

VIEWPOINT

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FDA Drug Approval and the Ethics of Desperation

In justifying the accelerated approval of aducanumab (Aduhelm; Biogen), US Food and Drug Administration (FDA) officials emphasized that many patients with Alzheimer disease and their families “made it clear that they are willing to accept the trade-off of some uncertainty about clinical benefit in exchange for earlier access to a potentially effective drug.”¹ This reasoning raises a critical question. When patients have a diagnosis of desperation that leaves them facing a life-limiting disease without good treatment options, what role should their willingness to try a drug of unproven benefit play in regulatory decision-making? In this Viewpoint, we argue that patient voices should be integrated into the drug approval process, but without such deference that the FDA abdicates its responsibility to ensure drugs are safe and effective.

Desperate Times

In November 2020, the FDA’s Peripheral and Central Nervous System Advisory Committee, a group of external experts, recommended against approving aducanumab in light of insufficient evidence that the drug slows cognitive decline. In the spring of 2021, FDA officials serving on the agency’s Medical Policy and Program Review Council acknowledged that some patients would want aducanumab “despite the uncertainties” but “stressed that this should not influence the regulatory decision,” according to meeting minutes obtained by the *New York Times*.² Nonetheless, in June 2021, the FDA granted accelerated approval of aducanumab on the basis of a reduction in amyloid- β plaques, an end point that has not been established to predict clinical benefit.

What happened between November 2020 and June 2021? Among other activities, the Alzheimer’s Association organized a meeting between senior FDA officials and patients, families, and association representatives, based on concerns that “the voices of those diagnosed with Alzheimer’s and their caregivers had not truly been heard.”³ Later, the chief executive officer of the Alzheimer’s Association stated his belief that this advocacy “had some influence” on the FDA’s decision, explaining “you cannot be unmoved by hearing the stories of people who face this disease, the crushing realities of it every day.”⁴

Although patient views should inform the balance between speed and certainty in regulatory decisions, approving drugs for which benefits have not been established can derail scientific progress, expose patients to medications with risks that outweigh benefits, and allow hope to be exploited for commercial benefit, with high costs to the health care system. Unfortunately, patient desperation in the face of crushing realities has no bearing on a drug’s effectiveness against disease; wanting a drug to work does not mean it will.

The difficult reality is that the FDA sometimes must make decisions at odds with the wishes of some patients. The ethics of desperation demand that the FDA navigate between the poles of excessive paternalism and excessive deference to patient autonomy.

Desperate Measures?

Accepting patients’ willingness to try unproven treatments as a touchstone for drug approval would dangerously erode the FDA’s regulatory role. Rigorous standards for the safety and effectiveness of approved drugs protect patients and enhance their autonomy by providing the evidence needed for informed judgments about available therapies.⁵ As the FDA applies these standards in drug approval decisions, it weighs a variety of factors, including scientific evidence and clinical context, as well as limits on its regulatory authority. The agency’s decisions, however, are not purely objective. Deciding whether a drug is safe and effective usually involves subjective, normative judgments about whether the product is safe and effective enough.

Patients have the greatest stake in drug approval, and it would be irresponsible for the FDA to ignore their input when making these decisions. Rigorous patient-reported outcomes can inform conclusions about treatment effects. Patients’ lived experience can also help contextualize clinical trial data when risks and benefits are not easily compared. For instance, with aducanumab, patients could offer insight into whether a small change in the Clinical Dementia Rating Scale Sum of Boxes, a score used to stage dementia severity, would translate to meaningful improvement in daily life—and how that benefit would compare with the risk of adverse events. Yet patient perspectives also should be balanced against other relevant data, including trial results, advisory committee input, the likelihood of quickly gathering additional meaningful evidence after approval, and the precedent set by weak approval standards.

Desperation and Regulatory Decisions

To inform the FDA’s regulatory decision-making in the face of patient desperation, we suggest 5 considerations.

First, patient input is most valuable in close cases, where available data and regulatory frameworks do not clearly indicate whether a drug should be approved. The accelerated approval of aducanumab was not a close case given conflicting trial results and a lack of evidence for the clinical benefit of reducing amyloid- β plaque.⁵ This regulatory pathway is meant to facilitate early access to promising drugs when further study to demonstrate clinical benefit would lead to significant delay, not to save drugs from regulatory rejection when clinical benefit has been studied but the evidence falls short.⁶

Second, the FDA should take into account the diversity of patient opinion and avoid generalizations about patient preferences. For example, support for aducanumab is not universal in the Alzheimer disease patient and caregiver community. The agency should seek out and hear from a range of patients rather than assume that the few who submit comments or speak at public meetings are representative. In addition, some patients may have ties to drug companies or patient advocacy organizations with financial conflicts of interest: in fiscal year 2020, the Alzheimer's Association received between \$250 000 and \$499 999 in financial support from both Biogen and Eisai, Biogen's partner in bringing aducanumab to market.⁷ The FDA should take care to discern the potential influence of industry on messages delivered by patients.⁸ It should also avoid favoring certain patient advocacy organizations with privileged access or outsized influence on its decisions.

Third, and closely related, the FDA has obligations to both current and future patients. The urgency of current patients' needs may lead them to push the FDA to facilitate immediate access to drugs of uncertain benefit. In contrast, future patients are more likely to favor approval standards that result in drugs with stronger evidence of benefit and that provide incentives for companies to expend the time and care needed to develop such evidence. From the FDA's perspective, the desperation of current patients is palpable and difficult to set aside, whereas the benefits of further research for future patients are abstract and easier to disregard. Nevertheless, as a public health agency, the FDA should account for and fairly balance all relevant patient interests.

Fourth, communication between the FDA, patients, families, and advocacy groups should be bidirectional. This means the agency should listen but also educate about relevant considerations that individuals or groups may not recognize, such as reasons for not ap-

proving a drug with conflicting evidence regarding benefit but clear potential for harm, gaps in available data, and the challenges of obtaining meaningful evidence after approval. Patients' informed preferences—based on an understanding of all the relevant information—are most pertinent to the agency's decision-making.

Finally, when approving drugs, the FDA should resist a "something is better than nothing" mindset. This mindset is understandable for desperate individuals, which is why the agency allows certain unapproved drugs to be used through expanded access programs.^{9,10} But relying on desperation to justify drug approval does more than simply leave treatment decisions to individual patients and their clinicians. Instead, it affects the drugs and clinical information likely to be available to all patients. The FDA's role as a gatekeeper forces companies to establish that their drugs are safe and effective before they can be marketed. When the FDA abdicates this responsibility, however, that evidence is much less likely to be forthcoming. That benefits companies, not patients, and shifts the responsibility for gatekeeping onto others, such as physicians and insurers.

Conclusions

The accelerated approval of aducanumab highlights a broader question: what role should desperation play in the FDA's decision-making? Although the FDA should listen to patients, caregivers, and advocacy groups, their views should not be treated as determinative. Being in service of patients—today's and tomorrow's, individuals and populations—sometimes requires the FDA to deny new drug applications. Approving only drugs with convincing evidence of safety and effectiveness enhances patients' autonomy by providing meaningful choices while affording important protections. Approving ineffective drugs is likely to make desperate patients more desperate.

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