

RECOMMENDATION 4: ENHANCE THE ACCELERATED APPROVAL PATHWAY

Key takeaways:

- FDA's accelerated approval program has led to early patient access to over 300 products.
- Despite this success, the program has proved controversial politically and publicly.
- FDA can improve the program through procedural reforms and enhancements to the advisory committee process. These efforts should be implemented in ways that maintain the program's success in accelerating availability to patients.
- Data from real-world clinical practice should play a larger role in efforts to ensure confirmatory studies are completed on a timely basis.
- FDA should leverage transparency to minimize unnecessary duplication with other agencies and improve regulatory predictability.

FDA's accelerated approval program, which enables medicines for some of the most serious diseases and conditions to be made available to patients sooner, has been the subject of recent controversy and reform efforts. New agency leadership has inherited a set of ongoing reforms and should work to ensure that they succeed in putting the program on a stronger footing and enhance the core goal of accelerating availability to patients.

The accelerated approval program, first instituted in 1992, grew out of activism by patients during the HIV/AIDS epidemic who lacked treatment options and argued that they not should suffer or die while waiting for multiyear studies to definitively verify the clinical benefit of promising medicines.^{140,141} Earlier access can be critical for patients in many circumstances, especially when timely treatment is important but the course of the disease is lengthy or variable enough that it may take many years before a drug's intended clinical benefit can be fully evaluated—a common fact pattern for many oncology and rare disease indications.

Under the accelerated approval pathway, a drug or biologic for a serious or life-threatening disease or condition may be approved based on evidence demonstrating that it has an effect on a surrogate or intermediate endpoint that is “reasonably likely to predict” clinical benefit, rather than waiting an extended period of time for completion of studies to fully measure clinical benefit.¹⁴² Although the evidentiary standard is the same as for traditional approval, the outcome being measured is different. Instead of providing evidence of a beneficial clinical outcome, the sponsor can instead provide evidence that the product has an effect on a biomarker (e.g., a laboratory measurement) or intermediate clinical measurement that is not itself beneficial enough to support approval but is thought to be predictive of actual clinical benefit.^{142,143}

By using these alternative endpoints, patients can access products that provide meaningful advantages over available therapies years earlier than would be possible through the traditional approval process. But because the approval is based on a prediction of clinical benefit rather than a demonstration

of benefit itself, FDA typically requires the sponsor to conduct post-approval studies to confirm benefit, and can withdraw approval if, among other things, the studies are not completed or the product fails to show benefit.^{142,144}

The program has been incredibly successful at accelerating the availability to patients of safe and effective products. Since its inception in 1992, FDA has granted accelerated approval to more than 300 products (over 100 of which are for rare disease) and, as of December 2021, has converted 50% of accelerated approvals into traditional approvals based on a demonstration of clinical benefit.^{145–147} For these converted drugs, the median time from accelerated approval to conversion was 3.2 years—meaning a median of 3.2 years of earlier availability to patients relative to traditional approval.¹⁴⁷ The accelerated approval has transformed cancer care,¹⁴⁸ turned HIV/AIDS into a controllable disease, and offers promise for rare disease.¹⁴⁹

Despite these successes, the program has proved controversial. FDA has faced well-founded criticism over whether it is doing enough to ensure that confirmatory studies are completed on a timely basis and that products are withdrawn as appropriate.^{146,150,151} (As of December 2021, 12% of accelerated approvals had been withdrawn.)¹⁴⁷ In addition, individual approval decisions have proven contentious due to disagreement over which endpoints are “reasonably likely to predict” benefit, or when accelerated approval should be used for products that initially came to the agency seeking traditional approval.^{150,152} These controversies can diminish public confidence in products approved through the accelerated approval pathway and have led payors including CMS to restrict coverage in some circumstances.^{153,153–155}

In December 2022, Congress passed a set of reforms to address some controversial elements of the program. These reforms included, among other things, expedited procedures for withdrawing approval and provisions to improve the completion rate for confirmatory studies, including the requirement for FDA to set study conditions before approval and authorizing the agency to require the studies be underway before accelerated approval.¹⁵⁶

FDA is now implementing these reforms. For example, it has published draft guidance on new statutory processes and established an intra-agency accelerated approval council to coordinate activities and promote consistent use of the pathway.^{143,157,158} As new leadership assumes responsibility for these works in progress, there are significant opportunities to enhance the program and ensure a well-functioning pathway for accelerating the availability of critical medicines.

Recommendation 4.1: FDA should facilitate more data from real-world clinical practice in confirmatory studies

Recent reforms have tried to address the completion rate for confirmatory studies by regulating how far along the study should be at the time of approval, but perhaps the most important tool FDA has to improve completion is in the design of the studies themselves. FDA has been working to facilitate studies that are designed to maximize the chance of success and avoid common pitfalls. Data from real-world clinical practice should play a larger role in these efforts.

One of the biggest challenges for confirmatory studies is that once a drug is approved and can be accessed on the market outside of the research setting, it becomes more difficult to recruit patients and conduct ongoing trials.¹⁵⁷ In addition, many studies require years of treatment and follow-up, making retention an issue.¹⁴³ FDA has been encouraging various innovative trial designs that can help overcome these challenges,¹⁴³ but it has provided little to no guidance on using data from real-world clinical practice for this purpose. The gap is surprising because RWE studies are a powerful tool for understanding how patients in real clinical settings may or may not be benefiting from a product, without having to ask patients to risk changing their care.¹⁵⁹

While it would be challenging to fully replace existing confirmatory requirements with RWE studies,¹⁶⁰ RWE can nonetheless be an important element of a confirmatory study plan—and, indeed, there are multiple examples in which FDA has agreed to confirmatory evidence that included real-world data elements such as registries, chart reviews, medical and claims records, and prospective data collection.¹⁶¹ FDA should update its guidance to highlight the important role that such evidence can play and help product sponsors identify appropriate use cases.

Recommendation 4.2: Pursue reform strategies that address programmatic concerns while prioritizing early availability to patients

As FDA continues to implement reforms to strengthen the accelerated approval program and address concerns with its operation, it is important that the agency do so in a way that respects and builds upon the pathway's considerable historical success in accelerating the availability of drugs to patients.

Process concerns with the accelerated approval pathway are generally limited to a narrow subset of total actions—a point underscored by a recent report from the HHS Office of Inspector General that identified concerns with FDA's actions in only a small percentage of total approvals, all of which related to FDA procedural decisions regarding the handling of scientific disagreement, documentation of meetings, and the use of analyses not included in sponsors' original analysis plans.¹⁵²

The challenge for FDA is to implement reforms that address high-profile concerns without disrupting a pathway that works well in the overwhelming number of cases. The agency can accomplish this through targeted reforms to the accelerated approval program in combination with broader reforms to the agency's advisory committee process.

Concrete steps the agency can take include:

- *Establishing regularized and flexible procedures:* FDA should work through the Accelerated Approval Council to develop and publicize updated procedures for evaluating endpoints and determining whether the accelerated approval standard has been met, including procedures on how to manage scientific disagreements. The procedures need not establish a formal role for the council, which could complicate intra-agency appeals,¹⁵² and should be flexible enough to allow for product-specific judgments and maintain a clear process for leadership to manage disagreement. The goal of these reforms should not be to make any substantive outcome more or less likely, but to establish a regularized, principled, and well-documented process that provides transparency and instills greater public confidence in the agency's scientific decision-making.
- *Updating guidance on withdrawal after a failed confirmatory trial:* FDA recently provided new guidance on the procedures for withdrawing accelerated approval, but the guidance is focused on process rather than explaining how FDA will apply the substantive standard for determining when withdrawal is appropriate.¹⁴³ The guidance should be updated to discuss when the failure of a confirmatory study to establish benefit will—and, importantly, will not—warrant withdrawal of approval. As senior FDA leaders recently explained, there are many reasons why a study might fail to show benefit, and it is important to understand to what extent the failure is attributable to problems with the study (e.g., methodology or dosage) as opposed to problems with the drug.¹⁶² Guidance on how FDA intends to apply this principle would provide needed clarity for product sponsors and the public alike.
- *Ensuring that new policies do not meaningfully delay patient access:* In recent draft guidance implementing the 2022 legislative reforms, FDA announced a new policy that “FDA generally intends to require that the confirmatory trial(s) be underway prior to the accelerated approval

action.”¹⁶² This policy is expected to facilitate more timely completion of confirmatory requirements, but depending on how it is implemented, it also carries the potential risk of delaying accelerated approvals by shifting activities from post-market to pre-market. FDA should carefully analyze this risk and closely track the timing of accelerated approval actions relative to the start of clinical studies so that the agency can understand and address any impact.

FDA can also strengthen the accelerated approval pathway by improving its use of advisory committees. FDA’s advisory committees are panels of outside scientific experts and community members (including industry, consumer, and patient representatives) who provide advice and recommendations to inform agency decisions. They provide this advice through both public discussion and nonbinding votes, which can not only improve the quality of FDA’s decisions by expanding the expertise and viewpoints that the agency considers, but also help build public confidence in those decisions by providing transparency into the deliberative process.^{163,164} However, FDA has been criticized as falling short of this ideal, including with respect to its recruitment of committee members and the procedures by which it conducts meetings and considers the committee’s advice.^{165,166}

As FDA evaluates potential reforms to its use of advisory committees—a process it has already initiated¹⁶⁴—it should include measures that would help address concerns with the accelerated approval program in particular. These include:

- *Requiring a written public statement explaining any decision to approve a product after an advisory committee voted against approval:* Whereas FDA almost always follows committee recommendations to approve a drug, it departs more frequently when the committee votes against approval (97% versus 67%).¹⁶⁷ A requirement to explain these departures would not change the bar for approval, but it would allow the public to better understand the agency’s rationale. In many cases, the explanation may reveal that the agency did not ignore the committee’s recommendation, but rather that the committee process revealed problems with an application that the sponsor was able to address.¹⁶⁸
- *Establishing clear rules for when to reconvene committees:* When an advisory committee votes against approval and the sponsor subsequently addresses issues with its application, or the agency decides to consider the application under a different approval pathway (e.g., accelerated rather than traditional approval), it should trigger a process for deciding whether to reconvene the advisory committee to consider the new information. While the agency should maintain flexibility with respect to its substantive decisions, clear rules about what types of changes warrant reconvening could help foster confidence in the ultimate decision.
- *Updating committee procedures to provide fair scientific consideration:* For advisory committee meetings to serve

their purpose, they must be organized around the principle of genuine scientific inquiry and not designed to achieve a preordained result. FDA has been criticized in this regard for, among other things, not providing enough time for the public to review meeting materials (which may be distributed as little as 48 hours before the meeting),^{165,169} or posing “leading” questions to the committee that appear weighted toward a particular outcome.¹⁷⁰ FDA should adopt standardized procedures that revise these practices and strengthen the advisory committees as a tool for appropriately managing divergent scientific views, such as those that may arise when evaluating whether an endpoint is predictive of clinical benefit.

Recommendation 4.3: FDA should minimize unnecessary duplication with other agencies

Although policies for the payment and reimbursement of accelerated approval drugs fall outside of FDA’s purview, these policies can have a significant impact on patient access. FDA can help CMS minimize duplicative scientific reviews and facilitate patient access by improving how it explains its accelerated approval decisions.

Once FDA approves a drug, coverage under Medicare is determined based on whether the product is “reasonable and necessary for the diagnosis or treatment of illness or injury.”¹⁷¹ Although historically CMS has applied this standard to cover drugs approved through the accelerated approval pathway in the same fashion as other drugs, more recently it has taken a different approach. In the context of a 2022 National Coverage Determination, CMS announced that Medicare coverage for accelerated approval drugs will depend on whether “there is scientific evidence that the surrogates directly affect [sic] the clinical outcomes,” and applied this standard to restrict coverage for a class of drugs based on CMS’s evaluation of the scientific evidence.¹⁵³ In 2023, CMS announced that it was working in consultation with FDA to develop a new payment model that would reduce Medicare Part B payments for accelerated approval drugs until they have generated confirmatory evidence.^{172,173}

These coverage policies may reduce federal spending and strengthen financial incentives for completing confirmatory studies,⁴⁶ but they also risk limiting access to treatments for serious diseases and conditions under circumstances where FDA has already reviewed the scientific evidence and determined that the product should be made available to address unmet need.¹⁷⁴ Over time, they may also depress developer interest in utilizing the accelerated approval pathway. While FDA does not have purview over how CMS applies the “reasonable and necessary” standard, and it should not modify its own review to account for considerations that CMS may bring to bear, FDA should update how it presents the information from the reviews it is already conducting to minimize the risk that coverage decisions will create duplicative work or undermine the broader access goals of the accelerated approval program.

Goals for this effort should include:

- *Minimizing duplication of effort:* Although accelerated approval and Medicare coverage are governed by different statutes, the underlying science for a given drug does not change between the two contexts. To the extent FDA has already analyzed a scientific question in the context of an approval decision, it is unnecessary and wasteful for CMS to relitigate the same scientific question when evaluating coverage. FDA should work with CMS to ensure that its scientific assessments are presented in a manner that improves CMS's ability to rely on them rather than relitigate the same question.
- *Focusing on what matters most to patients:* FDA should ensure that when patient preference information (PPI) is available as part of an approval package, it highlights that information to help inform CMS coverage decisions. Patient preferences are particularly important in the context of accelerated approval: When FDA evaluates whether an endpoint is reasonably likely to predict clinical benefit, the agency must determine—implicitly or explicitly—how much uncertainty is appropriate in a particular therapeutic context. Using quantitative PPI at the early stage of regulatory submissions (e.g., when applying for accelerated approval or in early trial phases) to identify patient priorities and tolerance for uncertainty would improve the transparency of FDA's decisions and facilitate CMS reliance. Likewise, by providing CMS with this information, FDA can help CMS focus its own evidentiary requirements on questions that are relevant and fit for purpose.
- *Maximizing predictability:* To the extent that FDA and CMS standards do not overlap, product sponsors should have clarity and predictability as to what the differences are and how they will be applied. The current approach does not meet this goal; under CMS's recently articulated position, it may restrict coverage even after FDA determines that the scientific evidence is strong enough to support accelerated approval, as long as the internal Medicare coverage group determines that the evidence is not sufficiently robust or “direct”—a standard that CMS has yet to define.¹⁵³ While it would be inappropriate for FDA to modify its own evidentiary requirements to require development of information to satisfy the “reasonable and necessary” standard, FDA should work with CMS to ensure that any differences between the approval and coverage standards are clearly identified and explained so that product sponsors can organize their development programs accordingly. Enabling sponsors to generate data with both agencies' review processes in mind would improve efficiency and potentially reduce the time and inconsistency between regulatory approval and coverage.
- *Maintaining appropriate incentives:* FDA should also provide input on how any novel payment models for

accelerated approval drugs might affect drug developers' use of the pathway. If CMS uses a new payment model to reduce reimbursement for accelerated approval drugs until the sponsor generates confirmatory evidence, it could potentially disadvantage use of the pathway when considered in combination with other laws. Price restrictions enacted under the IRA can take effect as early as nine or 13 years after a drug or biologic is first approved, regardless of whether the approval was under the traditional or accelerated approval pathway.⁴⁵ If a new payment model reduces reimbursement on the front end until there is confirmatory evidence, and the IRA reduces payment again on the back end, it could leave developers with a narrower opportunity for financial returns on accelerated approval drugs relative to other products. In some cases, it may also lead developers to forgo the accelerated approval pathway altogether in favor of traditional approval, which would carry fewer reimbursement risks. Given where FDA sits in the regulatory ecosystem compared with CMS, the agency can play an important role in monitoring development activity for signs of potential impacts, and make that information available on an aggregated basis to CMS and the public.