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The Delicate Balancing Act of Accelerated Approval for Cancer Medicines—Speed, Certainty, and Benefit

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Over a half century ago, the Kefauver-Harris Drug Amendments raised the regulatory bar for drug approvals in the US by requiring sponsors to submit evidence demonstrating efficacy rather than only safety. Over the following 6 decades, the US Food and Drug Administration (FDA) established programs to expedite development and review of the potentially most important new therapeutics.[1] One such initiative is the accelerated approval pathway, established in 1992, to shorten the time required for a drug to receive FDA approval. The pathway allows drug approval based on a surrogate end point that "is thought to predict clinical benefit but is not itself a measure of clinical benefit."[2] Approving drugs on intermediary measures increases uncertainty, but this is balanced by the expectation that these drugs will "offer meaningful therapeutic benefit to patients over existing treatments,"[3] for which sponsors would verify through postmarket studies.

In this issue, Tibau and colleagues[4] reveal a gap between the accelerated approval pathway's original intent and current practice. Among 102 cancer drug indications approved through the FDA accelerated approval pathway from its inception in 1992 to 2022, only 12% of pivotal trials were associated with substantial clinical benefit, as assessed by the European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Even among confirmatory trials, less than half demonstrated statistically significant improvements in overall survival (44%) or quality of life (40%).[4]

The accelerated approval pathway is a balancing act between speed, certainty, and benefit. Surrogate end points allow drugs to be approved faster, so long that sponsors conduct studies to confirm meaningful benefit to patients. Notably, the FDA has never explicitly defined meaningful benefit.[1] Per the FDA description, surrogate end points are not measures of clinical benefit themselves but rather are "thought to predict" patient-centered outcomes,[2] such as overall survival and quality of life. Indeed, Tibau et al[4] found 98% of cancer drug indications are initially approved on these measures (ie, progression-free survival). However, these putative surrogate measures often fail to reliably predict survival or quality-of-life improvements, as demonstrated by the fact that less than half of confirmatory studies demonstrated statistically significant improvements in overall survival or quality of life.[4] Moreover, there is increasing evidence that progression-free survival is a valid surrogate for overall survival in only a small number of clinical circumstances.[5]

The accelerated approval pathway involves not only rapid approval but also the timely validation of efficacy and safety to protect patients. When the pathway was first designed, an accelerated withdrawal process was included to ensure enforcement. Yet, the findings of Tibau et al[4] demonstrate that drugs with boxed warnings, those lacking substantial clinical benefit, and those without confirmatory trials at the time of accelerated approval took longer to validate, exposing patients to treatments with known safety concerns and unproven clinical benefit.

Over the past decade, cancer drugs have dominated the accelerated approval pathway, accounting for more than 85% of approvals.[6] Notable examples that highlight the benefit of the pathway are drugs such as imatinib, which dramatically improved survival for patients with chronic myeloid leukemia. However, Tibau et al[4] demonstrate these examples are rare, with over half (53%) of confirmatory trials failing to meet the ESMO-MCBS threshold for substantial clinical benefit (ESMO scores of 4 or 5 for palliative intent and A or B for curative intent). This study adds to a growing body of evidence showing the small incremental benefits provided by many new cancer drugs approved

through the FDA, raising questions about the overall impact of these treatments on patient outcomes. The clinical implications cannot be overstated: patients receiving some treatments might be exposed to clinical, financial, and time toxic effects without any meaningful improvements in how long they live or how they feel.

Tibau et al[4] focused on cancer drugs that had either converted to regular regulatory approval or were withdrawn, providing valuable insight into their ultimate outcomes. However, 20% of all cancer drug indications that received accelerated approval between 1992 and 2022 remain ongoing, with their outcomes still uncertain.[4] Alarmingly, some of these drugs have been on the market for over a decade, such as pralatrexate (15 years) and belinostat (10 years) for peripheral T-cell lymphoma, both of which are several years past their confirmatory study deadlines.[7] The study raises serious questions about the clinical value of these drugs and the impact of delayed validation on patients, who are left relying on treatments with unverified efficacy for extended periods.[4] A 2024 study[8] has demonstrated that patients with personal experience of cancer could be willing to wait up to 21 months longer for cancer treatments supported by strong evidence of survival benefit, highlighting a preference for certainty of benefit over rapid access to unproven therapies.

The growing body of research that consistently characterizes the benefits of FDA accelerated approvals as small and incremental leaves us with 2 questions: why do these trends continue despite widespread recognition and how can they be fixed? These findings reflect broader systemic issues within the FDA regulatory framework. In an analysis of the FDA internal dynamics, Mathew Herder found that the agency's reliance on established practices, entanglement with industry stakeholders, lack of resources, lengthy legal processes, and political pressures create an environment where meaningful regulatory change is difficult to achieve.[9] One former director that was interviewed about the bevacizumab withdrawal said that "it was so hard and so time consuming that if you suggest now that somebody take something off the market, they just roll their eyes at you."[9] Addressing systemic barriers—such as resistance from stakeholders, poor FDA resources, and inadequate enforcement mechanisms—is essential to aligning the pathway with its original promise.

Tibau et al[4] underscore the need for policy reforms to ensure timely completion of confirmatory trials, stricter criteria for surrogate end points, and stronger FDA oversight to prevent prolonged market time of unvalidated treatments. These recommendations are important and build on positive steps that the FDA has recently taken to address current challenges.[7] For example, reforms included in the Food and Drug Omnibus Reform Act, the Consolidated Appropriations Act, and Project Confirm have focused on strengthening FDA oversight and timelines to its original intention. Late last year, the FDA published draft guidance that clarifies standards for end points, confirmatory trial requirements, and withdrawal procedures.[10]

In addition to the recommendations suggested by Tibau et al,[4] we add that, in line with the original intention of the pathway, "meaningful therapeutic benefit" could be better defined. This would allow the FDA to meet their responsibility in ensuring drugs that are approved through the accelerated approval pathway genuinely benefit patients. Furthermore, given the growing evidence demonstrating the weak correlation between putative surrogate end points and patient-centered outcomes, such as overall survival and quality of life, we urge the FDA to reconsider its reliance on these measures. This is particularly important as demonstrated by the current study; drugs approved on these end points often remain on the market longer without validation.

The accelerated approval pathway was designed to expedite patient access to promising treatments for serious or life-threatening diseases, allowing approvals based on intermediary surrogate end points so long that sponsors verify meaningful clinical benefit through the timely completion of confirmatory studies. However, work by Tibau et al[4] and others demonstrate that most drugs are approved on unvalidated surrogate measures that fail to demonstrate meaningful benefit. In this sense, the pathway seems to prioritize speed for clinical benefit, leaving patients with substantial uncertainty, and potential harm.

ARTICLE INFORMATION

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