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How FDA Used Its Accelerated Approval Pathway Raised Concerns in 3 of 24 Drugs Reviewed

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REPORT HIGHLIGHTS

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How FDA Used Its Accelerated Approval Pathway Raised Concerns in 3 of 24 Drugs Reviewed

Why OIG Did This Review

- FDA can use the accelerated approval pathway to speed development and review of new drugs to treat serious and life-threatening conditions.
- Accelerated approval does not require that a drug demonstrate a clinical benefit prior to approval.
- As a result, there is risk that an accelerated approval drug will not ultimately provide a clinical benefit for patients, necessitating safeguards and transparency in FDA decision making.
- FDA's 2021 accelerated approval of aducanumab, a drug to treat Alzheimer's disease, raised concerns in Congress and the medical and research communities about FDA's judgment in approving the drug and the accelerated approval pathway in general.
- This review examines a sample of 24 drugs, including aducanumab, approved through the accelerated approval pathway for similar concerns.

What OIG Found

Our review identified concerns about FDA's use of the accelerated approval pathway in 3 of the 24 drugs we reviewed:

- For two of the three concerning approvals, FDA evaluated analyses not included in the sponsor's (i.e., pharmaceutical company's) original analysis plans, deviating from recommended practices.
- FDA approved these three drugs despite concerns from its own reviewers and/or advisory committees.
- For one drug, some meetings with the sponsor appeared to be missing from the administrative file and other meetings are not fully documented.

Additionally, two of the three drugs that raised concerns are now off the market, and completion of the confirmatory trial for the third drug is delayed.

What OIG Recommends

OIG recommends that FDA strengthen guardrails in certain circumstances to ensure appropriate and consistent use of the accelerated approval pathway. FDA should:

1. Define specific factors that would require FDA's accelerated approval council to advise on certain drug applications.
2. Take steps to ensure that appropriate documentation of meetings with sponsors is included in drug approval administrative files.

FDA concurred with the second recommendation but did not concur with the first recommendation.

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BACKGROUND

OBJECTIVE

To determine the extent to which the Food and Drug Administration's (FDA's) review of selected drugs and biologics (hereinafter referred to as drugs) varied through the accelerated approval pathway, resulting in outliers that raise concerns about accelerated approvals.

FDA's 2021 accelerated approval of aducanumab, a drug intended to treat Alzheimer's disease and marketed under the brand name Aduhelm, raised concerns about FDA's decision to approve the drug. Some FDA staff, as well as members of its scientific advisory committee and others in the medical and research communities, shared these concerns. Two congressional committees jointly investigated the matter and released a report in December 2022 that was critical of FDA's review of aducanumab.[1]

FDA approved aducanumab via the accelerated approval pathway. The evidence FDA evaluates to determine a drug's effectiveness differs in the accelerated approval and traditional approval pathways. Under both pathways, drugs must be proven safe and effective as conditions of FDA approval. However, for accelerated approval, Federal law requires that the sponsor (e.g., the manufacturer) show that the drug is reasonably likely to provide a clinical benefit,[2] whereas for the traditional approval pathway sponsors must demonstrate that the drug provides a clinical benefit prior to approval.

This evaluation examines FDA's review of a selection of drugs—including aducanumab—that it approved via the accelerated approval pathway to determine how FDA has used this approval process. Specifically, we determined whether and how FDA's review of these drugs deviated from its recommended or typical practices and whether the main issues of concern raised about aducanumab's approval were also present in the approvals of other drugs in our sample.

FDA's Drug Approval Processes: Traditional Approval and Accelerated Approval

FDA has multiple pathways available for a drug to gain approval for a new use, including a traditional approval pathway and an accelerated approval pathway. The

pathways share many basic steps, such as demonstrating that a drug is safe and effective by conducting clinical trials and submitting results for an FDA review. Clinical trials typically occur before FDA approves a drug and progress from smaller to larger populations to assess safety, determine dosage, identify side effects, and evaluate effectiveness. A drug's sponsor designs an analysis plan to study the effect of the drug on a specified endpoint.

For each pathway, a sponsor compiles the resulting data and analysis from its completed trials in an application (either a New Drug Application or a Biologics License Application, hereinafter called drug application) for submission to FDA. FDA staff, including physicians, statisticians, chemists, and pharmacologists then review the drug application while focusing on three areas: (1) the safety and effectiveness of the drug for its proposed use, including whether its benefits outweigh the risks; (2) the appropriateness of the proposed labeling; and (3) the adequacy of manufacturing methods to ensure the drug's identity, strength, quality, and purity.[3, 4] After FDA approves the drug application, a sponsor can generally market and sell the drug in the United States.

FDA has considerable flexibility in its approach to approving drugs regardless of the pathway taken. FDA reviewers and decisionmakers weigh a host of scientific and public health factors while striving to balance the potential risks and benefits of new drugs. These flexibilities are generally accepted as inherently necessary given the evolving nature of science, the complexity of FDA's charge to balance risk with benefit in its decision making, and its role in protecting public health. For accelerated approval, that flexibility includes, but is not limited to, how FDA interprets whether trial results demonstrate that a drug's effect is reasonably likely to predict a clinical benefit.

The evidence FDA evaluates to determine a drug's effectiveness differs in the two pathways. For the traditional pathway, sponsors generally design trials to assess an effect on a clinical endpoint that directly reflects patient benefits (i.e., how patients feel, function, or survive), and the trials need to demonstrate that the drug has a clinical benefit. In contrast, for the accelerated approval pathway sponsors can assess an effect on a surrogate endpoint (i.e., a marker) and demonstrate that the drug's effect is reasonably likely to predict a clinical benefit.[5] For example, FDA may grant accelerated approval to a drug based on evidence that the drug shrinks tumors because tumor shrinkage in that cancer is considered a surrogate endpoint reasonably likely to predict clinical benefit (i.e., predict an improvement in overall survival).[6] Neither Federal law nor FDA defines the precise threshold of what constitutes "reasonably likely."

There are risks and benefits to allowing a drug sponsor to use a surrogate endpoint in the accelerated approval process. A risk is that the drug may not ultimately provide the predicted clinical benefit in patients. A benefit is that a surrogate endpoint enables a drug to be approved on an accelerated timeline when the effect on a surrogate endpoint can be measured faster than its associated clinical benefit, which may not occur until years later.

Drugs that FDA approves through the accelerated approval pathway still must demonstrate safety and effectiveness according to statutory requirements. From 1992 to 2023, FDA's Center for Drug Evaluation and Research approved 307 drugs via the accelerated approval pathway.

Glossary of Terms

Accelerated approval pathway: Allows drugs to be approved using a surrogate endpoint rather than by assessing a drug's effectiveness based on direct measures of clinical benefit.

Clinical endpoint: An event or outcome that directly measures how a patient feels, functions, or survives, that can help determine whether an intervention, such as a drug, provides a clinical benefit.

Surrogate endpoint: A trial endpoint used as a substitute for a direct measurement of how a patient feels, functions, or survives.

Source: FDA, *Guidance for Industry Expedited Programs for Serious Conditions*, May 2014.

Primer: FDA's Accelerated Approval Pathway

- FDA's accelerated approval pathway facilitates and expedites the development and review of new drugs for serious or life-threatening diseases or conditions—especially when there are no satisfactory alternative treatments.
- Drugs approved via the accelerated approval pathway address unmet medical needs and include drugs that treat rare diseases, cancer, and human immunodeficiency virus (HIV), among other diseases.[7]
- The approval process is expedited because FDA may approve a drug based on its effect on a surrogate endpoint, which can be measured sooner than the clinical benefit.
- Because accelerated approval is generally based on a surrogate endpoint, that is reasonably likely to predict benefit, rather than a direct measurement of clinical benefit, that benefit would be unconfirmed at the time of a drug's approval. FDA requires sponsors to conduct additional clinical trials after an accelerated approval to confirm clinical benefit. Sponsors may complete confirmatory trials after the drug has been available to patients.

Legislative Changes to FDA's Accelerated Approval Authorities

On December 29, 2022, the President signed legislation that granted FDA new authorities regarding accelerated approval. The signing followed OIG's release of a report on the timeliness of confirmatory trials (see Related Work below for more details) and was concurrent with the release of a congressional investigation into FDA's review of aducanumab. The legislation provided FDA with the authority to require that confirmatory trials be underway before a drug's approval as well as the authority to use a more expedited process to withdraw an accelerated approval for a drug.[8] It also mandated that FDA, within a year, create an intra-agency accelerated approval council to ensure consistent and appropriate use of the accelerated approval pathway across the agency. Council members include the directors of seven specified centers and offices within FDA, as well as at least three directors of review divisions or offices overseeing products approved via the accelerated approval pathway. The council must meet at least three times a year and work with FDA product review teams. FDA must publish an annual report of the council's activities on the FDA website.[9] The council held two meetings in 2023.[10] FDA published a one-page report of the council's 2023 activities. This report indicated that the meetings included discussions of policy issues related to the new accelerated approval authorities contained in the 2022 legislation but provided no details of the policy discussion.

Resolving Scientific Disputes

A scientific dispute involves a disagreement among FDA staff that can concern how data are interpreted or whether evidence is adequate to support a decision, among other issues (e.g., if FDA staff disagree whether a drug should be approved). If FDA staff are unable to resolve a dispute informally, staff can elevate that dispute through FDA's formal Scientific Dispute Resolution program, which is intended to address disputes that could have a significant impact on public health. In these cases, a review board documents its findings and recommendations before the FDA Commissioner makes a final decision.[11]

Additionally, FDA has a formal dispute resolution process for sponsors. This process addresses scientific and/or medical disputes between a sponsor and FDA, such as disputes related to a sponsor's new drug application.[12]

Advisory Committees

FDA can use advisory committees to offer independent recommendations or advice on scientific, technical, or policy questions.[13] FDA guidance states that the agency "seriously considers" advisory committee recommendations, including deliberations and voting, before making an approval decision.[14]

Generally, these committees are composed of scientific experts who work outside of the Government.[15] According to FDA, advisory committees contribute to the quality of its decision making and provide public assurance of a responsible process.[16] During any stage of a drug's review process, FDA can convene an advisory committee meeting to, for example, help interpret clinical trial data when difficult scientific questions arise.[17] FDA determines a meeting's agenda and charges the committee with specific questions to discuss and/or vote on, although the committee chair can suggest in consultation with FDA additional questions on which to vote. The advisory committee typically concludes with recommendations based on the discussion and voting, although not every meeting includes a vote.

Meetings and Communication Between Sponsors and FDA

During a drug development process, FDA encourages meetings with sponsors if these meetings aid in evaluating a drug and help solve scientific problems concerning the drug.[18] For example, sponsors can seek feedback and communicate at critical points during the development process (e.g., as sponsors proceed from smaller to larger trials).[19] For drugs seeking approval through the accelerated approval pathway, FDA generally gives sponsors more intensive guidance and expects to have more interactions, including formal meetings, with sponsors.[20]

During drug development, sponsors may request a formal meeting with FDA when they need advice on the regulatory process.[21] These meetings may take place in any format (e.g., face-to-face, via teleconference, or via videoconference). Meeting minutes provide an official record of these formal meetings and capture outcomes,

agreements, disagreements, and action items.[22] FDA typically issues official minutes to a requester within 30 calendar days of a meeting. Although FDA characterizes meeting documentation as "critical" for future referencing, it does not specify how the staff should maintain such documentation.[23]

Concerns About FDA's Accelerated Approval of Aducanumab

FDA's approval of aducanumab was controversial for a number of reasons. Among the concerns that surfaced regarding FDA's review of aducanumab were the emergence of scientific disagreements among FDA staff on the interpretation of trial data, reliance on the surrogate endpoint used to assess the drug's effect, the weight of the advisory committee on approval decisions, and the nature and extent of the meetings between FDA and aducanumab's sponsor.

In December 2022, two congressional committees jointly released the results of an investigation that was critical of FDA's review and the sponsor's marketing of aducanumab. The committees found that FDA's review and approval of aducanumab consisted of atypical procedures and deviated from the agency's own guidance. The committees also cited a 2021 internal review FDA conducted into the interactions between the agency and the drug's sponsor, which found that the extent of collaboration between FDA and the sponsor was atypical and "exceeded the norm in some respects."[24]

Related Work

This report follows a 2022 companion report, *Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns* (OEI-01-21-00401), that focused on confirmatory trials for accelerated approval drugs. The companion report found that more than one-third of accelerated approval drug applications with incomplete confirmatory trials had passed their trials' original planned completion dates, including four that were more than 5 years past those dates. It also found that Medicare and Medicaid spent more than $18 billion from 2018 to 2021 for accelerated approval drugs with incomplete confirmatory trials past their original planned completion dates.[25] The companion report did not contain recommendations.

Methodology

In light of the concerns regarding aducanumab's approval, we selected 19 drugs and 5 biologics (hereinafter called drugs) approved via the accelerated approval pathway, including aducanumab. We assessed approvals to identify outliers in deviating from usual processes.

Specifically, we reviewed a sample of 24 of the 278 drugs approved by FDA's Center for Drug Evaluation and Research (CDER) through the accelerated approval pathway from the pathway's establishment in 1992 through December 2021. We purposively

sampled 10 drugs with approvals identified as concerning during interviews with stakeholders. These drugs included aducanumab. We then took a random sample of 14 of the remaining 268 approved drugs.

We requested from FDA the administrative files for the 24 drugs in our sample. FDA staff are required to document in administrative files the basis for each decision, including relevant evaluations, reviews, memoranda, and minutes of meetings.[26] We also reviewed agendas, minutes, and transcripts for advisory committee meetings convened by FDA for the drugs in our sample, as well as relevant FDA policies and procedures.

We focused our review on determining whether variation or outliers existed at the following points for the accelerated approval pathway:

- following the original analysis plans with regard to endpoints;
- when scientific disputes and/or informal disagreements arose, including instances when advisory committees voted that drug sponsors did not demonstrate effectiveness; and
- in meetings between FDA and sponsors.

This review focused on a sample of 24 drugs that went through the accelerated approval pathway; it is not a compliance review. We did not independently assess the appropriateness of the decisions made by FDA. See page 20 for the detailed methodology.

Limitations

Two drugs in our sample have approvals dating to the 1990s, and their administrative files did not contain enough information to determine whether the sponsors followed their original analysis plans.

Standards

We conducted this study in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

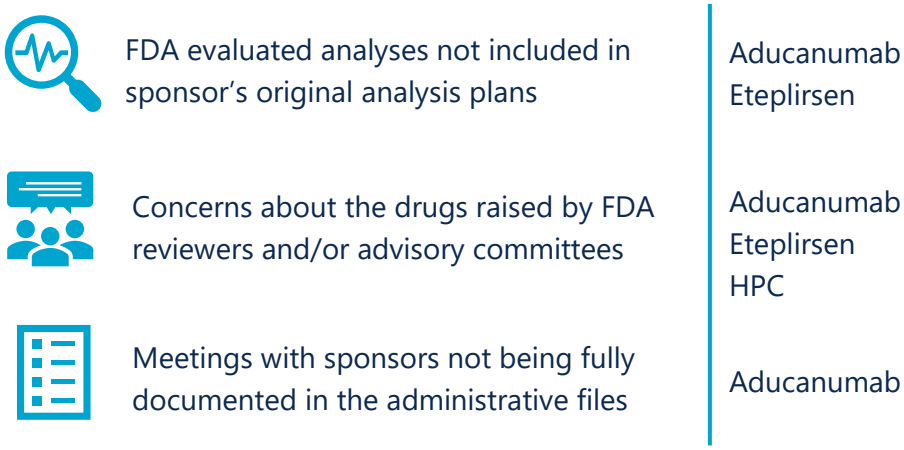
FINDINGS

Three of 24 drugs that received approval raised concerns about how FDA used the accelerated approval pathway

Our review revealed that 21 of the 24 drugs in our sample moved through the accelerated approval pathway without raising the kinds of concerns that surfaced during the review and approval of aducanumab. (See Appendix B for a snapshot of our analysis of the drugs in our sample concerning these areas.)

In contrast, we found that the processes for approving aducanumab (a drug to treat Alzheimer's disease), eteplirsen (a drug to treat Duchenne muscular dystrophy), and hydroxyprogesterone caproate (HPC, a drug to reduce the risk of preterm birth in certain women)[27] deviated from the other 21 approvals in our sample in ways that raised concerns.[28] (See Exhibit 1 for the three areas of concern and which of the three drugs' approvals raised concern.)

Exhibit 1: Areas of concern raised regarding the approval of three drugs



Source: OIG analysis of FDA administrative drug files, 2024.

For two of the three concerning approvals, FDA evaluated analyses not included in the sponsor's original analysis plans, deviating from recommended practices

For two drugs in our sample—aducanumab and eteplirsen—FDA evaluated whether the clinical data supported accelerated approval after concluding that the sponsors did not submit sufficient evidence to support traditional approval. FDA evaluated analyses that were not included in the sponsors' original analysis plans (i.e., changing the measure used to determine effectiveness and/or changing the approach to analyzing the data). This deviated from FDA's recommended practices. FDA

considers specifying a trial's endpoints (i.e., measures of clinical effectiveness) and related statistical analysis before the start of the trial to be a best practice.[29] Switching from the original analysis can increase the risk of error in interpreting clinical trial results and can raise questions about the evidence underpinning FDA's approval.

Aducanumab: FDA conducted analyses not included in the sponsor's original analysis plan

In the case of aducanumab, FDA veered from a best practice by conducting analyses related to a surrogate endpoint that were not included in the sponsor's original analysis plan. FDA examined trial data from the drug application seeking traditional approval to instead seek accelerated approval.

When it appeared that the drug could not achieve traditional FDA approval by demonstrating clinical benefit, FDA considered whether the drug had an effect on a surrogate endpoint that supported accelerated approval. Initially, the sponsor sought traditional approval by showing the drug was effective on a clinical endpoint (slower cognitive decline) through two clinical trials. After an interim analysis found that the drug may not demonstrate effectiveness in slowing cognitive decline, the sponsor terminated the trials before completion. However, final trial results came in after the decision to terminate was made. The final trial results demonstrated that one trial was, in fact, successful in demonstrating a positive effect on the clinical endpoint.

Because each of the two identically designed trials produced a different result, the sponsor went to FDA for guidance. FDA worked with the sponsor to identify potential causes for having different outcomes between the trials. FDA then conducted a new analysis focused on a surrogate endpoint (i.e., a reduction in amyloid plaques). FDA also considered data from an earlier, smaller clinical trial that was not primarily intended to measure aducanumab's ability to reduce amyloid plaques.

FDA's rationale for initiating the shift to accelerated approval for aducanumab was that one terminated trial found a clear relationship in the clinical data between reduction of amyloid plaques and improved outcomes for patients. The reviewers also noted that these results were consistent with similar drugs that were at that time under development. The reviewers found that the results of the post hoc analysis, along with support from the earlier trial's results, showed that aducanumab reduced amyloid plaques. FDA concluded that, therefore, aducanumab merited accelerated approval.

Eteplirsen: FDA request for additional analysis

In the case of eteplirsen, FDA also veered from best practices by redirecting the sponsor from the sponsor's original analysis plan. The sponsor originally sought accelerated approval based on a clinical endpoint (i.e., improved mobility). FDA decided this was not feasible and determined that the sponsor could instead focus on

a surrogate endpoint—production of dystrophin, a protein. The sponsor had been testing dystrophin production as a secondary measure in the clinical trial.

FDA's review team requested additional analysis not in the original analysis plan because the team concluded that the initial clinical trial data were not reliable or interpretable. The sponsor re-analyzed the data, with FDA's assistance, using a different analytic method. However, FDA continued to have concerns about the data as well as the clinical trial itself. FDA asked the sponsor to conduct yet more analysis, which was still focused on the surrogate endpoint, using data from another trial that was still in progress.

FDA approved 3 of the 24 drugs despite concerns from its own reviewers and/or advisory committees

Scientific debate plays an important role in ensuring robust decision making at FDA by exposing weaknesses or limits in analysis. As might be expected given the complexity of their task, FDA reviewers may not always reach consensus, and reviewers are not required to reach consensus before approving a drug. However, debates related to three drugs stood out.

Concerns related to eteplirsen escalated to a formal dispute, which was the only formal and internal dispute we observed for the 24 drugs in our sample. Concerns about aducanumab and HPC remained informal. However, concerns about aducanumab were not resolved before approval. Concerns about HPC ultimately were resolved before approval after an unusual number of rounds of review. We did not observe such significant concerns or lack of reviewer support for other drugs in our sample. Additionally, the advisory committees for aducanumab and eteplirsen did not believe that the drugs' sponsors provided sufficient evidence of effectiveness.

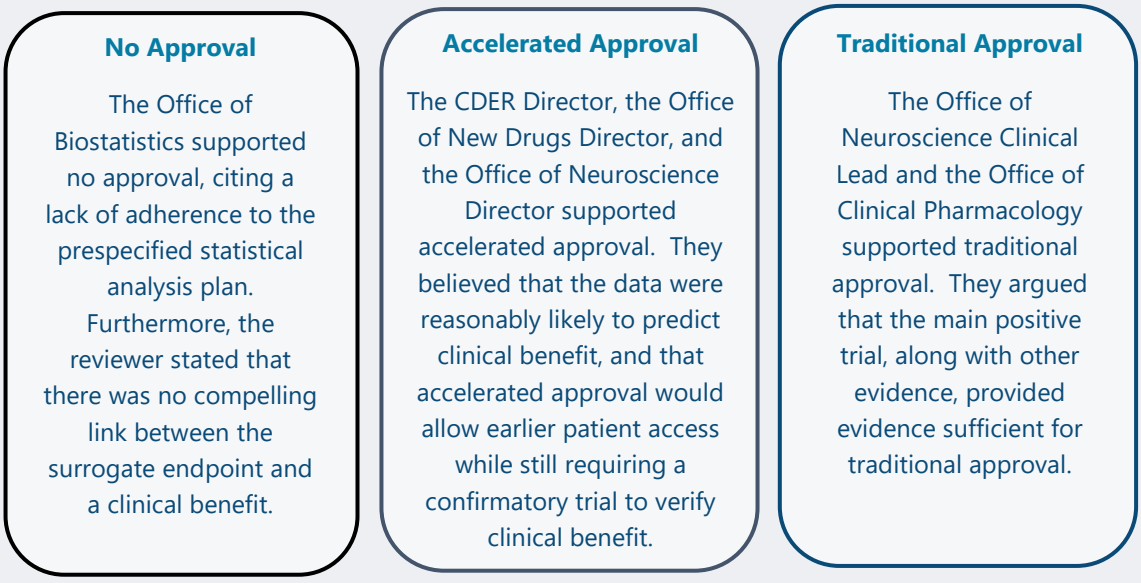
Aducanumab: Objections from an FDA reviewer and advisory committee concerns

Aducanumab was ultimately granted accelerated approval over objections from CDER's Office of Biostatistics. That office's statistical reviewer—whose concerns were not resolved before approval—found the results of the post hoc analysis to be unacceptable because the trials were designed to test the clinical endpoint and not the surrogate endpoint. The only valid analysis, according to the reviewer, stemmed from the original analysis plan's clinical trial data, which measured a clinical endpoint.

Other review team members, however, believed that the evidence from the trials warranted some type of approval—accelerated or traditional (see Exhibit 2). Furthermore, unlike any of the other drugs in our sample, aducanumab's administrative file included memoranda from the CDER Director and the Director of the Office of New Drugs. Their assessments were based on clinical trial data but also on the significant unmet medical need, including a need articulated by patients. Both

directors disagreed with the statistical reviewer and supported, based on the totality of evidence, that aducanumab should be approved via the accelerated approval pathway.

Exhibit 2: Reviewers did not agree on the appropriate pathway for approval of aducanumab



Source: OIG analysis of aducanumab administrative file, 2024.

Additionally, FDA chose to convene an advisory committee for aducanumab that largely voted against using the trials as evidence of effectiveness. FDA specified four questions for committee voting. In considering all studies and data, the committee voted overwhelmingly that the terminated positive trial was not primary evidence of effectiveness, given unaddressed criticisms of the analysis by the FDA statistical reviewer. (Ten of 11 committee members voted "no" and 1 voted "uncertain.") Second, a majority of the committee voted that the same terminated positive trial did not independently supply strong evidence for aducanumab's effectiveness (8 of 11 members voted "no," 1 voted "yes," and 2 voted "uncertain"). Third, a majority of the committee voted that the earlier, smaller-scale trial did not supply supporting evidence for the drug's effectiveness. (Seven of 11 members voted "no," none voted "yes," and 4 voted "uncertain.") Lastly, regarding whether the sponsor presented strong evidence that aducanumab had an effect on amyloid plaques, the committee was split but more positive. (Six of 11 members voted "uncertain" and 5 members voted "yes.")

But FDA never asked this advisory committee to vote on whether the application was suitable for accelerated approval. FDA has the authority to convene an advisory

committee and it specifies the questions for the committee to discuss or vote on. FDA ultimately granted aducanumab accelerated approval based on a surrogate endpoint that was not assessed by the advisory committee. Three members of the committee resigned in protest over the approval.

Eteplirsen: Disagreement on the drug's effect on the surrogate endpoint

Disagreement about whether eteplirsen was reasonably likely to predict a clinical benefit led to a formal dispute that was ultimately decided on by the FDA Commissioner.

In this case, FDA's review team had concluded that eteplirsen should not be approved because the measured effect on the surrogate endpoint (i.e., an increase in dystrophin protein production) was too small to be reasonably likely to predict a clinical benefit. However, the CDER Director concluded that, given the totality of the data, the drug warranted accelerated approval. The CDER Director also contended that if FDA did not approve the drug the sponsor would lack funding to continue researching it or similar drugs, which could have a negative impact on the patient population with Duchenne muscular dystrophy. The CDER Director invoked the need for "the greatest flexibility possible" under FDA's statutory authority to approve the drug, noting that Duchenne muscular dystrophy is fatal, the lack of available therapies, and that the population is a small subset of a population with a rare disease.[30]

As a result, the Office of Drug Evaluation I Director—the CDER office that led eteplirsen's review—formally disputed the decision to approve the drug. The dispute's primary issue was whether the measured effect on the surrogate endpoint was reasonably likely to predict a clinical benefit. Based on memoranda from FDA officials in the administrative file, the dispute also referred to atypical and excessive involvement by the CDER Director by means such as: (1) taking a large role in the early stages of the FDA review of the drug, (2) planning and speaking at the advisory committee meeting, and (3) making clear an intention to approve the drug regardless of the review team's conclusions.

Ultimately, the dispute was elevated to the FDA Commissioner, who upheld the decision to approve eteplirsen. The FDA Commissioner's decision also found that the CDER Director's involvement was appropriate.

Additionally, FDA chose to convene an advisory committee on eteplirsen. The committee voted 8-to-6 that the sponsor did not provide substantial evidence proving that the drug had an effect on a surrogate endpoint that was reasonably likely to predict a clinical benefit.[31] Committee members who voted favorably for eteplirsen largely cited the testimony of patients. In fact, three of the six members who voted in favor of accelerated approval were consumer and patient representatives.

HPC: Uncertainties due to limited trials

All of the HPC reviewers ultimately supported accelerated approval, but only after multiple review rounds and sponsor commitments to resolve concerns through confirmatory trials after approval. In the early stages of review, FDA reviewers were concerned about the choice of HPC's surrogate endpoint (i.e., the reduction in preterm births before a specific week of pregnancy) and the clinical trial. Given those concerns, FDA advised the sponsor that it would not approve the application and recommended the sponsor conduct additional trials. This feedback caused extensive discourse between the sponsor and FDA—enough discourse to warrant a formal dispute by the sponsor in opposition. However, FDA maintained the recommendation and, as a result, the sponsor agreed to submit the data.

After the second round of review, multiple reviewers still did not support accelerated approval for HPC because of concerns about the feasibility of the confirmatory trial. The drug's statistical reviewer was particularly concerned and remained unconvinced that the results were sufficient to support the drug's effectiveness due to the absence of a second trial. After HPC's final resubmission and a third round of review, the statistical reviewer eventually supported HPC's approval, although not all concerns had been resolved. The statistical reviewer agreed to have most of the concerns addressed by a post-approval confirmatory trial, and FDA approved HPC.

Some meetings with the sponsor appeared to be missing from the administrative file for one drug (aducanumab), and other meetings are mentioned but not fully documented for other drugs in our sample

Meetings needed for a drug's development and application can vary depending on the circumstances surrounding the drug. FDA expects that a drug developed under an expedited program such as accelerated approval may involve an increased number of interactions between FDA and sponsors.[32] FDA staff are required to document a basis for a decision, including relevant meeting minutes, in administrative files.[33]

Our review raised questions about whether the administrative file for aducanumab fully documented the basis for FDA's decision to approve the drug. The administrative files we reviewed documented 13 meetings between FDA and aducanumab's sponsor, 5 of which were held between July 2019 and July 2020, a period in which FDA and the sponsor worked together to analyze data from the clinical trials. The number of meetings documented in the administrative file appears at odds with the extent to which FDA and the sponsor reportedly collaborated toward the drug's approval. Another source cites a higher number of meetings, raising uncertainty about the extent and nature of the meetings. The 2022 congressional investigation, which was a focused inquiry into aducanumab's approval and marketing as opposed to our evaluation of the accelerated approval pathway, said FDA and the drug's sponsor convened at least 40 meetings during this time.[34] That investigation

also cited an internal FDA report stating that the total number of meetings between FDA and the sponsor during this time was unknown because FDA lacked a "clear record" of the meetings and did not properly document all of them.[35, 36]

Furthermore, the administrative files for aducanumab mentioned four meetings that occurred but for which there were no meeting minutes or summaries describing the meetings. The issue of meetings being mentioned but not further documented or summarized was not exclusive to aducanumab but was in fact something we noted that sometimes occurred for some of the other 24 drugs in our review. Although these meetings were documented as having happened, the lack of details regarding the meetings makes it difficult to determine whether the meetings contributed significantly to FDA's decision making. For example, the clinical reviewer for one drug wrote that "a follow up meeting to discuss items remaining from the pre-NDA meeting was held on February 2, 2012."

In fact, we saw that FDA documented meetings between the agency and a sponsor differently. We identified 152 meetings for the 24 drugs in our sample, and FDA documented them in 3 ways: (1) high-level summaries often recorded within the summary of a drug's development and application review (26 percent); (2) full meeting minutes, usually as part of correspondence sent to the sponsor (50 percent); and (3) references to meetings not documented with their own summaries or minutes (24 percent).

Although FDA characterizes meeting documentation as critical for future referencing, it does not specify how the staff should maintain such documentation.[37] Furthermore, FDA policy does not stipulate that the Agency should issue formal meeting minutes for every meeting with a sponsor. After the approval of aducanumab, FDA and others called for changes in FDA's practices, particularly practices concerning FDA's meetings with sponsors and documentation of those meetings. The 2022 congressional investigation stated that FDA was in the process of implementing these changes.

Two of three drugs that raised concerns are off the market, and the confirmatory trial for the third is delayed

All three of the drugs that raised concerns in our review of the accelerated approval pathway continued to do so after their approvals. Two of the drugs—aducanumab and HPC—were ultimately removed from the market, and eteplirsen's trial to confirm clinical benefit has been delayed.

Aducanumab: Sales stopped and confirmatory trial terminated

Three years after aducanumab's controversial accelerated approval and concerns about its high price, aducanumab's sponsor announced in 2024 that it would stop sales and terminate the confirmatory clinical trial of the drug.[38] This followed the 2022 decision by the Centers for Medicare & Medicaid Services to limit Medicare coverage of aducanumab to patients enrolled in certain clinical trials.[39] In January

2023, FDA granted accelerated approval for lecanemab, another drug for treating Alzheimer's disease. Lecanemab targeted the same surrogate endpoint as aducanumab—reduction of amyloid plaques—and was codeveloped by aducanumab's sponsor.[40] Later in 2023, FDA converted lecanemab to traditional approval after a confirmatory trial verified the drug's clinical benefit.[41] In 2024, FDA granted traditional approval to donanemab, which also treats Alzheimer's disease by reducing amyloid plaques.[42]

HPC: Approval withdrawn after hearing and second advisory committee

FDA withdrew approval of HPC and all its generics in April 2023, 12 years after HPC's accelerated approval. The drug's confirmatory trial had failed to verify the clinical benefit in 2019, 8 years after HPC's accelerated approval. Removing HPC from the market took 3 years, during which time patients had access to and were paying for the drug.

Once the confirmatory trial failed to verify the clinical benefit and failed to show an effect on the same endpoint that supported accelerated approval, FDA convened an advisory committee, which voted 9-to-7 to withdraw the drug's approval. The sponsor refused to withdraw the drug voluntarily and expressed the need for further study, underscored by the fact that HPC filled an unmet need. After extensive review of the data and considerations of public input, FDA announced in October 2020 that it intended to withdraw previous approval granted to HPC and its generics for reducing the risk of preterm birth. HPC's sponsor disagreed with FDA and requested a hearing. The hearing was not held for 2 years. At the hearing in October 2022, a second advisory committee voted 14-to-1 to recommend that FDA withdraw HPC's approval.

Eteplirsen: Confirmatory trial delayed, similar drugs approved

Eteplirsen was approved in 2016, but after 8 years its confirmatory trial had yet to provide evidence of clinical effectiveness. The trial, originally scheduled for completion in 2021, is delayed.

Furthermore, FDA referenced eteplirsen's approval and then granted accelerated approval to three other drugs to treat Duchenne muscular dystrophy in our sample between 2019 and 2021. All three drugs—two of which had the same sponsor as eteplirsen—used the same surrogate endpoint and showed a similar clinical effect as eteplirsen. FDA approved the first of these three drugs only after the sponsor, which was also eteplirsen's sponsor, prevailed in appealing a decision after a formal dispute with FDA. The clinical reviewer for another of these three drugs concluded that there was not clear evidence that the drug's effect on the surrogate endpoint met the reasonably likely standard, but that the reviewer felt bound by prior FDA approvals, including eteplirsen, based on similar effects.

CONCLUSION AND RECOMMENDATIONS

In using the accelerated approval pathway, FDA must balance the goal of expediting the development and review of new drugs when there are no alternative treatments with the risk of approving drugs without confirmed clinical benefit. Misjudging that balance has the potential to allow drugs that do not improve patient health and well-being to enter the market and incur costs to patients and the health care system. The FDA Commissioner said that, given the complex nature of these reviews and the expertise required, FDA has had "tremendous latitude" in making decisions for accelerated approvals.[43]

Our review revealed that for 21 of the 24 drugs in our sample there was a consistent approach through the pathway and the approval of advisory committees that had been convened, with no formal scientific disputes or informal disagreements. Our concerns were limited to three outlier drugs. Although FDA has latitude in making decisions, these three cases underscore the need for additional guardrails in certain circumstances.

Given these outliers and the importance of FDA's role in approving drugs for the public, it is critical that FDA have appropriate guardrails in place to offset risk and ensure consistent and appropriate practices. FDA's primary guardrail, the confirmatory trial, has been limited in execution. As we have also shown in previous work, many of these trials extend past their originally planned completion dates, and FDA faces challenges in withdrawing approval from a drug that fails to confirm clinical benefits.

In late 2022, Congress gave FDA new authorities that hold promise for additional protections. These include the authority for FDA to require that confirmatory trials be underway before a drug's approval or within a specified time period after the date of approval, and creation of a new intra-agency council to ensure the consistency of FDA's use of accelerated approval.

Our findings from this review indicate FDA should take further action. Therefore, we recommend that FDA:

Define specific factors that would require FDA's accelerated approval council to advise on certain drug applications

FDA's accelerated approval council, per statute, consists of FDA leadership across multiple centers, including at least three directors of review divisions or offices overseeing products approved via accelerated approval. The council is to work directly with product review teams to support the consistent and appropriate use of accelerated approval across FDA. It must meet at least three times a year.

FDA should define factors that, independently or combined, would require the council to meet and participate in certain drug application reviews. This OIG evaluation identified three potential factors:

- when FDA's review team does not reach consensus,
- when an advisory committee raises significant concerns (e.g., that clinical trial data do not support a drug's approval), and
- when a sponsor relies upon analyses outside prespecified analysis plans to support approval.

Although FDA should consider and could adopt these three factors, it might identify other factors that, like these, increase the risk associated with approving a drug for which clinical benefit is not confirmed. FDA should include those in a list of factors that warrant the council's review of a drug application.

Requiring the council to review drug applications with these FDA-defined factors can help FDA fulfill its statutory obligation to support consistent and appropriate use of accelerated approval. By engaging the council to assist with particularly challenging accelerated approval reviews, a broader group of FDA leaders, who may have perspectives outside of those within the center reviewing the drugs, will have visibility and input in accelerated approval decisions. FDA may choose to involve a subset of council members as it deems most appropriate or efficient.

Furthermore, FDA could also use the council's required annual report to provide greater transparency, to the extent appropriate, on efforts that the council undertakes to support consistent and appropriate use of accelerated approval. This increased transparency could bolster confidence in FDA's decision making.

Take steps to ensure appropriate documentation of meetings with sponsors in drug approval administrative files

As part of FDA's effort to improve documentation of the review and decision making associated with accelerated approvals, FDA should clarify in its procedures which types of meetings should be documented in a drug's administrative file and the appropriate manner in which they should be documented. Indeed, FDA reported to Congress that it has efforts underway that may be in line with this recommendation.

FDA efforts here can help uphold scientific integrity and strengthen transparency when concerns surface about FDA decisions. FDA's *Staff Manual Guide on Scientific Integrity* states that proper records management is an integral part of scientific integrity. Accordingly, a drug application's administrative file must document every significant decision—and the basis for that decision, including relevant meeting minutes.

AGENCY COMMENTS AND OIG RESPONSE

FDA did not concur with the first recommendation. FDA stated that requiring the accelerated approval council to evaluate specific drug applications would be inefficient. It further stated that, if a Center Director evaluated a drug application as part of the council, that Center Director would be unable to act as a designee of the Commissioner in cases where a drug sponsor appeals FDA's decision to withdraw that drug. FDA stated that it would concur with having Center leadership, rather than the accelerated approval council, advise on certain accelerated approval applications.

We continue to believe that drug applications warrant additional scrutiny before approval when both FDA's own reviewers and its advisory committees raise concerns. The accelerated approval council, which is charged to "engage with product review teams to support the consistent and appropriate use of accelerated approval" is an ideal venue to offer such scrutiny, as well as public accountability given its reporting requirement. Given that our evaluation identified three drugs that raised concerns, the burden on the council in reviewing specific drug applications seems unlikely to be excessive. Additionally, our recommendation accommodates FDA's need for flexibility for how it allows FDA to call on a subset of the council's membership as it sees fit. We ask that, in its Final Management Decision, FDA reconsider its position on our first recommendation.

Regarding the second recommendation, FDA concurred that it is important to ensure appropriate documentation of meetings with sponsors in drug approval administrative files. Additionally, FDA stated that it has recently taken steps to clarify appropriate documentation of substantive communications between the agency and external entities, including by updating internal procedures. FDA believes that these existing processes are sufficient and does not think additional steps are necessary at this time. Our recommendation acknowledges that FDA has steps underway in line with the recommendation. We ask that, in its Final Management Decision, FDA provide updates and documentation on its internal procedures.

For the full text of FDA's comments, see Appendix A.

DETAILED METHODOLOGY

Sample

Our sample of 24 approvals through the accelerated approval pathway was composed of 19 drugs and 5 biologics. FDA's CDER approved each drug between 1992 and 2022. The total population of drugs granted accelerated approval was 278, which we identified using public data from FDA's website. We took both a purposive sample and a random sample of these drugs. We purposively sampled 10 drugs with approvals identified as concerning during interviews with stakeholders. These included aducanumab, eteplirsen, and HPC (to reduce the risk of preterm birth in certain women). We then took a random sample of 14 of the remaining 268 approved drugs. Seven of these 14 were indicated to treat cancer and 7 were indicated to treat something other than cancer. This approach allowed us to include drugs in our sample that FDA approved to treat a variety of diseases and conditions while acknowledging that most accelerated approval drugs up to that date had been indicated to treat cancer.

Data Sources

This study used the following data sources: (1) administrative files for the 24 drugs in our sample and (2) advisory committee documentation for any of the 24 drugs for which FDA convened a committee. We also reviewed relevant FDA policies and procedures.

We requested from FDA the administrative files for the 24 drugs in our sample. These files officially document the basis of FDA's approval decisions as well as the recommendations and decisions of individual employees. The administrative files for the drugs in our sample typically contained items such as an approval letter, reviews (e.g., medical reviews, statistical reviews, and chemistry reviews), and administrative and/or correspondence documents.

We also requested from FDA the advisory committee documentation for any of the 24 drugs for which FDA had convened a committee. This documentation included advisory committee agendas and minutes, which documented discussions and committee votes.

Data Analysis

We focused our review on determining whether variation or outliers existed at certain points in the accelerated approval pathway including:

- Whether original analysis plans were followed: Whenever possible, we used FDA's history of a drug's development to determine whether a sponsor had deviated from its original clinical research plan, such as whether a sponsor switched to focusing on a surrogate endpoint that was not its original target.
- Whether scientific disputes and informal disagreements arose: We focused on FDA's cross-discipline review team, which is composed of clinical and statistical reviewers, with the Director of the CDER division leading the review. We considered informal disagreements when any reviewer concluded that a drug should not be approved but did not file a formal dispute; formal disputes were documented as such in the files. We also focused on advisory committees, using meeting agendas and minutes, to determine the extent to which the committees voted on or discussed specific questions, as well as the outcome of any votes.
- When meetings were held between FDA and sponsors: We reviewed all meetings documented in administrative files and all references to meetings in administrative files.

This review focused on a sample of 24 drugs that went through the accelerated approval pathway; it is not a compliance review. We did not independently assess decisions made by FDA.

APPENDICES

Appendix A: Agency Comments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

DATE: October 22, 2024

TO: Juliet T. Hodgkins, Principal Deputy Inspector General

FROM: Senior Advisor, Office of Economics and Analysis

SUBJECT: FDA's General Comments to OIG's Draft Report Titled "*How FDA Used Its Accelerated Approval Pathway Raised Concerns in 3 of 24 Drugs Reviewed*" (OEI-01-21-00400).

Enclosed are the Food and Drug Administration's general comments to the Office of Inspector General's OIG Draft Report, "*How FDA Used Its Accelerated Approval Pathway Raised Concerns in 3 of 24 Drugs Reviewed*" (OEI-01-21-00400).

We appreciate the opportunity to review and comment on this draft report prior to publication.

Lisa Rovin, J.D.
Senior Advisor, Office of Economics and Analysis

Attachment

FDA's General Comments to OIG's Draft Report, *How FDA Used Its Accelerated Approval Pathway Raised Concerns in 3 of 24 Drugs Reviewed*

The Food and Drug Administration appreciates the opportunity to review and comment on this draft report.

Recommendation 1

FDA should define specific factors that would require FDA's accelerated approval council to advise on certain drug applications.

FDA Response

FDA does not concur with OIG's recommendation. FDA would concur with having Center leadership, rather than the accelerated approval council, advise on certain accelerated approval applications if they meet certain factors.

The accelerated approval council consists of senior leaders from multiple centers, CDER, CBER, and OCE. Involving leaders from other Centers in a wide array of cases could waste scarce agency resources because they would need to spend considerable resources to evaluate a specific drug application before another Center. Additionally, if the accelerated approval council is responsible for advising on all drug applications whenever FDA's review teams do not reach a consensus or an advisory committee raises significant concerns, including after an application has been approved, consulting the accelerated approval council could prevent Center Directors on the council from later assisting the Commissioner in an appeal relating to proposed withdrawal of the application. Under the new FDORA process, if a Center proposes to withdraw approval of a drug approved under accelerated approval and the company appeals, this appeal may be decided by the Commissioner or by "a designee of the Commissioner who has not participated in the proposed withdrawal of approval." If a Center Director is consulted on a decision relating to a proposed withdrawal as a member of the accelerated approval council, they may not be eligible to serve as designee. Notably, in the recent withdrawal proceedings for Pepaxto, which was approved under accelerated approval, the Commissioner designated the appeal decision to the CBER Director, an option that FDA found useful. The proposed recommendation, if implemented, could remove this option.

Recommendation 2

FDA should take steps to ensure appropriate documentation of meetings with sponsors in drug approval administrative files.

FDA Response

FDA concurs that it is important to ensure appropriate documentation of meetings with sponsors in drug approval administrative files. FDA has recently taken steps to clarify appropriate documentation of substantive communications between FDA and external entities, including by updating internal procedures. FDA believes these existing processes are sufficient to ensure appropriate documentation moving forward, and we do not think additional steps are necessary at this time.

Appendix B: Details on Our Sample of Drugs

Our review revealed that for 20 of the 24 drugs in our sample, the research and analysis approach to demonstrating efficacy did not change from its originally intended goals. One drug's documentation did not allow for this assessment. For 21 of the 24 drugs, there were no formal scientific disputes or informal disagreements. For the 7 of 24 drugs in our sample that convened an advisory committee, 6 committees supported approval (1 advisory committee meeting covered 2 applications of the same drug). See table below for additional details on each drug in our sample.

	Drug Name and Application Type	Indication	Approval Year	Meeting Count	Did the sponsor analyze a surrogate endpoint (vs. clinical endpoint) when first seeking FDA approval?	Was an advisory committee convened for the drug and did it support the drug's approval?
1	ZALCITABINE, *NDA*	HIV	1992	0	✗	NO; N/A
2	MIDODRINE HYDROCHLORIDE, *NDA*	BLOOD PRESSURE	1996	1	✓	NO; N/A
3	MAFENIDE ACETATE, *NDA*	BACTERIAL INFECTION	1998	4	✓	YES; NO
4	INFLIXIMAB, *BLA*	CROHN'S DISEASE	1998	1	N/A	YES; YES
5	CIPROFLOXACIN (Supplement 38), *NDA*	ANTHRAX	2000	4	✓	YES; YES
6	CIPROFLOXACIN (Supplement 27), *NDA*	ANTHRAX	2000	4	✓	YES; YES
7	AGALSIDASE BETA, *BLA*	FABRY DISEASE	2003	0	✓	YES; YES
8	THALIDOMIDE, *NDA*	CANCER	2006	2	✓	NO; N/A
9	PRALATREXATE, *NDA*	CANCER	2009	0	✓	YES; YES
10	HYDROXY-PROGESTERONE CAPROATE (HPC), *NDA*	SPONTANEOUS PRETERM BIRTH	2011	11	✓	YES; YES
11	POMALIDOMIDE, *NDA*	CANCER	2013	7	✓	NO; N/A
12	PERTUZUMAB (Supplement 51), *BLA*	CANCER	2013	2	✓	YES; YES

	Drug Name and Application Type	Indication	Approval Year	Meeting Count	Did the sponsor analyze a surrogate endpoint (vs. clinical endpoint) when first seeking FDA approval?	Was an advisory committee convened for the drug and did it support the drug's approval?
13	ATEZOLIZUMAB, *BLA*	CANCER	2016	5	✓	NO; N/A
14	ETEPLIRSEN, *NDA*	DUCHENNE MUSCULAR DYSTROPHY	2016	18	✗	YES; NO
15	BRIGATINIB, *NDA*	CANCER	2017	15	✓	NO; N/A
16	BENZNIDAZOLE, *NDA*	CHAGAS DISEASE	2017	8	✓	NO; N/A
17	GOLODIRSEN, *NDA*	DUCHENNE MUSCULAR DYSTROPHY	2019	3	✓	NO; N/A
18	SELPERCATINIB (Supplement 8), *NDA*	CANCER	2020	2	✓	NO; N/A
19	VILTOLARSEN, *NDA*	DUCHENNE MUSCULAR DYSTROPHY	2020	3	✓	NO; N/A
20	PRALSETINIB, *NDA*	CANCER	2020	4	✓	NO; N/A
21	CASIMERSEN, *NDA*	DUCHENNE MUSUCLAR DYSTROPHY	2021	6	✓	NO; N/A
22	ADUCANUMAB-AVWA, *BLA*	ALZHEIMER'S DISEASE	2021	8	✗	YES; NO
23	BUDESONIDE, *NDA*	AUTOIMMUNE DEFICIENCY	2021	1	✓	NO; N/A
24	ALPELISIB, *NDA*	PIK3CA-RELATED OVERGROWTH SPECTRUM	2022	3	✓	NO; N/A

Source: OIG analysis of FDA administrative files, 2023.

ENDNOTES

[1] U.S. House Committee on Oversight and Reform and Committee on Energy and Commerce, *The High Price of Aduhelm's Approval: An Investigation into FDA's Atypical Review Process and Biogen's Aggressive Launch Plans*, December 2022. Accessed at https://democrats-energycommerce.house.gov/sites/evo-subsites/democrats-energycommerce.house.gov/files/documents/Final%20Aduhelm%20Report_12.29.22.pdf on June 19, 2024.

[2] Federal Food, Drug, and Cosmetic Act (FD&C Act) § 506(c)(1)(A). The statute allows for accelerated approval "upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit . . . taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

[3] FDA, "New Drug Application (NDA)." Accessed at https://www.fda.gov/drugs/types-applications/new-drug-application-nda on July 5, 2024.

[4] Under Section 351, licenses for biologics have been used only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. Potency has long been interpreted to include effectiveness. 21 CFR § 600.3(n).

[5] FDA, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, Draft Guidance for Industry*, Dec. 2019, p. 2. Accessed at https://www.fda.gov/media/133660/download on Nov. 19, 2021.

[6] FDA, *Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics*, May 2014, p. 18. Accessed at https://www.fda.gov/media/86377/download on Nov. 19, 2021.

[7] Institute for Clinical and Economic Review, *Potential Policy Reforms to Strengthen the Accelerated Approval Pathway*, Aug. 24, 2021. Accessed at https://icer.org/wp-content/uploads/2021/08/Kaltenboeck.-JCER.-2021.pdf on Sept. 25, 2023.

[8] Consolidated Appropriations Act of 2023 §§ 3210(a)(1)(D) and 3210(a)(1)(F).

[9] Ibid § 3210(e).

[10] FDA, *Accelerated Approval Council Activities Report CY 2023*. Accessed at https://www.fda.gov/media/174154/download on Mar. 1, 2024.

[11] FDA, *FDA Staff Manual Guides, Volume IV—Agency Program Directives, General or Multidiscipline, Dispute Resolution, Scientific Dispute Resolution at FDA*. Accessed at https://www.fda.gov/media/79659/download on Oct. 7, 2021.

[12] 21 USC § 360bbb–1 and FDA, *Formal Dispute Resolution: Sponsor Appeals Above the Division Level, Guidance for Industry and Review Staff,* Nov. 2017. Accessed at https://www.fda.gov/media/85613/download on Jan. 18, 2024.

[13] 21 CFR § 14.5.

[14] FDA, *Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings.* Accessed at https://www.fda.gov/media/75426/download.

[15] FDA, *Committees and Meeting Materials*, accessed at https://www.fda.gov/advisory-committees/committees-and-meeting-materials on Feb. 17, 2022; and *Learn About FDA Advisory Committees*, accessed at https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees on Nov. 22, 2021.

[16] FDA, *Advisory Committees: Critical to the FDA's Product Review Process*. Accessed at https://www.fda.gov/drugs/information-consumers-and-patients-drugs/advisory-committees-critical-fdas-product-review-process on Dec. 6, 2021.

[17] FDA, *Learn About FDA Advisory Committees*. Accessed at https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees on Nov. 22, 2021.

[18] 21 CFR § 312.47.

[19] 21 CFR § 312.82.

[20] FDA, *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*, December 2017. Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-communication-between-ind-sponsors-and-fda-during-drug-development on Oct. 4, 2021.

[21] FDA, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, December 2017. Accessed at https://www.fda.gov/media/109951/download on July 23, 2024

[22] FDA's administrative files contain all documents pertaining to a particular administrative action, including internal working memoranda and recommendations. 21 CFR § 10.3(a).

[23] FDA, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, December 2017. Accessed at https://www.fda.gov/media/109951/download on July 23, 2024.

[24] U.S. House Committee on Oversight and Reform and Committee on Energy and Commerce, *The High Price of Aduhelm's Approval: An Investigation into FDA's Atypical Review Process and Biogen's Aggressive Launch Plans*, December 2022. Accessed at https://democrats-energycommerce.house.gov/sites/evo-subsites/democrats-energycommerce.house.gov/files/documents/Final%20Aduhelm%20Report_12.29.22.pdf on June 19, 2024.

[25] OIG, *Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns* (OEI-01-21-00401), Sept. 29, 2022.

[26] 21 CFR § 10.70.

[27] Throughout this report, use of the drug name "hydroxyprogesterone caproate (HPC)" refers to HPC that was previously FDA-approved to reduce the risk of preterm birth in certain women. This drug product was marketed under the brand name Makena.

[28] FDA has latitude in reviewing drugs through the accelerated approval pathway. Such latitude does not imply noncompliance with law or regulation.

[29] FDA, *Guidance for Industry: E9 Statistical Principles for Clinical Trials*, September 1998. Accessed at https://www.fda.gov/media/71336/download on Jan. 17, 2024.

[30] FDA, *Center Director Decisional Memo*, July 14, 2016. Accessed as part of eteplirsen summary review file at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf on July 5, 2024.

[31] The official vote tally was eight "no" votes to five "yes" votes. One member who voted "no" stated that he had pressed the wrong voting button and that his vote should be changed to "yes" for the record.

[32] FDA, *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*, December 2017. Accessed at https://www.fda.gov/files/drugs/published/Best-Practices-for-Communication-Between-IND-Sponsors-and-FDA-During-Drug-Development.pdf on July 23, 2024. This guidance pertains to formal meetings between FDA and sponsors.

[33] 21 CFR § 10.70.

[34] The congressional committees gained access to documentation that went far beyond the administrative file we reviewed.

[35] U.S. House Committee on Oversight and Reform and Committee on Energy and Commerce, *The High Price of Aduhelm's Approval: An Investigation into FDA's Atypical Review Process and Biogen's Aggressive Launch Plans*, December 2022. Accessed at https://democrats-energycommerce.house.gov/sites/evo-subsites/democrats-energycommerce.house.gov/files/documents/Final%20Aduhelm%20Report_12.29.22.pdf on June 19, 2024.

[36] Because there are not similar investigations or other reporting for the other 23 drugs in our sample, we have no way of knowing whether the administrative files for those drugs were also missing documentation entirely for any meetings.

[37] FDA, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, December 2017. Accessed at https://www.fda.gov/media/109951/download on July 23, 2024. FDA updated this guidance in September 2023. The updated guidance can be found at https://www.fda.gov/media/172311/download.

[38] *The New York Times*, "Biogen Abandons Its Controversial Alzheimer's Drug Aduhelm," Jan. 31, 2024. Accessed at https://www.nytimes.com/2024/01/31/business/biogen-alzheimers-aduhelm.html on Sept. 6, 2024.

[39] Centers for Medicare & Medicaid Services, "Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease," Apr. 7, 2022. Accessed at https://www.cms.gov/newsroom/fact-sheets/medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment-alzheimers-disease on Sept. 6, 2024.

[40] FDA, "FDA Grants Accelerated Approval for Alzheimer's Disease Treatment," Jan. 6, 2023. Accessed at https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease on Sept. 6, 2024.

[41] FDA, "FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval," July 6, 2023. Accessed at https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval on Sept. 6, 2024.

[42] FDA, "FDA approves treatment for adults with Alzheimer's disease," July 2, 2024. Accessed at https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease on Sept. 6, 2024.

[43] Regulatory Focus, "Califf skates through nomination hearing," Dec. 2021. Accessed at https://www.raps.org/news-and-articles/news-articles/2021/12/califf-skates-through-nomination-hearing on June 14, 2024.

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