Association Between Preapproval Confirmatory Trial Initiation and Conversion to Traditional Approval or Withdrawal in the FDA Accelerated Approval Pathway

The accelerated approval pathway allows the US Food and Drug Administration (FDA) to approve drugs that demonstrate an effect on a surrogate end point that is reasonably likely to predict clinical benefit. Following accelerated approval, manufacturers are required to verify clinical benefit in confirmatory trials. Delays in confirmatory trial completion have led to proposals for reforming the accelerated approval pathway.1 One proposal would require a confirmatory trial initiation prior to accelerated approval.2 An FDA analysis found an association between pre-approval initiation and faster (from the date of accelerated approval) completion of confirmatory trials for oncology indications that ultimately received traditional approval or were withdrawn.3 We extended the FDA analysis by also including nononcology indications and evaluating whether preapproval initiation was associated with timelier conversion to traditional approval or withdrawal.

Methods | We identified all accelerated approval indications between September 1, 2002, and December 31, 2018, and their regulatory outcomes (ie, conversion to traditional approval or withdrawal) by December 31, 2021. For each indication, we extracted confirmatory trial requirements and target completion dates from approval letters at Drugs@FDAt. We linked trial requirements to corresponding information at ClinicalTrials.gov.4 We extracted the date on which the first participant was enrolled in the trial and noted whether this occurred before or after accelerated approval (eAppendix in Supplement 1). The Harvard Pilgrim Health Care Institutional Review Board determined the study exempt from review.

We used t tests to compare proportions of indications that were converted to traditional approval or withdrawn for drug indications with and without preapproval trial initiation and which had 3- or 5-year follow-up since accelerated approval or target completion dates before July 2021. These measures are in line with prior work on confirmatory trials making explicit the duration of patient exposure to drugs with uncertain benefits,4 and they assess compliance with timelines agreed on by sponsors and the FDA. A 2-sided P value of .05 was the threshold for statistical significance. We also used Kaplan-Meier methods, censoring studies that had not been completed by December 31, 2021, to evaluate the association between pre-accelerated approval trial initiation and regulatory outcomes. All analyses were performed using Stata version 17 (StatCorp).

Results | Among 127 accelerated approval indications with confirmatory trial requirements, 89 (70%) had confirmatory trials started before approval. Accelerated approval indications with confirmatory trials started before approval had higher proportions of conversion to traditional approval or withdrawal by 3 years (39.3% [35/89] vs 13.2% [5/38]; P = .003) and 5 years (76.2% [48/63] vs 26.9% [7/26]; P < .001) than indications that did not have pre-accelerated approval trial initiation.

Figure 1. Proportions of Indications With Conversion to Traditional Approval or Withdrawal by Preapproval Initiation Status of Confirmatory Trials

The numbers underneath the bars indicate the numbers of indications assessed.
Regulatory outcomes within target timelines were not statistically significantly different between indications with and without preapproval confirmatory trial initiation (42.0% [34/81] vs 23.8% [5/21]; P = .13) (Figure 1).

In the Kaplan-Meier analysis, indications with preapproval trial initiation had faster conversion to traditional approval or withdrawal than those without (P < .001) (Figure 2). Among indications with confirmatory trials started after approval, trial initiation took a median of 18.5 months (IQR, 13-30 months).

Discussion | Indications with accelerated approval between 2002 and 2018 that had confirmatory trials started before approval had faster conversion to traditional approval or withdrawal than those that did not, thereby reducing the duration of patient exposure to therapies with uncertain efficacy. However, there was no statistically significant difference in rates of regulatory outcomes within target timelines by preapproval trial initiation status. Target timelines may have taken into consideration other factors that affect confirmatory trial completion and allowed for delayed starts. That there was a substantial lag between approval and trial initiation for indications without pre-accelerated approval trial initiation suggests a need for policies mandating timely confirmatory trials. Such policies need to reduce total time to verify clinical benefit without delaying accelerated approval.

This analysis has limitations. First, some confirmatory trials may have been missed due to limitations in publicly available information. Second, reasons for starting confirmatory trials before or after accelerated approval are not known. Third, conversion to traditional approval was used as a proxy for verification of benefit but may not have been based on evidence of clinical benefit.

Overall, these results suggest that reforming the accelerated approval pathway by requiring preapproval initiation of confirmatory trials may result in timelier regulatory action on drugs initially approved on the basis of limited evidence.

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Accepted for Publication: January 17, 2023.

Published Online: January 27, 2023. doi:10.1001/jama.2023.0625

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Author Contributions: Ms Shahzad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shahzad.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Shahzad.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shahzad.

Administrative, technical, or material support: Shahzad.

Supervision: Naci, Wagner.

Conflict of Interest Disclosures: Dr Naci reported receiving grants from Health Foundation, National Institute for Health and Care Research, and UK Research and Innovation and personal fees from Pharmaceutical Group of the European Union and The BMJ (serving as an adviser). Dr Wagner reported receiving grants from the American Cancer Society. No other disclosures were reported.

Data Sharing Statement: See Supplement 2.


States’ Methods for Capturing and Reporting Local Responses to Suspected Nonfatal Drug Overdoses
Nonfatal overdose is a key predictor of future drug overdose death.1 State nonfatal overdose data can inform local communities about the dangers of the illicit drug supply and provide data-driven insights to inform the distribution of life-saving overdose-reversing drugs (eg, naloxone), harm-reduction resources, and treatment services.2 Current state-level surveillance methods track encounters with emergency medical services, visits to emergency departments (EDs), and hospital admissions to understand overdose trends; however, not all states publish data on nonfatal outcomes.3 This study identified the types of publicly available data used to surveil state-level drug overdoses and...