COMMENTARY

# Great Trees Require Strong Roots: Evaluating Data and Delegation Doctrine Underlying Proposed Reforms to FDA's Accelerated Approval Program

*Anjali D. Deshmukh*[1]

1: GEORGIA STATE UNIVERSITY, ATLANTA, GA, USA.

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**Abstract:** In "Missing the Forest for the Trees: Aduhelm, Accelerated Approvals & the Agency," Dr. Matthew Herder argues that agency capture and politicized discretion drive delays in confirmatory trials of accelerated approval drugs amongst other concerns at US Food and Drug Administration (FDA). In highlighting this important problem and offering nuanced insight into agency workings based in part on interviews with twenty-three unnamed FDA officials and a three-drug case study, Dr. Herder suggests two innovative solutions. However, amidst broader debates balancing agency expertise, data, and delegation, these proposed policy solutions would benefit from more corroborative evidence and consideration of institutional advantages within constitutional limits.

## Introduction

Just as drug efficacy cannot be demonstrated by a single patient, solutions to the problems underlying untimely completion of post-approval studies should not be based on a single drug. Doing so risks incomplete conclusions and misunderstandings. On this premise, Dr. Matthew Herder's article, "Missing the Forest for the Trees: Aduhelm, Accelerated Approvals & the Agency," advocates for reforms to user fee legislation as a solution to both delays in post-approval confirmatory trials for drugs approved under the Accelerated Approval Program and the overly "cooperative relationship between" industry and the US Food and Drug Administration (FDA).[1] As an alternative, he suggests delegating post-approval drug monitoring and withdrawal of approvals to independent external experts.[2]

Delays in completion of confirmatory trials for drugs approved under the Accelerated Approval Program is an important, multidimensional problem.[3] In a cross-sectional study examining the timeliness of all post-approval confirmatory studies for drugs granted accelerate approval between 2012-22, 54% of drugs were not completed by the initial agreed-upon deadline.[4] Most strikingly, the amount of time FDA projects a study to be completed varies by therapeutic area (mean 3.5 to 8.7 years).[5] Many FDA leaders, scholars, prescribers, and patients call for reforms to the Accelerated Approval Program to address these problems.[6] Dr. Herder's concerns about the scope of agency discretion are part of theses broader questions, but solutions should be connected to comprehensive data and within constitutional limits.

## In Consideration of Connection

Dr. Herder's three cases illustrates external and internal problems affecting FDAs drug approval and withdrawal decisions, highlighting difficulties in obtaining and acting on post approval clinical trial data and real-world evidence. He attributes confirmatory trial delays and limitations in post-approval drug monitoring programs to Congressionally mandated user fee legislation timelines, leading to improper distribu-

**Anjali D. Deshmukh, M.D., J.D.,** *is an Assistant Professor of Law at Georgia State University College of Law and a board-certified pediatrician practicing at Boston Children's Hospital.*



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tion of resources within the agency.[7] The Prescription Drug User Fee Agreements (PDUFA) is a law renewed every five years that collects large fees from pharmaceutical companies and mandates FDA review drugs designated Priority Review within specified timelines[8] These fees constitute a meaningful portion of the Agencies budget. Originally addressing concerns over inadequate staffing contributing to regulatory delays during the AIDS crisis, PDUFA has evolved over 30 years to address numerous issues such as post-approval monitoring, review cycles number, and transparency amongst others.[9] Despite some success, the program remains highly criticized.[10] In addition to concerns over potentially rushed decisions in attempts to meet mandatory review timelines echoed by Dr. Herder,[11] scholars worry about budgetary insufficiency creating agency dependance on user fees, unfulfilled FDA staffing needs, improper political oversight, and inappropriate industry influence.[12]

Although many scholars agree that PDUFA's user fee scheme may create a structural risk of agency capture, it is less clear PDUFA's timelines are the primary driver of delays in post-approval confirmatory trials and Agency priorities.[13] Additional research is needed to confirm Dr. Herder's theory that FDA intentionally does not prioritize post-confirmatory trials.[14] It would be helpful to understand why differential prioritization occurs, how often, relevant circumstances, and if they are related to PDUFA timeline pressures alone or in conjunction with the concerns raised by other scholars. Solutions based on limited evidence merit caution as revising PDUFA timelines may affect other regulatory concerns and have unintended impacts.[15] Solutions should be driven by comprehensive data and awareness of potential unintended impacts.

## Agencies, External Experts, and Constitutional Limits

Dr. Herder proposes a second "more radical" alternative, suggesting FDA should no longer be responsible for post-approval regulation of drugs granted accelerated approval. Instead, he suggests that responsibility should be delegated to a new congressionally created outside body of experts independent from the Agency, industry, and patients.[16] When an agency falters, many turn to outside sources like courts and Congress to reign in an inefficient or captured agency. Others like Dr. Herder envision outside experts as an efficient, scientifically sound replacement.[17] Yet such solutions may run afoul of the Constitutional.

Withdrawal of government benefits must comply with the Due Process clause of the Constitution, which requires reasonable notice, an opportunity to be heard, and decision by a neutral decision maker.[18] Revoking a license by external experts, without these features, would be unconstitutional. Due Process concerns are also intertwined with liberty objections. Accountability requires that citizens displeased with agency actions should be able to identify who took that action and express displeasure through their vote. While cooperation between public and private actors to achieve public policy goals is widespread, delegation to external experts without agency oversight lacks accountability.[19]

When private delegations were attempted at other agencies in the 1930s, the Supreme Court held reli-

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ance on outside experts without oversight, political accountability, and protections for minority views of regulated competitors to be problematic encroachments on liberty.[20] More recently, Justice Alito wrote "[i]f the arbitrator [of a government power] can be a private person, this law is unconstitutional. Even the United States accepts that Congress 'cannot delegate regulatory authority to a private entity.' [] It would dash the whole scheme if Congress could give its power away to an entity that is not constrained by those checkpoints."[21] While courts have not ruled on the legality of a statute authorizing a private party or independent experts to withdraw a license without agency participation, this line of cases suggest it may be unconstitutional.

The 1966 Drug Efficacy Study Implementation (DESI) cited by Dr. Herder included agency oversight.[22] There, FDA and experts at the National Academy of Sciences collaborated to evaluate the efficacy of over 16,000 therapeutic indications approved before the 1962 amendments to the Federal Food, Drugs, and Cosmetics Act required evidence of efficacy.[23] External experts reviewed data and presented a recommendation subject to FDA authorization.[24] As confirmed by the Supreme Court in 1973 in a quartet of cases,[25] the private nondelegation doctrine allows private participation in the regulatory process in a wide variety of supervised roles. It has never completely banned private party involvement in regulation.[26] Altogether, part of the distinction between unconstitutional delegation to private parties and expert collaboration with an administrative agency, who is subject to Congressional, executive, and judicial oversight.[27] External experts unquestionably add value to agencies, but as Dr. Herder highlights, drug approvals and withdrawals from market are scientific decisions with political consequences.[28] They benefit from accountability and Due Process. Agencies can provide accountability and objectivity to exercise authority amongst industry competitors.[29]

## Comparative Advantages Deserve Consideration

Finally, it is worth considering if external experts are better able to design and review post-approval for Accelerated Approval Program drugs compared to agency staff. Resources should be directed towards institutions most capable of providing high-quality, consistent, and fair determinations for post-approval drug reviews. As a federal agency, FDA has delegated legislative authority, political accountability through executive and judicial oversight, relatively independent internal experts vetted for financial conflicts, access to proprietary data, investigative authority, and the ability to consult with external advisors. While far from perfect,[30] these are institutional advantages. While I do not offer a conclusion on the preferability of investing scarce public resources in FDA's post-approval drug monitoring Office of Surveillance and Epidemiology within the agency, subdelegating to supervised external experts, or creating a new independent agency, institutional advantages merit examination.

Further data collection will illustrate if these new polices leads to improved outcomes in post-approval confirmatory trial timeliness or whether additional authority is needed to assure that confirmatory trials are completed in a timely manner for the benefit of patients. While Dr. Herder highlights important problems with timeliness of accelerated approval regulations and proffers creative solutions, reforms must identify and address root causes of problems in both a data informed and constitutionally sound manner.

## Conclusion

Reforms to the Accelerated Approval Program have a near universal goal: implementable policy solutions that will ensure patients benefit from accessible, safe, and effective medications. Dr. Herder insightfully connects broader concerns around accelerated approval and withdrawals to issues of regulatory capture, funding for post approval monitoring, and the impact of patient advocacy groups both influencing and being influenced by FDA. While he sees promise in the Food and Drug Omnibus Reform Act[31] reforms, he raises fears of unfettered agency discretion. Further data collection will illustrate if these new polices will lead


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to improved outcomes in post-approval confirmatory trial timeliness or whether additional authority is needed to ensure only safe and effective drugs are sold to patients. While Dr. Herder highlights important problems with the accelerated approval program, reforms should address the root of the problems in both a data informed and constitutionally sound manner.

## Note

The author has no conflicts to disclose.

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7. Herder, *supra* note 1, at 28.
8. S. Thaul, Cong. Research Serv., R42366, Prescription Drug User Fee Act (PDUFA): 2012 Reauthorization as PDUFA V 1 (2013), *available at* <https://sgp.fas.org/crs/misc/R42366.pdf> (last visited Dec. 6, 2023) at 10–11 ("At the core of PDUFA's history is FDA's commitment to completing review within a specified timeframe in exchange for an industry source of revenue to support that activity. Although subsequent PDUFA laws have added other kinds of commitments, the review time goals continue to be a focus of PDUFA Agreement negotiations.[ ] The urgency to pass PDUFA reauthorization stems from PDUFA revenue's accounting for more than half the FDA Human Drugs Program budget."); *see also* A. N. Monge, D. W. Sigelman, R. J. Temple et al., "Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021," *JAMA Network Open* 5, no. 11 (2022), *available at* <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798005> ("In October 1992, Congress passed the Prescription Drug User Fee Act, which established Priority Review designation for drugs that may provide a 'significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition.' The FDA's goal is to complete the review of drug applications meeting Priority Review requirements within 6 months instead of the standard 10 months.").
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20 *Carter v. Carter Coal Co.*, 298 U.S. 238, 311 (1936) ("This is legislative delegation in its most obnoxious form; for it is not even delegation to an official or an official body presumptively disinterested, but to private persons whose interests may be and often are adverse to the interests of others in the same business."); J. M. Rice, "The Private Nondelegation Doctrine: Preventing the Delegation of Regulatory Authority to Private Parties and International Organizations," *California Law Review* 105, no. 2, (2017): 539–572, *available at* <http://www.jstor.org/stable/24915721> (last visited Dec. 6, 2023).
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