MEDICAID EVIDENCE REVIEW AND COST INITIATIVE BRIEF

Impact of FDA Accelerated Approval on Medicaid

OVERVIEW

State Medicaid insurance coverage for individuals experiencing poverty or disability is a core component of our national health infrastructure, enabling access to care for vulnerable populations. Simultaneously, the US Food and Drug Administration (FDA) accelerated approval program is a faster pathway to approval for drugs that treat serious and life-threatening illnesses. These critical programs create access to treatment and support the health care needs of individuals made vulnerable by poverty, disability, and serious illness.

However, policymakers have struggled to address the unintended consequences of the FDA accelerated approval process for state Medicaid drug coverage. The mandate for Medicaid to cover FDA-approved drugs[1] results in barriers to Medicaid programs using evidence from clinical trials and peer-reviewed literature. In most cases, a state Medicaid program cannot restrict use of a drug, recommend dosage amounts, or curtail coverage when the FDA recommends a drug be withdrawn, or even when peer-reviewed literature demonstrates a drug's risks outweigh its benefits. The de facto Medicaid coverage mandate[1] means

MERCI Aims

The Medicaid Evidence and Review of Cost Initiative (MERCI) describes policy considerations for drugs approved by the US Food and Drug Administration (FDA) through the accelerated approval pathway. Each drug brief provides information on:

- The estimated prevalence of target diagnoses (the accelerated approval drug's indication[s]) among Medicaid members;
- The clinical trial population used to support FDA approval, and how similar it is to Medicaid members overall; and
- Projected drug costs for state Medicaid programs, including a breakdown of state and federal funds using the Federal Medical Assistance Percentage (FMAP).

MERCI analyses include national and state-level data where available to inform budget and policy decisions by state and federal policymakers.

that changes to FDA policy on how drug approvals are made directly affect Medicaid coverage policy nationwide.

In addition, Medicaid members, their families and care teams, and Medicaid program officials need better access to information about the status of required confirmatory drug trials, including safety and clinical outcomes. The lack of information about confirmatory drug trials makes informed decision making much more challenging, especially when weighing the risks and benefits of therapy with an accelerated approval drug. Further, since not all accelerated approval drugs go on to receive traditional approval, one consequence of the accelerated approval pathway is Medicaid members may receive drugs that are not actually effective, with taxpayer dollars covering the costs.

The Medicaid Evidence Review and Cost Initiative (MERCI) provides detailed case studies (see MERCI Drug Briefs) about a set of accelerated approval and expedited-pathway drugs so state and federal policymakers can craft a more deft combination of Medicaid drug coverage and FDA accelerated approval. Much of the policy literature about Medicaid and FDA accelerated approval focuses on issues of drug costs and patient access.[2-8] As a result, a dichotomy has emerged, pitting high costs to Medicaid and lack of timeliness in confirmatory trials against innovative drug development and patient access. Findings from the MERCI analyses can assist policymakers in side-stepping this unnecessary dichotomy. It is possible to simultaneously create access to life-saving drugs, protect patients from harm, and spend taxpayer dollars effectively. However, it requires policy enhancements that create better access to confirmatory trial information and permit state Medicaid programs to craft policies that use evidence effectively when uncertainty exists.

MERCI Drug Briefs

- *Sickle cell disease*: voxelotor (Oxbryta)
- *Duchenne muscular dystrophy*: casimersen (Amondys 45), eteplirsen (Exondys 51), golodirsen (Vyondys 53), and viltolarsen (Viltepso)
- *Non–small cell lung cancer*: sotorasib (Lumakras)
- *Cervical cancer*: tisotumab vedotin-tftv (Tivdak) (forthcoming)
- *Reduction of preterm birth*: hydroxyprogesterone caproate (Makena) (forthcoming)
- *Iron chelation*: deferiprone (Ferriprox) (forthcoming)
- *Cancer immunotherapy*: pembrolizumab (Keytruda) (forthcoming)
- *Spinal muscular atrophy*: onasemnogene abeparvovec-xioi (Zolgensma) (forthcoming)

What Is Accelerated Approval?

Needing to speed drugs to market during the HIV/AIDS crisis, the FDA created its accelerated approval program as a pathway for earlier approval of a drug that[9]:

- Treats a serious or life-threatening condition
- Fills an unmet need
- Has a surrogate endpoint reasonably likely to predict clinical benefit, and
- The manufacturer agrees to complete a post-marketing study to confirm clinical benefit

In the Final Rule creating the accelerated approval pathway published in December 1992, the FDA addressed public comments and its own considerations for shortening approval time.[10] This preamble foreshadowed many of the policy concerns that linger around the accelerated approval pathway today, including[10]:

- Diluting the substantial evidence requirement (§505(d) of the Act) for drug approval
- Defining what is a life-threatening disease and what is a meaningful benefit over existing therapy
- Latitude in claiming a correlation between a reasonably likely surrogate endpoint and a clinical endpoint
- Weak incentives for manufacturers to complete confirmatory trials in a timely manner

Between publication of the Final Rule in 1992 and 2012, more than 100 drug-indication pairs were approved through the accelerated approval pathway.[9] In 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act to codify in statute the FDA's authority to continue accelerated approval of drugs, as well as to formalize provisions for fast-track and breakthrough therapy approvals.[11] Congress instructed the FDA "to help expedite the development and availability to patients of treatments for serious or life-threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments."[11]

Further, Congress specified a "reasonably likely" standard for a surrogate endpoint to support a drug's accelerated approval by the FDA. The Act notes that a surrogate endpoint should be reasonably likely to predict clinical benefit, while accounting for the "severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."[11] This is an important point of flexibility for manufacturers, as surrogate endpoints like those used in accelerated approval, have been associated with study durations that are 11 to 19 months shorter, and with development costs for drug manufacturers that are 46% lower.[2]

As a result, the FDA's drug approval process has different evidence standards for the surrogate endpoints used in accelerated approval and traditional approval. A *validated surrogate endpoint* is used primarily for traditional drug approvals and a *reasonably likely surrogate endpoint* is used for accelerated approval drugs. Validated surrogate endpoints for traditional approval are "supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit."[12] For example, a validated surrogate endpoint for a drug used to treat hypertension is blood-pressure reduction, as blood-pressure reduction is directly linked to a decrease in rates of stroke, myocardial infarction, and mortality.[13]

The accelerated approval pathway uses the *reasonably likely surrogate endpoint* standard. The FDA-NIH (National Institutes of Health) Biomarker Working Group describes a reasonably likely surrogate endpoint as having "strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint."[14] Production of skeletal muscle dystrophin is an example of a reasonably likely surrogate endpoint for Duchenne muscular dystrophy because it does not have sufficient clinical data showing its direct association with a specific clinical benefit.[13]

What Are the Distinguishing Traits of Medicaid?

As an insurance program provided through a state-federal government partnership, Medicaid offers coverage to low-income people, including families and children, pregnant women, the elderly, and people with disabilities. Medicaid serves a population more diverse and with more special needs than the general US population[15,16]:

- 11% of the Medicaid population qualifies for coverage as a result of disability[17]
- 61% of the 37 million children enrolled in Medicaid are from racial and ethnic minority backgrounds[15,18]
- In 2019 Medicaid and CHIP (Children's Health Insurance Program) covered almost half of the 13.9 million children in the US with special health care needs[16]

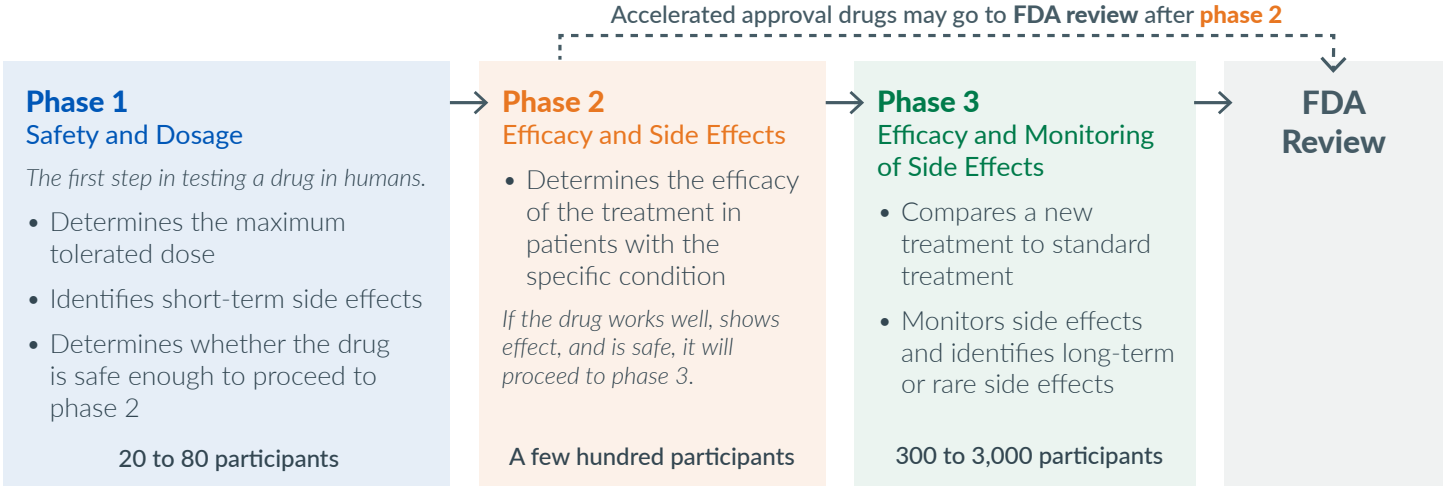
In addition to supporting its diverse and special-needs population, Medicaid has a unique role among health insurance payers in the US. The Centers for Medicare & Medicaid Services (CMS) acknowledges that Medicaid is the payer of last resort, and state Medicaid programs may be called upon to pay for covered care and services, including drugs, if no other third party is liable for coverage.[19] Moreover, the Medicaid Drug Rebate Program requires Medicaid to cover all FDA-approved drugs (including those that went through accelerated approval) for which the drug manufacturer has entered into a rebate agreement with the Secretary of Health and Human Services.[1]

How Do the Accelerated Approval Program and Medicaid Interact?

Drugs from the FDA's accelerated approval program interact with Medicaid's population and payment requirements in a manner different from traditionally approved drugs in private insurance or Medicare. Drugs receiving FDA traditional approval completed a phase 3 clinical trial measuring a clinical endpoint or a validated surrogate endpoint, meaning that patients, along with their families and care teams, have access to clinical outcome and safety data to help make treatment decisions. Accelerated approval drugs have a different standard of evidence. These drugs completed only a phase 2 clinical trial, often with a smaller number of participants and used a surrogate endpoint only reasonably likely to be correlated to clinical marker of the disease but without phase 3 trial evidence of outcomes (see Exhibit 1).

EXHIBIT 1

Clinical trial characteristics by phase[20]



Adapted from: Engelbak Nielsen Z, Eriksson S, Schram Harsløf LB, et al. Are cancer patients better off if they participate in clinical trials? A mixed methods study. BMC Cancer. 2020;20(1):401. doi:10.1186/s12885-020-06916-z

When considering treatment with an accelerated approval drug, patients, their families, and care teams must make their own calculation about whether the potential benefits of the drug outweigh its potential risks. This is no small matter, as postmarket safety events (new boxed warnings, safety communications, or withdrawal of drug from the market) are more frequent among drugs receiving accelerated approval.[21] Unlike Medicaid, private insurance companies and Medicare have the authority to exclude an accelerated approved drug from coverage if clinical trial evidence is weak. If the FDA-approved indication of a drug covers a population not studied in a clinical trial, private insurance may limit drug coverage to the population with clinical trial evidence.

Medicaid, however, must comply with the Medicaid Drug Rebate Program and cover all FDA-approved drugs, with limited exceptions.[1] So in nearly all cases, Medicaid cannot choose to exclude a drug from coverage, cannot limit coverage to exclude a population for which there is no clinical trial evidence, and cannot recommend a dose regimen deemed more effective or safer in peer-reviewed literature. These limitations curtail state Medicaid officials' ability to take common-sense steps to protect Medicaid members and ensure the covered drugs provide the best clinical care and value for the tax dollars spent.

What Are the Findings of the MERCI Analyses?

To date, the MERCI team analyzed 6 accelerated approval drug therapies:

- Sickle cell disease: voxelotor (Oxbryta)[22]
- Duchenne muscular dystrophy: exon-skipping drugs (casimersen [Amondys 45], eteplirsen [Exondys 51], golodirsen; [Vyondys 53], and viltolarsen [Viltepso])[23]
- Non–small cell lung cancer: sotorasib (Lumakras)[24]
- Cervical cancer: tisotumab vedotin-tftv (Tivdak)[25]
- Reduction of preterm birth: hydroxyprogesterone caproate (Makena)[26]
- Iron chelation for transfusional iron overload: deferiprone (Ferriprox)[27]

The number of Medicaid members taking one of these drug therapies varies widely, from 300 members receiving deferiprone (Ferriprox) to 20,000 members receiving hydroxyprogesterone caproate (Makena) per year. The smaller usage numbers speak to the success of the FDA's accelerated approval program in creating access to new therapies for serious or life-threatening diseases, but also highlight the need for vigilance about safety concerns during the confirmatory trial stage. In addition, this small number of therapies has substantial financial impact, as these this set of 6 drugs represent nearly $900 million in historical or future spending (see Exhibit 2).

EXHIBIT 2

Historical or estimated future costs of drugs analyzed in the MERCI briefs to date

	Years	Federal funds, $M	State funds, $M	Total costs, $M
Estimated historical costs to Medicaid				
Voxelotor (Oxbryta)[22]	2020 to 2021	82.9	32.2	115.2
Exon-skipping drugs for DMD[23]	2021	175.5	76.5	252.1
Hydroxyprogesterone caproate (Makena)[26]	2019 to 2021	251.7	110.6	362.3
Estimated future annual cost to Medicaid				
Sotorasib (Lumakras)[24]	-	16.7	6.4	23.1
Tisotumab vedotin-tftv (Tivdak)[25]	-	37.6	16.3	53.9
Deferiprone (Ferriprox)[27]	-	52.4	34.4	86.8

Abbreviations. DMD: Duchenne muscular dystrophy; M: million.

These drugs vary in current FDA-approval status, with 2 converted to traditional approval (tisotumab vedotin-tftv [Tivdak]; deferiprone [Ferriprox]), 2 awaiting confirmatory trial results (exonskipping drugs; sotorasib [Lumakras]), 1 voluntarily withdrawn by the drug manufacturer (voxelotor [Oxbryta]), and 1 withdrawn by the FDA (hydroxyprogesterone caproate [Makena]). Rather than viewing this as a failure of accelerated approval, the withdrawal from the market of drugs whose clinical benefit was not confirmed can instead be viewed as a trade-off for hastening drug development, potentially benefitting people with serious or life-threatening disease.[28]

However, the safety of people taking these therapies is paramount, along with the timely delivery of confirmatory trial results to patients and their care teams. When the confirmatory trial results for voxelotor, a drug used to treat sickle cell disease, showed the risks did not outweigh the benefits, the manufacturer voluntarily withdrew it from the market.[22] In another instance, when the FDA recommended that hydroxyprogesterone caproate (a drug to reduce risk of preterm birth; brand name Makena) be withdrawn from market, the manufacturer contested the recommendation. The review and appeals process kept the drug on the market for more than 3 years after the publication of evidence showing no clinical benefit.[26] As Medicaid is required to cover all FDA-approved drugs, even those for which the FDA has recommended withdrawal, we estimate that more than 60,000 Medicaid members took hydroxyprogesterone caproate but received no clinical benefit during the 3-year review and appeals process.[26] The costs of these drugs are substantial; we estimate the 2020-2021 costs for voxelotor at $115.2 million and the 2019-2021 costs of hydroxyprogesterone caproate at $362.3 million (see Exhibit 2).

The 2 drugs that converted to traditional FDA approval have black box safety warnings, and clinical evidence about the drugs' effectiveness compared with other therapies is still limited. A treatment for cervical cancer called tisotumab vedotin-tftv (Tivdak) carries a black box warning for vision loss, and a recent study has found it to be less cost-effective than chemotherapy.[29] Deferiprone (Ferriprox) treats transfusional iron overload in individuals needing regular blood transfusion for sickle cell disease or thalassemias. It converted to traditional approval using a noninferiority trial design, meaning the study only demonstrated that the drug is not any less effective than an existing therapy; it also carries a black box warning for serious infection and death.[27]

The picture is more nuanced for the drugs still moving through confirmatory trials. The FDA deemed the first sotorasib confirmatory trial insufficient in the strength of evidence to convert to traditional approval, and the manufacturer was given an opportunity to complete a second confirmatory trial by 2028.[24] In the meantime, peer-reviewed literature identified concerns about sotorasib's toxicity at the FDA-labeled dose, and demonstrated that a lower dose may have similar clinical effects with fewer toxicity effects to patients.[30] Medicaid, however, has limited ability to implement coverage policy or dosing recommendations that rely on peer-reviewed literature instead of the FDA label. The 4 exon-skipping drugs for Duchenne muscular dystrophy, a serious and life-threatening disease, were approved in 2016, 2019, 2020 and 2021.[23] In 2021, Medicaid treated 376 individuals with these exon-skipping drugs at a total cost of $252 million.[23] As confirmatory trial results for these drugs are still pending, these patients, their families, and care teams do not have concrete information about the benefit of these therapies already taken versus the risks.

EXHIBIT 3

Characteristics of the drugs analyzed in the MERCI briefs to-date

	Indicated as treatment for	FDA approval status	Surrogate endpoint(s)	Accelerated[b] or traditional[c] endpoint	Safety	Other considerations
Voxelotor (Oxbryta)[22]	Sickle cell disease	Voluntarily withdrawn by manufacturer	Increase in hemoglobin	Accelerated	Withdrawn for risks that out-weigh benefits	2,200 Medicaid members took drug before it was withdrawn by FDA
Exon-skipping drugs for DMD[a,23]	Duchenne muscular dystrophy	Accelerated approval, awaiting confirmatory trials	Skeletal muscle dystrophin	Accelerated	Precautions for kidney function, hypersensi-tivity reaction	Waiting on confirma-tory trial results for 3 to 8 years
Sotorasib (Lumakras)[24]	Non–small cell lung cancer	Accelerated approval, awaiting confirmatory trial	Objective response rate and response duration	Accelerated and traditional	Precautions for hepato-toxicity, interstitial lung disease, pneumo-nitis	Evidence shows a lower dose has similar clinical effects with fewer side effects
Tisotumab vedotin-tftv (Tivdak)[25]	Cervical cancer	Converted to traditional approval	Objective response rate and response duration	Accelerated and traditional	Black box warning for vision loss	Less cost-effective than chemo-therapy[29]
Hydroxy-pro-gesterone caproate (Makena)[26]	Reduction in risk for preterm birth	Withdrawn by FDA recom-mend-dation	Delivery prior to 37 weeks gestation	Accelerated	Withdrawn for no clinical benefit	Estimated 20,000 Medicaid members (per year) took drug while manufacturer contested withdrawal
Deferiprone (Ferriprox)[27]	Transfu-sional iron overload	Converted to traditional approval	Serum ferritin	Traditional	Black box warning for serious infec-tion and death	Confirmatory trial was a noninferior drug study

Notes. [a] Exon-skipping drugs included: casimersen (Amondys [45]), eteplirsen (Exondys [51]), golodirsen; (Vyondys [53]), and viltolarsen (Viltep-so). [b] Accelerated approval endpoints are *reasonably likely* to predict clinical benefit. [c] Traditional approval endpoints are *validated* to predict clinical benefit.
Abbreviations. DMD: Duchenne muscular dystrophy; FDA: US Food and Drug Administration.

Each MERCI drug brief is a case study which includes the clinical trial evidence used for FDA approval, the prevalence of the drug's indication among Medicaid members, and the costs to Medicaid. From those case studies, policy considerations emerge. These considerations are summarized in Exhibit 3 and include:

- Medicaid is unique among health insurers in the requirement to cover all FDA-approved drugs, including those undergoing manufacturer appeals before FDA-recommended withdrawal and those with black box warnings (e.g., vision loss, and serious infection and death), but also no evidence of superiority over current treatment
- Thousands of Medicaid members currently taking these accelerated approval drugs for serious and life-threatening illness wait as many as 8 years for the results of confirmatory trials
- Restrictions on Medicaid's ability to use evidence in coverage policy limit efforts to improve patient safety, such as dosing that maintains clinical effectiveness but reduces toxicity side-effects to patients

The fine-grained context of the individual MERCI drug briefs illustrates opportunities for the CMS and FDA to refine policy to safeguard patients while maintaining drug coverage and accelerating access to new drug therapies.

CONSIDERATIONS

To speed patient access to therapies, the FDA is already giving accelerated approval to drugs and Medicaid is already covering them. Opportunity exists to improve the policy framework between CMS and the FDA to better manage the risks inherent to accelerated approval, particularly safety risks to Medicaid members. This can be achieved by requiring more communication and sharing more information about confirmatory trials, aligning incentives for manufacturers to voluntarily withdraw drugs or refine the drug labels, and allowing Medicaid to craft coverage policy that reflects the evidence of clinical trials and peer-reviewed journals.

Based on MERCI briefs, specific opportunities to enhance Medicaid coverage of FDA accelerated approval drugs include:

- Requirements for manufacturers to complete and publicly disclose semiannual progress reports about confirmatory trials, including the number of participants recruited and estimated time remaining to complete the trial
- Using the existing Memorandum of Understanding between the FDA and CMS to enable information sharing with state Medicaid officials[31]
- Allowing Medicaid to have input about recommendations for confirmatory trial endpoints and targets for the demographic composition of trial participants that could enhance drug safety and applicability to Medicaid's vulnerable populations
- Implementing policy incentives and requirements that enable the FDA to achieve more manufacturer accountability to publicly disclose updated study statuses and results on ClinicalTrials.gov or in peer-reviewed journals
- Allowing latitude for Medicaid to craft coverage policies that reflect evidence from clinical trials and peer-reviewed literature, including limiting coverage to studied trial populations and permitting dosage changes

The FDA accelerated approval pathway and Medicaid interact in a profound way. FDA accelerated approval results in shorter study durations and lower development costs,[2] which can benefit both manufacturers and patients only if the drugs are safe and effective. Meanwhile, state Medicaid programs face a requirement to cover all FDA accelerated approval drugs despite lower standards of evidence of effectiveness, which can potentially expose Medicaid members to ineffective or unsafe drugs. There are opportunities to refine policy that enable the promise of accelerated approval while taking needed and appropriate steps to better protect people made vulnerable by serious and life-threatening disease.

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