Accelerated Approval

AV Health 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 30 years ago to speed the approval of drugs and biologics that treat serious conditions and fill an unmet need by permitting clinical trials to use surrogate endpoints[A] and requiring confirmatory clinical evidence be collected later. Some drugs and biologics approved through the accelerated approval pathway will have a strong, direct patient benefit on survival, symptoms and/or patient function, as is true with drugs used to treat HIV/AIDS.[1] Others, however, could turn out to have no direct clinical benefit, unnecessary costs, and pose considerable risk to patients after years of market access.

Accelerated approval is often based on indirect measures of patient health status (e.g., laboratory measurements, radiographic images, physical signs or other measures), rather than the effects on direct patient outcomes (e.g., survival, improved daily function, and symptom abatement). Indirect measures can be used as surrogates to predict whether an intervention affects patients but are not themselves direct measures of how well a drug treats a patient with a particular disease.

Central to the accelerated approval pathway is the need for post-approval studies to be conducted in a reasonable timeframe, using direct patient outcomes[B] to confirm clinical benefits to patients. Although the 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, it rarely does so.

There are inadequate incentives to ensure manufacturers complete confirmatory trials. Products granted accelerated approval can command high prices and generate significant profits before demonstrating clinical benefit. This means that the product's manufacturers have less incentive to complete confirmatory trials and risk being withdrawn from the market.[2]

$9.1 BILLION

Medicare net spending on drugs in 2019 with at least one accelerated approval indication was $9.1 billion (Part D: $3.2 billion; Part B: $5.9 billion).[3] 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.[4]

$1.4 BILLION

Medicaid net spending on drugs with at least one accelerated approval indication in 2020.[5]

The accelerated approval pathway was created to strike a careful balance: access to promising therapies today, obtaining confirmatory evidence of direct patient benefits later. This pathway can be highly beneficial to patients with an unmet medical need when well-designed clinical trials demonstrate promising evidence of a clinical benefit during earlier stages of drug development. However, there are other instances where the use of accelerated approval leads to patient harms and unnecessary spending when brand-name drug companies fail to confirm the predicted clinical benefit in a timely manner. For the public and medical community to trust the value of accelerated approval drugs to patients, reforms and timely completion of confirmatory trials are needed.

A Surrogate endpoints can be used as a substitute for a direct endpoint if they are expected to reflect changes in a clinically meaningful endpoint. This expectation must be supported by strong data ("validated"). Simple correlations between the surrogate and the direct endpoint, no matter how strong, are not enough. Unless validated, the relationship between surrogate and direct benefit may not be causal.

B 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.

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THE EVIDENCE

By June 2023, FDA issued 300 accelerated approvals, most for oncology drugs.[10] Some drugs or biologics are exclusively marketed for indications approved under the accelerated approval pathway, while others have several approved indications for which the accelerated approval pathway is used for a subset. As required by law and regulation, sponsors of drugs that use the accelerated approval pathway must verify and confirm the clinical benefit of the drug through adequate and well-controlled confirmatory trials after the drug is marketed.[11] However, post-approval confirmatory trials are often delayed.[12, 13,14] As shown over time, some surrogate endpoints can be poor predictors of the effects of drugs on patient health outcomes.[15] For example, in a study of 90 drug indications approved based on surrogate endpoints, at the time of approval, only 27 of the oncology indications and 8 of the non-oncology indications were found to have any added therapeutic benefit compared to alternatives.[16, 17]

In 2019, Medicare spent $9.1 billion (Part D: $3.2 billion; Part B: $5.9 billion) after estimated rebates on drugs with at least 1 indication that was approved using the accelerated approval pathway.[18] During 2015-2020, Medicaid spent $6.7 billion after estimated rebates on drugs with accelerated approval, of which 33 percent were on drugs exclusively marketed for indications approved under the accelerated approval pathway, and 31 percent on drugs approved under the accelerated approval pathway that, after at least five years, have yet to complete the confirmatory trial.[19] During this period, total Medicaid net spending on drugs with at least one accelerated approval indication doubled.

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.[20] However, continued congressional and FDA action is warranted to address outstanding concerns related to payment policy and FDA regulatory actions. As discussed during a recent National Academy of Medicine workshop, experts expressed an urgent need for continued congressional and FDA action to address patient safety concerns, elevate evidence standards, increase data transparency, and withdraw drugs that fail to confirm clinical benefit.[21]

15% INCREASE

The amount the Medicare actuary increased the standard monthly Medicare Part B premium (by $21.60) – the largest dollar increase in the history of the insurance program – at the time of approval in part because of expected cost and utilization of Aduhelm[6]. Despite a small premium decrease in 2023 because Aduhelm utilization and price were ultimately lower than expected, the majority of the 2022 increase remained.[7]

300

The number of accelerated approvals granted by the FDA to date.[8] Of the 278 drug applications granted accelerated approval from the start of this approval pathway, 104 have incomplete confirmatory trials.[9]

THE SOLUTIONS

Policymakers can create stronger incentives for manufacturers of accelerated approval drugs to collect meaningful, timely confirmatory evidence to inform provider, patient, and payer decisions. The following policy options are supported by research from a variety of experts, including the Institute for Clinical and Economic Review (ICER), the Medicaid and CHIP Payment and Access Commission (MACPAC), the Medicare Payment Advisory Commission (MedPAC), the Brookings Institution, and the Program on Regulation, Therapeutics, and Law (PORTAL) at Harvard Medical School and Brigham & Women's Hospital.

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.[22]
  - 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.[23]
  - Increase the Medicaid inflationary rebate on drugs that receive accelerated approval if the manufacturer has not completed the post-marketing confirmatory trial and been granted traditional FDA approval after 5 years.[24]
  - 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.[25]
- 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.[26]
- Allow government payers to limit reimbursement to an amount near the marginal or average cost of producing and delivering the drug if the trial sponsor fails to complete its confirmatory trial by the agreed upon completion date.[27]

FDA Policy Modifications

- Automatically withdraw accelerated approval drugs or indications when the confirmatory trial does not show clinically relevant, direct benefits for patients.[28]
- Restrict the use of accelerated approval so it is not a regulatory pathway for acute diseases.
- Ensure manufacturers comply with requirements for post-market studies in a timely manner.[29]
- Seek medical and scientific consensus regarding the use of clinician reported outcomes or other surrogate endpoints in any type of disease before it is used in drug development and drug approval (e.g., FDA advisory committee on the evidence supporting use of candidate surrogate outcomes), including how surrogate endpoints are chosen and what features allow them to serve as the basis for accelerated approval.[30]
- Mandate confirmatory trials use direct measures of patient outcomes.[31]
- Revise product labeling to ensure providers and patients know whether a surrogate endpoint was used to convert a drug from accelerated approval to traditional approval.[32]
- Require confirmatory trial protocols be finalized as a condition of accelerated approval.[33, 34, 35]
- 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.

ENDNOTES

1 https://www.fda.gov/media/86284/download
2 https://www.fda.gov/media/151146/download
3 https://jamanetwork.com/journals/jama-health-forum/articlepdf/2786897/rome_2021_ld_210024_1638463484.49075.pdf
4 https://oig.hhs.gov/oei/reports/OEI-01-21-00401.pdf
5 https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2021.00762
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