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The accelerated approval pathway in oncology: Balancing the benefits and potential harms.

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Introduction

The Food and Drug Administration's regulation of new cancer drugs is a vital public health resource. The FDA is singularly responsible for shielding patients from low-value and outright harmful therapies and they must make evidence-based decisions to approve or deny market authorization to novel compounds. One commonly used pathway for FDA approval is that of Accelerated Approval (AA). AA is a flexible approval pathway, created to give patients early access to promising drugs. AA is used only for drugs that are "reasonably likely" to have a clinical benefit [1]. In this viewpoint we consider the proposition that the AA pathway has deviated from its intended purpose of providing patients earlier access to drugs with likely favorable benefit-harm ratios. Instead, AA has become a pathway for drugs with less favorable benefit-harm profiles to gain access to the same healthcare marketplace based on clinical endpoints that matter less to patients. The flexibility in approval under AA may have led to a low-bar for approval for drugs that are unlikely to produce data that is clinically meaningful. We believe that two changes are required to begin improving the current AA regulatory pathway and ensure maximal treatment benefit for patients with cancer.

First, a shift in what is considered evidence of drug efficacy must occur in the oncology community. A review by the FDA Office of Hematology and Oncology Products, noted that 64 malignant hematology and oncology products for 93 new indications were approved over a 25-year period [2]. This review purportedly showed that drugs approved under the AA pathway had proven clinical benefit the majority of the time. The authors demonstrated that radiographic or laboratory surrogate endpoints are most often used for drug approval and suggests these are evidence of drug efficacy. One common surrogate endpoint used as confirmatory data in the FDA's review was response rate, which is a measure of drug activity, but not necessarily a measure of clinical benefit that matters most to patients. Remission is a clinical goal that should be pursued and may come with important benefits like more time out of the hospital and less time on chemotherapy. However, if remission does not improve the longevity or quality of life overall, then its usefulness in clinical medicine is diminished. Similarly, endpoints like progression-free survival primarily measure tumor growth on CT scan and do not consistently predict survival or quality of life in most cancers [3].

In the FDA's review, a majority of initial drug approvals using a surrogate endpoint were shown to be "confirmed" by another (or the same) surrogate endpoint. The purpose of AA is to allow flexibility in the initial AA approval under the condition that confirmatory studies show improvement in an endpoint that matters to patients, most often overall survival or quality of life. If confirmatory trials do not validate the AA approval, the AA system crumbles. Similarly, if patients do not value surrogate endpoints, the AA system crumbles. A recent pilot discrete-choice experiment was conducted in 20 patients with metastatic cancer which asked patients about two treatment regimens with equal survival benefit [4]. The first regimen was the standard of care and the second regimen was the standard of care plus a drug that increased toxicity and delayed tumor growth. Seventeen of 20 patients chose the first regimen and would not tolerate toxicity without improved survival, even if tumor progression was delayed. In the FDA's own analysis of the AA pathways, a majority of drugs never demonstrated improved survival, but all had toxicities.

Second, more explicit guidance on the criteria for AA would improve transparency in FDA decision making and likely improve patient outcomes. Currently, there is no clear pattern for what is sufficient evidence for AA. This lack of clear standards opens the FDA to regulatory capture by the pharmaceutical industry. Regulatory capture is a phenomenon where the most interested parties, those that have the most to gain, focus their efforts on obtaining their desired outcome, often by overwhelming the defense of less-interested parties [5]. In this case, the pharmaceutical industry increasingly dominates the drug approval landscape and is one of the parties that stands to gain the most from drug approval. After all, a drug manufacturer can only viably offset research and development

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costs if their drugs are approved. Concerns arise when the pharmaceutical industry repeatedly seeks approval for drugs based on surrogate endpoints without confirming clinical benefit [6], fails to properly study quality of life [7], chooses suboptimal control arms [8], influences drug advisory committee meetings [9], and advertises a biased message about drug efficacy [10].

The current dilemma facing the FDA is that the majority of its new drug applications come from the pharmaceutical industry who has numerous incentives to design trials that are most likely to achieve favorable results. The FDA must therefore mediate the needs of patients and drug manufacturers. Patients need more and better drugs approved, while drug manufacturers only need the former. It is the role of the FDA to regulate the drug manufacturers to ensure the quality of new drugs is appropriate. Clearer standards related to basic trial design may include items such as mandating a valid, contemporary control arm or studying quality of life the correct way [7]. Where nuance is required, such as for optimal endpoint selection, the FDA has a trove of literature to draw from to make informed policy decisions. In short, it is time to leave the flexibility of "reasonably likely" in the past.

In summary, the AA pathway is one that has enormous potential to benefit patients by granting them early access to promising novel drugs. Determining which drugs are likely to improve patient-centered endpoints is difficult when surrogate endpoints are used, control arms often do not reflect standard of care, and regulatory capture takes place. For that reason, in an effort to reform AA in a way that improves patient survival and quality of life we propose reforms to AA to maximize the treatment benefit to patients and hinder regulatory capture.

Contributors and sources

CW and VP conceptualized the viewpoint expressed herein. CW, GRM, and VP both equally participated in the writing of the analysis and all approve of the manuscript in its final form.

Conflicts of interest

CW has no conflicts of interest and has received no funding from drug companies. GRM has no conflicts of interest and has received no funding from drug companies. VP has no conflicts of interest with drug companies; he has received publishing royalties from Johns Hopkins University Press, Medscape, and MedPage; he has received consulting fees from UnitedHealthcare; he has received speaking fees from Evicore, New Century Health, and Patreon Plenary Session podcast outside the submitted work.

Conflicts of interest

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