The FDA Accelerated Approval Program: Data Transparency for Public Health

Zhuoying Lin
University of California, Los Angeles, Department of Chemistry and Biochemistry, Los Angeles, CA, USA
https://doi.org/10.38126/JSPG230107
Corresponding author: zylin@g.ucla.edu
Keywords: clinical trial data; data transparency; Accelerated Approval Program; FDA

Executive Summary: The Accelerated Approval Program (AAP) of the US Food and Drug Administration (FDA) authorizes earlier approval of drugs based on surrogate endpoints to fulfill unmet medical need. Compared to the standard approval process, drugs approved through the AAP have greater uncertainty in clinical benefits due to the reliance on surrogate endpoints and lack of initial confirmatory studies, which raises concerns regarding the rigor and transparency of the program. While the Consolidated Appropriations Act enacted on December 29, 2022 requires the FDA to start reporting its postmarket analysis and decision making publicly, it is neither sufficient nor comprehensive to inform the public of the existing public health risks and benefits of the accelerated approved drugs when the preliminary clinical trial data remains confidential. The lack of data transparency and inherent uncertainty surrounding accelerated approved drugs prevents patients from making fully informed choices and puts public health at greater risk. Thus, we propose that the FDA proactively release the de-identified clinical trial data upon accelerated approval. Disclosure of de-identified clinical trial data would strengthen independent, public health-prioritized data interpretation and analysis, which allows physicians and patients to make better informed decisions about their medical treatment.

I. Accelerated approval program

The Accelerated Approval Program (AAP) was adopted by the Federal Drug Administration (FDA) in 1988 and officially legislated by the U.S. Congress in 2012 "to allow for earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint." (FDA 2023). Unlike the standard FDA approval process, which requires direct measure of a clinical endpoint to verify the long-term clinical benefit of a drug upon approval, the AAP expedites the new drug authorization by basing the clinical benefit on a surrogate endpoint (e.g., biomarkers, laboratory measurements) that is considered reasonably likely to predict the long-term clinical benefit of symptom control and reduced mortality (Federal Food, Drug and Cosmetic Act 2018). Only after the accelerated approval does the FDA require manufacturers to verify the long-term clinical benefits through postmarket confirmatory clinical trials. If proven beneficial, the accelerated approval will be converted to a traditional approval. Otherwise, the drug will be withdrawn from the market (Figure 1).

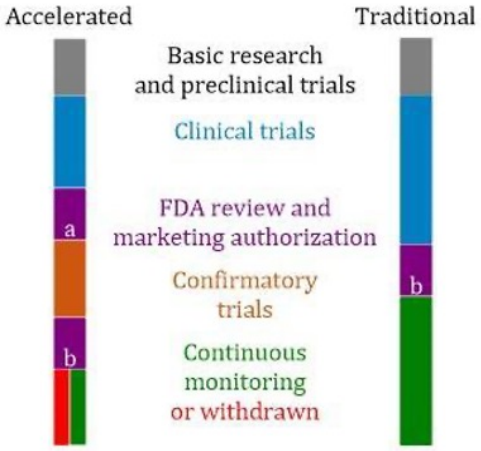

Figure 1: Timelines of trial endpoints in accelerated drug approval and traditional approval process. The trial endpoints are a. surrogate endpoint and b. clinical endpoint. Under accelerated approval, a drug is approved earlier by allowing for confirmatory trials to be conducted after market authorization.

Under the AAP, the postmarket confirmatory studies and long-term clinical benefit may take a considerably long time to verify. From 1992 to 2021, the FDA approved 278 drugs through the AAP, among which the median time for an accelerated approval to convert into traditional approval was 3.2 years (Beakes-Read et al. 2021). The median time has significantly shortened to 2.3 years for the 51 accelerated approvals in the last decade (2012 to 2021), which is attributed to FDA's 2014 guidance that formalized AAP protocols and the agency's proactive efforts to increase public involvement and discussion through the Advisory Committee (FDA 2014). Nevertheless, the time it takes to conclude confirmatory trials is highly variable. Furthermore, unforeseen challenges and special circumstances can also lead to potential delays and extensions of confirmatory trials, which extends the period of uncertainty before the safety and efficacy of the accelerated approval drug is confirmed. (Naci et al. 2017).

II. Lack of data transparency risks public health

Informing the public of the drug's progress to date—before the conclusive results of postmarket approval are available—becomes exceptionally important to public health when patients are in immediate need of medical treatment. In particular, clinical trial data submitted to the AAP is a significant component of the research progress to date; it is the primary evidence and serves as a baseline for postmarket clinical studies. Yet clinical trial data submitted under the AAP have never been disclosed proactively and openly by FDA, limiting public interpretation and analysis by those whose lives are directly impacted. While the FDA is subject to confidentiality obligations and baseline disclosure requirements established by Congress, the FDA is the only regulatory agency that determines what information will be made publicly available, and much of the data the FDA receives are kept confidential from public examination (Institute of Medicine 2015).

This leaves the FDA's evidence-based scientific reasoning subject to potential cherry-picked datasets and experimental designs that favor a desired outcome. This lack of transparency also bars data-based scientific inquiries by the public, which makes FDA's analysis difficult to validate. Without public access to its clinical trial data, the AAP leaves holes in the approval process and jeopardizes public health by withholding the comprehensive information about the current knowledge of the drug.

Efforts to improve transparency were enacted in 2023 under the Modernizing Accelerated Approval Act, also known as the Food and Drug Omnibus Reform Act (FDORA) of the Consolidated Appropriations Act, which reforms the AAP's regulatory framework. Highlights of transparency-focused reforms under this act include:

- Requirements for the accelerated approval council to publish an annual report of its activities on the FDA's website;
- Requirements for the FDA to publish on its website the rationale for not requiring a postapproval study, if deemed unnecessary;
- Requirements for the FDA to publish the expedited withdrawal proposal on its website for public comments, as well as a summary of the comments and the agency's response when available;
- Requirements for sponsors of drugs approved under accelerated approval to submit a report of progress on required postapproval studies to the Secretary every six months, with the FDA being required to share the information in an easily accessible format; and
- Increases to the frequency and timing of the postapproval reporting period for sponsors from annually to every six months, with the FDA required to publish the reported information on its website (Cooley 2023).

While it is encouraging that the FDORA requires the FDA to disclose its postmarket analysis and explain its decision making to the public, the changes are insufficient. De-identified clinical data, from which the FDA's decisions are derived, remain private. Therefore, despite the FDORA's efforts to improve transparency, limited data accessibility continues to prevent the public from being fully informed.

III. Adulhem case study

The FDORA was enacted partially in response to the FDA's controversial approval of the Alzheimer's drug Aduhelm (aducanumab) through the AAP in 2021. Aduhlem's manufacturer Biogen used the AAP's

surrogate endpoint-based mechanism. The FDA approved the drug despite the Advisory Committee concluding the clinical data was not convincing. The FDA also gave Biogen more than 8 years to complete the postapproval confirmatory trials while the drug remains on the market (Rubin 2021).

In late 2020, clinical data for Aduhelm was made available for public release in the Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting Briefing Document and claimed to be without redaction (FDA 2020). Review of the data by independent sources generated significant controversy; reviewers were unable to assess the drug efficacy in both the high-dose and low-dose groups based on the prespecified experimental plan. Reviewers also found the potential introduction of bias due to the ways data were presented and interpreted through post hoc selection of the randomized controlled trial (Tampi et al. 2021). Many Alzheimer's experts and doctors also disagreed with the FDA's approval and justification of Aduhelm (Belluck 2022). As a result, major health systems including Cleveland Clinic and New York's Mount Sinai Health System have declined to offer Aduhelm, while some physicians refuse to prescribe it to their patients or will leave the decision to the patients after informing them fully of the risks and benefits (Rubin 2021).

As the Aduhelm case demonstrates, reporting of clinical trial data is essential for public health-prioritized data analysis and interpretation independent from the FDA. Transparent clinical trial data also allows physicians and patients to make better informed decisions that ensure they choose the appropriate medical treatment, to the best of their knowledge, before FDORA-required postapproval reports become publicly available every six months.

IV. Policy options

To address public health concerns, the FDA could enact policies to ensure public access to clinical trial data and improve the transparency and rigor of the AAP. Options include:

i. Option 1: Status quo

Follow the current rules of the AAP, which keeps raw clinical data confidential.

Advantages

- No additional effort or cost needed to prepare de-identified data in a publicly accessible format before the AAP application.

Disadvantages

- Leaves the AAP more subject to bias and favorable outcomes without data examination and analysis by the public and independent researchers.
- Limits public interpretation and analysis of the clinical trial data, preventing a more informed medical treatment decision.

ii. Option 2: Expedited approval of data requests

As FDORA created the expedited withdrawal procedure for the AAP, expedited approval for data requests specific to the AAP under Freedom of Information Act (FOIA) should also be made available.

Advantages

- Allows access to original data upon request at reasonable cost and in a timely manner for urgent research questions and immediate prescription.
- Only released upon request, minimizing impact on regulators and corporations.

Disadvantages

- Relies on individual requests, which is not maximally efficient data sharing.
- Data shared upon request may not provide a comprehensive analysis.
- Increases the burden on regulatory agencies through increased use of time and money.

iii. Option 3: Disclosure of de-identified clinical trial data upon accelerated approval

Release de-identified clinical trial data to the public when the FDA approves the drug through the AAP.

Advantages

- Allows public access to clinical data and evidence that are important for clinical care and scientific understanding.
- Facilitates external evaluation and enhances the rigor of the AAP through outside analysis.
- Increases understanding of the program and clinical trials protocols for companies who are interested to apply and sequentially

increase the efficiency of the AAP during pressed time.
- Decreases liability to the corporations by having all data publicly available.

Disadvantages
- Requires additional input of labor, time and cost for manufacturers to submit de-identified clinical data in a publicly accessible format for the application of AAP.
- Requires FDA to set up data policies and protocols for data transparency.
- Additional evaluations may result in further confirmatory trials studies, slowing down the overall process of conclusively resolving an accelerated approval.

V. Policy recommendation

We recommend increasing transparency through proactive disclosure of clinical trial data upon accelerated approval (Option 3), as creating an expedited data request and approval mechanisms (Option 2) would only offer a partial solution. Currently, the only existing option to access clinical trial data from the FDA is through the FOIA, enacted in 1966, which provides a mechanism for individuals to submit requests for copies of records that are not distributed publicly. However, the FOIA is not designed for immediate data access. Requests for clinical trial data may take years to fulfill due to a wait list. Though "expedited processing" was granted by the FDA in 2014 and 2015, it took 693 days and 862 days to complete the data requests respectively (FDA 2015, U.S. Health and Human Services 2016). An expedited version of FOIA could help fulfill the data requests exclusive to the AAP by creating a separate FOIA request pipeline. However, the nature of FOIA is not designed to share clinical data for clinical care and public health (Kapczynski and Kim 2018). Additionally, FOIA does not result in the systematic release of data, and fulfilled requests are not required to be shared with others. Therefore, we believe having the FDA proactively release the clinical trial data upon accelerated drug approval (Option 3) would be most beneficial for public health.

Option 3 will allow the public to evaluate the safety and efficacy of the drug using existing clinical trial data. This data is especially relevant, as confirmatory trials are an extension of the preapproval trials. Having this data freely available will enhance public understanding of surrogate endpoint-based studies and safeguard the rigor of the AAP.

We recommend the FDA to distribute the standard types of clinical trial data: 1) patient-level raw data which contains identifiable information for analysis, 2) metadata about study protocol and statistical methods, and 3) summary-level data which includes clinical trial reports that provide comprehensive description of the research (Institute of Medicine 2015). These can be uploaded online through existing federal repositories such as the ClinicalTrials.gov and the Biologic Specimen and Data Repository, both run by the National Institutes of Health (NIH). Patient and commercially sensitive information could be removed to protect privacy and ensure confidentiality. The European Medicines Agency (EMA) currently publishes similar scopes of clinical data submitted by pharmaceutical companies (Tsang and Kerr-Peterson 2023). The EMA and NIH both have established standards on clinical study reports and protocols for de-identification of patients to protect privacy, which can serve as existing models to safeguard data privacy upon disclosure (EMA 2019). The FDA would also need to create legal policies on data disclosure and user agreements.

Manufacturers will be responsible for the main costs of data transparency. If the cost can be budgeted into the funds available for clinical research, clinical trial data availability can further benefit funders by serving as a primary source for determining cost-effectiveness of the research (Rosenberg 2022). We recommend the manufacturers to coordinate with the FDA in submission of the de-identified data along with the raw data. Manufacturers should also plan and create documentation for data disclosure along with the consent of clinical trials participants from the start instead of the very end.

In summary, lack of data transparency in the AAP puts public health at risk by restricting public analysis of the accelerated approved drug and limiting fully informed prescription choices. To improve public health and the rigor of the AAP, the FDA should proactively share clinical trial data upon accelerated drug approval. Doing so would enhance the public's understanding of and confidence in accelerated approved drugs.

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Zhuoying Lin is a Ph.D. student in Materials Chemistry at the University of California, Los Angeles, where she conducts battery research for energy storage applications. She enjoys science journalism and is a news writer for her home department.

Acknowledgements

The author thanks the Science Policy Group at UCLA and Ge Yang for their valuable feedback on the manuscript.

Disclaimer

The author declares no conflicts of interest.