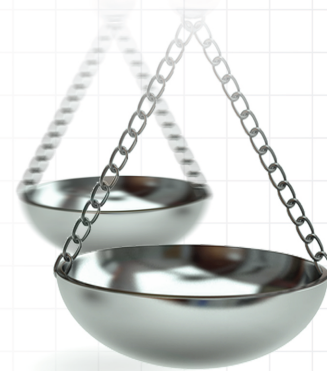




Potential policy reforms to strengthen the accelerated approval pathway

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The accelerated approval pathway for new drugs in the United States is often praised but faces growing criticism of whether it is finding the appropriate balance between uncertainty, access and cost. To support efforts to strengthen the pathway, this paper provides an analysis of key concerns and the advantages and disadvantages of ten potential policy reforms – those achievable through the US FDA action alone, and those that would require a combination of government, payer and life science industry actions. Accelerated approval sits at the heart of many of the controversies regarding drug approvals and pricing, and this analysis provides perspectives on how best to strengthen the pathway within the broader landscape of an innovative US healthcare system.

Tweetable abstract: New ICER policy analysis evaluates ten potential policy reforms to strengthen FDA's accelerated approval pathway for prescription drugs.

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The accelerated approval pathway (AAP) at the US FDA is in flux, and many would say, in crisis. This approval pathway is meant to expedite marketing authorizations of treatments that would otherwise face prohibitive logistical, feasibility or cost challenges in demonstrating efficacy and safety [1]. The distinguishing feature of accelerated approval is its reliance on surrogate endpoints, intermediate measures that must be 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.

When viewed broadly across all of the drugs approved through the AAP since its inception, the FDA has stated that it considers the pathway to be a success, particularly in oncology, where it points to the relatively small number of accelerated approvals that have failed later to confirm clinical benefits [2]. The agency's view is shared by many members of the patient community, who tout the program's ability to deliver access to groundbreaking treatments more rapidly [3,4].

However other patient groups and many policymakers view the AAP and its implementation as having lost the balance needed to ensure overall benefits to the patients and society [5–7]. The recent controversial approval of aducanumab through the AAP has highlighted many of these concerns [8–10]. Strongly worded condemnations claim that the FDA's use of the AAP has now fully succumbed to a gradual erosion in the standard of evidence deemed adequate for approval. In addition, there are longstanding concerns that the regulatory mechanism to ensure that drug sponsors perform high-quality confirmatory trials is ineffective, undermined by the lack of financial incentives and the apparent lack of will within the FDA to exercise their existing powers to withdraw approval when trials are not conducted expeditiously or fail to confirm the intended clinical benefit. Compounding the concerns of many stakeholders is the high price of most drugs approved through the AAP, a reflection of the lack of any mechanism to modulate pricing despite the greater uncertainty regarding clinical benefits for patients.

Thus, as the AAP nears the beginning of its fourth decade, the time is ripe to examine whether the intended balance between uncertainty and access is being achieved; 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 would benefit from reform.

We provide elsewhere a more comprehensive examination of the track record of accelerated approvals over many years, the core challenges of balancing uncertainty and early access with adequate incentives for confirmatory trials, and perspectives on whether the AAP is currently meeting its broader goals [11]. The goal of this paper is to focus on the analysis of potential options for reform of the AAP as policymakers re-examine how best to strengthen the pathway within the broader landscape of an innovative US healthcare system.

Methods

To inform this work, we performed a literature review focusing on the US experience with accelerated approval and surrogate endpoints. We also conducted 10 stakeholder interviews with representatives from patient community organizations, the life science industry, pharmacy benefit managers and commercial health plans.

From this background work, we developed a set of potential policy reforms reflecting different approaches to address some of the underlying areas in which the AAP could be strengthened. These potential policy reforms underwent further exploration in stakeholder interviews before being presented for formal discussion at a 2-day policy summit in March 2021. At this meeting, participants from 29 payer and life science companies discussed the proposed solutions and provided further suggestions for revisions to a draft version of this paper.

Policy reforms achievable through FDA action

Strengthen the selection of surrogate endpoints

We believe that greater clarity, transparency and consistency are needed in the process of judging whether surrogate endpoints will be accepted by the FDA as ‘reasonably likely’ to lead to patient benefit. Regulatory discretion in this process helps accommodate the breadth of treatments and potential endpoints the agency considers. However, 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 [12–14].

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 [15]. 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 have felt was exemplified by the approval decisions for eteplirsen in 2016 and aducanumab in 2021. 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.

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 rest 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 [16].

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.

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 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 [17]. 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.

Create a new label alert & 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 [18]. 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 gray 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 [19].

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 [20].

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.

Increase enforcement of requirements to complete confirmatory trials

This policy proposal calls on the FDA to maximize the 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 [21,22]. The agency could also wait to grant accelerated approval until there is a proof that confirmatory trials are either initiated or in progress [21,23].

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. However, 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 the FDA would find support from other stakeholders adequate to withstand the negative pressure from directly affected patients, clinicians and companies is not clear.

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. A law or regulation could be changed to automatically withdraw marketing authorization for an accelerated approval drug should its confirmatory evidence not be available for the FDA review by a predetermined 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 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 EMA, which requires that drugs with conditional approval be re-reviewed to ensure that they continue to justify the risk–benefit tradeoff [24]. However, as with any proposal for enhanced monitoring and enforcement, this approach would almost certainly require additional staff and resources.

Create a separate ‘Safety-only’ approval pathway that waives public or private insurance coverage requirements

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 for 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, 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 & life science industry actions

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

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 [25]. The MDRP could be modified for drugs with accelerated approval to require a higher rebate during the time between accelerated and full approval [21,26]. 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 [27,28].

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, but at a set level and regardless of benefit phase. In the Medicare Part B benefit, the policy would mirror a recent Centers for Medicare and Medicaid Services proposal to lower Medicare reimbursement for drugs acquired under the 340B program [29].

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.

Use pricing at marginal cost to incentivize completion of confirmatory trials, with consideration of a federal carve-out

Another reimbursement-driven approach for addressing cost concerns and 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 be able to move to full market pricing and could also receive a ‘prize’ payment to compensate for some of its ‘lost’ revenue since initial accelerated approval.

Implementation of this approach would require that drug makers report their marginal costs on a per-unit basis to Centers for Medicare and Medicaid Services, who would use the information to develop a benchmark for reimbursement, similar to the Average Sales Price. 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) [30].

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 could be too strong a disincentive to develop drugs for less well-understood diseases and therapeutic targets. The financial return might be insufficient to maintain innovation for ultrarare conditions and others that rely on surrogate endpoint trials to be developed within a reasonable timeframe. Companies that invest in ultrarare 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.

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 would be complex to implement given the fragmentation of healthcare provision and financing in the USA. 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 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 would struggle to manage.

Require payment be based on outcomes-based contracts

Outcomes-based contracts (OBCs), described as 'value-based' agreements by the industry, make some or all of the payment for a drug contingent on patient benefit. OBCs have been proposed as a way to reduce barriers to access while limiting some of the downside financial risk to health plans [31]. 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.

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 ability of OBCs to accomplish these goals is in question. Although a number of such arrangements are currently in place across different manufacturers and private payers in the USA, their use remains limited, particularly for accelerated approval products [32,33]. 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 [34].

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 the 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 the clinical performance.

Still, the complexities of OBCs that have made them difficult to launch in the private sector 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, Medicaid Best Price and the antikickback 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 [35].

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 the medical science.

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 toward drugs that do not help them and that contribute to healthcare 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 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 have analyzed ten 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 the 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 the 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.

Summary points

- The accelerated approval pathway (AAP) at the US FDA is in flux, and many would say, in crisis. This approval pathway is 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 must be 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.
- While the FDA and many members of the patient community consider the pathway to be a success, other patient groups and many policymakers view the AAP and its implementation as having lost the balance needed to ensure overall benefits to the patients and society.
- This paper presents ten potential policy reforms – those achievable through the FDA action, and those that would require payer and life science industry actions – and the advantages and disadvantages of each.
- These policy reforms include: strengthening the selection of surrogate endpoints; developing standardized accelerated approval review templates; requiring greater use of randomized controlled trials; creating a new label alert and patient material for accelerated approval drugs; increasing enforcement of requirements to complete confirmatory trials; creating an annual renewal cycle or sunset accelerated approvals lacking confirmatory evidence; creating a separate 'safety-only' approval pathway that waives public or private insurance coverage requirements; increasing mandatory federal rebate levels until time of full approval; using pricing at marginal cost to incentivize completion of confirmatory trials, with consideration of a federal carve-out; and requiring payment be based on outcomes-based contracts.
- Some of these policy reforms are straightforward in their aim of increasing institutional consistency and accountability in the FDA decision-making. Solutions in this category can largely be built on the existing scaffolding of the 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.
- As the AAP enters its fourth decade of striking a balance between uncertainty, access, innovation and cost, policy reforms are needed to strengthen its role in an innovative healthcare landscape.

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