ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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FDA Regulatory Pathways for Expedited Drug Development and Approval

Aaron S. Kesselheim, MD, JD, MPH
Professor of Medicine
Brigham and Women's Hospital/Harvard Medical School
Boston, Massachusetts

H&O What are the main expedited pathways for drug approval?

ASK The main expedited regulatory pathways for the development and approval of prescription drugs by the US Food and Drug Administration (FDA) are Priority Review, Fast Track, Accelerated Approval, and Breakthrough Therapy. In Priority Review, the FDA reviews a completed application in a maximum of 6 months instead of the standard review deadline of 10 months. Fast Track designation is intended to expedite the clinical testing process and allows the FDA to approve a drug on the basis of even a single phase 2 study if the drug meets certain criteria, including treating a serious and life-threatening condition. Accelerated Approval is also directed at the clinical testing process. It allows a drug to be approved if studies show changes to surrogate measures such as laboratory test results rather than clinical endpoints such as how a patient feels, functions, or survives if his or her condition is serious and life-threatening, and if the drug appears to represent a true advance over currently available therapy. Finally, the Breakthrough Therapy designation directs more FDA review resources toward a drug in development; manufacturers can apply for this designation at any point in a drug's preapproval period. In many cases, the same drug qualifies for more than one of these expedited pathways.

An additional pathway that applies specifically to regenerative medicine products is the Regenerative Medicine Advanced Therapy (RMAT) designation. In oncology, for example, the RMAT designation has been applied to chimeric antigen receptor (CAR) T-cell therapy.

H&O How has the FDA's use of expedited approval affected oncology drugs over the past decade?

ASK A growing number of cancer therapies are being reviewed via expedited approval pathways. When the pathways were created, they were invariably intended to be exceptions that would apply just to the most important new therapies. These days, however, most drugs are approved via at least one of the expedited designations. An analysis of the 49 novel therapeutics approved in 2020 showed that 57% received Priority Review, 45% Breakthrough Therapy designation, 33% Fast Track designation, and 25% Accelerated Approval.[1] We can expect these percentages to be even higher for oncology drugs, which generally qualify for more than one designation. The effect on the development of cancer therapy has been profound, although not always for the best.

H&O What concerns exist regarding the use of expedited pathways in oncology drug approvals?

ASK The pathways are designed to give the FDA the flexibility it needs to allow highly promising products to be tested and approved as quickly as possible to benefit patients. The problem is that drugs that appear promising sometimes do not actually turn out that way. In recent years, multiple cancer drugs that received Accelerated Approval were later found not to work or to have risks that were not initially apparent, causing that indication to be withdrawn. When that happens, it means that patients have been taking a drug whose risks may outweigh its benefits. They also may have missed out on a

different treatment that would have worked better. Drugs that are approved through expedited pathways are much more likely to have subsequent safety issues identified and require label changes to clarify those safety issues. A review of FDA public records from 1997 to 2016 found that of 382 new drugs, 35% received an expedited development or review pathway.[2] The annual rate of safety-related label changes was 0.94 for expedited pathway drugs, whereas it was 0.68 for non-expedited pathway drugs. Expedited pathway drugs also had a 48% higher rate of changes to boxed warnings and contraindications. Of course, we would take these extra risks for extremely important new products that work very well, but that is not always the case. As a result, it is important that we follow up on drugs subject to expedited development and approval and make adjustments as needed. However, we do not put as many resources into this process as we should—close monitoring of drug effectiveness and safety after approval should be increased, with rapid updating of labeling as needed.

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H&O What are some examples of oncology drugs that have been approved through Accelerated Approval and then been withdrawn?

ASK One of the prominent examples was the use of bevacizumab for metastatic breast cancer, which received Accelerated Approval in 2008 on the basis of progression-free survival results. This indication was withdrawn 3 years later, in 2011, when a more rigorous trial showed disappointing overall survival results. In recent years, indications for approximately 2 dozen drugs that received Accelerated Approval have been withdrawn. In particular, 3 oncology drugs that received Accelerated Approval in 2021 were removed from the market in 2024: mobocertinib (Exkivity, Takeda), which had been approved for use in patients with non–small cell lung cancer; infigratinib (Truseltiq, QED Therapeutics), which had been approved for use in cholangiocarcinoma; and melphalan flufenamide, which had been approved for use in multiple myeloma. Sacituzumab govitecan-hziy (Trodelvy, Gilead) received an indication for metastatic urothelial cancer via Accelerated Approval in 2021, but this indication was withdrawn in 2024. These days, Accelerated Approval of a drug or indication is withdrawn in approximately 15% of cases.[3]

H&O Should oncologists be more cautious when prescribing drugs that have been approved through expedited pathways?

ASK Oncologists should be aware of the possibility that agents approved in this way may subsequently be found not to work or to have safety issues that we were not aware of, and they should communicate these issues to patients. Patients should understand that certain agents are the subject of ongoing confirmatory studies or were approved on the basis of an early-phase study rather than a more-definitive study. That information may affect whether a patient decides to use a drug.

H&O Should oncologists watch for certain red flags when a cancer drug is approved through an expedited pathway?

ASK Such red flags are described in a recently published study led by a colleague of mine, Dr Ariadna Tibau, that defined predictors of withdrawal of Accelerated Approval cancer indications.[4] For example, we found that the risk of withdrawal was higher for agents receiving a lower score on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) at the time of approval. By contrast, receiving a Breakthrough Therapy designation or a genome-targeted indication was associated with lower withdrawal rates.

H&O Would you say that the FDA is moving too fast or too slowly when it comes to expedited approvals for cancer drugs?

ASK That is the classic debate, with some people saying that the FDA is moving too fast and others saying that it is moving too slowly. I do think that these expedited programs are important in giving the FDA flexibility to ensure that extremely promising treatments filling an unmet medical need can be prioritized in the regulatory review process. Still, it does seem as if their use is far more widespread that what was originally intended—and that we should pay far closer attention to confirming the effectiveness and safety of drugs after approval.

H&O Do you have suggestions for improving the expedited approval system so that patients with cancer will be better served?

ASK We could have greater clarity from the FDA about why certain drugs qualify for expedited approval. That information, in turn, should be communicated to patients more effectively so that they can take it into account when they make decisions about drugs. An important reform would be to make sure that confirmatory trials are conducted as efficiently as possible, with the use of clinical endpoints rather than surrogate measures whenever possible. Another improvement would be to accelerate the rate at which labels are updated when new information emerges.

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References

1. Mitra-Majumdar M, Gunter SJ, Kesselheim AS, et al. Analysis of supportive evidence for US Food and Drug Administration approvals of novel drugs in 2020. *JAMA Netw Open*. 2022;5(5):e2212454.
2. Mostaghim SR, Gagne JJ, Kesselheim AS. Safety related label changes for new drugs after approval in the US through expedited regulatory pathways: retrospective cohort study. *BMJ*. 2017;358:j3837.
3. Withdrawn | cancer accelerated approvals. US Food & Drug Administration. Updated December 2, 2024. Accessed July 10, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals.
4. Tibau A, Hwang TJ, Romano A, Borrell M, Gich I, Molto C, Kesselheim AS. Factors in time to full approval or withdrawal for anticancer medicines granted accelerated approval by the FDA. *JAMA Netw Open*. 2025;8(3):e252026.