Trends in Time to Withdrawal and Full Approval of Accelerated Approval Cancer Drug Indications (1992–2024)

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Abstract

The US Food and Drug Administration (FDA) accelerated approval program facilitates earlier access to therapies for serious illnesses based on surrogate endpoints reasonably likely to predict clinical benefit given sponsors conduct post marketing studies to confirm clinical benefit. Over the past decade, concerns have emerged about the pace and quality of post marketing evidence generation. We analyzed regulatory outcomes of oncology indications granted accelerated approval between 1992 and 2024, using publicly available FDA data. Median time to conversion to regular approval decreased from 4.3 to 2.3 years and time to withdrawal decreased from 9.5 to 3.2 years between the 1992–2013 and 2014–2024 periods (both $p<0.001$). The proportion of indications with confirmatory studies underway at the time of accelerated approval increased from 63% to 85% ($p=0.003$). Findings remained consistent across sensitivity analyses. Although these trends may reflect stronger oversight, advances in clinical trial design and regulatory coordination may also contribute. Future efforts should ensure that faster regulatory timelines are consistently accompanied by demonstrable clinical benefit to maintain the integrity of the accelerated approval pathway.

In 1992, the US Food and Drug Administration (FDA) established the accelerated approval Program to streamline access to innovative medicines for patients with serious illnesses.[1] Originally designed as a response to the HIV/AIDs crisis, the program expanded to include drugs from other therapeutic areas, such as cancer, which now comprise over 85% of accelerated approvals over the past 10 years.[2] Approvals are based on surrogate endpoints that are reasonably likely to predict clinical benefit, such as quality of life or improved survival. Drugs granted accelerated approval must complete confirmatory studies that could lead to conversion to regular approval or, if negative, could lead the FDA to seek withdrawal of the indication.[3]

Over the past decade, the accelerated approval pathway has received growing criticism. Research has found that several cancer drug indications remain on the market despite negative confirmatory trials, exposing patients to ineffective therapies and financial toxicities.[4–6] Since 1992, only 12% of pivotal trials supporting cancer drug approvals are associated with substantial clinical benefit, and only half of the confirmatory trials demonstrated statistically significant improvements in overall survival.[7] Recent analyses of oncology indications between 2013 and 2023 similarly found that fewer than half of converted indications demonstrated clinical benefit, and that many conversions relied on surrogate endpoints rather than overall survival.[4] Despite these findings, the pathway remains widely used.

In recent years, the FDA has been more active in encouraging manufacturers to remove such indications from their labeling. Recent reforms, including the Food and Drug Omnibus Reform Act (FDORA) passed in 2022, among other ongoing FDA initiatives have sought to strengthen the approval process by requiring confirmatory trials be underway at the time of initial approval and streamlining withdrawal procedures.[3,8] Although recent studies have suggested that regulatory timelines for conversion or withdrawal may be shortening, these analyses were limited to more recent approvals and did not examine trends across the full history of the program.[4,5] There, broader temporal trends in regulatory outcomes, including time to withdrawal or conversion, across the entire accelerated approval program remain unknown.

We therefore analyzed trends in time to regulatory action and confirmatory trial practices among oncology indications granted accelerated approval between program inception (1992) and 2024, using publicly available FDA databases.[9] For each indication, we assessed the time from accelerated approval to withdrawal or conversion to regular approval, and determined the proportion of confirmatory studies that were ongoing at the time of accelerated approval by identifying study start dates on ClinicalTrials.gov. Ongoing accelerated approvals were censored in time-to-event analyses but excluded from the confirmatory trial status analysis, as their final regulatory outcomes were not yet determined as of December 31, 2024. Data are current as of December 31, 2024.

We divided the dataset in 2014 to reflect a period of increased scrutiny of the accelerated approval pathway, which preceded statutory reforms such as FDORA in 2022.We compared medians with interquartile ranges (IQRs) and proportions between 1992–2013 and 2014–2024 to assess differences in market time and confirmatory study status. Time-to-event data were analyzed using Kaplan-Meier methods, censoring studies without final outcomes as of December 31, 2024. Pearson's χ^2 test assessed differences in proportions of ongoing studies. To address right-censoring, we performed three sensitivity analyses: (i) a 4-year Kaplan-Meier and χ^2 comparison of 1992–2013 vs. 2014–2020; (ii) a 6-year Kaplan-Meier and χ^2 comparison of 1992–2013 vs. 2014–2018; and (iii) a Mann-Whitney test for non-normal market time distributions between 1992–2013 and 2014–2024 (Supplement). Analyses used SPSS 26.0, with two-sided p-values <0.05 considered statistically significant. The study was exempt from review under the Common Rule (45 CFR 46).

Between 1992 and 2024, we identified 205 cancer drug indications received accelerated approval. Of these, 106 (52%) converted to regular approval, 31 (15%) withdrawn, and 68 (33%) with ongoing confirmatory trials (Supplementary Tables S.1 to S.3). The median market time for withdrawn indications was 3.8 years (IQR: 2.8-7.6) and 3.1 years (IQR: 1.89-4.8) for indications converted to regular approval. Of the 137 indications converted or withdrawn, 104 (76.0%) had confirmatory studies ongoing at accelerated approval.

Among converted or withdrawn indications, 57 (42%) were from 1992–2013 and 80 (58%) from 2014–2024, while most ongoing accelerated approvals (67 of 68; 99%) were granted in the later period (**Table).** The median time to conversion to regular approval decreased from 4.3 years (IQR, 2.9–6.6) to 2.3 years (IQR, 1.5–3.4) ($p<0.001$), and the median time to withdrawal decreased from 9.5 years (IQR, 8.8–10.1) to 3.2 years (IQR, 2.6–4.9) ($p<0.001$) (**Figure**). The proportion of approvals with confirmatory studies already underway increased from 63% (36 of 57) in 1992–2013 to 85% (68 of 80) in 2014–2024 ($p=0.003$). Findings remained consistent across sensitivity analyses with 4-year, 6-year, and non-parametric comparisons (Supplementary Tables S.4–S.6).

In the three decades since the inception of the accelerated approval pathway, we found that the time for oncology indications to achieve conversion to regular approval or be withdrawn has shortened. Simultaneously, the proportion of confirmatory studies underway at the time of approval has increased. These trends extend prior findings that certain drug characteristics predict faster regulatory action and suggest that broader systemic changes[7], including evolving FDA guidance and statutory reforms, may be contributing to earlier regulatory decisions. Our results are also consistent with efforts by the FDA to tighten confirmatory study requirements and streamline post marketing oversight.[2] Although our study is limited by right-censoring of the most recent approvals, the consistency across multiple sensitivity analyses strengthens the validity of the observed patterns.

Alternative explanations for these trends must be considered. Over the past two decades, there have been substantial advances in clinical trial design, such as the use of basket trials, smaller targeted patient populations, and surrogate endpoints. These evolving trends may have contributed to shorter times to regulatory action by enabling faster patient accrual, earlier efficacy assessments, and more rapid trial completion independent of reforms. Furthermore, improved coordination between drug sponsors and regulatory authorities may also have played a role. While these developments may facilitate faster conversions, they also raise concerns about whether accelerated timelines are accompanied by robust evidence of long-term clinical benefit.

Faster regulatory action, while potentially reducing patient exposure to ineffective therapies, does not guarantee meaningful clinical improvement. Structural challenges within the FDA, including political pressures, resource constraints, and competing priorities between expediting access and ensuring post marketing evidence generation, may limit the agency to enforce rigorous confirmatory standards.[11] Indeed, prior studies have demonstrated that many drugs granted accelerated approval demonstrate only marginal improvements in survival or quality-of-life endpoints even after confirmatory studies.[4,5,7] Recent analyses of oncology indications granted accelerated approval between 2013 and 2023 similarly found that fewer than half of converted indications demonstrated clinical benefit, and that most conversions relied on surrogate endpoints rather than overall survival.[4]

Strengthening standards for confirmatory evidence will remain essential to maintaining the balance between timely access and patient-centred outcomes within the accelerated approval pathway. Future research could evaluate the clinical magnitude of benefit at the point of conversion and monitor post conversion outcomes to ensure that regulatory efficiencies translate into meaningful survival gains as sustaining public and clinician trust will depend on ensuring that faster regulatory timelines are consistently accompanied by demonstrable clinical benefit.

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Table. Trends in Time to Withdrawal and Full Approval of Accelerated Approval Cancer Drug Indications (1992–2024) [a]

	1992-2013 (n=57)	2014-2024 (n=80)	p-value
Time to full approval (years, IQR) [b]	4.3 (2.9-6.6)	2.3 (1.5-3.4)	<0.001
Time to withdrawal (years, IQR) [b]	9.5 (8.8-10.1)	3.2 (2.6-4.9)	<0.001
Confirmatory studies ongoing at time of AA (%) [c]	36 (63)	68 (85)	0.003

Abbreviations: AA, Accelerated Approval; IQR, Interquartile Range.

Notes: This table presents the time from AA to either withdrawal or full approval for cancer drug indications granted AA, as well as differences in the proportion of ongoing confirmatory studies across two periods: 1992–2013 and 2014–2024.

[a] Of the 137 indications (68%) that were either converted to regular approval or withdrawn, the distribution across periods was as follows: 57 (42%) in the early period (46 converted to regular approval, 8 withdrawn) and 80 (58%) in the later period (57 converted to regular approval, 23 withdrawn). Among the 68 indications (33%) still under AA, only 1 originated from the early period, while 67 belong to the later period.

[b] Time-to-event analyses were performed using Kaplan-Meier curves, with censoring for indications that remained ongoing as of December 31, 2024.

[c] Ongoing accelerated approvals were omitted from the confirmatory trial analysis due to a lack of information. Differences in the proportion of ongoing confirmatory studies were assessed using Pearson's χ^2 test.

[d] Statistical significance set at $p < 0.05$.