Pink Sheet
Pharma Intelligence

Aduhelm, One Year Later: US FDA's Credibility, Accelerated Approval Pathway Feel The Bite From Alzheimer's Drug Approval

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Executive Summary

June 7 marks the one-year anniversary of the accelerated approval of Biogen's aducanumab, an event that still reverberates throughout the drug development community. While the FDA continues to defend the approval, experts say the backlash has caused the agency to become more reluctant to use the expedited pathway. Meanwhile, Alzheimer's patients find themselves where they were a year ago: without ready access to a disease-modifying therapy.

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One year after the US Food and Drug Administration's accelerated approval of Biogen, Inc.'s Aduhelm (aducanumab-avwa), the Alzheimer's treatment remains a hot and divisive topic in drug development circles.

Reflecting back on the controversy, it appears the approval and the following pricing and reimbursement decisions could have long-lasting implications, including how the public views the FDA's role as the arbiter of drug safety and efficacy, how the FDA uses the accelerated approval pathway, and how payers view the quantum of efficacy evidence for such drugs.

In addition, Aduhelm's approval may have created an expectation – among patients with degenerative or other serious diseases with high unmet need – of approval for late-stage drugs regardless of data package quality given the great efforts the FDA took to get Aduhelm across the regulatory finish line.

Aduhelm is, without a doubt, one of the most controversial drug approval decisions in the FDA's history. (Also see "US FDA's Most Controversial Drug Approval Decisions, From A To Z" - Pink Sheet, 4 Jun, 2021.)

But looking back at the events of the past year, the big question is if the pursuit of the approval was worth the reverberations that it has delivered.

For Biogen, the answer is probably not. Given outstanding questions about the drug's safety and efficacy, coupled with the Centers for Medicare and Medicaid Services' decision to restrict reimbursement, Aduhelm has seen little commercial use and is not widely accessible to Alzheimer's patients.

As a result of the financial investment without near-term revenues to offset the cost, the company is in a precarious financial position – cutting expenses, preparing for layoffs, and recruiting a new CEO.

Although aducanumab set a precedent for the future accelerated approval of other late-stage monoclonal antibodies for Alzheimer's, CMS' coverage decision assures that any such drug granted accelerated approval will only be reimbursed in the context of a randomized clinical trial. (Also see "Medicare Alzheimer's Decision Varies Evidence Mandate For Accelerated vs. Traditional Approvals" - Pink Sheet, 7 Apr, 2022.)

There were predictions at the time of Aduhelm's approval that it would lead to increased use beyond Alzheimer's of the FDA's regulatory flexibility and the accelerated approval mechanism. (Also see "Aducanumab Accelerated Approval Reflects US FDA Flexibility But Raises Doubts About Confirmatory Trial" - Pink Sheet, 7 Jun, 2021.)

However, experts who regularly interact with the agency are reporting the opposite, finding review staff more reluctant to consider use of the expedited pathway.

And caught in the tangled web of controversies created by the FDA's approval, CMS' unprecedented coverage determination and Biogen's much criticized commercial strategy are Alzheimer's patients, many of whom cannot readily access what has been touted as the first drug that could actually modify the course of their disease.

[*Editor's note: This story is part of our package marking the one-year anniversary of the approval of Aduhelm. See the box for links to all the articles.*]

A Landmark Approval, Then A Torrent Of Criticism

The FDA, Alzheimer's patient community and specialists hailed Aduhelm's approval on 7 June 2021 as groundbreaking, the first of several monoclonal antibodies in the pipeline that are aimed at slowing or halting progression of the devastating neurodegenerative disease. Yet, the backlash from consumer groups, academics and others was immediate and multipronged.

The agency faced criticism for approving Aduhelm despite the strongly negative recommendation of its advisory committee, three members of which ultimately resigned in protest. (Also see "Aduhelm Approval Firestorm Raises Question: What Are US FDA Advisory Committees For, Anyway?" - Pink Sheet, 11 Jun, 2021.)

Critics objected to the FDA's decision, arrived at late in the review process, to use the accelerated approval pathway on the basis of a surrogate endpoint. (Also see "As Aducanumab's US FDA Review Progressed, Support Grew For Accelerated Approval" - Pink Sheet, 22 Jun, 2021.)

Reliance upon amyloid as a surrogate for efficacy was explicitly disclaimed by Office of Neuroscience director Billy Dunn at the November 2020 advisory committee meeting. (Also see "Biogen's Aducanumab: Why Accelerated Approval Might, And Might Not, Be An Option For US FDA" - Pink Sheet, 13 Nov, 2020.)

The very broad population for which Aduhelm initially was approved stunned many, as the indication was not restricted by stage of disease. (Also see "Biogen Gets 'Almost Shockingly Broad' Label For Alzheimer's Drug Aducanumab" - Pink Sheet, 7 Jun, 2021.)

Aduhelm's First Birthday

Below are links to the Pink Sheet's stories marking the one-year anniversary of one of most consequential approvals in FDA history.

Aduhelm, One Year Later: US FDA's Credibility, Accelerated Approval Pathway Feel The Bite From Alzheimer's Drug Approval

Medicare Coverage Restrictions For Expensive Drugs: Did Aduhelm Let The Genie Out Of The Bottle?

How Biogen's Aduhelm Bet Became A Commercial Bust

The Story of Aduhelm, From Early Studies To Commercial Demise

The FDA quickly took a step back on this issue, clarifying the indication a month after approval to specify the drug should be initiated in patients with mild cognitive impairment or mild dementia. (Also see "'Embarrassing About-Face': FDA's Aduhelm Labeling Change Does Little To Improve Frustration Over Alzheimer's Approval" - Pink Sheet, 8 Jul, 2021.)

The nearly nine-year timeframe allowed for conducting the required confirmatory trial made for bad headlines for the FDA and Biogen alike. (Also see "3,189 Days: Aduhelm Phase IV Timeline Is Long Among Alzheimer's Drugs And Other Accelerated Approvals" - Pink Sheet, 12 Jul, 2021.)

This extended runway added to the growing conversation around timely completion of confirmatory trials under the accelerated approval program – a conversation that has resulted in legislative proposals aimed at tightening study timelines and authorizing the FDA to be able to require that confirmatory trials are underway at the time of approval.

Both the FDA and Biogen took pains to emphasize that the confirmatory trial would be completed as quickly as possible. In December, Biogen announced plans to begin enrolling patients in May 2022, with the expectation that data would be available in 2026. (Also see "Biogen Pledges Aduhelm Confirmatory Data By 2026, Renewing Spotlight On FDA's Lengthy Original Plan" - Pink Sheet, 16 Dec, 2021.)

That study began recruiting on 2 June, according to a 6 June update on ClinicalTrials.gov. "Site activation and patient scheduling for screening in the Phase IV ENVISION trial has begun," Biogen told the *Pink Sheet*. "We will provide further updates at a future time, as patient dosing is initiated."

The FDA went to extraordinary lengths to defend its approval decision, including holding media calls, quickly releasing review documents and authoring journal articles. Nevertheless, within months, it faced a joint investigation by two House committees looking into the approval and questioning the propriety of its interactions with Biogen on the application.

The HHS Office of Inspector General also initiated a review looking more broadly at the FDA's use of the accelerated approval pathway. (Also see "Beyond Aduhelm: OIG Review Will Put FDA's Entire Accelerated Approval Program Under Microscope" - Pink Sheet, 4 Aug, 2021.)

'Serious Damage To Reputation'

The recoil from the Aduhelm approval has affected how the public views the FDA and how the agency internally is handling other drug reviews, experts said.

"The first thing that resulted from that decision was, I think, serious damage to the agency's reputation, and certainly from our perspective raised concerns about the integrity of the process for reviewing and approving new drug applications," said Michael Carome, director of Public Citizen Health Research Group, which staunchly opposed the drug's approval.

Carome said Aduhelm's approval likely was one factor that pushed Congress to consider changes to the accelerated approval pathway as part of user fee reauthorization legislation that must be signed into law by 30 September.

User fee legislation marked up by the House Energy and Commerce Committee in May would streamline the withdrawal process and require the agency to specify postapproval study conditions no later than the time of approval. (Also see "User Fee Bill's Accelerated Approval Reform Provisions Watered Down, But Could Speed Withdrawals" - Pink Sheet, 4 May, 2022.)

Legislation introduced in the Senate contains similar provisions but also would require the FDA to set up an internal council to ensure the consistent and appropriate use of accelerated approval. (Also see "US FDA Accelerated Approval Council Required Under Senate User Fee Bill" - Pink Sheet, 30 May, 2022.)

Public Citizen has advocated for more changes on the pathway's premarket side, asserting there should be widespread, evidence-based agreement in the research community that an effect on a particular surrogate endpoint is reasonably likely to predict clinical benefit. "In the case of aducanumab

and other drugs that target amyloid in the brain, that's just not the case," Carome said "And that's one of the problems with the FDA's decision to use accelerated approval for aducanumab."

Carome said Aduhelm's accelerated approval dramatically lowered the bar for Alzheimer's treatments to come to market under the expedited pathway, but it remains to seen what effect this will have on drugs in other disease areas.

Course Correction

Those who interact with the agency on drug applications and development programs beyond the Alzheimer's space said the Aduhelm approval and resulting backlash have made the agency more risk-averse and less inclined to use accelerated approval.

The Aduhelm approval has frayed the relationship between the FDA and industry, said Marc Scheineson, co-head of the FDA practice at Alston and Bird in Washington, DC who previously served as FDA associate commissioner. He characterized Aduhelm as a case where "bad facts are making bad regulatory policy."

The FDA deviated from its normally conservative approach in deciding to grant accelerated approval, Scheineson said, adding that he now believes the agency is moving in the opposite direction.

The FDA is "steering its ship in a wide berth now to not be criticized in future designations of accelerated approvals or approvals based on surrogate endpoints, or maybe taking into account the desires of patients and physician groups." – Alston and Bird's Marc Scheineson

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"I'm seeing in my practice that there's a bit of a reaction, that FDA had its hand slapped for being too lenient and kind of bending a little bit to patient groups and medical groups that were lobbying it a bit for lenient treatment to get an unmet medical need addressed," Scheineson said. "Now FDA, as it normally does, in my experience anyway, is reacting to it disproportionately and not allowing accelerated approvals when maybe it otherwise would."

"I think it's steering its ship in a wide berth now to not be criticized in future designations of accelerated approvals or approvals based on surrogate endpoints, or maybe taking into account the desires of patients and physician groups," Scheineson said.

When asked whether he thought Aduhelm's accelerated approval spurred more companies to pursue the expedited pathway than otherwise might have been expected, Scheineson replied: "I think that might have been true within months of the Aduhelm approval, but then with the reaction and the ultimate shutting of the door on the reimbursement side, I think it's had the opposite effect, that companies are steering away from accelerated approval to go more traditional routes in Phase III research."

Another veteran industry observer used a different seafaring metaphor in describing how the Aduhelm action has had a chilling effect on the FDA's use of accelerated approval and its exercise of regulatory flexibility, especially for rare diseases.

While it is said that a rising tide lifts all boats, "we're in a situation with rare diseases since Aduhelm, a receding tide has lowered all boats," the expert said.

When Is Accelerated Approval Appropriate?

The Aduhelm decision also has raised questions about the appropriate use of accelerated approval.

Ellis Unger, principal drug regulatory expert at Hyman, Phelps and McNamara and former director of the FDA's Office of Cardiology, Hematology, Endocrinology and Nephrology, noted the agency's 2014 guidance on expedited programs for serious conditions states that the pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure a drug's intended clinical benefit, or a very large study would be needed to quantify and compare changes in clinical endpoints.

The implication, Unger said, was that accelerated approval should not be used when it is feasible to conduct a development program based on clinical endpoints that would support regular approval. "That's not what I remember as being the appropriate use of that pathway," he said.

In Aduhelm's case, it gained accelerated approval despite failing the primary clinical efficacy endpoint, a measure of cognitive and functional decline, in one of two similarly designed Phase III trials.

'We Stand By That Decision'

Although the FDA declined to respond to questions for this story, its representatives continue to defend the approval decision.

At the Senate Health, Education, Labor and Pensions Committee's 26 April hearing on user fee programs, Susan Collins, R-ME, asked Center for Drug Evaluation and Research director Patrizia Cavazzoni whether, given CMS' national coverage determination, the FDA's accelerated approval decision should be questioned.

The FDA is committed "to continue to utilize expedited pathways, including accelerated approval, to bring medicines to underserved populations, such as people suffering from Alzheimer's, and our decision on aducanumab exemplifies our commitment. And we stand by that decision." – FDA's Patrizia Cavazzoni

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"I would like to emphasize how committed we are to continue to utilize expedited pathways, including accelerated approval, to bring medicines to underserved populations, such as people suffering from Alzheimer's, and our decision on aducanumab exemplifies our commitment," Cavazzoni said. "And we stand by that decision."

"We believe that the data are solid, and that the drug is appropriately made available to patients based on FDA's decision. It is important to distinguish FDA's role and CMS' role. FDA is squarely and solely responsible for determining whether a drug is safe and effective. And we made that determination when we approved aducanumab. And that determination … represented our belief that the drug can be made available to patients."

‘Dark Year For Patients’

Yet, some have questioned whether, by approving Aduhelm, the agency created false hopes in the Alzheimer’s patient community about the drug’s clinical benefits, as well as the expectation among patients with other neurodegenerative and serious diseases that they, too, deserved the same kind of flexibility and regulatory help the FDA gave to Aduhelm.

This viewpoint was evident at the March advisory committee meeting on Amylyx Pharmaceuticals, Inc.’s AMX0035 for treatment of amyotrophic lateral sclerosis. During the open public hearing, an ALS patient advocate questioned why the FDA’s generally negative review of the data for AMX0035 was lacking the “humanity and urgency” afforded to Aduhelm. (Also see "One Difference Between Amylyx’s ALS Drug And Aduhelm: A Biomarker Endpoint" - Pink Sheet, 30 Mar, 2022.)

Alzheimer’s patient advocacy groups, who strongly supported the FDA’s accelerated approval and opposed CMS’ coverage decision, said their communities are in the same, or even worse, position than before Aduhelm’s approval one year ago.

“The primary way that individuals with Alzheimer’s, early stage or mild cognitive impairment due to AD, can access a new treatment is through participating in a clinical trial, which is ultimately where we were prior to the approval,” Alzheimer’s Association president Joanne Pike said. “It’s been certainly a year where we have seen advancements in treatment for Alzheimer’s. But at the same time we unfortunately also are in a place where equitable access to those treatments is not available” due to CMS’ coverage restrictions.

“The accelerated approval mechanism, I think, has been essentially denuded. It’s been nullified by CMS’ decision.” – UsAgainstAlzheimer’s George Vradenburg

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George Vradenburg, chairman and co-founder of UsAgainstAlzheimer’s, said patients with Alzheimer’s or other serious diseases are worse off than a year ago given the backlash against the FDA’s approval, followed by CMS’ coverage restrictions.

“The accelerated approval mechanism, I think, has been essentially denuded. It’s been nullified by CMS’ decision,” Vradenburg said. “Whatever scientific judgment is that the FDA has come to about the safety and effectiveness of a drug approved under the accelerated approval mechanism will be ignored by Medicare, and effectively denied access to a marketplace, notwithstanding the FDA approval.”

“This is a sign that Medicare is going to be a second layer of review, a second set of trials or studies,” he said. “So we’re in a worse position today than we were a year ago.”

Drug sponsors and patients in other therapeutic areas are extremely concerned about the precedent CMS’ decision sets for patients getting access to accelerated approval drugs, he said. In addition, congressional measures aimed at tightening use of the accelerated approval pathway, such as the Senate proposal for an intra-agency council, will create additional bureaucratic obstacles and delays in other therapeutic areas, Vradenburg said.

Vradenburg worries that the “trauma” everyone went through with Aduhelm is going to affect the future behavior of some of the key players involved, including the FDA.

“Is FDA going to have the same positive attitude toward using the accelerated approval mechanism to accelerate innovation in this space and to create the innovation that we got in HIV/AIDS and cancer? Or are they going to be a gun-shy? … What is the consequence of a set of things that have happened on future behavior as it affects FDA, CMS, industry, other therapeutic areas?”

“It has ended up being a dark year for Alzheimer’s patients,” Vradenburg said. “Not just Alzheimer’s patients, but potentially for patients in other therapeutic areas.”