ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Approval Versus Coverage: The Differences Between FDA and CMS Standards



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H&O What is the standard that the US Food and Drug Administration (FDA) uses to evaluate a new drug or device?

DH The FDA uses safety and efficacy as its standard. The real question is, what kind of proof does the FDA require to satisfy that standard? The traditional answer for regular approvals has been that the drug sponsor—typically the manufacturer—must present the FDA with the results of 2 well-conducted controlled studies that focus on clinical outcomes in a defined population that is large enough for us to have confidence in the results. The FDA uses that evidence to weigh whether the sponsor has presented sufficient evidence of safety and efficacy, and it determines whether the drug or medical device has a favorable risk-to-benefit ratio.

The answer is a bit different for accelerated approvals, in which the FDA balances the value of less evidence and less compelling evidence (usually relying on "surrogate" outcomes in a single trial instead of clinically focused outcomes in 2 trials) against the severity of the disease in question and whether treatments that are good enough are available. Although accelerated approval requires less compelling evidence than "traditional" approvals, an accelerated approval is usually coupled with an obligation for the sponsor to conduct a study after the drug or device is launched to determine whether the FDA's initial judgment should be sustained or reversed.

H&O Does FDA approval automatically guarantee coverage by the Centers for Medicare & Medicaid Services (CMS)?

DH Coverage by CMS is not automatic after FDA approval. Sometimes, an express statutory prohibition exists, such as with weight loss drugs, although the current administration is in the middle of launching a demonstration project for glucagon-like peptide-1 (GLP-1) drugs. The key point to understand is that the FDA criteria of "safe and effective" are not the criteria that CMS uses in making decisions about whether to pay for something. For CMS, the standard is whether the drug or device is "reasonable and necessary." Many of the things that are safe and effective are also reasonable and necessary, meaning that they will qualify for payment by CMS, but CMS payment is not a given after FDA approval.

H&O How does CMS determine whether it will cover a drug or device?

DH The CMS decision to provide coverage depends on several factors; these vary according to whether the drug or device is covered under Medicare Parts A and B, Medicare Part D, or Medicaid. Coverage is also affected by whether a statutory mandate exists that requires coverage for certain classes of drugs under Medicare Part D, and whether CMS has made a "national coverage decision." In the absence of a statutory requirement or national coverage decision, a lot of coverage decisions are pushed downstream to regional Medicare Administrative Contractors for Medicare Parts A and B and to individual plan sponsors who design their own formularies for Medicare Part D. The rules are different for Medicaid because the drug manufacturer typically signs a rebate agreement with Medicaid requiring the program to cover every drug from

that manufacturer. Medicaid is still able to impose step therapy requirements or other utilization constraints, but it cannot exclude a drug outright if a rebate agreement exists. For obvious reasons, most drug manufacturers have a rebate agreement with Medicaid.

The FDA is basically prohibited from considering the cost of a drug, which is a reasonable policy choice given its limited role. But it is neither sensible nor sustainable for CMS not to consider costs.

Multiple evaluations have found low rates of completion of postmarketing studies for both drugs and devices.

H&O What problems can arise when the FDA grants accelerated approvals for oncology drugs?

DH When the FDA is making a decision that is based on less evidence than the traditional standard, we should expect to see some errors—approval of some drugs that should not be approved and failure to approve some drugs that should be approved. The challenge is how quickly the FDA can acquire good evidence to either back up their original decision or persuade them that they made the wrong decision, which is why the timely completion of postmarketing studies is an essential part of accelerated approval. Unfortunately, we have seen persistent problems with getting these postmarketing studies done. Multiple evaluations have found low rates of completion of postmarketing studies for both drugs and devices. That is very disconcerting.

One problem with accelerated approval is that dose optimization may not be part of the approval process, potentially causing the FDA to approve the agent at a higher dose than is required. Approval of a dose higher than necessary can be a major issue when it comes to cytotoxic agents, leading to unnecessary adverse effects and wasted health care dollars. It can also be a problem with targeted agents. Giving people higher doses of drugs than are necessary is just not good practice.

At the same time, it is important to remember that accelerated approvals are a reasonable response to a real problem, which is that some people may miss out on the benefits of a new agent while it remains in the FDA approval pipeline. So how do we make the correct trade-off between acquiring gold standard information and having timely access to treatment? Reasonable people can disagree, but no perfect state of the world exists in which we get traditional approvals in the same time frame as accelerated approvals.

H&O How did the Food and Drug Omnibus Reform Act seek to address the problems that can occur with accelerated approvals?

DH The Food and Drug Omnibus Reform Act was part of the Consolidated Appropriations Act, passed in December 2022. The Act contained several provisions related to accelerated approvals that provided the FDA with a couple more "sticks" to ensure that postmarketing studies are done on a timely basis. For example, the FDA can insist that the confirmatory trial be underway at the time of approval rather than accept a promise that the trial will start at some point in the future. At the same time, the Act gives manufacturers more due process rights if the FDA decides to withdraw an accelerated approval.

H&O How does CMS decide whether to issue a national coverage determination, and when does it defer to local Medicare Administrative Contractors?

DH How CMS decides is similar to how the Supreme Court decides to take a case—it may be important for fiscal or political reasons to have a single answer for the entire country. Although one might assume that coverage decisions are national because Medicare is a federal program, we do see a lot of variation in coverage decisions. Local coverage decisions are made by Regional Administrative Contractors, who are charged with implementing the rules as they understand them. Sometimes local variations are excessive, however, especially when use of a drug is politically sensitive or very expensive.

When CMS is sorting out whether a specific drug or device should be covered, they have the option of granting "Coverage with Evidence Development." This is a way for CMS to say that Medicare will provide coverage, but only for patients participating in a clinical trial. After the trial ends, CMS can revisit coverage of the drug. One high-profile example of this situation is aducanumab, a drug for the treatment of Alzheimer disease. Aducanumab controversially received FDA approval in 2021 despite weak evidence of benefit and a significant adverse event profile. CMS apparently did not feel comfortable covering aducanumab, especially given its cost, so their compromise was to grant Coverage with Evidence Development. The manufacturer ended up discontinuing the drug after disappointing sales.

H&O For drugs, how do Part B and Part D drug coverage rules and statutory requirements like "medically accepted indication" affect CMS decision making?

DH Statutory requirements on CMS are binding, so CMS must follow the decisions that Congress has made regarding coverage or noncoverage. CMS also has a lot less leeway under current administrative law than it used to have in interpreting statutory language. The drug coverage regulations are the attempt of CMS to make national coverage decisions; if they want to change them, they must jump through some procedural hoops.

H&O How has the Inflation Reduction Act (IRA) affected coverage decisions?

DH The IRA addresses multiple factors that affect the prices being charged and the way in which those costs are shared between beneficiaries and Part D programs. The IRA does not on its face affect specific coverage decisions, but it does create downstream effects because sponsors of Part D plans are going to make different decisions on formularies according to the prices that they must pay. The Medicare Modernization Act requires Medicare Part D to cover all antineoplastic agents, which removes the ability of plan sponsors to extract lower prices by excluding certain agents from their formulary.

H&O What further reforms or alignment between FDA and CMS standards would you like to see?

DH Although coordination between the 2 agencies could be closer, I think it is appropriate for FDA and CMS to be applying differing standards for approval and payment policy. We also see differing standards in countries other than our own, in which a drug or device receives approval but the national health authority decides not to pay for it. Patients are still allowed to receive the treatment, but they must pay out of pocket to do so.

Disclosures

Dr Hyman has served as an expert in several lawsuits involving pharmaceuticals, pharmacy benefit managers, and drug pricing.

Suggested Readings

Epstein WN, Hyman DA, Silver C. Better drugs and devices through private contracts. *UC Davis Law Rev.* 2026;59:2407-2477.

Brown BL, Mitra-Majumdar M, Darrow JJ, et al. Fulfillment of postmarket commitments and requirements for new drugs approved by the FDA, 2013-2016. *JAMA Intern Med.* 2022;182(11):1223-1226.

Moneer O, Brown BL, Avorn J, et al. New drug postmarketing requirements and commitments in the US: a systematic review of the evidence. *Drug Saf.* 2022;45(4):305-318.

Mitra-Majumdar M, Powers JH III, Brown BL, Kesselheim AS. Evidence at time of regulatory approval and cost of new antibiotics in 2016-19: cohort study of FDA approved drugs. *BMJ Med.* 2022;1(1):e000227.

Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US Food and Drug Administration accelerated approval of malignant hematology and oncology drugs and biologics: a review. *JAMA Oncol.* 2018;4(6):849-856.

Naci H, Smalley KR, Kesselheim AS. Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *JAMA.* 2017;318(7):626-636.

Pease AM, Krumholz HM, Downing NS, Aminawung JA, Shah ND, Ross JS. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ.* 2017;357:j1680.

U.S. Government Accountability Office. Medical devices: FDA ordered postmarket studies to better understand safety issues, and many studies are ongoing. GAO-15-815. Published September 30, 2015. https://www.gao.gov/products/gao-15-815.