

Insights on FDA's controversial approval of Alzheimer's drug

June 21 2021, by Patrick Ercolano



Supriya Munshaw. Credit: Johns Hopkins University

The U.S. Food and Drug Administration's recent approval of aducanumab, a treatment for Alzheimer's disease, has drawn decidedly mixed reviews.

Advocates for patients, such as the Alzheimer's Association, applauded the FDA's green light for the [drug](#) (though the group later decried the high price tag set by Biogen, the U.S. manufacturer selling the drug under the brand name Aduhelm). On the other side, critics assessed the trial data as inconclusive. Indeed, three of the scientists on the advisory committee resigned in protest over the FDA's move, with one calling it "probably the worst drug approval decision in recent U.S. history."

In a conversation with the Hub, Johns Hopkins Carey Business School Senior Lecturer Supriya Munshaw—an expert in the commercialization of early-stage technologies, especially in the [life science](#) and medical device industries—considers the recent controversy and offers her insights into the FDA's rationale, the price set by Biogen, the future of FDA leadership, and other related topics.

Despite the FDA advisory committee's nearly unanimous decision against approving aducanumab—they said there was not enough evidence that the drug provided clinical benefit—the FDA gave its OK to the drug. Is it unusual for the FDA to ignore a clear-cut recommendation from an advisory group?

While this is not the first time the FDA's final action has disagreed with the advisory committee's recommendation, we know that this happens rarely. A 2019 study showed that between 2008 and 2015, the FDA and the advisory committee disagreed about 22% of the time. Only 25% of disagreements were in cases where the advisory committee had an unfavorable decision. So, this situation we have with aducanumab is not the norm.

It is also essential to know that the FDA does not engage an advisory committee with all [drug approvals](#). The FDA seeks their advice only in some cases, such as if the drug is first-in-class or first for a given indication such as for Alzheimer's.

Why do you think the FDA decided to approve the drug?

The FDA considers other factors beyond the science and technical aspects of the drug (which is what the advisory committee focuses on). If we simply look at the science behind this drug, it is not compelling. While one study demonstrated marginal improvements in clinical outcomes, another did not.

The approval is also based on a surrogate marker, not on a clinical outcome. A surrogate marker is a biological marker that is used instead of a clinical outcome. For example, oncology drugs may use a reduction in tumor size as a marker for improved overall survival. The link between the two is well accepted, so companies don't have to wait till patients have survived longer but can apply for approval based on the surrogate marker of tumor size. In the case of aducanumab, clinical trials showed that patients had significantly decreased levels of amyloid plaques. However, the link of this marker to clinical outcomes is not well-established and has even been questioned, so all in all, the science behind the approval is weak.

However, the disease burden from Alzheimer's is immense. There are more than 6 million patients in the United States alone with no treatments for the disease. The FDA considers this a substantial unmet need. In addition, patient advocacy groups such as the Alzheimer's Association were highly vocal in favor of this approval. The FDA had to balance the risk of the drug with the benefits it could provide, making it a highly complicated decision. The FDA's perspective could be to put this drug on the market, at least for those whom it can help, while the company conducts confirmatory trials to ensure that it works.

In my Pharmaceutical Strategy class at Carey, students discuss a similar

2016 case of the approval of a drug called Exondys51 for Duchenne muscular dystrophy. The FDA also approved this drug despite the unfavorable decision by the advisory committee. The case gives students an idea of the complexities of the drug approval process.

Some supporters of the approval have said this is a first step to help some patients and spur continued research into a drug for Alzheimer's. Is there validity in that viewpoint?

The drug provides immense hope to patients and patients' families who have been waiting for treatment for many years. Still, the question is whether this gives them false hope, given the drug's disputed efficacy. In terms of continued research, there are two sides to this: one, yes, the approval could set the path for future investment, drug research, and approvals. Still, it could also send companies toward the wrong target (given the controversial connection between the pathway this drug works on and clinical outcomes), and patients could drop out of clinical trials to take this approved drug.

Looking ahead, how might the resignations of advisory board members affect the process in which experts examine research data and give their opinions on possible FDA approvals?

I don't think that the resignations will change the way advisory committees will provide recommendations. The committee provides a third-party, unbiased review of the scientific data, and the remaining and new members will continue to do so. How these resignations change the way the FDA may approach recommendations from the committee and approvals of such controversial drugs is a different question. A lot of this

depends on the outlook of the FDA commissioner and the heads of the agency's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

A recent *New York Times* article noted that the FDA continues to be run by an acting commissioner, Janet Woodcock, and that the FDA's "long-term agenda for drug approvals or new issues is languishing without a permanent commissioner." Do you think this situation with FDA leadership might have been a factor in what has transpired with aducanumab?

I think getting a permanent commissioner is important for a long-term strategy as the Times article suggests, but in this case, I don't think that having only an acting commissioner had an adverse effect. Dr. Janet Woodcock has been with the FDA since 1986. She is well-positioned to serve as the acting commissioner and even the permanent commissioner, for that matter. Interestingly, Dr. Woodcock was the director of CDER during the Exondys51 approval and played an essential role in that decision. She has broad support from the drug industry and patient advocacy groups. So, while the permanency of leadership may not be an issue, the type of leadership and their outlook are essential in setting the direction for the FDA.

Another controversial aspect of the drug is that Biogen, which developed the drug with Japanese pharmaceutical company Eisai, has set the price at \$56,000 for a year's worth of treatment per patient, much higher than what industry experts were expecting. What's more, it's the kind of treatment that many people would need for years. Can you offer insight as to why Biogen set the price at that level?

Many experts were expecting a price around \$10,000 based on current Alzheimer's treatments, but honestly the high price was not a shock to me. First, this is a biologic drug, and Biogen views it as a specialty drug, so given the prices of such specialty drugs in recent years, this high price was not atypical.

One thing to note is that the drug received a much broader approval label from the FDA than expected. Based on the trials and data, Biogen expected that the FDA would approve the drug for a subset of Alzheimer's patients, specifically those in the early stages of the disease. Biogen was expecting a population of around 1 million to 2 million patients to be eligible for the drug. Instead, the FDA approved the drug under a much broader label, making all 6 million U.S. patients eligible. The original, smaller patient population was probably a consideration in the higher list price. Even with the new label, I don't expect that the list price is going to be lowered unless Biogen faces significant backlash or if the drug faces hurdles with patient access.

Because the drug was OK'd as part of the FDA's "accelerated approval" process, Biogen must conduct a randomized controlled trial to verify aducanumab's efficacy. Is that a routine procedure? And is it possible the FDA will rescind its approval if this subsequent trial shows poor results?

The Accelerated Approval pathway is an essential piece to this story. This pathway was initiated in 1992 specifically for conditions with a high unmet need. The idea is to approve the drug based on a surrogate marker to start helping patients and then have companies perform confirmatory trials. So, yes, this pathway is routine for many oncology drugs and others where, again, there is a high unmet need. If these

confirmatory trials fail to demonstrate the clinical benefit, the drug is pulled from the market.

For example, Bristol-Myers Squibb withdrew its drug Opdivo for a particular subset of lung cancer patients in December 2020 after confirmatory trials did not meet the endpoint of overall survival. The drug was granted accelerated approval for this indication in 2018 based on a surrogate endpoint.

One major issue in the aducanumab decision is that the FDA has given Biogen until 2029 to complete these confirmatory trials, so this drug can potentially be on the market for at least until 2030, costing the health care system significantly before any decision might be made to withdraw. The FDA has come under scrutiny for failing to enforce these confirmatory trials. For example, confirmatory trials for Exondys51 have not been complete yet, although the completion date in their letter was November 2020.

Provided by Johns Hopkins University

Citation: Insights on FDA's controversial approval of Alzheimer's drug (2021, June 21) retrieved 4 May 2024 from

<https://medicalxpress.com/news/2021-06-insights-fda-controversial-alzheimer-drug.html>

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