HPR15

Trends and Postmarketing Outcomes of Accelerated Approvals (AAs) in FDA New Drug Applications and Biologic License Applications (NDAs/BLAs) from 1992-2025

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INTRODUCTION

- The United States Food and Drug Administration (FDA) introduced the Accelerated Approval (AA) designation in 1992 to expedite the development and regulatory review of New Drug Applications and Biologic License Applications (NDAs/BLAs).
- AA designation is requested in the drug development process and is intended for treatments that provide a meaningful advantage over available therapies in serious conditions.
- AA designation enables approval based on a surrogate endpoint (i.e., conditional approval) but requires confirmatory trials for conversion to traditional approval (i.e., verified clinical benefit). A conditional approval may be withdrawn if a confirmatory trial is not conducted or if no clinical benefit is observed in the confirmatory trial.
- The objective of this study was to review the features, review time, and regulatory outcomes of NDAs/BLAs approved between 1992-2025 within the FDA Center for Drug Evaluation and Research (CDER).

METHODS

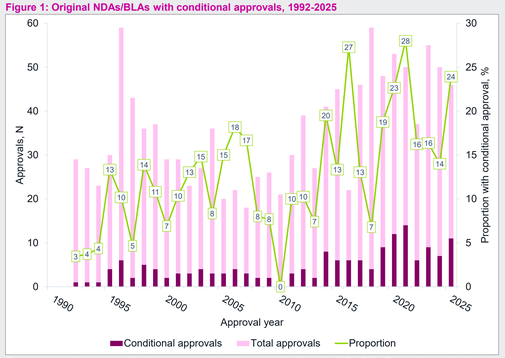
- Trends in AA designations were examined among original NDAs/BLAs within CDER.[1] Applications with multiple indications were considered to have AA if any indication had AA. Relative risks (RR) with 95% confidence intervals (CI) were calculated for comparisons of interest.
- All original and supplemental NDAs/BLAs within CDER with verified clinical benefit, ongoing, or withdrawn status from January 1992-December 2025 were reviewed using FDA data.[2] The Federal Register was searched for details regarding the initiator and rationale for withdrawn applications.[3] Vaccines, blood products, gene/cell therapies, and different formulations or dosing for the same drug-indication pair were excluded from analysis.

RESULTS

Original NDAs/BLAs within CDER:

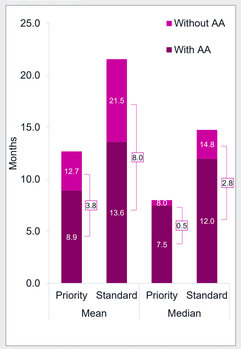
- Among 1,208 original NDAs/BLAs approved between 1992-2025, 160 had AA designation and received conditional approval (13%). The proportion of conditional approvals generally increased during the timeframe (**Figure 1**).
- Applications with AA were more likely to receive priority review; 95% of applications with AA received priority review, while 46% of applications without AA received priority review (RR [95% CI] = 2.08 [1.93, 2.25]).
- Irrespective of priority or standard review status, applications with AA had shorter mean and median application review time within CDER than applications without AA. AA designation saved a mean (median) of 3.8 (0.5) months for applications under priority review and saved 8.0 (2.8) months for applications under standard review (**Figure 2**).

Figure 1: Original NDAs/BLAs with conditional approvals, 1992-2025



Each bar represents the annual conditional approvals (purple) and total approvals (pink) of original NDAs/BLAs. The green line and data labels refer to the proportion of annual approvals with AA designation.

Figure 2: Time to conditional approval among original NDAs/BLAs based on priority or standard status

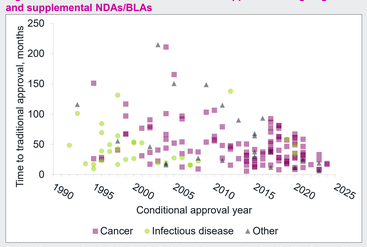


Bars represent the time from application receipt to approval with priority (n = 630) and standard (n = 578) review.

Figure 3: Application status for original and supplemental NDAs/BLAs with conditional AA

Graph represents 291 original and supplemental NDAs/BLAs, including applications related to cancer (n = 205; 70% of total), infectious disease (n = 37; 13% of total), and other conditions (n = 49; 17% of total).

Figure 4: Time from conditional to traditional approval among original and supplemental NDAs/BLAs

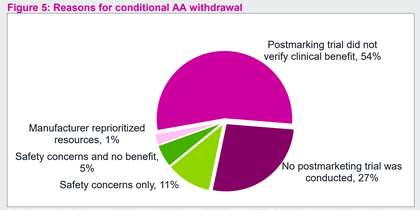


Each marker represents an individual application's time between conditional and traditional approval in months for cancer (n = 120), infectious disease (n = 31), and other conditions (n = 23).

Original and supplemental NDAs/BLAs that received conditional approval within CDER:

- Across 291 original and supplemental NDAs/BLAs with conditional approval, 60% of approvals have been verified, while 26% are ongoing and 14% have been withdrawn (**Figure 3**).
- Among verified applications, the mean (median) time from conditional to traditional approval between 1992-2025 was 48.4 months. The time to traditional approval trended longer in the period between 1992-2014 (57.0 [45.9] months) versus 2015-2025 (37.8 [33.6] months; **Figure 4**).
- For indications that received conditional approval between 2021-2025 and are ongoing, the mean (median) projected time to complete postmarketing requirements is 46.5 (47.4) months.

Figure 5: Reasons for conditional AA withdrawal



Graph represents withdrawn applications with details available in the Federal Register (n = 37). Only three instances were identified in which the manufacturer appealed the FDA's recommendation for voluntary withdrawal.

- Among withdrawn AA indications, key reasons for withdrawal included a lack of clinical benefit (7% of all AAs), no trial being conducted (3%), safety concerns (2%), or resource reallocation (<1%; **Figure 5**).
- Manufacturers voluntarily withdrew applications in 92% of instances after receiving the FDA's recommendation.

CONCLUSIONS

- The AA program accelerates patient access to therapies that treat serious and life-threatening conditions. More than half of all conditional approvals have converted to traditional approvals, and ongoing conditional approvals are expected to complete requirements within four years. Withdrawals are uncommon, and withdrawals due to safety issues are rare (2% of all conditional approvals).
- The uncertainty regarding clinical benefit of a conditional approval is balanced against the earlier access enabled by AA's use of surrogate endpoints. The reduction in the postmarketing requirement period that has occurred in recent years mitigates this uncertainty.[4,5] In oncology, both the National Comprehensive Cancer Network (NCCN) guidelines and clinical practice patterns demonstrate rapid awareness of a lack of benefit from confirmatory trials.[6,7]
- The dramatic increase in survival gains that has been ascribed to the AA program is an essential consideration in evaluations of the value of AA.[8,9] However, verifying clinical benefit through confirmatory trials is critical to patients and prevents unnecessary spending on therapies that do not enhance survival.[10,11]

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