a proxy for preventing progression to AIDS. According to the FDA, over 75% of product approvals that are based on a surrogate endpoint have come through the traditional pathway using a validated surrogate endpoint.<sup>31</sup>

However, the AAP does not use validated surrogate endpoints. It was designed to consider surrogate endpoints that meet a lower standard of being “reasonably likely to predict clinical benefit.” The FDA describes a reasonably likely surrogate endpoint as one with a “strong

mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, *but without sufficient clinical data to show that it is a validated surrogate endpoint.*<sup>32</sup> This is the only difference between a surrogate endpoint that is considered validated and one that is not validated but can be used for accelerated approval.

To give more substance to these terms and support a shared understanding across different governmental agencies, the FDA and NIH formed the Biomarker Working Group. This effort produced the BEST (Biomarkers, EndpointS, and other Tools) Resource with a glossary of terms that has effectively become the standard for distinguishing between different concepts and endpoint types used in federal databases and in regulatory policy in the US.<sup>27</sup> These definitions are shown in Table 1 on the following page.

**Table 1. FDA-NIH BEST Taxonomy of Endpoints and Related Concepts**

Term	FDA Definition (Verbatim) <sup>27</sup>	FDA Examples
<b>Biomarker</b>	<i>A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives.</i>	Kidney injury molecule <sup>33</sup>
<b>Surrogate Endpoint</b>	<i>An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.</i>	
<b>Validated Surrogate Endpoint</b>	<i>An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit. A validated surrogate endpoint can be used to support marketing approval of a medical or tobacco product in a defined context without the need for additional studies to demonstrate the clinical benefit directly. Although the term has been used in a conceptually broader way, from a U.S. regulatory standpoint, a validated surrogate endpoint almost always refers to a biomarker.</i>	HbA1c reduction as a proxy for long-term reduction in complications of T2DM  Reduction in number of HIV-RNA copies as a proxy for disease control in HIV <sup>30</sup>
<b>Reasonably Likely Surrogate Endpoint</b>	<i>An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints may be used for accelerated approval for drugs and potentially also for approval or clearance of medical devices. In the case of accelerated approval for drugs, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.</i>	Radiographic confirmation of tumor response as a proxy for improved overall survival in cancer  6-month sputum culture as a proxy for resolved pulmonary tuberculosis <sup>32</sup>

## How Does the FDA Determine Whether a Candidate Surrogate Endpoint Meets Criteria to be a “Reasonably Likely” Surrogate Endpoint?

By the AAP’s design, a surrogate endpoint that is not validated due to lack of “sufficient clinical data” can still be eligible for use in accelerated approval as long as it is “supported by [a] strong mechanistic and/or epidemiologic rationale.” To determine whether a candidate surrogate endpoint meets this threshold for use as a reasonably likely surrogate within the AAP, the FDA applies five distinct evidence criteria to evaluate the biological relationship of the candidate endpoint to the disease and the degree to which it may be suitable for measuring disease levels and changes (See Table 2). The FDA language specifies that reasonably likely surrogate endpoints must show correlation with disease severity, as well as provide prognostic value for disease progression and disease severity. But it is unclear whether these criteria are applied consistently in practice across therapeutic areas, as no compendium exists of decisions with explanation of FDA’s interpretation of the criteria over time and across different treatment areas.

**Table 2. Key Criteria for Assessing Candidate Surrogate Endpoints<sup>34</sup>**

<b>Criterion</b>	<b>Key Considerations</b>
<b>Causality</b>	Is there evidence that the surrogate is on the single direct causal pathway to a disease outcome? (greater evidence implies less need for evidence of universality)
<b>Biological Plausibility</b>	Is the biology so compelling that it adds to the weight of the empirical evidence to support its use?
<b>Specificity</b>	Is there reason to believe it may be confounded, or does it appear robust to other factors affecting disease outcome and off-target effects? Are there potential complicating effects?
<b>Proportionality</b>	How well does the magnitude or change in magnitude of a candidate surrogate endpoint explain the disease or change in disease burden or clinical outcome?
<b>Universality</b>	Is there evidence supporting use of the candidate surrogate endpoint across different patient groups or drug mechanisms of action?

# Challenges with Accelerated Approval

---

## Managing Uncertainty

### Selecting Surrogate Endpoints for Accelerated Approval

Central to concerns about the AAP is the level of uncertainty associated with studies using surrogate endpoints, and what threshold of certainty about safety and effectiveness should be satisfied before accelerated approval is granted. Though all clinical studies remain vulnerable to questions about their internal and external validity, major uncertainty frequently characterizes the evidence produced by studies using “reasonably likely” surrogate endpoints – endpoints for which there is insufficient clinical evidence to demonstrate that the surrogate accurately predicts clinical outcomes. One aspect of this uncertainty pertains to whether there is, in fact, any relationship between the selected surrogate endpoint and the intended clinical outcome.

Although, as noted above, the FDA has specific criteria by which to judge when a surrogate endpoint can be considered “reasonably likely” to serve as a suitable endpoint for an AAP, experience is mixed in demonstrating that surrogate endpoints accurately estimate the relative effects of treatment on the ultimate clinical outcomes of interest.<sup>35</sup> A meta-analysis examining the relationship between surrogate endpoints and overall survival (OS) in RCTs of cancer treatments found that more than half of the tested correlations between surrogate endpoints and OS were weak; 25% and 23% were moderately and highly correlated, respectively.<sup>36</sup> Meanwhile, publication bias, incomplete reporting, and poor study design continue to produce a glut of peer-reviewed journal articles on biomarkers and candidate surrogate endpoints with irreproducible results.<sup>37</sup>

Drawing the wrong conclusions from poorly understood or selected surrogate endpoints can have serious consequences for patients. The adoption of ventricular arrhythmia (VA) as a surrogate endpoint for mortality in patients with a prior heart attack offers an example. Studies conducted in the 1980’s showed that patients who experienced VA after having a heart attack were at greater risk of death.<sup>38</sup> Expecting that treatment of VA would reduce mortality, the FDA approved three drugs for this purpose based on studies that measured suppression of VAs as a surrogate endpoint. Fortunately, a randomized controlled trial (RCT) was conducted to quantify the effect of treatment on mortality. When the results were published, the medical community was stunned: patients treated with drugs that successfully suppressed VA were nearly three times more likely to die than those treated with placebo.<sup>39</sup> Estimates attribute more than 50,000 excess deaths to the widespread use of these drugs following FDA approval before the clinical outcome study results were available.<sup>40</sup>



## Threshold for Meaningful Change in Surrogate Endpoints

Within the FDA’s rubric for evaluating potential surrogate endpoints for the AAP, even if a measure has a strong case built on knowledge of the condition’s cause and the corresponding biological plausibility of the surrogate endpoint, it can be more difficult to establish the minimum change in the surrogate to be considered “reasonably likely” to translate into a meaningful clinical improvement. This is the criterion of “proportionality” in the FDA rubric, and even though it is of great importance, there is no accompanying language in FDA documents to help define the process for establishing the threshold for meaningful change. The closest available language available comes from the FDA guidance on biomarker qualification, but this language is vague:

*“There are no set quantitative criteria for determining whether the relationship between the biomarker and the clinical outcome is sufficiently strong to support biomarker qualification. Criteria based on parameters used to quantify the relationship (e.g., clinical performance change as a function of biomarker quantity) can provide confidence that a finding is likely to be relevant, reliable, and statistically robust.”*<sup>41</sup>

In practice, it is likely that expectations for a threshold for change in the surrogate endpoint do play a role in the accelerated approval process, but transparency and consistency in how they are determined and applied is utterly lacking. For example, documents made available by the FDA from its eteplirsen review suggest that reviewers considered a 10% increase in dystrophin levels to be a meaningful increase. When the trials showed a median increase of only 0.1% in truncated dystrophin levels over 48 weeks of treatment, the failure to achieve a change anywhere near the previously discussed threshold was at the heart of the intense internal disagreement with the ultimate decision to grant accelerated approval.<sup>42</sup> Other approvals are known in which the change in surrogate endpoint appeared far lower than likely to produce meaningful clinical improvement. In one recent example, pembrolizumab received accelerated approval for the treatment of advanced cervical cancer on showing an objective response rate (ORR) of 14.3% in 77 patients.<sup>43</sup> The median response rate for 85 regular or accelerated approvals between 2006 and 2018 was 41%, but 16% of the approvals were on the basis of a response rate below 20%.<sup>44</sup> The FDA has no consistent framework for determining an a priori threshold for meaningful change nor in communicating the rationale for outcomes that fall below these thresholds. In many of these cases, unless these surrogate endpoints do not fully reflect the benefits of treatment, the promise of a significant clinical improvement for most patients appears to be relatively low.

## Uncertainty and the Lack of Randomization

Uncertainty also increases when pre-approval studies are inadequately controlled, enrolled, or blinded. A review of studies supporting 24 accelerated approvals granted between 2009-2013 found that only 40% were based on randomized trials, with only half of those able to be double-blind.<sup>25</sup> A more recent study suggests that over time, the FDA has granted approvals on the basis of

clinical trials that are on average longer, but fewer in number and with greater likelihood of a single arm.<sup>45</sup>

Requiring randomization and blinding might be seen as creating the need for larger, longer studies, acting in opposition to the overall goal of accelerated approval to achieve more rapid access for patients. But abandoning randomized trial designs invariably adds to the uncertainty surrounding treatment effects. Single-arm studies are extremely vulnerable to selection bias, among other biases. Historical controls or simultaneous “synthetic” controls can be useful in certain circumstances, but the absence of a randomized comparator arm still limits the ability to measure changes attributable to the course of disease, the treatment effect, and the placebo effect. This is a problem not only for identifying the driver of an observed effect; it also limits insight in instances when no change is observed.<sup>46</sup>

Proposals have been made to use real world observational data (RWOD) and real world clinical trials (RWCT) to support regulatory approval,<sup>17</sup> and the FDA is exploring how to use such data as a supplement or possibly as a replacement for traditional clinical trials.<sup>47</sup> However, recent studies attempting to replicate clinical trial results with RWOD have met with mixed results.<sup>48</sup> Given current understanding of the strengths and limitations of RWOD, it is difficult to argue that these data would be adequate for regulatory decision making in smaller patient populations with greater uncertainty surrounding the studied endpoints.

## **Delayed and Inadequate Confirmatory Studies**

Pre-approval uncertainty often remains unaddressed well after drugs with accelerated approval have entered the market, despite requirements that confirmatory evidence be produced for full approval. Post-marketing studies to generate this evidence are required of manufacturers by the FDA, which outlines the needed studies in the approval letter.

As noted earlier, in practice, performance and reporting on these postmarketing requirements often falls short. Executing on postmarketing requirements can be difficult for a number of reasons. One is that products with accelerated approval cease being purely investigational agents, and become part of the therapeutic landscape.<sup>49</sup> This can complicate enrollment into further clinical trials, whether because of concerns about the ethics of placebo-controlled trials following FDA approval, or because it is difficult to interest patients and clinicians in randomized trials when patients can obtain whichever treatment they prefer without the constraints of being enrolled in a study. The entry of further new treatments can also complicate matters. Confirmatory trials become difficult to complete and interpret if the role in therapy of the treatment of interest is shifting.<sup>50</sup> Despite these challenges, the FDA appears to have no formal process for exploring these issues with study sponsors following accelerated approval.

Misaligned financial incentives for study sponsors only further complicates the issue. Absent credible threats of withdrawing approval for failing to comply with postmarketing requirements, there may be little upside for study sponsors to spend the resources to seek rapid completion of confirmatory trials. Only when the drug is competing directly with other treatments that have established direct clinical benefit does the study sponsor have a true incentive to push forward with their own confirmatory trial.

The FDA has also been relatively generous in evidence development timelines set forth in postmarketing commitments. Accountability for disclosing the results of studies, either in peer-reviewed journals or on [clinicaltrials.gov](https://clinicaltrials.gov), also appears to be underenforced.<sup>12</sup> Serious concerns about these issues and other areas of lax oversight were documented in a 2009 GAO report criticizing the FDA for failing to ensure that treatment effects estimated through surrogate endpoints are eventually verified.<sup>51</sup> This scrutiny brought no visible change to internal FDA procedures or to their external actions within their existing AAP framework.

Although the FDA can fine companies or withdraw approval to penalize non-compliance with postmarketing requirements, it acts with significant restraint in deploying these measures. In some instances, it has also publicly reversed or deferred recommendations to withdraw on the basis of inadequate data. This was the case in 2010, when the agency proposed removing midodrine hydrochloride (Proamatine) from the market after the company marketing the drug failed to conduct the post-marketing studies required as a condition of its accelerated approval for symptomatic orthostatic hypotension 14 years earlier in 1996. However, patients and professional societies opposed the withdrawal, leading the FDA to reverse its decision.<sup>52</sup> Twenty-four years after it was initially approved, midodrine and its generics remain on the market without conversion to full approval.

The FDA's reversal on midodrine sparked concerns that the agency was setting a dangerous precedent.<sup>52</sup> The agency now finds itself in a similar bind with another product, synthetic hormone 17-hydroxyprogesterone caproate (Makena). In 2011, it granted the drug accelerated approval for the prevention of pre-term birth, on the basis of a randomized, placebo-controlled trial showing that the drug reduced the risk of this outcome. However, because the study failed to show an improvement against placebo on the desired clinical endpoint of improved neonatal outcomes, the agency required that the manufacturer confirm the effect in a post-marketing study. In 2019, when this subsequent trial failed to show either an improvement in neonatal outcomes or in pre-term births, the FDA's Center for Drug Evaluation and Research (CDER) recommended that approval for the drug be withdrawn.<sup>53</sup> The maker of the drug, AMAG pharmaceuticals, could agree to withdraw, or request a hearing with the FDA. The company requested the hearing. Although the FDA review committee considered additional evidence from the company, and subsequently reiterated its recommendation that the drug be withdrawn, the drug and its generics remain on the market.<sup>54</sup>

## Inconsistent Regulatory Decisions

Inconsistent decisions following negative or ambiguous confirmatory data have also drawn scrutiny. Barring safety concerns, the agency has generally preferred to steer clear of withdrawing approval, even when postmarketing trials do not support a treatment effect on the primary clinical endpoint, as was the case for bevacizumab in the treatment of glioblastoma.<sup>26,55,56</sup> Bevacizumab was granted full approval despite failure to demonstrate improvements in overall survival. Although the FDA justified this decision by citing patient input that gains in PFS and reduction in corticosteroids were meaningful benefits, the rationale was questioned as being inconsistent with the stated goals of the confirmatory trial, contributing to a sense of a lack of consistency in decision-making.<sup>57</sup>

Although accelerated approval had been granted on a positive early signal in response rate, the confirmatory study failed to show an improvement in OS over lomustine alone.<sup>55</sup> Nevertheless, the drug was granted full approval for this indication; in its press release, Genentech pointed to improvements in PFS and a reduction in the need for corticosteroids observed in the trial.<sup>58</sup> The decision was controversial - patients treated with bevacizumab experienced a higher rate of high grade adverse events than those on lomustine alone. It also stands in notable contrast to an earlier FDA decision to rescind accelerated approval for bevacizumab in the treatment of metastatic breast cancer, after confirmatory trials failed to show an improvement in OS.<sup>26</sup>

Another example of seeming inconsistency in FDA actions is shown with atezolizumab (Tecentriq). After this drug was granted accelerated approval in 2016 for the treatment of urothelial carcinoma, one post-approval study failed to show improvements in OS among patients previously treated with platinum-based therapy who were subsequently treated with atezolizumab, as compared with chemotherapy. However, atezolizumab did appear to be better tolerated than chemotherapy.<sup>59</sup> Following other precedents this might be expected to be adequate confirmatory information to support full approval. To date, however, no updates to the prescribing information or other materials have been made. Other postmarketing commitments to study the effect of atezolizumab in urothelial carcinoma are either listed as ongoing or delayed.<sup>5</sup>

Problems also exist within the consistency of the timeline and specific requirements for confirmatory trials. Bedaquiline, marketed as Sirturo, offers an interesting example. The drug was granted accelerated approval for multi-drug resistant tuberculosis in 2012, based on data showing a greater rate of negative sputum culture among treated patients as compared to placebo. However, five times as many patients who received bedaquiline in the pre-approval trial died than in the placebo arm. In addition to scrutiny of the FDA's decision to weight the surrogate endpoint more heavily than the observable clinical outcomes, the case also prompted questions about whether the FDA had been too generous in its postmarketing requirements. These allowed the confirmatory trial to begin a year after approval, and did not require results until 2022, 10 years later.<sup>60</sup> Though the FDA's analysis that the benefits outweighed the risks may well have been robust,<sup>61</sup> mitigating

measures, such as requiring additional study and a more rapid plan for producing the confirmatory evidence, might have been appropriate, given the risks.

## High Costs

Concerns about uncertainty and delayed confirmation of safety and efficacy are magnified by the ongoing trend towards higher launch prices for pharmaceutical products. The trend is particularly pronounced for specialty drugs, a category that overlaps meaningfully with those granted accelerated approval. Although specialty drugs accounted for only 2.2% of prescriptions in 2018, they constituted nearly half of per capita spending on medicines in the US.<sup>62</sup>

Within specialty drugs a growing proportion are treatments for rare diseases.<sup>63,64</sup> A report by Evaluate Pharma examining the 100 drugs with greatest US sales found that the average cost of treatment for orphan drugs is 4.5 times that of non-orphan drugs (\$150,854 vs. \$33,654 per year).<sup>65</sup> Not surprisingly, many of these drugs are oncology drugs, and overall US spending on cancer drugs doubled to \$56 billion from 2013 to 2018.<sup>66</sup> More than \$9 billion of that growth is attributable to PD-1/PD-L1 inhibitors alone, a class of drugs which in recent years have been frequent recipients of accelerated approvals.<sup>66</sup>

These trends toward orphan indications, and the increased prices and use of oncology drugs, are reflected in the general trends of prices of products with accelerated approvals. For drugs approved through the AAP in 2020, 4-week list price treatment costs ranged from \$13,420 to \$22,661, with the exception of one drug for the treatment of DMD, viltolarsen (Viltepso), which is priced at \$54,144 per month. (See Table 3 below).<sup>13,67</sup> For many of these drugs, even after rebates, the cumulative annual cost would be well over \$150,000. Among all new oncology drugs approved in 2020, the average cost for 4 weeks of treatment was comparable for those with and without accelerated approval.<sup>68</sup> A number of drugs have multiple indications, and the prices do not vary depending on whether the indication represents a full approval or one under accelerated approval. Keytruda, for example, has a fixed treatment regimen across all indications, so that it costs the same amount regardless of the level of certainty in its treatment effects.

**Table 3. Four-week Wholesale Acquisition Treatment Costs for Products with Accelerated Approval for One or More Indications in 2020<sup>†</sup>**

Brand Name	Generic Name	Approval Date	Indication for Accelerated Approval	Price per 4 Weeks <sup>68</sup>
Gavreto	Pralsetinib	12/1/2020	Advanced medullary thyroid cancer	\$21,552
Viltepso	Viltolarsen	8/12/2020	DMD	\$54,144

<sup>†</sup> Notes: Includes all unique combinations of drugs and dose that received accelerated approval in 2020. Where there were both adult and pediatric indications, the adult indication was used. Costs for drugs with weight- or mass-based dosing were calculated assuming an 80 kg average for adults, and 30 kg average for children.

Brand Name	Generic Name	Approval Date	Indication for Accelerated Approval	Price per 4 Weeks <sup>68</sup>
<b>Blenrep</b>	Belantamab mafadotin-blmf	8/5/2020	Multiple myeloma	\$24,524
<b>Monjuvi</b>	Tafasitamab-cxix	7/31/2020	DLBCL	\$16,500
<b>Zepzelca</b>	Lurbinectedin	6/15/2020	NSCLC	\$13,364
<b>Rubraca</b>	Rucaparib	5/15/2020	Prostate cancer	\$17,297
<b>Pomalyst</b>	Pomalidomide	5/14/2020	Kaposi's Sarcoma, HIV-negative & AIDS-related	\$40,553
<b>Retevmo</b>	Selpercatinib	5/8/2020	NSCLC, RET+ thyroid cancer, RET+ medullary thyroid cancer	\$21,404
<b>Tabrecta</b>	Capmatinib	5/6/2020	NSCLC	\$19,911
<b>Keytruda</b>	Pembrolizumab	4/23/2020	Alternate dosing regimen for 15 different cancer types	\$14,411
<b>Trodelvy</b>	Sacituzumab govitecan-hziy	4/22/2020	Breast cancer	\$26,482
<b>Pemazyre</b>	Pemigatinib	4/17/2020	Cholangiocarcinoma	\$25,179
<b>Istodax</b>	Romidepsin	3/13/2020	Peripheral T-cell lymphoma	\$16,958
<b>Tazverik</b>	Tazemetostat	1/23/2020	Epithelioid carcinoma	\$16,073

Against this backdrop, the negative financial consequences of drugs that are ultimately shown not to have a clinical benefit have become more pronounced. For example, olatumab, which was granted accelerated approval in late 2016 for the treatment of metastatic soft tissue sarcoma, was shown after two and a half years to convey no survival benefit, leading the FDA rescind the approval.<sup>69</sup> While it was on the market, the drug cost \$106,100 for six months of treatment. It generated \$305 million in sales in 2018 alone – a small number by most earnings standards, but a significant sum for a product that ultimately failed to benefit patients.<sup>23</sup>

## Potential Policy Reforms

---

The goal of accelerated approval is to hasten access to treatments that promise meaningful advantages for patients with serious conditions but would take too long to evaluate if evidence on clinical outcomes is required. The solution the AAP provides for this problem is to offer a shortcut tied to a promise: earlier approval for treatments can be considered if they show positive effects on “reasonably likely” surrogate endpoints, with meaningful clinical benefits to be confirmed after market entry.

This compromise rests on the idea that the perfect can be the enemy of the good; its success lies in ensuring that the “good” - an overall net-positive benefit to patients and society - is maintained. But despite notable successes in accelerating access to treatments that have demonstrated substantial clinical benefits, many view the AAP and its implementation as having lost the balance needed to ensure overall benefits to patients and society. A gradual erosion in the standard of evidence FDA accepts as adequate for accelerated approval has increased the uncertainty at launch about whether drugs work at all, and whether they are even safe. The existing regulatory mechanism to ensure rapid generation of high-quality confirmatory evidence lies in ruins, undermined by a lack of specific powers to withdraw approval when evidence is not generated at all, and by the apparent lack of will within the FDA to exercise consistently their existing powers to withdraw approval, even when evidence is generated that fails to confirm the intended clinical benefit. Compounding these failures is the lack of pricing or other market incentives to modulate pricing in relation to increased uncertainty and to reward companies for investing the time and resources to conduct high-quality confirmatory trials. Meanwhile, as the number of drugs approved through the AAP continues to increase,<sup>70</sup> the combination of high uncertainty and high prices for many of these drugs has been driving an erosion in access to these drugs that is the fundamental goal of the entire pathway.

Building from our analysis of the current challenges with the AAP, we present below a list of policy reform proposals and explore their potential advantages and disadvantages. Because the AAP is meant to strike a balance, no policy reform is without potential negative consequences. We present some proposals that would be viewed as minor adjustments to the current AAP. Others will be considered radical reconstruction of the entire process, including requirements for new Congressional statute and major shifts in the landscape of pricing and coverage for new drugs. Our goal is to provide a broad palette of policy reform ideas to stimulate dialogue about the areas with the most urgent need of change, whether these changes should be incremental or tectonic in their design and implementation, and what their consequences might be for characteristics of the pathway seen as largely beneficial. We hope that these options for policy reform will help all policymakers and stakeholders reconsider some of the fundamentals that led to the creation of the AAP and provide new insights into ways it can be strengthened for the future.

# Policies that could be achieved through FDA action

## 1. Strengthen the Selection of Surrogate Endpoints

Greater clarity, transparency, and consistency are needed in the evaluation and acceptance of “reasonably likely” surrogate endpoints by the FDA. Regulatory discretion helps accommodate the breadth of treatments and potential endpoints the agency considers. But current guidance and biomarker working group documents appear too vague to support a consistent approach within the FDA, especially when there is no internally or publicly available compendium of the rationale FDA has used in previous cases.<sup>41,71,72</sup>

To address this issue, the FDA could consider a series of actions. First, before approving the use of a surrogate endpoint within the AAP, the FDA could publish publicly a preliminary justification for the basis of its decision, including a “scorecard” of the surrogate endpoint against each of the criteria that FDA has already established to support a “reasonably likely” designation. This preliminary judgment could be posted for public comment to ensure that clinical experts and other stakeholders have the opportunity to see the FDA’s thinking and contribute to the final decision on whether to deem the surrogate endpoint as “reasonably likely.”

Importantly, this preliminary scorecard would require the FDA to make public its thinking on the threshold for change in the surrogate endpoint that would be considered likely to be substantial enough to translate into meaningful clinical improvement. This threshold need not be interpreted as a mandatory threshold for accelerated approval, but it will set a public marker to help guide future discussion inside and outside the FDA, should the drug not produce the threshold level of change in the surrogate endpoint. It would strengthen the hand of the FDA in determining that a promising treatment does not meet the evidentiary standard for accelerated approval, even in the face of strong political or stakeholder pressure. Assuring that the FDA clarifies not only biological plausibility but proportionality in advance of pivotal trials would enhance internal consistency at the FDA in the condition area while also contributing to a publicly available compendium of justifications that would guide policy discussion and the planning for future research by clinical researchers and life science companies.

This policy reform thus would have several potential benefits. It would strengthen the consistency of scientific judgments within the FDA and likely avoid the kind of debacle that many observers felt was exemplified by the approval decision for eteplirsen. At the same time, this reform would preserve the FDA’s existing flexibility to ask for additional study to support accelerated approval, rather than deferring to full approval or declining approval for treatments whose treatment effects fall below the surrogate endpoint threshold. And the clearer and more public standard would have positive ramifications for innovation, strengthening the competitive advantages of companies doing rigorous science and reducing uncertainty about whether to invest in less promising pipeline candidates.



The potential disadvantages of this approach begin with the risk that limited understanding of a candidate surrogate endpoint could lead the FDA to establish a prespecified threshold for change that is too high, thus leading to the regulatory failure of drugs that, if approved, would have been ultimately proven to help patients. Another drawback, as with any guidance, is that public engagement and comment may enhance external pressure on the FDA and erode the flexibility and regulatory discretion it needs to administer the AAP.

## **2. Develop Standardized Accelerated Approval Review Templates**

The FDA can take steps to increase consistency and clarify evidence standards within AAP reviews by updating its review template to include a section specific to the assessment of surrogate endpoints in accelerated approvals. This section would serve as a way to organize the information, assumptions, and reasoning that inform the FDA's decision to accept a surrogate endpoint as reasonably likely. Used systematically and published on accelerated approval with the reset of the review template, this information could then be assembled in a compendium for both internal and external purposes. If needed there could be variations on the template depending on indication, including oncology, or rare genetic disorders.

This surrogate endpoint information (once finalized following public comment) would be part of a broader template made available at the time of accelerated approval that includes a structured explanation for why accelerated approval was deemed appropriate over regular review, and which provides details about the timing and design of trials for postmarketing commitments, including information currently absent in postmarketing requirement disclosure, such as study design, comparator types, specific endpoints, and study duration.<sup>12</sup>

Developing a more formal and public template for AAP reviews would have several benefits. One is that more disciplined reporting can lead to more consistent decisions across therapeutic areas, acting as a forcing function to align practices across different groups within the FDA. Another benefit is improved transparency: providing insight to all stakeholders about the rationale and considerations underlying the decision to use the AAP and the study design and key details that will be expected of persuasive confirmatory trials. Systematically providing these details would create a public record that can be referenced for later accountability.

The most notable drawback to this approach is the burden it would add for FDA reviewers. Some of this information is occasionally available in the approval documents provided at Drugs@FDA, albeit not at the desired level of detail, but systematically compiling the information would require additional effort. Another potential concern is that the level of information provided could infringe on what the drug maker would consider proprietary trade secrets, but it seems unlikely that this level of information would pose a significant commercial risk.

### 3. Require Greater Use of Randomized Controlled Trials

The cause of the greater uncertainty about the safety and effectiveness of drugs in the AAP is not solely due to surrogate endpoints; the shift to greater reliance on single-arm trials has also played an important part. In some ways, the greater uncertainty associated with surrogate endpoints could be attenuated by requiring that these endpoints be used only in rigorously conducted randomized trials. Therefore, it is worth considering whether the FDA should adopt a formal shift in posture toward requiring randomized controlled trials (RCTs) within the AAP unless there are clear and persuasive reasons that render this impossible.

The benefits of shifting toward a “RCT default” position start with a greater ability to discern before launch whether approved drugs are reasonably likely to be safe and effective. The chance of approving a drug on the basis of evidence undermined by selection bias and other vulnerabilities would be greatly diminished.

Another benefit of randomized data, even when coming from a placebo-controlled trial, is that they often allow for more robust indirect comparisons with other active comparators. This information helps patients and clinicians better judge the comparative clinical effectiveness of new treatments. It also helps insurers exercise more precision in targeting their coverage criteria and other utilization management policies, potentially reducing unnecessary constraints on access.

Nevertheless, it is clear that RCTs are infeasible in some situations. Among the most notable are when there are too few patients to randomize and retain a modicum of statistical power. Ethical concerns are sometimes raised that patients without other treatment options should not be randomized when there is a particularly promising treatment under evaluation; Randomization might also reduce the willingness of patients and clinicians to participate. However, the experience with treatments such as those for Spinal Muscular Atrophy (SMA) demonstrates that the patient community can be allies in efforts to conduct randomized trials because patients share the goal of ensuring that rigorous evidence is generated on the treatments that may save their lives or those of their family members.<sup>73</sup> Early engagement with the patient community would be essential in order for them to comment and consider whether randomization could ultimately be the best way for patients and clinicians to gain the information they need.

As the FDA weighs whether RCTs are the best way forward for any particular emerging treatment, it could also consider the evolving ability of real-world observational data (RWOD) to provide complementary information, whether as a component of initial approval or as a defined approach to rapidly obtain confirmatory data on safety and effectiveness. However, the current limitations of RWOD make it unlikely that many stakeholders, especially payers, would view it as helpful in reducing uncertainty at the time of launch, and increased requirements for RCTs will remain a bedrock position for many who believe the evidence standards for the AAP have slipped in recent years.

## 4. Create a New Label Alert and Patient Material for Accelerated Approval Drugs

Another potential reform is to include a clear visual alert of accelerated approval on drugs' prescribing information. Clinicians have become very accustomed to the implications of an FDA black box warning that signals a risk of specific serious side effects.<sup>74</sup> The goal of these warnings is to ensure that clinicians and patients discuss these risks as part of the shared decision-making that weighs the risks and benefits of treatment options in light of an individual patient's clinical status and other factors. To mirror this goal, the FDA could adopt a new visual signal, perhaps a yellow triangle or a grey box, for drugs approved through accelerated approval. The intent of this label warning would be to highlight the relative degree of uncertainty about an accelerated approval drug prior to the completion and evaluation of its confirmatory trials. The information could also include the status of postmarketing requirements, what uncertainties they are meant to resolve, and their expected dates of completion. This would represent an advance over current practice, in which information about accelerated approval status does not feature prominently in the labeling material; in some instances, it is buried in footnotes.<sup>75</sup>

Patient communication materials could be changed as well. A study of drugs with accelerated approvals that submitted promotional materials for FDA found that, although 73% of them included a disclosure about their AAP status, the accompanying information required reading skills at the high school level or above to understand. The basis for approval and the key uncertainties surrounding the product were also communicated inconsistently. Borrowing from the clinician-oriented approach, albeit using simplified language accessible to a lay audience, this information could be made a mandatory part of any direct-to-consumer advertising.<sup>76</sup>

The strength of this approach is that it would make explicit the limitations of current evidence to patients, providers, and others involved in dispensing or administering the drug. Ideally, it would foster discussion about the uncertainties in the evidence between clinician and patient, and might restrain inappropriate prescribing.

This approach could also increase the incentive for drug makers to complete their required confirmatory studies in order to be able to remove the warning label. In particular, companies that fail to perform the required studies might be at a disadvantage against competitors who do, and can thus position themselves as having more robust data.

Despite its intuitive appeal, however, the impact of this approach may also be limited. Payers are likely to already be aware of this information because they use it to develop coverage and utilization management policies, and it stands to reason to assume that the physicians most likely to prescribe or administer such products are up to date on the approval status and uncertainties surrounding treatment options. It is unclear whether patients would find this information helpful or that it would change their expectations or approach to treatment.

## **5. Increase Enforcement of Requirements to Complete Confirmatory Trials**

This policy proposal calls on the FDA to maximize use of its existing powers to enforce the completion of required confirmatory trials. These powers include issuing administrative action letters, assessing financial penalties, and withdrawing approval, should expected evidence not materialize in a timely manner.<sup>77,78</sup> The agency could also wait to grant accelerated approval until there is proof that confirmatory trials are either initiated or in progress.<sup>77,79</sup>

The benefits of the FDA aggressively exercising its existing powers are relatively obvious. Just as the ability to market a drug creates an incentive to develop it, the threat of removing it from the market would serve as an incentive to comply with confirmatory requirements. However, this only works if the agency can follow through; it has been challenged successfully on several occasions in recent years by industry and patients. The agency would also have to tread carefully to avoid penalizing study sponsors for delays that are beyond their control. To ensure that technical issues in confirmatory studies are understood and addressed in a timely manner, the FDA might commit to a more hands-on post-approval process for giving scientific advice.

One downside of this approach is that vigorous monitoring and enforcement may require additional staff and resources. In addition, withdrawal of a drug or even stiff financial penalties might threaten the survival of small companies marketing drugs for rare diseases. But perhaps the greatest concern is that enforcement leading to withdrawal of approval for accelerated approval drugs would trigger powerful pushback from industry and potentially from patient groups as well, raising the risk that Congress would lean in to pressure the FDA. Whether FDA would find support from other stakeholders adequate to withstand the negative pressure from directly affected patients, clinicians, and companies is not clear.

## **6. Create an Annual Renewal Cycle or Sunset Accelerated Approvals Lacking Confirmatory Evidence**

Another way to fortify requirements for confirmatory evidence is to avoid putting the FDA in the position of having to decide how to proceed when study sponsors fail to produce it. Law or regulation could be changed to automatically withdraw marketing authorization for an accelerated approval drug, should its confirmatory evidence not be available for FDA review by a pre-determined date set at the time of approval. This kind of formal “sunset” policy would give the clearest signal to industry of what is required, and protect the FDA from pressure to change decisions when it makes them at its discretion.

Nevertheless, the potential advantages of this policy would also come with several important drawbacks. Legitimate extensions to study timelines are sometimes needed to resolve scientific problems affecting confirmatory studies for promising drugs. Without this flexibility, desirable

treatment options may be removed from the market prematurely, and if requests for extensions are allowed as part of a sunset policy then the FDA could be vulnerable to the same pressures that the policy was meant to address.

An alternative that offers a bit more FDA discretion would be to periodically renew approval after reviewing the available evidence for drugs with accelerated approval. This is the practice at the European Medicines Agency (EMA), which requires that drugs with conditional approval be re-reviewed to ensure that they continue to justify the risk-benefit tradeoff.<sup>80</sup> However, as with any proposal for enhanced monitoring and enforcement, this approach would almost certainly require additional staff and resources.

## **7. Create a Separate “Safety-only” Approval Pathway That Waives Public or Private Insurance Coverage Requirements**

The case of eteplirsen raised the question for some observers of whether the FDA was trending toward the adoption of a “safety-only” evidence standard for the AAP, at least in situations in which patients had no available treatments for a life-threatening condition, and perhaps when the financial survival of the drug’s sponsor hung in the balance.

Conceptually, a safety-only approval pathway could be designed to allow the FDA to approve drugs solely on the basis of a judgment that adequate evidence exists of a reasonable safety profile in the context of the severity of the condition. Removing any requirement for reasonably likely evidence of efficacy, this vision of a safety-only pathway would mirror to some extent the intent of the FDA “right to try” program, although that program provides limited access to patients to drugs that have not yet received any form of FDA approval.

The presence of a separate safety-only approval pathway could, through contrast with the AAP, serve to strengthen the evidence standards for the evidence on effectiveness required within the AAP. Concerns about health system costs could be addressed if a safety-only approval pathway was explicitly designed to release public and private insurers from requirements to cover the drugs. Patients would be required to pay the drugs themselves unless their health plan or employer opted to provide coverage (perhaps through an insurance rider) for drugs with safety-only approval.

This approach would tilt the balance far in the direction of access and put patients at significant risk of using drugs that would produce no benefits, still pose a degree of risk, and cause financial stress. Patients, especially those with significant illnesses, are vulnerable, and it is likely that this approach would see more drugs approved of unproven benefit while doing more harm than good.

However, right to try proponents, supported by many politicians, have been pushing for similar policies for years. An important, if theoretical, consequence of this approach would be that it would

effectively require manufacturers to market their drugs on the basis of price, putting it either at a level commensurate with patients' ability to pay out of their own pocket, or insurers willingness to consider coverage. It is possible that a combination of these factors would push manufacturers to perform confirmatory trials more rapidly in order to gain insurance coverage; however, it might also reduce the incentive to develop drugs that offer only incremental benefits, or that only help a small subset of patients.

As noted, however, any theoretical benefits would be obtained at great risk that vulnerable patients would feel themselves compelled to try treatments without a shred of evidence to suggest likely clinical benefits. It would put individual patients in the difficult position of deciding whether to spend their own money on an unproven therapy. And it would not ultimately serve to answer the question at the heart of the AAP: what level of evidence is sufficient to suggest "reasonably likely" clinical benefit?

## **Policies that would require payer and life science industry actions**

Another avenue through which policies might strengthen the AAP is reimbursement. These approaches could be initiated by payers at the federal or state government level, or implemented through the commercial market.

### **8. Increase Mandatory Federal Rebate Levels Until Time of Full Approval**

In order to link pricing to levels of certainty and to create greater incentives for completion of confirmatory trials, one policy reform option would be to grant Medicare and Medicaid higher minimum mandatory rebates on drugs approved through the AAP than given for drugs with regular approval. Already established federal reimbursement pathways would serve as the means to accomplish this.

In exchange for mandatory coverage under the Medicaid Drug Rebate Program (MDRP), manufacturers are currently required to pay rebates to state Medicaid programs so that their net prices do not exceed the lower of either the Best Price in the market, or a statutory rebate amount of 23.1% of the Average Manufacturer Price (AMP).<sup>81</sup> The MDRP could be modified for drugs with accelerated approval to require a higher rebate during the time between accelerated and full approval.<sup>77,82</sup> This approach has recently been recommended by the Medicaid and CHIP Payment and Access Commission (MACPAC), which voted 16-1 to recommend to Congress that they consider an increased Medicaid rebate for AAP drugs before confirmatory trials are done.<sup>83,84</sup>

Medicare Part D plans can also make use of already established pathways, although legislation to mandate specific rebate levels would be necessary. To implement this policy option, Part D plans would be required to collect mandatory rebates as they do for the Coverage Gap Discount Program

(CGDP), but at a set level and regardless of benefit phase. In the Medicare Part B benefit, the policy would mirror a recent CMS proposal to lower Medicare reimbursement for drugs acquired under the 340B program.<sup>85</sup>

The potential advantages of this policy stem from shielding Medicare and Medicaid from the full financial burden of the high prices for drugs approved through the AAP. By reducing the net price for Medicare and Medicaid this approach would also provide a potentially large financial incentive for drug makers to conduct rapid confirmatory trials in order to seek a shift to full regulatory approval and thereby move to a lower mandatory rebate for public payers.

However, deeper fixed rebates can also always be overcome by higher list prices. In addition, one well known downside of reducing revenue from public payers is that it creates an incentive for drug makers to increase their list and/or net pricing for commercial payers. How these countervailing incentives would influence the overall financial impact of drugs approved through the AAP is difficult to judge.

## **9. Use Pricing at Marginal Cost to Incentivize Completion of Confirmatory Trials, with Consideration of a Federal Carve-Out**

Another reimbursement-driven approach to addressing cost concerns, while also enhancing incentives for confirmatory evidence, would be to regulate pricing at the time of accelerated approval and limit pricing to the marginal or average cost of producing and delivering the drug. This price ceiling would stay in effect until confirmatory evidence is produced. At that time, if the evidence supports full approval, the company would move to full market pricing and could also receive a “prize” payment to compensate the compensate for some of its “lost” revenue since initial accelerated approval. This prize approach borrows from the prize model originally proposed by the economist Joseph Stiglitz as a replacement for patents.<sup>86</sup>

Marginal cost pricing would limit the profit opportunity during a drug’s confirmatory period, while still offsetting some costs. Mechanically, implementation would require that drug makers report their marginal costs on a per-unit basis to Centers for Medicare and Medicaid Services (CMS), who would use the information to develop a benchmark for reimbursement, similar to the Average Sales Price (ASP).

There are precedents in the healthcare system for indexing reimbursement to the cost of production – prospective bundled payments by Medicare to hospitals delivering inpatient care are based on the costs these hospitals report. The FDA also has a provision that allows companies to recover costs for investigational products if these would otherwise prevent their study. Manufacturers seeking cost recovery must submit an estimate of costs of production and

verification of their statement by a certified public accountant.<sup>87</sup> The resulting prices could be extended to both public and commercial payers by levying financial penalties on manufacturers who decline to offer the same price across the market, as proposed under the Elijah Cummings Lower Drug Prices Now act (also known as H.R.3).<sup>88</sup>

The expected outcome of this approach would be to greatly reduce the financial consequences of newly launched accelerated approval drugs for payers, patients, and taxpayers. It would also likely provide a substantial incentive for drug makers to launch and complete confirmatory trials.

However, marginal cost pricing, even with a prize for completion of confirmatory trials, could also be too strong a disincentive to develop drugs for less well understood diseases and therapeutic targets. The financial return might be insufficiently certain or large to maintain innovation for ultra-rare conditions and others that rely on surrogate endpoint trials to be developed within a reasonable timeframe. Companies that invest in ultra-rare treatments are often small, and less diversified and capitalized than large pharmaceutical manufacturers, making it even more likely that marginal cost pricing at launch would leave them without the resources needed to survive. It is therefore possible that companies would shift their investments primarily to pipeline candidates in the regular approval pathway.

However, there is a similar, if less draconian option: allow for manufacturer-determined pricing at launch, but include in the approval the requirement that reimbursement fall to marginal cost on the date confirmatory trial data are expected to become available. This approach would provide the initial return on investment to ensure that companies are not financially hamstrung, while retaining the strong incentives for companies to get confirmatory data as early as possible in order to ensure continuation of its freedom from regulated pricing. A possible downside would be that companies could seek even higher launch prices to accommodate for the possibility of losing pricing power in several years' time, and there would still be some risk of reduced investment in emerging drugs that need surrogate endpoint trials to get to market in a relatively short time horizon.

Even if an incentive structure could be developed that minimizes potential rewards to bad actors, it is complex and difficult to implement effectively, given the fragmentation of healthcare provision and financing in the US. These pitfalls might be avoided by aggregating and centralizing buyer power under a federal carve-out benefit that acts as the single US payer for indications and products with accelerated approval. In addition to increase negotiating leverage, this would reduce the exposure of small health plans to large budget variances that they struggle to absorb. Unfortunately, the UK experience with the Cancer Drugs Fund suggests that this solution also falls short. From 2010 to 2015, the fund spent £1.3 billion to pay for cancer treatments that had failed to gain NICE approval, of which only 38% demonstrated an effect on OS, at a median of 3.1 months. The authors of the study examining its performance concluded that the fund had “not delivered meaningful value to patients or society”.<sup>89</sup>



## 10. Require Payment Be Based on Outcomes-based Contracts

Outcomes-based contracts (described as “value-based” agreements by the industry), which make some or all of the payment for a drug contingent on patient benefit, have been proposed as a way to reduce barriers to access while limiting some of the downside financial risk to health plans.<sup>90</sup> One potential policy reform option, therefore, would be to create a requirement for Medicare and Medicaid to cover drugs approved through the AAP only under the terms of an outcomes based contract.

A requirement for outcomes-based contracts could be framed as a way to support the conduct of confirmatory trials while reducing payer concerns regarding the high prices for accelerated approval drugs. If such contracts focused on achievement of the meaningful clinical outcomes that would be the target for confirmatory trials, and if the contract shifted enough financial risk to drug makers, this option could provide shift incentives to align with the broader goals of the AAP. This could be achieved either through clawbacks on payments already made for drugs that proved to be ineffective, or by holding payments in escrow until the treatment effect is confirmed.

However, the capacity of OBCs to accomplish these goals is in question. Currently, although a number of such arrangements are in place across different manufacturers and private payers in the US, their use remains limited, particularly for accelerated approval products.<sup>91,92</sup> This likely reflects the fact that many payers lack the negotiating leverage that would grant them the power to achieve meaningful sharing of financial risk on outcomes that payers believe best represent the real-world effectiveness of treatment. Single payer systems are perhaps in a better position to benefit from such arrangements because they have aggregated buyer power and the ability to collect the requisite data. But even in single-payer health systems the experience with outcomes based contracts is checkered; they have a reputation for yielding little additional data, adding significant administrative burdens, and saving payers little money even when performance is less than expected.<sup>93</sup>

If there were a universal mandate for outcomes-based contracts for initial payment of AAP approvals, it is possible that a system could be developed to overcome some of these limitations. An independent party, with input from FDA, could be empowered to set the terms of the contract, including the selection of endpoints and the price rebate that would flow back to payers based on clinical performance.

Still, the complexities of OBCs that have made them difficult to launch in the private setting would still obscure the prospects for successful implementation at a broader scale. The new bureaucracy needed to design and implement them would be significant. The timeframe over which outcomes must be measured in confirmatory trials may stretch years; patients often switch payers on a much shorter timeframe. Interim evaluations might be possible, but would burden patients, and would, by definition, not measure the true clinical outcome that would confirm the benefits of treatment.

This is further complicated by an absence of rich clinical data, as well as inadequate information about demographics and social determinants of health.

Their logistical complexities aside, whether such arrangements are practical under current policies is another question. Some argue that OBCs would only be practical under modifications to the calculation of Average Sales Price (ASP), Best Price, and the anti-kickback statute. However, it appears unlikely that the potential benefits of such contracts justify altering these mechanisms, which are in place to protect public payers, including Medicare and Medicaid.<sup>94</sup>

## Conclusion

---

Since its inception in 1992, the AAP has provided an important policy vehicle through years that have witnessed a series of profound advances in medical science. Its performance has been mixed, bookended by clear successes, such as imatinib, as well as decisions that have set precedents ripe for abuse, including controversial decisions to approve Sarepta's portfolio of products for DMD, and the agency's lack of action to withdraw products like midodrine and Makena.

Some degree of failure of drugs to move from accelerated to full approval is not only expected, but considered a marker that the AAP is finding a balance between early access and the risk of approving drugs that ultimately are shown not help, or even to harm, patients. Nevertheless, there are reasons to examine closely whether the pathway's unique combination of scientific uncertainty and risk acceptance, combined with the market's rich incentives in the form of high prices, provides a rationale for policy reforms.

Concerns identified over the course of this review include inconsistencies in the level of uncertainty deemed to qualify surrogate endpoints as reasonably likely to predict a clinically meaningful treatment effect; a lack of clarity over what magnitude of change in such endpoints justifies accelerated approval; and the high prices commanded by these products despite their relative lack of evidence. Ultimately, these concerns reflect a central risk: that patients will be harmed by having their care diverted towards drugs that do not help them and that contribute to health care cost escalation that itself causes patient harm. Although the majority of accelerated approvals convert to full approval within a reasonable timeframe of 3 years, many products take significantly longer, and those that fail to produce evidence or that have evidence that fails to confirm patient benefit do not always leave the stage quickly. Expedited approval seems to be working in most cases, but the vision of a matching expedited withdrawal has not been realized.

These concerns coincide with other trends that are by no means unique to the AAP. Increasing reliance on single arm trials and other statistical concessions to study design have added uncertainty across approval types, with accelerated approvals being no exception. This has raised questions about whether the FDA has allowed its evidence standards to become too permissive and inconsistent. Nevertheless, specialty, oncology, and orphan drugs are also commanding historically

high prices, and there is no evidence that the prices for those with accelerated approval reflect any temperance reflecting the uncertainty in their benefits.

These concerns aside, many consider the AAP to be working as intended in the majority of cases. Those who seek to reform the program will thus have to balance the goals of improving aspects of the AAP without undermining its benefits. In this paper we identify 10 potential policy changes that have some rationale as ways to strengthen the AAP. Some will appear more hypothetical than practical, but all may help policymakers push their own thinking beyond traditional boundaries in understanding the tradeoffs involved with any policy reform. Some of the policy reforms are relatively straightforward in their aim of increasing institutional consistency and accountability in FDA decision-making. Solutions in this category, such as formally documenting the reasoning behind accepting a surrogate endpoint for a particular accelerated approval, can largely be built on the existing scaffolding of FDA regulation and practice. Other policies would require a much broader set of actions by payers and the life sciences industry to make changes in reimbursement that can produce compelling incentives for the completion of confirmatory trials. These are likely to generate the greatest controversy, as they surface questions about the right balance between incentives for innovation and affordability.

None of these policies are mutually exclusive, and many have significant overlap or synergies if bundled together. At the same time, none are perfect, and many come with tradeoffs that make them politically challenging. Policymakers should explore all of these considerations when addressing the challenge of renewing and strengthening the AAP as it enters its fourth decade of balancing between uncertainty, access, innovation, and cost.

## References

---

1. Keng MK, Wenzell CM, Sekeres MA. A drug's life: the pathway to drug approval. *Clinical advances in hematology & oncology : H&O*. 2013;11(10):646-655.
2. Dagher R, Johnson J, Williams G, Keegan P, Pazdur R. Accelerated Approval of Oncology Products: A Decade of Experience. *JNCI: Journal of the National Cancer Institute*. 2004;96(20):1500-1509.
3. Institute for Clinical and Economic Review. *Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value*. 2019.
4. Dearment A. Documents give inside view of FDA's rejection, and surprise approval, of Sarepta Duchenne's drug. 2020. <https://medcitynews.com/2020/01/documents-give-inside-view-of-fdas-rejection-and-surprise-approval-of-sarepta-duchenne-drug/>. Accessed 2020-02-02.
5. Postmarket Requirements and Commitments. 2021. <https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=3&StepSize=1&Paging=Yes>.
6. Food and Drug Administration. NDA 211970 Accelerated Approval. In:2019.
7. Food and Drug Administration. FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation. 2021; <https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0>. Accessed 4/20/2021.
8. Grayling MJ, Mander AP. Do single-arm trials have a role in drug development plans incorporating randomised trials? *Pharmaceutical statistics*. 2016;15(2):143-151.
9. Ladanie A, Speich B, Briel M, et al. Single pivotal trials with few corroborating characteristics were used for FDA approval of cancer therapies. *Journal of clinical epidemiology*. 2019;114:49-59.
10. Vokinger KN, Kesselheim AS. Characteristics of trials and regulatory pathways leading to US approval of innovative vs. non-innovative oncology drugs. *Health Policy*. 2019;123(8):721-727.
11. National Breast Cancer Coalition. Call to Action Online - April 5, 2021 - National Breast Cancer Coalition. 2021; <https://www.stopbreastcancer.org/call-to-action-online-april-5-2021/>.
12. Wallach JD, Egilman AC, Dhruva SS, et al. Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross sectional analysis. *BMJ (Clinical research ed)*. 2018;361:k2031.
13. CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint. 2020. <https://www.fda.gov/media/88907/download>. Accessed 1/10/2021.
14. De Gruttola VG, Clax P, DeMets DL, et al. Considerations in the evaluation of surrogate endpoints in clinical trials. summary of a National Institutes of Health workshop. *Controlled clinical trials*. 2001;22(5):485-502.
15. Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. *JAMA oncology*. 2018;4(6):849-856.
16. Ladd V. The FDA's accelerated approval process is working. *Morning Consult* 2021; <https://morningconsult.com/opinions/fdas-accelerated-approval-process-working/>.
17. Friends of Cancer Research. Optimizing the Use of Accelerated Approval. 2021; [https://friendsofcancerresearch.org/sites/default/files/2020-11/Optimizing the Use of Accelerated Approval-2020.pdf](https://friendsofcancerresearch.org/sites/default/files/2020-11/Optimizing%20the%20Use%20of%20Accelerated%20Approval-2020.pdf).

18. Institute for Clinical and Economic Review. Cornerstones of “fair” drug coverage: Appropriate cost-sharing and utilization management policies for pharmaceuticals. 2020; <https://icer.org/wp-content/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage--September-28-2020-corrections-1-5-21.pdf>.
19. Food and Drug Administration. Guidance for industry: Expedited programs for serious conditions - drugs and biologics. 2014; <https://www.fda.gov/media/86377/download>.
20. Food and Drug Administration. Kefauver-Harris Amendments Revolutionized Drug Development. 2020; <https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development>.
21. Kepplinger EE. FDA's Expedited Approval Mechanisms for New Drug Products. *Biotechnology law report*. 2015;34(1):15-37.
22. McCaughan M. Expedited Approval Pathways. *Health Affairs*. 2017.
23. Grover N. As it takes Lartruvo off the shelves, Lilly is setting up program to provide drug access to current patients. 2021; <https://endpts.com/as-it-takes-lartruvo-off-the-shelves-lilly-is-setting-up-program-to-provide-drug-access-to-current-patients/>.
24. Loftus P. Fast-Track Drug Approval, Designed for Emergencies, Is Now Routine. 2021.
25. Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636.
26. Gyawali B, Hey SP, Kesselheim AS. Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval. *JAMA Internal Medicine*. 2019;179(7):906-913.
27. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource 2016; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>. Accessed 1/21/2021.
28. Amur S. Biomarker terminology: speaking the same language. 2020; <https://www.fda.gov/files/BIOMARKER-TERMINOLOGY--SPEAKING-THE-SAME-LANGUAGE.pdf>. Accessed 1/2/2021.
29. Zhuang SH, Xiu L, Elsayed YA. Overall Survival: A Gold Standard in Search of a Surrogate: The Value of Progression-Free Survival and Time to Progression as End Points of Drug Efficacy. *The Cancer Journal*. 2009;15(5):395-400.
30. FDA-NIH Biomarker Working Group. Validated Surrogate Endpoint. [Text]. 2020; <https://www.ncbi.nlm.nih.gov/pubmed/>. Accessed 1/21/2021.
31. Food and Drug Administration. Surrogate Endpoints That Were the Basis of Drug Approval or Licensure | FDA. 2020.
32. FDA-NIH Biomarker Working Group. Reasonably Likely Surrogate Endpoint. [Text]. 2020; <https://www.ncbi.nlm.nih.gov/pubmed/>. Accessed 1/21/2021.
33. FDA-NIH Biomarker Working Group. Contents of a Biomarker Description. [Text]. 2020; <https://www.ncbi.nlm.nih.gov/pubmed/>. Accessed 1/21/2021.
34. McShane LM. Concepts and Case Study Template for Surrogate Endpoints Workshop. *Biomarkers Consortium - Workshop: Defining an Evidentiary Criteria Framework for Surrogate Endpoint Qualification* 2018; <https://fnih.org/sites/default/files/final/pdf/6-McShane-Case%20Study%20Overview.pdf>. Accessed 11/18/2020, 2020.
35. Vanderweele TJ. Surrogate measures and consistent surrogates. *Biometrics*. 2013;69(3):561-569.
36. Prasad V, Kim C, Burotto M, Vandross A. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. *JAMA Internal Medicine*. 2015;175(8):1389-1398.
37. Scherer A. Reproducibility in biomarker research and clinical development: a global challenge. <http://dxdoi.org/102217/bmm-2017-0024>. 2017.

38. Lauer M. Be Skeptical About Biomarkers and Surrogate Endpoints. 2018; <https://www.ncbi.nlm.nih.gov/pubmed/>. Accessed 1/23/2021.
39. Fleming TR. Surrogate Endpoints And FDA's Accelerated Approval Process. *Health Affairs*. 2005;24(1):67-78.
40. Moore TJ. *Deadly medicine : why tens of thousands of heart patients died in America's worst drug disaster*. New York: Simon & Schuster; 1995.
41. Food and Drug Administration. Biomarker Qualification: Evidentiary Framework 2021; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biomarker-qualification-evidentiary-framework>.
42. Food and Drug Administration. Exondys 51 prescribing information. 2016; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/206488lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf). Accessed 1/5/2021.
43. Food and Drug Administration. FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy 2021; <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-cervical-cancer-disease-progression-during-or-after-chemotherapy>. Accessed 4/20/2021.
44. Chen EY, Raghunathan V, Prasad V. An Overview of Cancer Drugs Approved by the US Food and Drug Administration Based on the Surrogate End Point of Response Rate. *JAMA Internal Medicine*. 2019;179(7):915-921.
45. Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017. *JAMA Network Open*. 2020;3(4):e203284-e203284.
46. Evans SR. Clinical trial structures. *Journal of experimental stroke & translational medicine*. 2010;3(1):8-18.
47. Food and Drug Administration. Framework for FDA's real-world evidence program. 2018; <https://www.fda.gov/media/120060/download>. Accessed 4/20/2021.
48. Herper M. Real-world evidence trial generates real-world criticism, too. *Stat News* 2019; <https://www.statnews.com/2019/07/03/replicate-clinical-trials-real-world-evidence/>. Accessed 4/20/2021.
49. Naci H, Wouters OJ, Gupta R, Ioannidis JPA. Timing and Characteristics of Cumulative Evidence Available on Novel Therapeutic Agents Receiving Food and Drug Administration Accelerated Approval. *The Milbank quarterly*. 2017;95(2):261-290.
50. Nagai S, Ozawa K. Drug approval based on randomized phase 3 trials for relapsed malignancy: analysis of oncologic drugs granted accelerated approval, publications and clinical trial databases. *Investigational New Drugs*. 2018;36(3):487-495.
51. Office of Government Accountability. FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints. 2009; <https://www.gao.gov/assets/300/295762.pdf>. Accessed 4/20/2021.
52. Dhruva SS, Redberg RF. Accelerated Approval and Possible Withdrawal of Midodrine. *JAMA*. 2010;304(19):2172-2173.
53. Chang CY, Nguyen CP, Wesley B, Guo J, Johnson LL, Joffe HV. Withdrawing Approval of Makena — A Proposal from the FDA Center for Drug Evaluation and Research. *New England Journal of Medicine*. 2020;383(24):e131.
54. Food and Drug Administration. CDER perspective on recently published results of EPPPIC meta-analysis. 2021; <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information>. Accessed 4/20/2021.
55. Wick W, Gorlia T, Bendszus M, et al. Lomustine and Bevacizumab in Progressive Glioblastoma. *New England Journal of Medicine*. 2017;377(20):1954-1963.

56. Food and Drug Administration. Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. 2020; <https://www.fda.gov/media/113361/download>. Accessed 2/5/2021, 2021.
57. Pollack A. Two Studies Challenge Avastin’s Effectiveness Against a Rare Brain Cancer. *New York Times*. 2013-06-02, 2013.
58. Genentech. Press Release. <https://www.gene.com/media/press-releases/14695/2017-12-05/fda-grants-genentechs-avastin-full-appro>. Accessed 4/20/2021.
59. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet (London, England)*. 2018;391(10122):748-757.
60. Avorn J. Approval of a Tuberculosis Drug Based on a Paradoxical Surrogate Measure. *JAMA*. 2013;309(13):1349-1350.
61. Cox E, Laessig K. FDA Approval of Bedaquiline — The Benefit–Risk Balance for Drug-Resistant Tuberculosis. *New England Journal of Medicine*. 2014;371(8):689-691.
62. IQVIA Institute. Medicine use and spending in the US. A review of 2018 and outlook to 2023. 2019; [https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?\\_=1611031457906](https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?_=1611031457906). Accessed 4/20/2021.
63. Sarpatwari A BR, Abdurrob A, He M, Kesselheim AS. Evaluating The Impact Of The Orphan Drug Act’s Seven-Year Market Exclusivity Period. *Health Affairs*. 2018;37(5):732-737.
64. Chambers JD, Silver MC, Berklein FC, Cohen JT, Neumann PJ. Orphan Drugs Offer Larger Health Gains but Less Favorable Cost-effectiveness than Non-orphan Drugs. *Journal of General Internal Medicine*. 2020;35(9):2629-2636.
65. Evaluate Pharma. Orphan Drug Report 2019. [https://www.evaluate.com/sites/default/files/media/download-files/EvaluatePharma\\_Orphan\\_Drug\\_Report\\_2019.pdf](https://www.evaluate.com/sites/default/files/media/download-files/EvaluatePharma_Orphan_Drug_Report_2019.pdf). Accessed 4/20/2021.
66. IQVIA Institute. Global oncology trends 2019. 2019; [https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2019.pdf?\\_=1611693976013](https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2019.pdf?_=1611693976013). Accessed 4/20/2021.
67. SSR Health. US Brand Rx Net Pricing Tool. 2021; <https://www.ssrhealth.com/dataset/>. Accessed 4/20/2021.
68. Bach P. Price & Value of Cancer Drugs. 2021; <https://www.mskcc.org/research-programs/health-policy-outcomes/cost-drugs>.
69. Food and Drug Administration. Announcement of the Revocation of the Biologics License for LARTRUVO. *Federal Register*. 2020.
70. Darrow JJ, Avorn J, Kesselheim AS. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA*. 2020;323(2):164-176.
71. Food and Drug Administration. The biomarker qualification process: a roadmap for requestors. 2021; <https://fda.report/media/107876/The-Biomarker-Qualification-Process--A-Roadmap-for-Requestors.pdf>.
72. Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. *Clinical pharmacology and therapeutics*. 2015;98(1):34-46.
73. Cure SMA. Our Strategy. 2021; <https://www.curesma.org/our-strategy/>.
74. Food and Drug Administration. A guide to drug safety terms at FDA. 2012; <https://www.fda.gov/media/74382/download>.
75. Food and Drug Administration. Prescribing information for Keytruda. 2020; [https://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf). Accessed 4/20/2021.

76. Sullivan HW, O'Donoghue AC, David KT, Patel NJ. Disclosing accelerated approval on direct-to-consumer prescription drug websites. *Pharmacoepidemiology and drug safety*. 2018;27(11):1277-1280.
77. Gellad WF, Kesselheim AS. Accelerated Approval and Expensive Drugs — A Challenging Combination. *New England Journal of Medicine*. 2017;376(21):2001-2004.
78. Dauner DG, Dauner KN, Peterson ALH. FDA's Unimproved Enforcement of Postmarketing Requirements and Commitments: Implications for Providers and Patients. *Research in Social and Administrative Pharmacy*. 2020;16(6):844-847.
79. DiMagno SSP, Glickman A, Emanuel EJ. Accelerated Approval of Cancer Drugs—Righting the Ship of the US Food and Drug Administration. *JAMA Internal Medicine*. 2019;179(7):922-923.
80. Detela G, Lodge A. EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation. *Molecular Therapy - Methods & Clinical Development*. 2019;13:205-232.
81. Dolan R. *Understanding the Medicaid Prescription Drug Rebate Program*. KFF; 2019-11-12 2019.
82. Sachs RE, Donohue JM, Dusetzina SB. Confronting State Medicaid Drug Spending Pressures. *JAMA*. 2020;324(18):1831-1832.
83. Medicaid and Chip Payment and Access Commission. April 2021 MACPAC Public Meeting. 2021; [https://www.macpac.gov/public\\_meeting/april-2021-macpac-public-meeting/](https://www.macpac.gov/public_meeting/april-2021-macpac-public-meeting/). Accessed 4/20/2021.
84. Medicaid and Chip Payment and Access Commission. High-Cost Specialty Drugs: Review of Draft Chapter and Recommendations. 2021; <https://www.macpac.gov/wp-content/uploads/2021/04/High-Cost-Specialty-Drugs-Review-of-Draft-Chapter-and-Recommendations.pdf>. Accessed 4/20/2021.
85. Centers for Medicare and Medicaid Services. Billing 340B Modifiers under the Hospital Outpatient Prospective Payment System (OPPS). 2018; <https://www.cms.gov/medicare/medicare-fee-for-service-payment/hospitaloutpatientpps/downloads/billing-340b-modifiers-under-hospital-opps.pdf>. Accessed 4/20/2021.
86. Stiglitz JE. Prizes, Not Patents. 2007; <https://www.project-syndicate.org/commentary/prizes--not-patents>. Accessed 4/20/2021.
87. Food and Drug Administration. Charging for Investigational Drugs Under an IND. 2016; <https://www.fda.gov/media/85682/download>. Accessed 4/20/2021.
88. Pallone F, Jr. H.R.3 - 116th Congress (2019-2020): Elijah E. Cummings Lower Drug Costs Now Act. 2019; <https://www.congress.gov/bill/116th-congress/house-bill/3>. Accessed 4/20/2021.
89. Aggarwal A, Fojo T, Chamberlain C, Davis C, Sullivan R. Do patient access schemes for high-cost cancer drugs deliver value to society?—lessons from the NHS Cancer Drugs Fund. *Annals of Oncology*. 2017;28(8):1738-1750.
90. Kaltenboeck A, Bach PB. Value-Based Pricing for Drugs: Theme and Variations. *JAMA*. 2018;319(21):2165-2166.
91. Kaltenboeck A. Pharmaceutical Products and Their Value: Lessons Learned and the Path Ahead. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2020;23(4):421-424.
92. Value-Based Contracts: 2009 - Q4 2019. 2020. <https://www.phrma.org/Fact-Sheet/Value-Based-Contracts-2009-Q4-2019>. Accessed 2/4/2021.
93. Garattini L, Curto A. Performance-Based Agreements in Italy: 'Trendy Outcomes' or Mere Illusions? *PharmacoEconomics*. 2016;34(10):967-969.
94. Kaltenboeck A, Bach PB. Outcomes-Based Drug Contracts Do Not Move Us Closer to Value - Morning Consult. *Morning Consult*. 2021.



# Appendix A: 2021 ICER Policy Summit

## Attendees

Representatives from the following companies attended ICER's 2021 Policy Summit, which was held virtually from March 11-12, 2021:

- AbbVie
- America's Health Insurance Plans
- Alnylam Pharmaceuticals
- Anthem Blue Cross Blue Shield
- AstraZeneca
- Biogen
- Blue Shield of California
- Boehringer Ingelheim
- CVS Caremark
- Envoke Pharmacy Solutions
- Express Scripts
- Genentech
- GlaxoSmithKline
- Harvard Pilgrim Health Care
- Health Care Service Corporation
- Humana
- Kaiser Permanente
- LEO Pharma
- Mallinckrodt Pharmaceuticals
- Merck & Co.
- National Pharmaceutical Council
- Novartis
- Pfizer
- Premera Blue Cross
- Prime Therapeutics
- Regeneron
- Sanofi
- uniQure
- UnitedHealthcare