

CMS VS. FDA

**HOW MEDICARE & MEDICAID COVERAGE DECISIONS
LIMIT ACCESS TO FDA-APPROVED TREATMENTS**

CONTENTS

Executive Summary	3
Accelerated Approval Program	5
Background.....	5
History of Accelerated Approval.....	6
FDA Approval & CMS	10
Background.....	10
Coverage with Evidence Development.....	10
New Territory for CMS—Alzheimer’s Treatments.....	11
Beyond Alzheimer’s.....	12
AAP & Medicaid.....	13
Patients Are Casualties in the War Between CMS and FDA	15
Agency Hostility Toward AAP and Surrogate Endpoints.....	15
Different Agencies with Different Missions.....	16
Delayed Access for Vulnerable Patients.....	16
Stifling Innovation.....	18
Conclusion: Let the FDA Do Its Job	19



Patients Rising Now is a national 501c(4) nonprofit organization dedicated to advocating for the rights of all patients. We work at federal, state, and community levels to activate patients in support of reforms and legislation aimed at advancing patient access to quality healthcare, at a transparent and affordable price.

EXECUTIVE SUMMARY

The Food and Drug Administration's Accelerated Approval Program (AAP) is an instrumental pathway offering faster approval of new therapies to treat serious conditions with unmet medical needs. By relying on surrogate endpoints instead of traditional clinical endpoints, the program expedites treatment access for patients suffering from severe and potentially terminal illness. Originating in response to the HIV/AIDS crisis of the 1980s and 1990s, the AAP has evolved into a pivotal pathway for approving new cancer treatments and providing access to therapies for rare diseases.

By most objective standards, the AAP has been a success. Since the program officially began in 1992, the vast majority of drugs granted accelerated approval from the FDA have either already been converted to traditional approval or are well within the expected time frame for achieving that objective. Only a small portion of accelerated approvals have been withdrawn or went beyond anticipated timelines for receiving traditional approval.

The Centers for Medicare and Medicaid Services (CMS) has typically deferred to the FDA's rigorous standards to assess whether an item or service is "reasonable and necessary" for coverage under Medicare. As a result, CMS has opted to provide nationwide coverage for most FDA-approved products or allowed such determinations to be made by regional contractors. However, in some cases, CMS has issued national coverage determinations (NCDs) stipulating conditions or limitations on coverage. Until recently, virtually all NCDs issued by CMS were for medical devices, and only rarely applied to medications. In exceptional cases, CMS has issued NCDs requiring coverage with evidence development (CED), meaning the item or service must be part of a CMS-approved clinical study in order to receive coverage. As with the more typical NCDs, these designations have largely been reserved for medical devices, not FDA-approved drugs.

However, CMS has recently taken a different approach toward coverage for AAP medications, starting with Aduhelm, a promising new treatment for Alzheimer's disease. Following the FDA's accelerated approval of the drug in 2021, CMS issued a broad NCD requiring CED for Aduhelm and any drugs in the same class subsequently receiving accelerated approval, marking the first time CMS restricted coverage for a whole class of FDA-approved drugs. Indeed, when Leqembi, a drug in the same class, was granted accelerated approval in early 2023, it was subject to the same restrictive coverage requirements. Despite a published phase 3 study and its subsequent conversion to traditional approval, CMS has refused to reconsider the NCD with CED.

In February 2023, in response to an executive order on prescription drug pricing, CMS also proposed an "Accelerating Clinical Evidence" payment model that would reduce physician reimbursements under Medicare Part B for some or all AAP medications. This was suggested both as a cost-cutting measure and a supposed incentive for manufacturers to complete their confirmatory trials more rapidly after obtaining accelerated approval.

There have also been recent proposals to restrict access or reimbursements for AAP medications in state Medicaid programs. A handful of states have requested waivers from CMS to allow them to decrease reimbursements or refuse coverage for AAP drugs. While the agency has not approved any of these measures, the Medicaid and CHIP Payment and Access Commission recently recommended that Congress grant states this type of authority.

Underpinning efforts at CMS and elsewhere to expand CED, demand reimbursement concessions, or ration access to AAP drugs is an apparent hostility and skepticism toward medications receiving accelerated approval as well as the use of surrogate endpoints. While most observers see them as cost-saving measures, CMS's justifications for these proposed restrictions are largely based on concerns over the quality of evidence showing the effectiveness of treatments. In making these kinds of judgments, CMS is exceeding its mandate to make "reasonable and necessary" determinations and undermining the purpose of the AAP.

The FDA is science-based agency focusing on clinical assessments of the safety and effectiveness of new medications. In contrast, CMS is a healthcare payer charged with setting reimbursement and coverage policies. Yet, when CMS sets restrictions and requires additional evidence to offer coverage of new medication, it is effectively overruling the scientific judgments of FDA experts in favor of its own views.

Patients are the ones who will suffer the greatest harm under this ongoing impasse between FDA and CMS. New restrictions on AAP medications will significantly limit access to potentially life-saving treatments. The impact will be particularly harmful toward vulnerable patient populations, including elderly patients and those suffering from rare diseases. Moreover, available data strongly suggest that approval delays significantly decrease the economic value of new medications. As a result, this new direction will likely create disincentives for investment in new and innovative treatments.



I have hugely benefitted from a drug that received accelerated approval. In fact, I believe I would not be alive without it. I have taken Tagrisso (osimertinib) for almost seven years—six years as a single agent and nearly one year in combination with another targeted therapy medication. In December 2013, at age 47, I was diagnosed with stage IV lung cancer that had spread to my bones. After initially taking a different targeted medication, my cancer started growing again in November 2016. If Tagrisso didn't have accelerated approval at that time, I would have had no option other than traditional IV chemotherapy, which likely would not have worked nearly as well and might not have extended my life long enough for Tagrisso to reach full approval. I will celebrate my 10 year "cancer-versary" in a few months and the Accelerated Approval Program made this possible.

Ivy Elkins, Lung Cancer Patient and Advocate; Co-Founder [EGFR Resisters](#)

ACCELERATED APPROVAL PROGRAM

The Food and Drug Administration's (FDA) Accelerated Approval Program (AAP) allows for earlier approval of drugs developed to treat serious conditions and fill unmet medical needs. On average, successfully moving a new treatment from its initial research stages through final FDA approval takes more than a decade. This difficult and onerous process is designed to ensure the safety and effectiveness of new drugs before they enter the marketplace. However, it can also leave those suffering from serious—and potentially terminal—diseases without any meaningful therapies or cures. The AAP was implemented to allow those patients to access new and innovative treatments on a shorter timeline.

Background

For any new medication, FDA approval requires demonstrating that it is “safe and effective” based on evidence obtained from clinical trials. The AAP allows for treatments to be more rapidly approved by using surrogate endpoints to show their safety and effectiveness rather than the clinical endpoints used for traditional FDA approval. Put simply, clinical endpoints are results from clinical trials that demonstrate the direct clinical benefit—such as absence of disease, decreased pain, or survival—from a new treatment. Surrogate endpoints are markers—like laboratory measurements, radiographic images, or physical signs—that can predict a clinical benefit but are not themselves measures of that clinical benefit.

Surrogate endpoints are particularly useful in cases where it would be impractical or unethical to rely on clinical endpoints due to time or the immediate need for new treatment options. This is particularly essential when dealing with progressively debilitating diseases where measuring a clinical milestone would take years. Examples of surrogate endpoints approved by the FDA to assess new treatments include CD4 counts for AIDS patients, blood pressure for cardiovascular disease, intraocular pressure in glaucoma patients, and reduction in tumor size in cancer patients.

To qualify for the AAP pathway, manufacturers are required to produce data to demonstrate the surrogate endpoint is “reasonably likely” to predict the intended clinical benefit. Once accelerated approval is granted, drug companies must still conduct studies to confirm whether a treatment produces the anticipated clinical benefit. If additional trials confirm predictions made at earlier phases, the FDA grants traditional approval for the medication. When confirmatory trials do not demonstrate the drug's clinical benefits, the FDA can withdraw its approval.

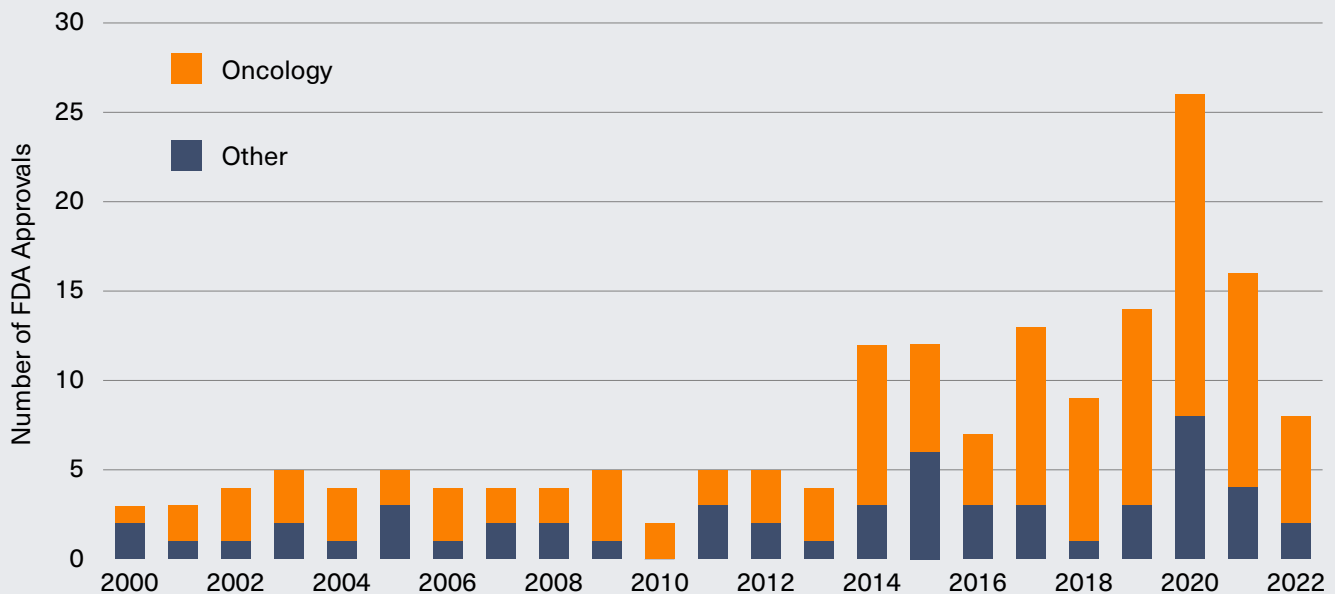
History of Accelerated Approval

The AAP was established via [FDA regulation](#) in 1992 and was formally codified in 2012 as part of the [Food and Drug Administration Safety and Innovation Act](#). The initial regulation was largely a response to HIV/AIDS crisis, which, by the early 1990s, was a [rapidly-growing epidemic](#) with no effective treatments. Advocacy groups like ACT UP [spent years](#) putting pressure on federal health agencies, making the case that testing new therapies was itself a form of health care and demanding new pathways for both expedited approval and coverage for the latest treatment breakthroughs.

With [support from regulatory agencies](#), researchers began to streamline clinical trials for new HIV/AIDS medications by focusing on improved T-cell counts or viral loads where data showed a strong correlation with improved clinical outcomes. This approach allowed zidovudine (AZT) to be the first antiretroviral medication approved by the FDA to treat HIV/AIDS in 1987. The first medication officially approved once the AAP rule was in effect was zalcitabine, another key early HIV/AIDS treatment. During the [first 10 years](#), nearly two-thirds of the drugs approved under the AAP were treatments for HIV/AIDS and other infectious diseases. The program played a pivotal role in the rapid development and approval of antiretroviral therapies that eventually changed the status of HIV/AIDS from terminal to a chronic but manageable condition.

In subsequent years, the program has become a key pipeline for the approval and introduction of [new cancer treatments](#). Since 2000, as the total number of drugs receiving accelerated approval has increased dramatically, oncology medications

Figure 1. Accelerated Approvals by Year (2000–2022)



SOURCE: [GlobalData, Pharma Intelligence Center](#)

account for roughly 66% of all accelerated FDA approvals. Since 2010, that figure has increased to more than 80 percent (see figure 1).

The AAP has also been instrumental in giving patients with rare diseases access to new treatments. Rare diseases present **many unique challenges** for researchers when designing clinical trials to establish direct clinical benefits. These challenges include small patient populations, long timelines for disease progression, poor understanding of disease natural history, and a shortage of prior clinical studies. These types of obstacles can extend the time it takes to gather the evidence required to produce meaningful study results. By allowing for the use of surrogate endpoints, **the AAP helps rare disease patients** gain access to the latest treatments during these longer periods of study and data collection. Recognizing these benefits, the FDA **recently announced** a new effort to encourage the use of the AAP, along with other initiatives, to expedite approval of more rare disease treatments through the use of surrogate endpoints. Unfortunately, not all federal agencies are as forward-thinking when it comes to accelerated approval (see below).

There are several high-profile examples where the AAP has offered new hope to those suffering from rare and debilitating diseases. For example, in 2016, the FDA granted accelerated approval for **Exondys 51**, the first drug approved to treat Duchenne

Case Study: Truvada

Truvada, developed by Gilead Sciences, was a key milestone in HIV treatment. It is a combination two drugs, tenofovir and emtricitabine, and is used to both treat and prevent transmission of HIV/AIDS. Truvada works by inhibiting reverse transcriptase, a critical enzyme that HIV needs to reproduce, thereby preventing the virus's progression in the body.

Timeline:

- **August 2004:** The FDA granted accelerated approval for Truvada as a treatment for HIV-1 infection in adults using reduction in viral load and increased CD4 cell counts among HIV-positive individuals as surrogate endpoints.
- **March 2006:** After additional clinical trials providing confirmatory evidence of its sustained efficacy and safety, Truvada received traditional approval from the FDA.
- **July 2012:** The FDA granted accelerated approval for Truvada as a pre-exposure prophylaxis (PrEP) based on surrogate endpoints from clinical trials showing a significant reduction in the risk of HIV infection among high-risk populations.
- **August 2013:** Truvada received traditional approval as a PrEP from the FDA after successful confirmatory trials.

Results: Truvada dramatically improved the treatment landscape for HIV. Before its approval in 2004, managing HIV was often complicated, requiring the administration of multiple antiretroviral drugs, usually with serious side effects and complicated dosing schedules. With Truvada, a single pill combining two effective antiretroviral agents, patients' adherence to treatment and overall quality of life have greatly improved. Truvada's subsequent approval as a preventative measure also revolutionized HIV prevention, highlighting the drug's versatility and the critical role it has played in managing global HIV/AIDS.

Muscular Dystrophy, a rare, incurable, and fatal genetic disorder. Three similar Duchenne treatments have received accelerated approval in subsequent years. And, in June 2023, the first gene therapy for Duchenne was approved via the AAP. While some have considered these approvals controversial, they have demonstrated how, by allowing the use of surrogate endpoints, the AAP can offer potential lifelines to small patient populations with high unmet needs.

By most objective measures, the AAP has largely been successful. According to a 2022 study published in *Therapeutic Review & Regulatory Science*, the FDA gave accelerated approval to 278 drugs in the first 30 years of the program. As of last year, half of all accelerated approvals had been converted to traditional approval after additional studies confirmed their clinical benefits. That percentage is lowered by the significant increase in accelerated approvals in recent years, which means a significant number of medications are currently still within the typical window for traditional approval (see below). The median time for conversion from accelerated to traditional approval over the life of the program is 3.4 years and has gotten significantly shorter over the last ten years (see figure 2).

Critics of the program point out that some drugs that received accelerated approval were later shown to be ineffective. However, such cases are the exception. According to the study, only 12% of accelerated approvals had been subsequently withdrawn—either voluntarily or after agency action—as of the end of 2022. The vast majority—77 out of 107—of accelerated approvals still awaiting conversion were still within the average conversion period. Of the 30 AAP medications that had been on the market longer than 3.4 years, all but eight were considered on-time, proceeding in accordance with their established milestones and timelines (see figure 3).

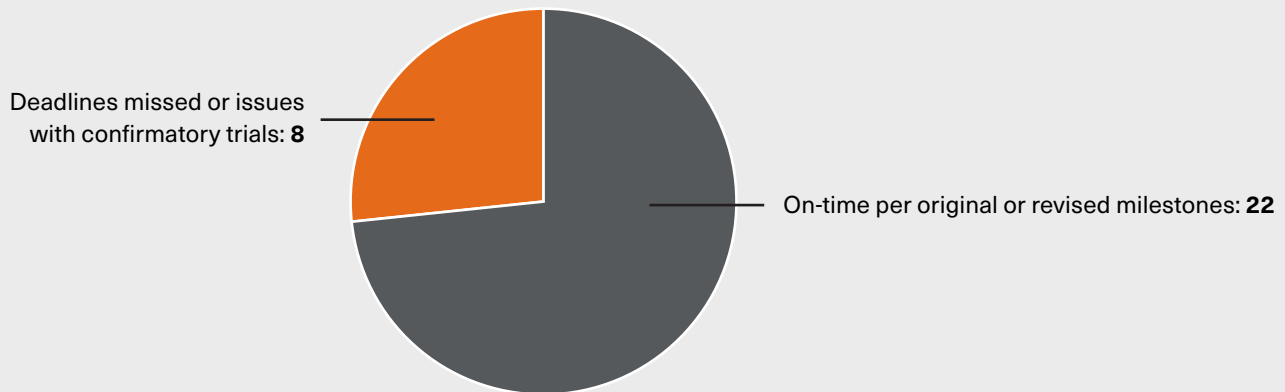
The AAP has been a lifeline for patients suffering from serious and life-threatening illnesses with few available treatment options. While no program is perfect, the AAP has a strong track record of allowing effective new treatments to enter the market years ahead of the normal FDA approval schedule. In most cases, the clinical benefit of approved therapies has been confirmed in short order on a predictable timeline and the FDA has proven to be efficient in dealing with those cases where the benefits fail to materialize.

Figure 2. Accelerated Approvals by Decade

Decade	1992–2001	2002–2011	2012–2021
Total Accelerated Approvals Granted	52	59	167
Median time for conversion to traditional approval	3.9 years	4.1 years	2.3 years

SOURCE: Therapeutic Innovation & Regulatory Science

Figure 3. Status of Confirmatory Trials Pending (1992–2021)



SOURCE: [Therapeutic Innovation & Regulatory Science](#)

Case Study: Keytruda

Keytruda, developed by Merck & Co., was a significant advancement in the field of oncology. It is a programmed death receptor-1 (PD-1) blocking monoclonal antibody, designed to help the body's immune system fight cancer cells.

Timeline:

- **September 2014:** The FDA granted accelerated approval for Keytruda to treat patients with advanced or unresectable melanoma no longer responsive to other drugs. This decision was based on surrogate endpoints of tumor shrinkage rate and duration of response.
- **December 2015:** After further clinical trials showed its efficacy and safety, Keytruda received full FDA approval for treating patients with unresectable or metastatic melanoma.
- **August 2016–Present:** FDA has since approved Keytruda to treat many other forms of cancer, including lung cancer, head and neck cancer, Hodgkin lymphoma, stomach cancer, cervical cancer, and certain types of breast cancer.

Results: Keytruda has greatly impacted cancer treatment, particularly in melanoma and solid tumors with MSI-H or dMMR. Prior to its approval, treatment options for these conditions were limited and often came with severe side effects. Keytruda, as an immunotherapy, leverages the body's immune system, leading to more targeted treatment with less harmful side effects. Moreover, the approval of Keytruda for any tumor with specific genetic features, regardless of its origin, paved the way for a new era of personalized medicine, underscoring its pivotal role in cancer treatment evolution.

FDA APPROVAL & CMS

Background

Section 1862 of the Social Security Act limits Medicare coverage to items and services that are “reasonable and necessary for the diagnosis or treatment of illness or injury” and fall within the scope of a defined Medicare benefit category. Such determinations are made by the Centers for Medicare and Medicaid Services (CMS).

Historically, CMS has deferred to the FDA’s rigorous, data-centric approval standards when making these assessments. As a result, the agency has **deemed** most FDA-approved products and services to “reasonable and necessary,” and either provided nationwide Medicare coverage or allowed for regional contractors to make coverage decisions. Until recently, CMS has held the same posture with regard to medications approved through both the traditional and accelerated pathways.

Coverage with Evidence Development

Federal law also **authorizes** CMS to issue “national coverage determinations” (NCDs) to establish conditions or limitations on coverage for specific items or services under Medicare Part B. The vast majority of NCDs issued by CMS have applied to medical devices. In those few cases where NCDs have been issued for FDA-approved medications, CMS has **virtually always** provided coverage in accordance with the drugs’ labels.

In a limited number of cases, CMS has issued NCDs that approve **coverage with evidence development** (CED). Put simply, this means CMS declines to cover an item or service unless it is administered as part of a CMS-approved clinical study. The agency’s CED policy is not specifically authorized by federal statute. Instead, it was **created by CMS** via regulation in 2005 and subsequently updated in 2014.

The goals of the CED policy are ostensibly similar to the AAP. Both are supposedly meant to provide access to promising therapeutics while additional evidence is generated. However, in practice, the two programs are dramatically different. The FDA has established clear standards for “graduating” a new treatment from accelerated to traditional approval. As noted above, drugs brought to market via the AAP typically obtain final approval in just a few years. By comparison, CED is **“a never-ending purgatory for innovators,”** as critics continually fault CMS for its lack of transparency and uniformity for determining whether and how CED-labeled items and services can eventually receive full national coverage.

The process of setting up an approved study to satisfy an NCD requiring CED can be extremely burdensome. There are about **30 complex steps** required just to establish a program and begin testing. These steps include identifying investigators, getting approval from both CMS and an institutional review board, and preparing a registry or database to which data can be submitted, among many others. In most cases, there are relatively few administering centers, which can place strict geographical limits on who is

able to participate. In addition, data collection and follow-up investigation requirements often put **added burdens** on patients and prescribing doctors.

Worst of all, the vast majority of CED determinations are never removed. According to a **2022 study** in the *American Journal for Managed Care* (AJMC), CMS issued 27 CED determinations from 2005 to 2022. Only four had their CED status retired while retaining national Medicare coverage. In two cases, CMS removed the NCD and deferred coverage decisions to regional administrative contractors. The remaining 21 items and services are still subject to CED requirements with no established schedule or standard for reaching a final coverage decision. After reviewing the six instances where CED requirements were removed, the researchers concluded that “there were no clear programmatic characteristics suggesting greater or lesser likelihood of progressing to an NCD without CED requirements vs. revocation of the NCD.”

New Territory for CMS—Alzheimer’s Treatments

For the most part, CMS has limited its use of CEDs to medical devices and services. Prior to 2022, CMS had issued **only one** NCD requiring CED for a prescription drug. That determination, issued in 2005, applied restrictions only to off-label uses of a single anticancer agent.

However, last year, CMS **issued** an NCD requiring CED for aducanumab (Aduhelm), a first-of-its kind treatment for Alzheimer’s disease utilizing anti-amyloid monoclonal antibodies (mAbs) developed by Biogen and Eisai. The decision to restrict coverage was extraordinarily broad, subjecting the entire class of FDA-approved mAbs—both present and future—to severe coverage limitations. Prior to this decision, **CMS had never declined** to cover a medication for its FDA-approved use or restricted coverage for an entire class of drugs based on the data available for a single drug.

The FDA granted accelerated approval for Aduhelm in 2021. While there was some controversy surrounding the decision, the FDA clearly **recognized the significance** of approving the first new Alzheimer’s treatment in decades and its potential for meeting



What is really remarkable about the AAP relates to its outcomes—while it was conceived in 1992 as a “Hail Mary” endeavor for very serious afflictions with uncertainty about whether a majority of such approved drugs would progress to full approval, the results have exceeded the expectations of patient communities as well as care practitioners. Multiple studies clearly document the significant impact of accelerated approval on care practices and patient outcomes, showing an estimated acceleration of patient access for AA oncolytics by a median 3.4 years earlier than traditional pathways. To have compelled drug developers to perform traditional clinical studies instead of pursuing accelerated approval would have meant many years and lives lost for those in dire need.

Timothy Franson, M.D., FACP, FIDSA; Principal–Health and FDA Practice, **Faegre Drinker Consulting**

unmet needs. Indeed, Congress granted FDA regulatory flexibility in the AAP precisely for these types of situations.

Initially, CMS justified its coverage restrictions for Aduhelm on a claimed shortage of direct clinical data proving its effectiveness. However, in January 2023, the **FDA granted accelerated approval** to lecanemab (Leqembi)—a second Alzheimer’s therapy from the same manufacturers utilizing the same class of mAbs—without any major objections. Even though the accelerated approval of Lequembi included significantly more data to demonstrate its efficacy, **CMS declined** to revise the previous NCD. In July 2023, **Eli Lilly presented clinical trial data** showing that a third drug in this class slowed cognitive and functional decline for Alzheimer’s patients. Lilly has submitted its application for traditional FDA approval.

Skepticism at CMS toward FDA-approved Alzheimer’s treatments extends beyond the AAP. In July 2023, Leqembi received **traditional approval** from the FDA after agency experts determined the drug showed significant clinical benefit for Alzheimer’s patients. In advance of that decision, **CMS issued guidance** for coverage of mAbs treatments receiving traditional FDA approval. While the guidance was purported to “ensure availability” of approved Alzheimer’s medications, it limited coverage to patients treated by physicians participating in CMS-approved registries. Many **industry leaders and patient advocates** had serious concerns when the guidance was announced. While CMS seemed to address some of their concerns with the registries it created when Leqembi **received traditional approval**, it is too soon to tell how this will work in practice. To date, CMS hasn’t shown any sign that it intends to reconsider its posture despite all the new evidence published since its initial decision in 2022.

Beyond Alzheimer’s

The restrictive approach taken by CMS toward Alzheimer’s treatments will almost certainly impact future coverage decisions for other types of medication. In fact, that appears to be the plan as CMS appears poised to use this approach to create additional restrictions for both AAP medications and others receiving traditional approval.

Leaders at CMS laid groundwork for a more expansive CED approach in **guidance** issued in 2014 that declared: “We believe that CED can be applied to drugs and biologics.” A **draft update** to this guidance issued in June 2023 seems to suggest CMS intends to broadly increase scrutiny toward AAP drugs going forward. In October 2022, the presiding chair and co-chair of Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) wrote **an article** for *The New England Journal of Medicine* (NEJM) entitled “Medicare’s National Coverage Determination for Aducanumab — A One-Off or a Pragmatic Path Forward?” In the article, the officials acknowledged CMS’s Alzheimer’s decision required a “rigorous interpretation of its authority to determine a therapy is ‘reasonable and necessary,’” but argued that it “shouldn’t be a one-off example of the agency exercising this authority.”

Later in 2022, President Biden issued an **executive order** directing the Department of Health and Human Services (HHS) and CMS to recommend “additional actions to...drive down prescription drug costs.” The agencies **responded** in February 2023 by selecting three new payment models for testing by the Centers for Medicare and Medicaid

Innovation (CMMI), one of which was “Accelerating Clinical Evidence Model.” Under this model, CMS would lower physician reimbursements under Medicare Part B for some or all AAP medications.

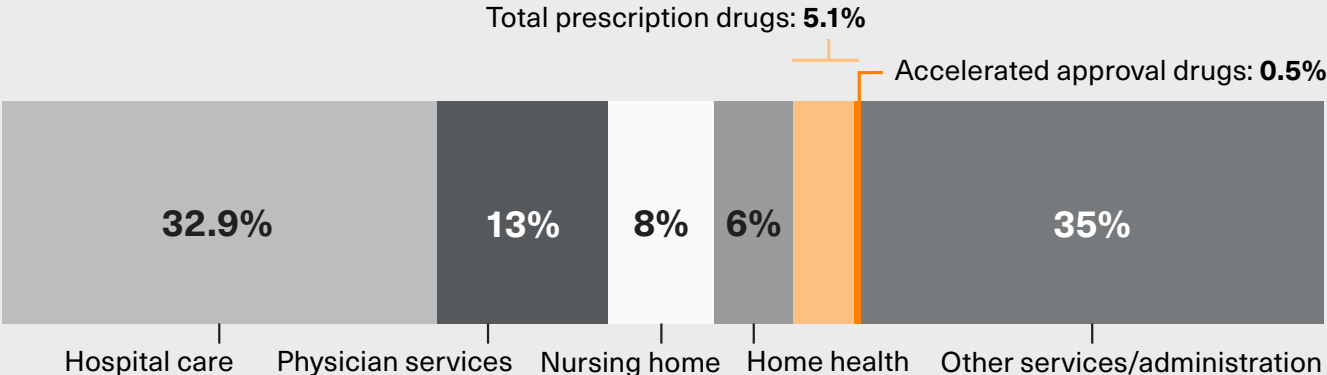
AAP & Medicaid

Efforts to restrict coverage for AAP therapies have also extended into state Medicaid programs. Under the Medicaid Drug Rebate Program (MDRP), manufacturers agree to pay steep rebates to states on payments they receive from Medicaid. In return, states are **required** to cover any drugs produced by participating manufacturers when they are prescribed for a medically accepted indication. Some have proposed changes to these restrictions to help states control program costs.

Most notably, the Medicaid and CHIP Payment and Access Commission (MACPAC), an independent board advising Congress on state-run health programs, recently **recommended** allowing states to limit coverage for drugs cleared under the AAP. This change—which would require an act of Congress to implement—would essentially allow states to impose CED-like requirements for drugs covered under Medicaid. This came a year after MACPAC recommended assessing higher rebates for AAP drugs—essentially a tax on innovation—until their confirmatory studies are complete. In addition, a few states have **submitted requests** to CMS in recent years asking to waive Medicaid drug coverage requirements for AAP therapies. The most recent request was **submitted by Oregon** in 2022. To date, CMS has denied all these requests.

While these changes have largely been couched as cost-savings measures, a **2022 data analysis** from the Partnership to Fight Chronic Disease found that AAP drugs accounted for less than one percent of overall Medicaid spending (see figure 4). Ultimately, these proposals reflect a growing suspicion toward AAP among policymakers (more on that below) more than any measurable impact of AAP medications on Medicaid costs.

Figure 4. Distribution of Medicaid Spending (FY2020)



SOURCE: Partnership to Fight Chronic Disease

Case Study: Gleevec

Gleevec (imatinib) is a groundbreaking treatment for various types of cancer. Developed by Novartis, Gleevec specifically targets abnormal proteins leading to the suppression of cancer cell growth and improved patient outcomes.

Timeline:

- **May 2001:** FDA granted accelerated approval for Gleevec to treat chronic myeloid leukemia (CML). Surrogate endpoints included hematologic and cytogenetic response rates.
- **December 2002:** Gleevec received traditional approval after a series of confirmatory trials.
- **February 2003–Present:** FDA subsequently approved Gleevec to treat patients with gastrointestinal tumors (GIST), dermatofibrosarcoma protuberans, acute lymphoblastic leukemia, systemic mastocytosis, and hypereosinophilic syndrome.

Results: Gleevec has had a transformative effect on cancer treatment, vastly improving patients' prognoses and quality of life. Before it was approved 2001, the average five-year survival rate for CML patients was around 30%. Today, thanks to Gleevec, those rates exceed 90%. Similarly, for GIST patients, the average five-year survival rate prior to Gleevec was roughly 40%. Today it is over 85%.



I was diagnosed with CML in January 1995 and started the clinical trial for Gleevec in August of 1998. With CML three years was a very important time span. Some of the people who were diagnosed at the same time—if they weren't in that trial—they most likely were not alive because they usually only had about three years to live. It took another three years for Gleevec to get accelerated approval—when I was at like six and a half years. If I had to wait for traditional approval, studies have shown that it would have taken another three years. That would have been nine years. And there was no way I was going to survive nine years. So, it was good I got on the trial. But, because of accelerated approval there were all these other patients—three years' worth of people—who were also able to take advantage of the drug.

Mel Mann, Cancer survivor

PATIENTS ARE CASUALTIES IN THE WAR BETWEEN CMS AND FDA

The purpose of the AAP is to advance science to make more innovative treatments available to patients with serious or life-threatening illnesses. As noted previously, the program has helped patients gain access to effective new therapies treating wide range of diseases—including HIV/AIDS, cancer, and sickle cell disease—years ahead of their traditional approval. Recent efforts at CMS to expand the use of CED, demand reimbursement concessions, or ration access to AAP drugs essentially penalize patients—including some of the most vulnerable among us—who rely on treatments approved through this program.

Agency Hostility Toward AAP and Surrogate Endpoints

Strictly speaking, federal law limits CMS's coverage discretion to determining what is “reasonable and necessary,” preventing the agency from explicitly considering cost when deciding whether Medicare will pay for a particular drug, device, or service. This is due largely to the reluctance of legislators to specifically authorize the rationing of care. However, many acknowledge the agency has often skirted this restriction by simply interpreting data in a manner that supports cost-limiting coverage policies. Indeed, former senior CMS officials have recently acknowledged that NCD's are “the most powerful coverage tool Medicare has and have generally been reserved for Medicare services that are costly...”

Recent efforts to expand CED—whether its limiting coverage for Alzheimer's treatments or agency recommendations to accelerate the program—are clearly motivated by cost concerns. However, because the law limits the role cost can play in CMS's coverage decisions, the agency has justified its new approach by focusing on concerns over the quality of evidence showing the effectiveness of treatments receiving accelerated approval. In doing so, they undermine the purpose of the AAP and cast doubts on the legitimacy of surrogate endpoints as measures of effectiveness. For the most part, those who support this approach rarely seem worried about these implications.

Virtually all of CMS's proposed restrictions and concessions on AAP medications are clearly premised on the assumption that FDA approvals based on surrogate endpoints are innately suspect—and therefore less valuable—despite decades of data showing otherwise. Indeed, the stated purpose of the proposed CMMI model is to incentivize additional clinical trials for AAP drugs and “reduce Medicare spending on drugs that have no confirmed clinical benefit.”

Though its authors don't explicitly call for added scrutiny for ALL drugs receiving accelerated approval, former senior CMS officials have argued for more robust use of CED primarily “to address residual uncertainty about benefits and harms for an increasing number of FDA-regulated products by ensuring that evidence is generated using clinically meaningful end points...” The notion that spending on AAP drugs

is presumptively wasteful has shown up in other agency documents and reports produced under the Biden administration.

Different Agencies with Different Missions

When considering these issues, it is important to remember the FDA and CMS have very different roles and priorities when it comes to the evaluation and regulation of prescription medications. Those differences are reflected in the structure of the two agencies as well as the authorities granted to them by Congress.

The FDA is responsible for regulating and approving drugs for the U.S. marketplace. It is a science-based agency, made up of experts in numerous disciplines, including pharmacology, toxicology, clinical research, and biostatistics. The agency has a wealth of knowledge and experience in the evaluation of drug efficacy through well-designed clinical trials and data analysis and its infrastructure is designed to serve that purpose.

While CMS plays a crucial role in federal health policy, it is healthcare payer, not a scientific agency. It is charged with administering and overseeing the programs under its jurisdiction, with a focus on reimbursement policies and coverage decisions. Compared to the FDA, CMS's expertise on the safety and effectiveness of any medication is extremely limited and its "approval" process is not nearly as transparent or consistent.

The FDA approves new medications based on finding of sufficient evidence that it is "safe and effective." The same standard applies whether the drug receives traditional or accelerated approval. When CMS bases a decision to limit or refuse coverage on concerns about the quality of the evidence for a newly approved drug, it is effectively supplanting the clinical and scientific assessments of FDA experts with the opinions of CMS officials whose expertise and priorities lie elsewhere. And, when CMS determines surrogate endpoints are not "meaningful," it substitutes its judgement for that of Congress, which has formally authorized FDA to approve new treatments on the basis of such evidence.

Delayed Access for Vulnerable Patients

By its very nature, increased restrictions and concessions for drugs receiving accelerated approval can dramatically limit patient access to potentially life-saving medications. For example, a typical CED can delay—for many years, if not indefinitely—the availability of cutting-edge treatments for Medicare beneficiaries. The impact of restrictions coming in the form of a new reimbursement model for AAP drugs will be less direct as more doctors will simply steer Medicare patients away from the latest treatments to avoid lower reimbursements. Both approaches will inflict disproportionate harms on some of the most vulnerable patients, including those suffering from rare diseases with few, if any, treatment options or seniors suffering from progressive illnesses who could lose valuable years and quality of life waiting for access to new treatments.

For example, every day, upwards of 3,000 patients can progress from mild to advanced Alzheimer's disease. While this degeneration is irreversible, available evidence strongly suggests recently approved medications can significantly slow the cognitive decline

Case Study: Xalkori

Xalkori, developed by Pfizer, was a major step forward in lung cancer treatment. It is an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor, designed to obstruct the growth and spread of cancer cells in patients with non-small cell lung cancer (NSCLC).

Timeline:

- **August 2011:** The FDA granted accelerated approval for Xalkori for the treatment of patients with specified forms of late-stage lung cancer detected by an FDA-approved test. Approval was based on surrogate endpoints of objective response rate and duration of response.
- **November 2013:** After additional clinical trials confirmed its efficacy and safety, Xalkori received full FDA approval.
- **March 2016–Present:** Xalkori has subsequently been approved for expanded uses, including the treatment of non-small cell lung cancer and ALK-positive anaplastic large cell lymphoma in children and young adults.

Results: Xalkori has substantially advanced lung cancer treatment, particularly in NSCLC with ALK and ROS1 positive mutations. As a targeted therapy, Xalkori provides more precise treatment with fewer harmful side effects than most of the previously available options. This was another big step forward into more personalized cancer treatment, where therapies can be tailored to match the genetic makeup of an individual patient's tumor.

in Alzheimer's patients, most of whom receive their primary health coverage through Medicare. By severely limiting coverage for these new treatments, CMS has placed insurmountable barriers between millions of patients and the first promising Alzheimer's treatment innovations seen in decades.

While CMS's Alzheimer's decisions have garnered the most headlines, the agency's new posture toward AAP drugs will likely be even more harmful for cancer patients. Once again, the vast majority of medications approved via the AAP over the past decade have been for oncology indications. Therefore, whether it is restricting access to the latest treatments through the established CED system or limiting reimbursements in a new payment model, seniors suffering from cancer will be the ones who most likely to end up in CMS's crosshairs.

In addition, because the current CED approach often limits coverage to those living near a few approved academic centers, patients living in lower income regions or underserved communities are often the first to be denied access to a new treatment. Those fortunate enough to get coverage by qualifying for an approved CED study often incur all new costs just to participate. These may include travel costs or time off work for added visits.

Stifling Innovation

For companies developing treatments for the senior population, CMS's recent posture will likely make the AAP pathway much less attractive. If a company chooses to forego the possibility of accelerated approval, it will delay any returns on its research and development investments. Yet, if CMS's recent decision on lecanemab is any indication, getting traditional approval by the FDA is no longer a guarantee for traditional coverage under Medicare.

By any measure, the CED process adds additional complexity, time, and costs to the process of bringing new drugs to market. Whether a drug receives accelerated or traditional approval, the FDA process is rigorous and time-consuming. Requiring manufacturers to navigate a second level of bureaucracy using a different set of arbitrary and unpredictable evidentiary standards increases risk and reduces incentives for investment in new and innovative therapies.

Numerous studies show the impact of approval delays on the economic value of new medications. For example, [recent analysis](#) from Vital Transformation, LLC found that a two-year delay in FDA market approval would leave 28% to 54% of accelerated approval drugs with a negative net present value (NPV), depending on what approach is used to factor development costs. Delaying approval for three to four years—the average time between accelerated approval and traditional approval—would eliminate any NPV for 35% to 68% of AAP treatments (see figure 5).

Policies that refuse or severely limit coverage under Medicare for AAP drugs would effectively eliminate any market incentives to seek accelerated approval for medications targeting illnesses that primarily affect older patients, including Alzheimer's disease and many forms of cancer. Ultimately, if a drug is projected to have a negative NPV, manufacturers will simply opt not to invest in its development.

For other AAP treatments, including many developed to treat rare diseases, refusal by CMS—the world's largest health insurer—to offer coverage would particularly harmful impact. Indeed, given the inherent difficulties associated with clinical trials for rare disease treatments, additional regulatory delays would likely make them economically unviable. In the end, this would mean reduced investments in these types of innovations and fewer treatment options for the most at-risk patient populations.

Figure 5. Impact of Approval Delays on the Net Present Value of Accelerated Approval Medications

Length of Delay	2 years	3 years	4 years
% of AAP drugs with negative NPV	28% to 54%	35% to 65%	41% to 68%

SOURCE: [Therapeutic Innovation & Regulatory Science](#)

CONCLUSION: LET THE FDA DO ITS JOB

While understanding the value patients receive from new a medication requires a long-term focus on evidence generation and analysis between manufacturers and payers, this apparent impasse between agencies has a relatively simple solution: CMS should default to covering FDA-approved drugs for their on-label uses. The process for obtaining FDA approval—for both the traditional and accelerated pathways—is science-based and requires extensive data collection to meet the same high evidentiary standards. The FDA factors all relevant safety and efficacy data into its approval decisions and addresses them its labeling process. After a drug is approved, FDA continuously monitors and adjusts the label after factoring in any new developments.

Critics of the AAP point to examples of medications that received accelerated approval but failed to obtain traditional approval and were eventually withdrawn. However, in many ways, those relatively few cases demonstrate the strength of the program. If every AAP drug eventually obtained traditional approval, it would strongly suggest that the overall FDA approval process is far too stringent. Moreover, in 2022, Congress passed the **Food and Drug Omnibus Reform Act**, which gave FDA additional authority to hold manufacturers accountable for completion of confirmatory trials. Whether it is assessing the evidence gathered in these trials or monitoring the long-term safety and efficacy of any approved medications, the FDA's processes for post-approval monitoring and clinical reevaluation are far more effective tools than CEDs and other CMS-driven interventions.

Recent scientific advances have vastly increased our understanding of diseases and the long-term value of new and innovative therapies. This progress has allowed for the development of medications and treatments with the potential to significantly improve quality of life for patients across a broad spectrum of diseases and populations. Policymakers should focus on encouraging this type of progress instead of burdening innovators with inappropriate restrictions and placing barriers between patients and the latest treatments.



Surrogate endpoints have a clear role in clinical trial design and approval pathways; this has been the case for decades. Not all surrogate endpoints are equal in validity, but this is the FDA's role to work with clinical trialists and determine whether an endpoint is sufficiently defined and validated to meet the standards for approval. We should let the FDA do its work here.

Jennifer Hinkel, MSc, Managing Director, [The Data Economics Company](#);
Chair, [Patient Access & Affordability Project Advisory Board](#)



patientsrising.org | patientsrisingnow.org | 800-685-2654 | info@patientsrising.org