The U.S. Food and Drug Administration (FDA) established the Accelerated Approval Program 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 and requiring confirmatory clinical evidence be collected at a later date. 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. Others, however, may not show a direct clinical benefit and could 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 meant as a substitute or “surrogate” for direct patient outcomes), rather than the effectiveness on direct patient outcomes (e.g., survival, improved patient function in their daily lives, and symptom abatement). Surrogate endpoints can be used to predict the treatment effect of an intervention on direct patient clinical outcomes, 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 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 outweighs its risks, it rarely does so.

There are inadequate incentives to ensure manufacturers complete confirmatory trials. Sponsors often charge unjustifiably high prices based on an assumption that direct patient benefits have already been demonstrated, when this is not typically the case. If companies are granted approval with the ability to launch at high prices before they’ve demonstrated a clinical benefit, they have less incentive to complete confirmatory trials. This is especially true if these studies fail to confirm a clinical benefit and lead to the product’s market withdrawal.

The accelerated approval pathway was created to strike a careful balance: access to promising therapies today, obtaining confirmatory evidence of direct patient benefits later. But for the public and medical community to trust the value of drugs approved through the accelerated approval pathway, reforms and timely completion of confirmatory trials are needed.

From 1992 - 2020, FDA granted more than 250 accelerated approvals, most for oncology drugs. Some drugs or biologics are exclusively marketed for indications

### THE EVIDENCE

- **$9.1 BILLION**
  Medicare net spending on drugs in 2019 with at least 1 accelerated approval indication (Part D: $3.2 billion; Part B: $5.9 billion)

- **$1.4 BILLION**
  Medicaid net spending on drugs in 2020 with at least 1 accelerated approval indication

- **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 because of expected cost and utilization of Aduhelm.

- **253**
  The number of accelerated drug approvals the FDA has granted to date. From 1992 – 2020, nearly half (112) of the 253 drugs that received accelerated approval have not been confirmed clinically effective.
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.\(^9,10\) However, post-approval confirmatory trials are often delayed and many have been found to use the same incompletely validated surrogate endpoints from the preapproval trials.\(^11\) As shown over time, some surrogate endpoints can be poor predictors of the effects of drugs on patient health outcomes.\(^12\) As of July 2021, of the 18 accelerated approval indications with negative post-approval trials (those that did not confirm a clinical benefit), six remained on formal FDA approved drug labelling and continued to be recommended in clinical guidelines.\(^13\)

In 2019, Medicare spent $9.1 billion (Part D: $3.2 billion; Part B: $5.9 billion) on drugs with at least 1 indication that was approved using the accelerated approval pathway.\(^14\) From 2015 – 2020, Medicaid spent $6.7 billion 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.\(^15\) During this time period, total Medicaid net spending on drugs with at least 1 accelerated approval indication doubled.

**THE SOLUTIONS**

Policymakers have a variety of options to 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 can be used alone or in combination and 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), Dr. Richard Frank, and Dr. Aaron Kesselheim.

**Payment Policy Modifications**

- Require manufacturers to offer additional price concessions to public insurance programs for drugs receiving accelerated approval until the confirmatory trials are completed.\(^16\)
  - 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.\(^17\)
  - 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 a specified number of years.\(^18\)
  - 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.
- Direct CMMI to test an approach to incentivize rapid completion of confirmatory trials, particularly for drugs that treat cancer, to ensure that Medicare is paying for drugs with the most clinical value to patients.\(^19\)
- Require accelerated approval drugs to be eligible for government negotiation.\(^20\)
- Set Medicare reimbursement for accelerated approval drugs at the same price as drugs approved through traditional, non-expedited pathways with the same indication until confirmatory trials are completed and show direct clinical benefit.\(^21\)
- 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.\(^22\)

**FDA Regulatory Modifications**

- Limit use of accelerated approval and surrogate endpoints to chronic diseases where it may take years to ascertain direct patient benefits.
- Ensure manufacturers comply with requirements for postmarket studies in a timely manner.\(^23\)
- 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 a candidate surrogate outcomes in a specific disease in a specific patient population prior to use in a confirmatory trial), including how surrogate endpoints are chosen and what features allow them to serve as the basis for accelerated approval.\(^24\)
• Require clinical trial sponsors to outline the use of any surrogate endpoint and the supporting evidence and reach agreement with FDA on their use prior to beginning confirmatory trials.

• Mandate confirmatory trials use direct measures of patient outcomes, not biomarkers that have not undergone validation.25

• 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.26

• Require confirmatory trial protocols be finalized, and agreed upon, as a condition of accelerated approval.27, 28

• Require that drugs granted accelerated approval be made available via expanded access between the time accelerated approval was granted and the initiation of the confirmatory trial as an incentive to initiate confirmatory trials in a timely manner.

• Publicly report the status of confirmatory trials at least annually, and when the confirmatory trial is completed and reported, require that trial findings be promptly released.29

• Automatically withdraw accelerated approval drugs or indications when the confirmatory trial does not show clinically relevant, direct benefits for patients.30

• Launch public initiatives and include wording in drug labeling so that patients and providers are aware that the evidence for drugs that receive accelerated approval lacks evidence of the drugs effect on direct patient outcomes and that the indication will be revoked, but still made available via expanded access, if confirmatory trials fail to verify clinical benefit.31

ENDNOTES

1 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.


3 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.

4 https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals


8 https://www.fda.gov/media/88907/download

9 https://www.bmj.com/content/374/bmj.n1898.full


13 https://jamanetwork.com/journals/jama_internmedicine/fullarticle/2764287


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


20 https://jamanetwork.com/journals/jama/fullarticle/2785217


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


25 https://jamanetwork.com/journals/jama_internmedicine/fullarticle/2782120

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28 https://jamanetwork.com/journals/jama_internmedicine/fullarticle/2782120

29 https://www.nature.com/articles/s41571-018-0066-3

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