Accelerated Approval

AV HEALTH CARE POLICY BRIEF

Improving FDA Evidence Standards for Drugs and Biologics Approved Under the Accelerated Approval Pathway

THE ISSUE: The U.S. Food and Drug Administration (FDA) established the accelerated approval pathway over 30 years ago with a careful balance in mind: allowing access to promising therapies today, while obtaining confirmatory evidence of direct patient benefits later. Specifically, the pathway allows earlier approval through the use of surrogate endpoints, which substitutes for direct clinical outcome measures. Sponsors then need to verify the clinical benefit of the drug through adequate and well-controlled confirmatory trials.[1]

The pathway has shown that it can be highly beneficial to patients with an unmet medical need when well-designed clinical trials produce early, promising evidence of clinical benefit. However, some surrogate endpoints are poor predictors of the effects of drugs on patient health outcomes.[i,2]

In addition, post-approval confirmatory trials are often delayed.[3] As a result, there have been cases where accelerated approval led to patient harms and unnecessary spending[4] after drug companies failed to confirm[5] the predicted clinical benefit in a timely manner.[6]

Given the careful balance described above, FDA has the authority to withdraw a product from the market if the drug ultimately fails to show direct patient benefits that outweigh its risks; however, the agency rarely does so. In addition to the need for additional FDA resources, there are also inadequate incentives in place to motivate manufacturers to complete confirmatory trials in a timely manner. Products granted accelerated approval can command high prices and generate significant profits before demonstrating clinical benefit. This means that manufacturers are more incentivized to delay actions that may ultimately result in withdrawing their product from the market.[7]

For the public, patients, and the medical community to trust the value of accelerated approval drugs, reforms are needed.

THE EVIDENCE: To date, FDA has granted 375 accelerated approvals.[8] In a 2022 review, HHS' Office of the Inspector General (OIG) found that of the 278 drug applications granted accelerated approval at the time, 104 had incomplete confirmatory trials.[9] In a 2025 report, HHS OIG highlighted the example of eteplirsen, was approved in 2016 to treat Duchenne muscular dystrophy.[10] As of January 2025, its confirmatory trials remain unfinished, despite an original deadline of November 2020.[11] Eteplirsen can cost more than $1 million per year for a one-time treatment and patients and payers in the U.S. spent $2.6 billion over 2017-2022 period on this drug.[12]

Further:

- In 2019, Medicare net spending on drugs with at least 1 accelerated approval indication was $9.1 billion (Part D: $3.2 billion; Part B: $5.9 billion).[13] From 2018 to 2021, Medicare and Medicaid spent billions on accelerated approval drugs that were past their planned confirmatory trial completion date and had yet to verify a clinical benefit.[14]
- In 2020 alone, Medicaid net spending on drugs with an accelerated approval indication was $1.4 billion.[15]
- From 2015–2020, Medicaid spent $6.7 billion after estimated rebates on drugs with accelerated approval. Of the $6.7 billion, 33 percent was for drugs exclusively marketed for indications approved through the accelerated approval pathway. Another 31 percent was for drugs with accelerated approval that, after at least five years, had yet to complete confirmatory trials.[16] During this period, total Medicaid net spending on drugs with at least 1 accelerated approval indication doubled.

i In contrast, direct endpoints are clinically meaningful endpoints that directly measure how a patient feels, functions, or survives. Direct endpoints are customarily the basis for traditional approval of new drugs and biologics.

The Food and Drug Omnibus Reform Act (FDORA) of 2022 ushered in important first steps towards reforming the accelerated approval pathway. Specifically, FDORA modified the accelerated approval pathway by (1) requiring confirmatory trials be underway at time of accelerated approval, (2) requiring sponsors to submit bi-yearly progress reports on these trials, and (3) encouraging FDA to withdraw drugs that fail to confirm clinical benefit.[17] However, continued Congressional and FDA action is warranted to address patient safety concerns, elevate evidence standards, increase data transparency, and withdraw drugs that do not confirm clinical benefit.[18]

THE SOLUTIONS: Policymakers should create stronger incentives for manufacturers of accelerated approval drugs to collect meaningful, timely confirmatory evidence to inform provider, patient, and payer decisions. This includes several options:

FDA Policy Modifications

- Premarket
  - Delineate a clearer framework to ensure more consistent and appropriate use of the accelerated approval program
  - Seek medical and scientific consensus (e.g. consult FDA advisory committees) regarding the use of surrogate endpoints approval.[19]
  - Publicly display a standardized accelerated approval review template that includes a structured explanation for why accelerated approval was deemed necessary and the justification for use of the chosen surrogate endpoint.
- Postmarket
  - Automatically withdraw accelerated approval drugs or indications when the confirmatory trial does not show clinically relevant, direct benefits for patients.[20]
  - Provide FDA the ability to levy fines and other penalties for developers who fail to complete postmarket studies in a timely manner.[21]
  - Mandate that confirmatory trials focus on a primary endpoint.[22]
  - Revise product labeling to ensure providers and patients know whether a product was approved using a surrogate endpoint via the accelerated approval pathway.[23]
  - Streamline the expedited withdrawal process to avoid dangerous or ineffective drugs staying on the market for longer than necessary (e.g. allow for notification and withdrawal when there is a serious public health concern).

Payment Policy Modifications

Policymakers have several options to incentivize the timely completion of confirmatory trials for accelerated approval drugs by modifying reimbursement for public payers:

- Require manufacturers to offer additional price concessions to public insurance programs for drugs receiving accelerated approval until the confirmatory trials are completed.[24]
  - Increase the Medicaid minimum rebate percentage on drugs that receive accelerated approval until the manufacturer has completed the post marketing confirmatory trial and been granted traditional FDA approval.[25]
  - Increase the Medicaid inflationary rebate on drugs that receive accelerated approval if the manufacturer has not completed the postmarketing confirmatory trial and been granted traditional FDA approval after 5 years.[26]
  - Provide a mandatory discount to Medicare on drugs that receive accelerated approval until the manufacturer has completed the post-marketing confirmatory trial and been granted traditional FDA approval.
- Set Medicare reimbursement for accelerated-approval drugs at the same or lower price as drugs approved through traditional, non-expedited pathways with the same indication until confirmatory trials are completed and show direct clinical benefit.[27]
- Allow government payers to reimburse accelerated approval drugs or indications based on the cost of manufacturing the drug plus an agreed-upon markup, until confirmatory trials demonstrate clinical benefit.[28]
- Allow government payers to limit reimbursement to an amount near the cost of manufacturing and delivering the drug if the trial sponsor fails to complete its confirmatory trial by the agreed upon completion date.[29]

ENDNOTES

1 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.500.

2 https://jamanetwork.com/journals/jama/fullarticle/2648631.

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5 https://www.bmj.com/content/374/bmj.n1959.

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7 https://www.fda.gov/media/151146/download.

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9 https://oig.hhs.gov/oei/reports/OEI-01-21-00401.pdf.

10 https://oig.hhs.gov/documents/evaluation/10160/OEI-01-21-00400.pdf

11 Ibid.

12 https://jamanetwork.com/journals/jama/fullarticle/2816420.

13 https://jamanetwork.com/journals/jama-health-forum/articlepdf/2786897/rome_2021_ld_210024_1638463484.49075.pdf.

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23 Ibid.

24 https://www.nejm.org/doi/10.1056/NEJMp1700446.

25 https://www.macpac.gov/wp-content/uploads/2021/06/Chapter-1-Addressing-High-Cost-Specialty-Drugs.pdf.

26 Ibid.

27 https://www.commonwealthfund.org/blog/2021/reducing-spending-prescription-drugs-limited-clinical-evidence.

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