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Building Public Trust in Scientific Decision Making through Expert Advisory Committees:

Lessons from the FDA

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Harvard Medical School

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FOREWORD

On behalf of the IBM Center for The Business of Government, we are pleased to release this new report, Building Public Trust in Scientific Decision Making through Expert Advisory Committees: Lessons from the FDA, by Joseph Daval and Aaron Kesselheim with Harvard Medical School and Brigham and Women's Hospital.

When faced with difficult decisions about new drugs or medical devices, the Food and Drug Administration (FDA) is authorized to consult with advisory committees of independent experts. Advisory committees provide critical scientific insights and credibility for FDA efficacy and safety determinations.

Leveraging data on the frequency, outcomes, and deliberative process of FDA advisory committees, this new report describes the impact of expert advisory committees on FDA decision making. The research discussed the roles that expert advisors play in this essential public health agency, and the report makes evidence-based recommendations that policymakers can implement to make advisory committees optimally useful for the FDA. The FDA case serves as a framework for recommendations about how other expert agencies can best engage with expert independent advisory committees.

DANIEL J. CHENOK

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We hope that this report helps leaders in science-focused agencies to leverage expert advice in a way that informs and improves decision making.

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INTRODUCTION

When federal agencies develop policy or make regulatory decisions, they often consult external advisory committees—panels convened to advise agency decision makers.

Expert advisory committees, comprised primarily of advisors with technical qualifications in a certain subject area, frequently convene in advance of key decisions at scientific agencies. By providing independent recommendations to agency decision makers in a transparent public forum, such committees can bolster trust in the integrity of the agency's processes and lend credibility to its decisions.

Using the Food and Drug Administration (FDA) as a case study, this report evaluates the use of advisory committees by expert scientific regulatory agencies. Drawing from empirical findings on FDA's use of advisory committees and a comparative analysis of advisory committee procedures at the Centers for Disease Control and Prevention (CDC), Environmental Protection Agency (EPA), and Centers for Medicare & Medicaid Services (CMS), the report distills practices implementable through policy reforms at FDA and elsewhere. Specifically, the study identifies the following characteristics as essential to supporting the effectiveness of independent expert advice in regulatory settings:

- Consistency in which issues are reviewed by advisory committees
- Reliable wording of questions presented to the advisors
- Sufficient time for free deliberation among advisors
- Availability of procedures for thorough explanation and clarification in the case of disagreement between the agency and its advisors
- Clear understanding by the advisors of the agency's proposed regulatory action

By taking steps to follow the above principles, agencies making policy on technical scientific matters can improve the usefulness of advisors while maintaining public trust.

The research and recommendations presented here draw from the context of expert scientific agencies consulting independent expert advisors. The report focuses on technical expertise in scientific contexts due to the unique position that science-based agencies occupy among federal administrative agencies. Broadly speaking, such agencies (including FDA, EPA, CMS, CDC) share certain characteristics.[1] They make time-sensitive technical decisions with widespread effects on the health and well-being of populations, often based on imperfect information and facing pressure from industry actors. Their wide ambits—including air quality standards (EPA), drug approvals (FDA), coverage determinations (CMS), and vaccine recommendations (CDC)—all relate directly to public health. For this reason, their actions rely on public trust, a widely acknowledged cornerstone of U.S. public health policy.

1. Of the four agencies, CDC arguably plays the least "regulatory" role, because its vaccine recommendations are merely guidance for states and other policymakers. However, its public health mission and scientific remit were sufficiently similar with the others to merit inclusion.

Scientific agencies frequently explain their decisions by reference to rigorous scientific methods, multiple rounds of peer review, and the results of studies such as clinical trials. Political interference can obstruct their activities and erode trust, as can undue industry influence. Expert advisory committees, in these settings, can be invaluable tools to promote trust, transparency, and legitimacy. In addition to a thorough assessment of these issues in the FDA context, the fact that these agencies share broadly similar mandates, rely on similar methods, and face similar obstacles allows a limited comparative analysis on how they can best leverage expert advice.

This analysis does not address the use of expert advisory committees in nonscientific settings such as immigration or economic policy, where considerations may differ with regard to how experts can best support agency policy, or nontechnical advisory committees such as those comprised primarily of industry representatives. These advisory committees may serve important purposes, such as helping agencies to understand the priorities of the interested public in a transparent setting, but the question of how to evaluate and optimize their use falls beyond the scope of the issues addressed here.

Background: The Evolution of Advisory Committees at FDA

The Food and Drug Administration plays numerous essential public health roles, of which perhaps the most prominent is reviewing evidence relating to the efficacy and safety of new drugs and medical devices before they can be made available on the U.S. market. Determining whether a product's benefits outweigh its risks for U.S. patients is frequently a complicated task with numerous competing considerations. To aid its decision making, the FDA has created 34 standing advisory committees of independent experts covering different subject matter areas that it can convene to offer input on key regulatory decisions.[2]

The physicians, researchers, statisticians, and other public health experts who comprise these panels offer discussion and recommendations on whether data support product approval, whether various safety actions should be taken (such as drug labeling changes to incorporate new warnings), and the appropriateness of new FDA policies (such as study requirements for drugs in a certain class). While the FDA is not required to follow advisory committee recommendations, FDA decisions aligned in 78 percent of cases from 2008-2015,[3] and greater consensus in favor of approval among the advisory committee members corresponded with the likelihood of a concordant FDA decision from 1997-2006.[4] Advisory committees remain integral to FDA decision making, although their use has decreased in recent years, as discussed in this paper.

With the emergence of COVID-19, advisory committees now play an even more important role at FDA. After some missteps early in the pandemic, the credibility and trustworthiness of FDA decisions came increasingly under scrutiny. In this context, the support that advisory committees provided for regulatory legitimacy and their avenue for engaging the expert and non-expert public in FDA decisions proved essential, particularly around approval of new vaccines and booster schedules.

FDA faces a period of heightened scrutiny and skepticism from both experts and nonexperts. Public confidence in FDA is reportedly at low levels,[5] and pervasive vaccine skepticism illustrates the consequences of decreased trust in federal public health agencies.[6] Advisory committees can play a central role in changing this dynamic in numerous ways. First, when the FDA makes impactful decisions without first consulting with an advisory committee, it can raise the risk of perceived inappropriate political influence. In March of 2020, FDA hastily issued an emergency use authorization (EUA) for hydroxychloroquine to treat COVID-19 without convening an advisory committee, and despite a lack of reliable evidence that it reduced mortality or morbidity.[7] The move was widely perceived as being driven by the exigencies of the Trump administration, contributing to mistrust in other FDA COVID-19-related decisions around the time (the EUA was revoked just six weeks later). By contrast, the FDA very quickly convened advisory committees in December 2020 to discuss the recently obtained data on the Pfizer-BioNTech and Moderna COVID-19 vaccines, which helped support more widespread acceptance of the emergency use authorization of those products.

2. Although this report focuses primarily on advisory committees that offer recommendations on specific medical products, other FDA advisory committees advise on other product areas, such as tobacco, as well as the development of FDA policy or issues that cut across product areas, such as the Risk Communication Advisory Committee and the Patient Engagement Advisory Committee.
3. Zhang, Audrey, Jason Schwartz, and Joseph Ross. Association between Food and Drug Administration advisory committee recommendations and agency actions, 2008–2015. Milbank Q 2019;97:796-819.
4. Lavertu, Stéphane, and David Weimer. Federal advisory committees, policy expertise, and the approval of drugs and medical devices at the FDA. J Pub Admin Res Theory 2010;21:211-237.
5. Simmons-Duffin, Selena. Poll finds public health has a trust problem. NPR (May 13, 2021). Accessed Dec 5, 2023. https://www.npr.org/2021/05/13/996331692/poll-finds-public-health-has-a-trust-problem.
6. SteelFisher, Gillian, et al. Trust in US Federal, State, and Local Public Health Agencies During COVID-19: Responses and policy implications. Health Affairs 2023;42(3):328-337.
7. Thomson, Kyle, Herschel Nachlis. Emergency use authorizations during the COVID-19 pandemic: lessons from hydroxychloroquine for vaccine authorization and approval. *JAMA* 2020;324(13):1282-1283. .

Second, when the FDA disagrees with the scientific insights brought up during advisory committee meetings, substantial reputational harm can result if such insights are inadequately addressed. For example, the FDA in 2021 approved the Alzheimer's drug aducanumab (Aduhelm) after a heavily scrutinized advisory committee meeting in which no member of the committee voted in favor of its approval.[8] The resulting outcry from medical, legal, and public health experts was unprecedented in FDA history. Although aducanumab ended up being rejected broadly in the U.S. market, this incident cast a shadow over FDA decision making related to other investigational Alzheimer's disease drugs.

Although the regulatory decisions on which advisory committees consult, such as whether to approve a drug, authorize a vaccine, or ban a medical device, can affect the health of millions of people—and have implications for billions of dollars in commerce—advisory committee use at FDA is largely unguided by formal process. FDA leadership decides whether to convene an advisory committee, whether to take their advice, and what questions to ask them. Under the Federal Advisory Committee Act, which imposes requirements and restrictions on the use of advisory committees by federal agencies, the transcript and other materials from the meetings must be made public. Although FDA follows these requirements, it does not routinely give reasons for deciding 1) whether to convene an advisory committee, 2) what questions to ask, and 3) what to do with the advice.[9] All of these considerations impact the quality of the scientific advice and the credibility imparted on the FDA by advisory committees.

History

FDA began consulting external advisors on its own initiative in the 1960s, with the aim of receiving scientific and technical advice on product evaluations.[10] In particular, FDA sought independent advice and assistance on new drug approvals in the wake of FDA's expanded premarket review authority for new drugs under the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act (FDCA), which required FDA to ascertain the effectiveness, as well as the safety, of drugs before approving them.[11] At the time, FDA lacked sufficient in-house expertise to evaluate product safety and efficacy, and advisors filled that gap in capacity.[12]

In addition to ad hoc consultations with advisors for prospective drug approvals, FDA initiated a formal, ongoing collaboration with panels of independent experts in the form of the Drug Efficacy Study Initiative (DESI)—a large-scale efficacy assessment of thousands of drugs approved from 1938-1962 on the basis of their safety alone. To accomplish this task, FDA sought the assistance of panels of expert advisors, contracting with the National Academy of Sciences and the National Research Council to create a multi-panel advisory committee for this purpose.[13] From 1966 to 1970, the panels reviewed over 4,000 drug formulations. The panels made categorical recommendations on the effectiveness of drugs, providing the basis for ineffective drugs' withdrawal by FDA from the market. FDA's current advisory system directly

8. November 6, 2020: Meeting of the peripheral and central nervous system drugs advisory committee meeting announcement. Accessed Dec 5, 2023. https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-meeting.
9. FDA sometimes acknowledges advisory committee recommendations in the context of the package of materials accompanying new drug approvals. In the case of the negative advisory committee vote in its approval of aducanumab (Aduhelm), it even published a short, separate response to some of the topics raised at the committee meeting. If the product is not approved, FDA does not respond to advisory committee recommendations.
10. Institute of Medicine 1992. Food and Drug Administration Advisory Committees. National Academies Press, 1992. [hereinafter "NAS Report"].
11. NAS Report, 37.
12. NAS Report, 47-48.
13. Carpenter, Daniel, Jeremy Greene, and Susan Moffit. *The Drug Efficacy Study and Its Manifold Legacies in FDA in the 21st Century* (ed. Holly Fernandez Lynch and I. Glenn Cohen).

descends from the National Academies' DESI model, where panelists make categorical recommendations on products using the available evidence, which FDA then tends to follow.[14]

Even after FDA gained the necessary technical expertise to evaluate efficacy in new drug applications, it continued consulting advisors on product evaluations, and in the 1970s FDA consolidated its advisory system into formal standing advisory committees.[15] This formalization occurred with the passage of the Federal Advisory Committee Act (FACA) in 1972.[16] The Act reflected Congress's concern, spurred by the proliferation of advisory committees after World War II, that many advisory committees were duplicative and wasteful, and were improperly influencing regulatory policy.[17] The explicit design and aim of FACA was therefore to restrict agency access to advisory committees overall, to publicize advisory influence on policy through transparency requirements, and to limit the influence of industry-favorable views on agency decisions.[18]

Congress appeared to recognize the value of advisory committees in FDA policymaking when it required extensive consultation between FDA and advisory committees in the 1976 Medical Device Amendments for approving, banning, and classifying medical devices.[19] The Act marks the first time Congress required FDA to use advisory committees in particular circumstances. These requirements were amended in 1990, so that FDA today retains substantially more discretion over whether to convene committees in decisions relating to medical devices.[20]

Four major reports between 1976 and 1990 dealt with the issue of FDA advisory committees, each recommending a number of reforms relating to when FDA should use advisory committees, how it should handle conflicts of interest, and committee procedures.[21] However, none of these reports led to substantial reforms to FDA's advisory committee system.

The most comprehensive report on FDA advisory committees, published in 1992, was commissioned by FDA Commissioner David Kessler, who "requested that the Institute of Medicine (IOM) examine the optimal use of FDA's advisory committees in product evaluation and in relation to agency management and agency accountability."[22] The report largely endorsed FDA's use of advisory committees at that time, but made a series of recommendations related to the usefulness and independence of the committees. Among other reforms, the report recommended:

- Consistently conducting votes on questions of importance[23]
- Updated and expanded criteria and procedures for handling conflicts of interest
- Regular reminders for advisory committee members evaluating drugs and biologics of FDA's regulatory standards (i.e., weighing risk/benefit and "substantial evidence" to support effectiveness claims)
- Uniform procedures across FDA for convening advisory committees

14. Schwartz, Jason. Fifty years of expert-advice—pharmaceutical regulation and the legacy of the drug efficacy study. *N Engl J Med*. 2016;375(21):2015-2017. https://www.nejm.org/doi/full/10.1056/NEJMp1609763.
15. NAS Report, 54-55.
16. Federal Advisory Committee Act Pub L 92—463 (1972).
17. Croley, Steven, and William Funk, The federal advisory committee act and good government. 1997;14 The Yale J on Regulation. 451, 458-460 [hereinafter "Croley and Funk"].
18. Croley and Funk, 460-65.
19. Dormer, Robert. Use of Advisory Committees by the Food and Drug Administration under the Medical Device Amendments. 40 *Food Drug Cosmetic Law Journal*, 103-111 (1985).
20. Merrill, Richard. The Architecture of Government Regulation of Medical Products. 82 *Va. Law Rev*. 1753-1866, 1821, n. 218 (1996).
21. NAS Report, 100-108.
22. NAS Report, page v.
23. NAS Report, 23-24.

The IOM issued another report in 2007 on FDA's regulation of prescription drugs, prompted by the withdrawal of rofecoxib (Vioxx) from the market in 2004 due to increased risk of heart attacks that ultimately resulted in an estimated 38,000 deaths.[24] In response to this crisis, the report recommended that FDA "have its advisory committees review *all* [new molecular entities] either prior to approval or soon after approval."[25] (emphasis added). The IOM report further recommended that FDA "establish a requirement that a substantial majority" of its advisors "be free of significant financial involvement with companies whose interests may be affected" by their recommendations.[26]

Non-Technical Membership

FDA advisory committees usually include participation by members representing the interests of industry, patients, or the general public, in addition to members appointed by virtue of medical, statistical, or scientific expertise. FDA has formally invited participation by nontechnical committee members since (at least) the 1976 Medical Device Amendments, which required the appointment "as nonvoting members" of two nontechnical members to advise on the regulatory classification of medical devices, including "a representative of consumer interests and a representative of interests of the device manufacturing industry."[27] The Amendments also created a nontechnical committee comprised of representatives of government, industry, the medical community, and the general public to advise on regulations relating to manufacturing requirements.[28]

In the 1997 FDA Modernization Act amendments to the Food, Drug, and Cosmetic Act, Congress provided that in addition to the standard expert members, the FDA "shall" appoint to each committee "a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel." The FDA interpreted the legislation as permitting the Commissioner, in his or her discretion, to appoint these representatives "to supplement the core membership on an ad hoc basis." As to the contribution to committee votes, FDA distinguished between "core members" (i.e., voting members appointed "based on their scientific or technical expertise") and "ad hoc committee members who are representatives of consumer or patient interests" who may vote only if they possess "the requisite scientific or technical expertise" and their participation is "not prevented by conflict of interest laws and regulations."[29] This policy followed from FDA's existing practice of allowing consumer representatives to vote on human drug committees if they had technical qualifications.[30]

24. Prakash, Snigdha, and Vikki Valentine. Timeline: The rise and fall of Vioxx. Nov 10, 2007. Accessed Dec 5, 2023. https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx.
25. Institute of Medicine. 2007. The Future of Drug Safety: Promoting and protecting the health of the public. Washington, D.C.: The National Academies Press, 9. [Hereinafter "2007 Report"].
26. 2007 Report, at 10.
27. 1976 Medical Device Amendments 513(b)(2).
28. 1976 Medical Device Amendments 520(f)(3).
29. Guidance for Industry. Advisory Committees: Implementing section 120 of the food and drug administration modernization act of 1997 (1998).
30. Lakshmanan, Joseph. Nontechnical Representation on the FDA's Advisory Committees: Can there be more? 44 *Food & Drug Law Journal*, 181, 181 n. 2 (1989).

Conflicts of Interest

Since the 1990s, FDA's conflict of interest procedures and requirements for advisory committee members have changed multiple times.[31] Major changes and regulations include:

- Federal law generally prohibits "rendering . . . advice" in government decisions if the advisors have a financial conflict of interest, unless a waiver is granted on the basis that "the need for the individual's services outweighs the potential for a conflict of interest."[32]
- The FDA Modernization Amendments in 1997 prevented advisors from voting if the advisor or a family member "could gain financially from the advice," although a waiver could be granted if the conflict is disclosed and the waiver "is necessary to afford the panel essential expertise."[33]
- In 2000, FDA published guidance with criteria for when it would grant a waiver for advisory committee conflicts. The guidance employed multiple tables identifying different factors, including the type and degree of financial interest and type of meeting, with the aim of achieving consistency across the agency in how waivers were issued.[34]
- After the 2004 Vioxx crisis, the FDA Amendments of 2007 instituted a stricter approach by capping the overall portion of advisors for which FDA could provide waivers.[35]
- In its 2008 guidance implementing the new provisions, FDA sought to correct the perceived shortcomings of its 2000 waiver criteria by creating more rigorous and streamlined procedures for consistently identifying and granting waivers when appropriate.[36]
- In 2012, Congress removed the cap on the overall portion of advisors who could be granted waivers, as well as the FDCA's specific prohibition on conflicts for advisors.[37] This legislation left in place the existing general federal prohibition on advisor financial conflicts without waivers, as well as the requirement that all waivers be published online with the "type, nature, and magnitude" of the financial interest, as well as the FDA's reasons for granting the waiver.[38]

In current practice, there is no limit on the number of waivers FDA can grant for conflicts of interest, and FDA must post all waivers on its website.[39] However, FDA data show that the portion of FDA advisors participating with waivers remained below 1 percent from 2012-2018.[40] FDA screens advisors for conflicts before they are appointed, collecting information on potential members' financial interests as part of the online application for membership on an FDA advisory committee.[41]

31. This section discusses conflicts regulated under 18 USC 208, and not "Section 502" conflicts, which relate to financial or other relationships that could create the *appearance* of a conflict. One study found section 502 conflicts to be much more common, and FDA in 2016 considered requiring disclosure of these as well. Xu J, Emenanjo O, Ortwerth M & Lurie P. Association of appearance of conflicts of interest with voting behavior at FDA advisory committee meetings—a cross-sectional study. *JAMA* Internal Med. 2017;177(7):1038-1040.
32. 18 USC § 208.
33. FDCA 505(n)(4).
34. FDA Guidance on conflict of interest for advisory committee members, consultants and experts. (February 2000). Accessed Dec 6, 2023. http://web.archive.org/web/20010618055137/http://www.fda.gov/oc/advisory/conflictofinterest/guidance.html.
35. FDA Amendments Act of 2007, § 701.
36. Guidance for the public, FDA advisory committee members, and FDA staff on procedures for determining conflict of interest and eligibility for participation in FDA advisory committees. (August 2008).
37. Wood, Susan, and Jillian Mador. Policy Forum: Uncapping Conflict of Interest? Science 2013;340(6137):1172-1173.
38. FDCA § 712(c)(1). (21 USC § 379d-1).
39. Guidance for the public, FDA advisory committee members, and FDA staff: public availability of advisory committee members' financial interest information and waivers. (March 2014). Accessed Dec 6, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/public-availability-advisory-committee-members-financial-interest-information-and-waivers#_ftn7.
40. Lurie, Peter. Suggestions for improving conflict of interest processes in the U.S. Food and Drug Administration advisory committees—past imperfect. *JAMA* Internal Med. 2018;178(7):997-998.
41. U.S. FDA. Applying for membership on FDA advisory committees. (March 27, 2018). Accessed Dec 6, 2023. https://www.fda.gov/advisory-committees/advisory-committee-membership/applying-membership-fda-advisory-committees.

Meeting Procedures

As of 2023, FDA lists on its website 34 standing advisory committees, including 18 for human drugs, five for biologics, one for medical devices split into 18 panels, and 10 others. Each committee has a charter that must be renewed every two years. Meetings are announced in advance in the Federal Register, and have traditionally been held in person at the FDA's offices in Maryland. Since the COVID-19 pandemic, most meetings have taken place virtually, with live streaming and posting on YouTube. The meeting itself must be announced at least two weeks in advance, with briefing materials sent to committee members 2-3 weeks in advance and posted online at least 48 hours in advance.[42] Additional meeting materials, including the briefings, presentations, transcript, minutes, and roster, are made publicly available on the FDA website after the meeting, as required by the Federal Advisory Committee Act (FACA).

Officials at the relevant FDA Center set the meeting agenda, which typically includes presentations by the product sponsor and the FDA, followed by questions, discussion, and voting on questions written by FDA staff. Voting is simultaneous and electronic, and usually followed by discussion. Meetings also typically include a public hearing portion lasting one hour, where private individuals who sign up in advance may speak for an allotted period of time.

42. Guidance: Advisory Committee Meetings—Preparation and Public Availability of Information Given to Advisory Committee Members. (2008).

Regulatory Framework for FDA Advisory Committees

The FDA's regulatory authority to protect consumers and promote public health derives primarily from the Food, Drug, and Cosmetic Act (FDCA). The FDCA frequently mentions—but rarely *requires* the use of—advisory committees in FDA's regulatory decision making. The FDCA explicitly contemplates advisory committees in multiple areas of FDA regulation, including prescription drugs, medical devices, manufacturing standards, and tobacco products (see Table 1).

In a few narrow circumstances, the FDCA requires consulting advisory committees. For example, FDA must consult advisory committees before issuing regulations on drug compounding, at the sponsor's request in expedited withdrawal proceedings for accelerated approval drugs, and for changing performance standards for medical devices if a petition is filed. The FDCA also requires that the Drug Safety and Risk Management Advisory Committee be consulted "at least biannually."

But while the FDCA requires consultation with advisory committees in some circumstances, the Act leaves to the Commissioner's discretion whether to convene an advisory committee to review routine actions relating to prescription drugs, including review of drug approvals, supplemental indications, and safety actions. The FDCA contemplates that the FDA will establish expert advisory committees, that they will "meet regularly," and that they will provide "expert scientific advice and recommendations to the Secretary" relating to drug approvals. The Act further requires that FDA provide a "summary of reasons" for declining to refer certain drug or biologic applications to an advisory committee in its decision letter to the sponsor. However, federal law does not specify the circumstances under which a committee should, or must, be used in most circumstances, and for unapproved drugs this decision letter is not made public.

FDA regulations promulgated in 1979 state that the Commissioner retains discretion over whether to convene an advisory committee for any human prescription drug, and to set the meeting agenda. They also list "high priority" drug categories for referral to advisory committees, including drugs with a narrow benefit-risk profile and drugs that are the subject of "major scientific or public controversy." However, these priorities are functionally nonbinding and are not generally referred to when FDA declines to convene an advisory committee.

For decisions on medical devices as well, FDA generally retains discretion over whether to convene them. Although consultation with advisors was required under the Medical Device Amendments of 1976 for most regulatory decisions relating to medical devices, a 1990 law repealed this requirement.[43] Today, advisory committees for medical devices are required for rare classifications of pre-1976 devices, but not for general submissions, such as premarket approval applications for Class III devices.[44]

43. This requirement may never have been practical, given the large number of devices FDA reviews. Gibbs JN & Gibbs DA, PMA Advisory Panels: Do Their Votes Matter? Food & Drug Law Institute. (April/May 2019) Accessed Dec 6, 2023. https://www.fdli.org/2019/05/pma-advisory-panels-do-their-votes-matter/.
44. FDA Guidance: Procedures for meetings of the medical devices advisory committee: guidance for industry and food and drug administration staff. (Sept 2017).

Table 1. Summary of Federal Laws, Regulations, and Guidances Impacting Advisory Committee Function at the FDA

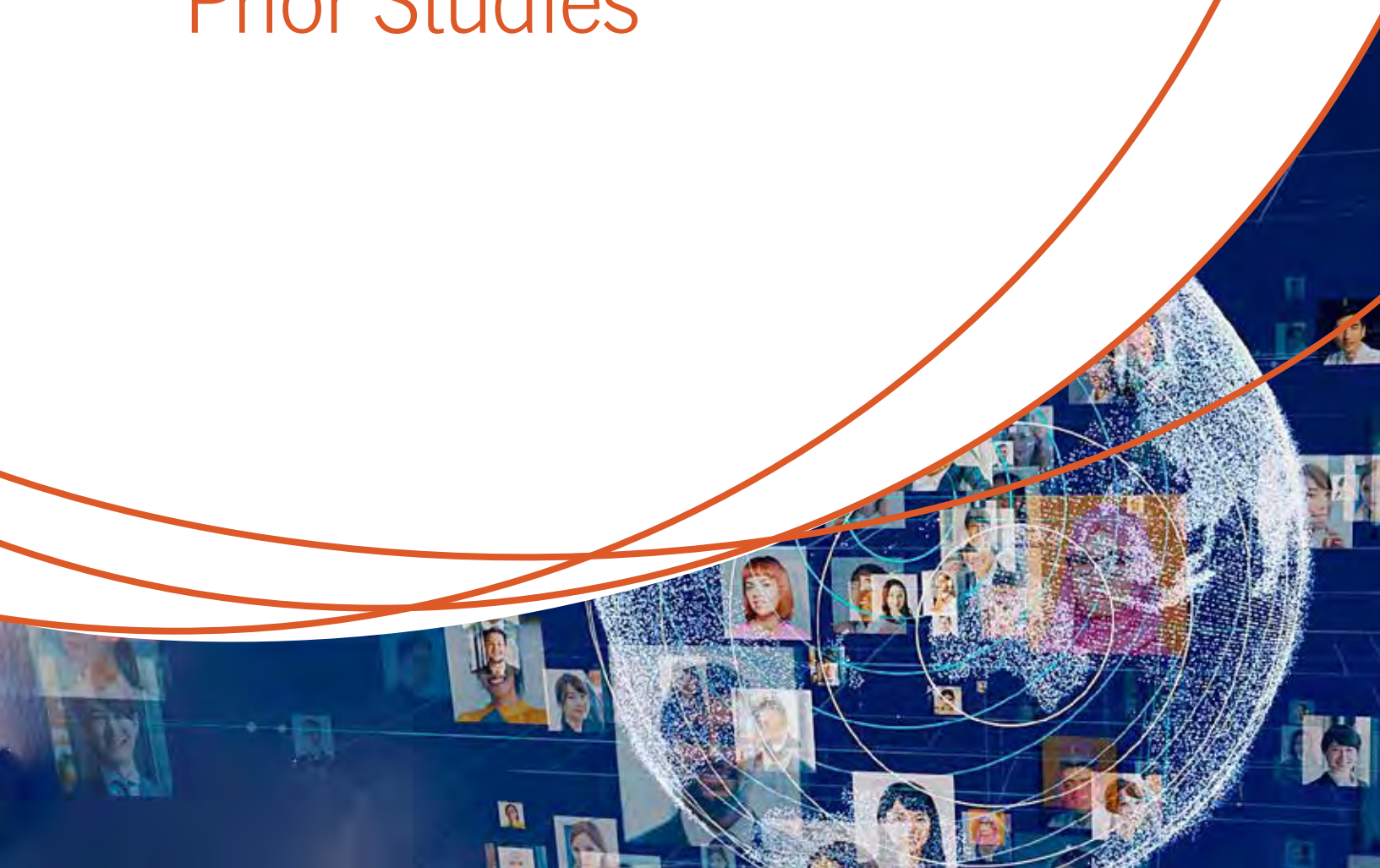
Federal Law	Effect
21 USC 355(n), enacted by the FDA Modernization Act of 1997[45]	FDA shall "establish" advisory committees to "meet regularly," and document the "rationale" for final agency decisions on their recommendations. The committees exist "for the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug."
21 USC 355(s), enacted by the FDA Amendments Act of 2007[46]	FDA must refer new drugs or biological product applications to advisory committees if the product includes no already approved active ingredient or provide a "summary of the reasons" for declining to do so.
10(b)-(c) of the Federal Advisory Committee Act of 1972, (5 U.S.C. App. 2)	Requires the public availability of all relevant documents used during advisory committee meetings, including meeting minutes verified by the chairperson
§ 3210 of Consolidated Appropriations Act, 2023	FDA must convene advisory committees at the request of the sponsor in expedited withdrawal proceedings for accelerated approval drugs.
21 USC 353a(c) FDCA (§ 503B(c)(2)), enacted by the FDA Modernization Act of 1997	Before issuing regulations on pharmacy compounding, "the secretary shall convene and consult an advisory committee on compounding."
21 USC § 355 (k)(4) (c), enacted by the FDA Amendments Act of 2007	"At least biannually, the Secretary shall seek recommendations from the Drug Safety and Risk Management Advisory Committee."
21 USC 360d(b)(5)(a), enacted by the Medical Device Amendments of 1976	When establishing, amending, or revoking performance standards for medical devices, FDA does not have to consult advisors unless someone petitions for them to do so.
§ 520 21 USC 360j, enacted by Medical Device Amendments of 1976	Creates advisory committees for setting current Good Manufacturing Practices (cGMPs) for medical devices, which FDA "shall" consult for recommendations before promulgating regulations
21 USC 379d-1, enacted by the FDA Safety and Innovation Act of 2012	Requires FDA to conduct outreach to potential committee members, disclosure of financial interests and rationale for including them anyway, as well as regular reports to Congress on FDA's use of advisory committees, and periodic review of guidance on advisory committees

45. Pub. L. 105–115, November 21, 1997, 111 Stat 2296.
46. PL 110–85, September 27, 2007, 121 Stat 823.

FDA Regulations	Effect
21 CFR § 14.160, promulgated 1979, Fed Reg 44, 73 (22365)	Establishes advisory committees for human prescription drugs
21 CFR § 14.171, promulgated 1979, Fed Reg 44, 73 (22365)	Reserves to the FDA Commissioner the discretion to convene an advisory committee for human prescription drugs and set its agenda Identifies "high-priority" categories of prescription drugs for advisory committee review, including new drug applications that represent: "Potential therapeutic advances" "Significant safety hazards" "Narrow benefit-risk considerations" "Novel delivery system or formulation" "Major scientific or public controversy" "Subject to special regulatory requirements" As well as already approved drugs: "For which an important new use has been discovered or which pose newly discovered safety hazards" "Which are the subject of major scientific or public controversy" "Which may be subject to important regulatory actions such as withdrawal of approval"
21 CFR 330.10, promulgated 1974, Fed Reg 39, 62 (11742).	Advisory review panels "shall be established for each designated category of OTC drugs and every OTC drug category will be considered by a panel."

FDA Guidance	
2017 Guidance	Procedures for Meetings of the Medical Device Advisory Committee: Guidance for Industry and Food and Drug Administration Staff
2016 Draft Guidance	Procedures for Evaluating Appearance Issues and Granting Authorizations for Participation in FDA Advisory Committees
2014 Guidance	Public Availability of Advisory Committee Members' Financial Interest Information and Waivers
2013 Guidance	The Open Public Hearing at FDA Advisory Committees: Guidance for the Public, FDA Advisory Committee Members, and FDA Staff
2010 Guidance	Summary of Changes to CDRH's Advisory Committee Process
2008 Guidance	Guidance for Industry: Advisory Committee Meetings—Preparation and Public Availability of Information Given to Advisory Committee Members (Explains how FDA will handle the disclosure of FOIA-exempt information, including making briefing materials available to the public at least two business days before the time of the meeting)
2008 Guidance	Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings (Introduces uniform voting procedures, including simultaneous voting, replacing sequential "hand-raising" voting)
2008 Guidance	FDA Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees
2000 Guidance	FDA Waiver Criteria for Conflicts of Interest
1998 Guidance	Advisory Committees: Implementing Section 120 of the Food and Drug Administration Modernization Act of 1997

Purposes of FDA Advisory Committees: Insights from Prior Studies



FDA, perhaps more than any other federal regulatory agency, relies on the trust of patients, the medical community, and other branches of government to support its regulatory decisions. In his history of FDA and its regulation of medical products, Harvard University Professor Daniel Carpenter describes how FDA has cultivated a reputation of excellence throughout its history that has allowed it to wield extraordinary regulatory power in service of its public health mission.[47] Other scholars, such as Harvard Kennedy School of Government Professor Sheila Jasanoff, have constructed thorough accounts of how scientific advisors inform and legitimize regulatory policy.[48]

Our review of academic literature on the FDA, federal advisory committees, and technical regulatory decision making identified four interrelated purposes served by FDA's use of advisory committees, each of which supports public trust: information gathering, transparency, credibility, and accountability.

Information Gathering

A frequently discussed value of FDA advisors is to provide the agency with additional,[49] high-quality information in the form of expert interpretations and recommendations.[50] This is premised on the understanding that a better-informed agency will make better decisions, especially on complex scientific matters. Because FDA makes regulatory decisions requiring specialized knowledge, the agency benefits from advisors who can "[p]rovide it with technical assistance related to the development and evaluation" of the products it reviews.[51] This consensus view—in which advisors supplement, but do not replace, FDA's in-house expertise—has its roots in the DESI program of the 1960s discussed above.[52]

47. Carpenter, Daniel. *Reputation and Power: Organizational image and pharmaceutical regulation at the FDA*. (Princeton University Press, 2010) [hereinafter "Reputation and Power"].
48. Jasanoff, Sheila. *The Fifth Branch: Science advisers as policymakers*. (Harvard University Press, 1998) [hereinafter "Fifth Branch"].
49. The information is "additional" in the sense that without the advisory committee the agency would not have the interpretations and recommendations at its disposal.
50. Lavertu, Stéphane, and David Weimer. Federal Advisory Committees, Policy Expertise, and the Approval of Drugs and Medical Devices at the FDA. J Public Administration Research and Theory, 2010;21:211-237.
51. NAS Report, 2
52. Schwartz, Jason. Fifty years of expert advice—pharmaceutical regulation and the legacy of the Drug Efficacy Study. N Engl J Med 2016;375:2015-2017.

Transparency

Brown University Professor Susan Moffitt writes that, across regulatory agencies, "[c]ommittee deliberations can shine light on agencies' regulatory decisions and bring policy issues into visible, permeable venues."[53] At FDA, Moffitt notes how the two advisory committee meetings on rofecoxib led to the first reports in the popular press of the drug's link to adverse cardiovascular events, preceding the drug's withdrawal from the market on that basis.[54] The Institute of Medicine report from 1992 also notes that FDA advisory committees can "provide a forum for public discussion of certain controversial issues,"[55] and can "expose the agency's decisions to public scrutiny" that they may otherwise lack.[56]

Credibility

Scholars, policy advisors, and the FDA itself often link the presence of advisory committees with the credibility of FDA's decisions in the eyes of the public and the medical profession. In the aftermath of the rofecoxib withdrawal, the Institute of Medicine advised, "[The] FDA's credibility is its most crucial asset and recent concerns about the independence of advisory committee members . . . along with broader concerns about scientific independence in the biomedical research establishment, have cast a shadow on the trustworthiness of the scientific advice received by the agency[.]"[57]

Carpenter notes that "observers of FDA advisory committees often detect that the administration chooses to invite an advisory panel's judgment when the case before the agency is scientifically or politically more difficult."[58] By choosing to bolster such decisions with the added support of an independent advisory committee, FDA enhances its credibility in contexts that it knows will receive close scrutiny. FDA has held in regulations dating to 1985 that its use of advisors "adds to the quality and credibility of the decision-making process,"[59] an observation reiterated on the FDA website in 2016: "The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision making and lend credibility to the product review process."[60]

Accountability and Independence

Another common thread in the literature on advisory committees is ensuring the independence of agency decisions, with the understanding that open discussion with independent experts can provide the public with an additional degree of assurance that FDA's decisions are not being inappropriately influenced by political or industry considerations. The broader discourse on federal advisory committees across agencies also reflects a preoccupation with their independence from both political actors and industry pressure. An illustrative comment by Robert Steinbrook notes, "To maintain the integrity of federal advisory committees, advocates insist that the appointment process and subsequent committee deliberations should emphasize relevant scientific or clinical expertise and be free of ideological, political, and economic bias."[61]

53. Moffitt, Susan. The Policy Impact of public advice: the effects of advisory committee transparency on regulatory performance, at 181, in *Regulatory Breakdown: The Crisis of Confidence in U.S. Regulation*. (University of Pennsylvania Press, 2012) (ed. Gary Coglianese).
54. Moffit, Susan. Inviting Outsiders In: Choosing Access to Bureaucratic Implementation. (2005 dissertation, University of Michigan) 2-3.
55. NAS Report, 2.
56. NAS Report, 64.
57. 2007 Report, 9.
58. *Reputation and Power*, 498.
59. 50 Federal Register 7481. (Feb 22, 1985).
60. U.S. FDA. Advisory Committees: Critical to the FDA's product review process. (May 4, 2016). Accessed Dec 6, 2023. https://www.fda.gov/drugs/information-consumers-and-patients-drugs/advisory-committees-critical-fdas-product-review-process.
61. Steinbrook, Robert. Science, Politics, and Federal Advisory Committees. *N Eng J Med*. 2004;350(14):1454-1460.

For example, in the aftermath of the controversial 2016 approval of the drug eteplirsen (Exondys 51, discussed in more depth below), Yale School of Public Health Professor Jason Schwartz noted how "Advisory committee recommendations are so routinely reflected in subsequent FDA decisions that in the rare cases in which the agency does not follow them—such as the recent approval of eteplirsen for the treatment of patients with Duchenne's muscular dystrophy—it invariably receives additional scrutiny, and allegations of political interference in science are not uncommon."[62] Former FDA Associate Chief Counsel Robert Dormer similarly wrote in 1985 how the 1976 Medical Device Amendments, which required advisory review of most medical device decisions, aimed to "open up the agency to greater public scrutiny" and "improve the quality of FDA decision making."[63]

Jasanoff, writing in 1990, observed that both EPA and FDA "are served by, and are accountable to" their advisory committees.[64] FDA has appeared to welcome the accountability function of advisors, stating on its website in 2016: "Advisory committee meetings often receive considerable media attention, and the agency welcomes such scrutiny because it helps provide public assurance of a responsible process."[65]

62. Schwartz. Supra note 48.
63. Dormer, Robert. Use of advisory committees by the food and drug administration under the medical device amendments at 103. *Food Drug Cosmetic Law Journal*, 1985;40:103-111.
64. *Fifth Branch*. 229.
65. U.S. FDA. Advisory Committees: Critical to the FDA's product review process. (May 4, 2016). Accessed Dec 6, 2023. https://www.fda.gov/drugs/information-consumers-and-patients-drugs/advisory-committees-critical-fdas-product-review-process.

Impacts of FDA Advisory Committees: A Review of Empirical Work

This section summarizes empirical research on FDA's use of advisory committees prior to 2021. Most studies addressed the impact of conflicts of interest on committee recommendations, or alignment between advisor recommendations and FDA action.

Alignment and Frequency

Empirical research shows strong alignment between advisor recommendations and FDA action. Of the FDA advisory committees convened from 2008-2015, only 22 percent were followed by discordant actions from FDA within a year, and the majority of discordance, when it occurred, was the result of FDA being more restrictive than its advisors (i.e., rejecting a drug for which the advisors supported approval).[66] A review of advisory votes on Pre-Market Approvals for medical devices from 2005-2016 similarly found that positive votes were significantly associated with approval,[67] and a study of drug and device approval votes from 1997-2006 found that an "increase in the proportion of committee members voting for drug approval" corresponded with an increased likelihood of approval and a decreased time to approval after the meeting.[68]

An analysis of new drugs approved 1986-2009 found that consultation with an advisory committee was associated with fewer post-marketing safety problems when the advisory committee had few or no conflicts of interest.[69] 11.5 percent of votes cast on new drug approvals by the Oncology Drug Advisory Committee between 2006 and 2019 were followed by discordant agency action.[70]

Existing research on the frequency of advisory meetings is sparse, but one study found that 44 percent (251/571) of new molecular entities approved between 1985 and 2006 were reviewed by an advisory committee before approval.[71] Another found that "35 (24 percent) of 147 new molecular entities . . . approved between 2000 and June 30, 2006, were preceded by advisory committee meetings," representing a "decrease from 1998 and 1999 when 40 percent and 52 percent, respectively, of approved NMEs [new molecular entities] were preceded by meetings."[72]

Conflicts of Interest

One study on drug advisory committee meetings between 2001-2004 found a weak association between conflicts of interest and individual votes which did not affect voting outcomes overall.[73] However, a larger study looking at FDA advisory committees from 1997-2011 found a significant relationship in which advisors with exclusive financial ties to the firm sponsoring the product at issue exhibited a pro-sponsor voting bias:

66. Zhang, Audrey, Jason Schwartz, and Joseph Ross. Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008-2015. Milbank Q, 2019;97(3):796-819.
67. Gibbs, Jeffrey, and David Gibbs. PMA Advisory Panels: Do Their Votes Matter? Food & Drug Law Institute. (April/May 2019) Accessed Dec 6, 2023. https://www.fdli.org/2019/05/pma-advisory-panels-do-their-votes-matter/.
68. Lavertu, Stéphane, David Weimer. Federal advisory committees, policy expertise, and the approval of drugs and medical devices at the FDA. J Pub Admin Res Theory 2010;21:211-237.
69. Moffitt, Susan. The Policy Impact of public advice: the effects of advisory committee transparency on regulatory performance, in *Regulatory Breakdown: The Crisis of Confidence in U.S. Regulation*. (University of Pennsylvania Press, 2012) (ed. Gary Coglianese).
70. Haslam, Alyson, Jennifer Gill, and Vinay Prasad. Oncology Drug Advisory Committee Recommendations and the U.S. Food and Drug Administration's Actions. Mayo Clin Proc. 2020;95(2):417-426.
71. Moffitt, Susan. Promoting Agency Reputation Through Public Advice: Advisory committee use in the FDA. *Journal of Politics*, 2010;72(3):880-893.
72. Tapley, Asa, Peter Lurie, and Sidney Wolfe. Suboptimum use of FDA drug advisory committees. *Lancet,* 2006;368:2210.
73. Lurie, Peter, Cristina Almeida, Nicholas Stine, Alexander Stine, Sidney Wolfe. Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings. *JAMA* 2006;295(16):1921-1928.

> Individuals with financial interests solely in the sponsoring firm are more likely to vote in favor of the sponsor than are members who have no financial ties; moreover, this pro-sponsor bias appears to be larger when we look at non-unanimous votes—cases in which the scientific evidence may be more ambiguous. At the same time, however, individuals with ties to both the sponsor and its competitors do not appear to vote differently from those with no financial ties.[74]

A study looking at a sample of 16 meetings from 2005-2006 found that advisors who required conflict of interest waivers also had slightly higher overall rates of publication, citation, and years of experience.[75] An analysis of drug evaluation meetings between 1997-2012 found that 12 percent of votes were cast by conflicted members (using FDA's definition), and that experts cast 88 percent of all votes, while consumer representatives cast 7 percent and patient representatives 5 percent.[76] The authors did not find a difference between conflicted members, who voted for drug approval 65.3 percent of the time, and unconflicted members (62.3 percent). However, they found that "consumer representatives have 25 to 30 percent lower odds than non-conflicted permanent experts . . . of voting for approval. Patient representatives, on the other hand, have 26 to 54 percent greater odds of voting for approval."[77]

Findings on FDA's Use of Advisory Committees in Prescription Drug Regulation

To understand the role of advisory committees in FDA's regulation of prescription drugs, this study assesses 1) the frequency of advisory committee meetings, 2) the alignment between advisory recommendations and FDA, 3) the questions that FDA asks advisors to vote on, and 4) the timing and circumstances of when advisory committees are convened.

Methods

The following results draw on data presented in two studies recently published by the authors—one looking at FDA new drug approvals,[78] and another looking at human drug advisory meetings[79]—both from 2010-2021. The methodology is briefly described here; more detail is available in the prior publications.

To determine the frequency of meetings, this analysis draws on advisory committee meeting minutes for all human drug advisory committees convened from 2010-2021 from FDA's website archives. These documents summarize the meetings held by the FDA as required by FACA, and include the roster, discussion topics, voting questions, and outcomes.

74. Pham-Kanter, Genevieve. Revisiting Financial Conflicts of Interest in FDA Advisory Committees at 459. Milbank Q. 2014;92(3):446-470.
75. Ackerley, Nyssa, John Eyraud, and Marisa Mazzotta. Eastern Research Group, Inc. Measuring Conflict of Interest and Expertise on FDA Advisory Committees. 2007.
76. Cooper, James, and Joseph Golec. Conflicts of Interest on Expert Committees: The Case of FDA Drug Advisory Committees.
77. Id.
78. Daval, C. Joseph, Ameet Sarpatwari, and Aaron Kesselheim. Unwanted Advice? Frequency, Characteristics, and Outcomes of Negative Advisory Committee Votes for FDA-Approved Drugs. *Health Affairs*, 2022;41(5):713-721.
79. Daval, C. Joseph, Theodore Teng, Massimiliano Russo, and Aaron Kesselheim. Association of Advisory Committee Votes with U.S. Food and Drug Decision-Making on Prescription Drugs, 2010-2021. *JAMA* Health Forum 2023;4(7)e231718.

The number of drug approvals is based on a review of approval letters, drug approval packages, and product labels from Drugs@FDA. Meetings were classified by whether the committee voted on a regulatory question, and by the type of regulatory question. The categories included new drug approval, supplemental indication, safety action, accelerated approval withdrawal, and different regulatory action. Corresponding FDA actions were determined from the online Risk Evaluation and Mitigation Strategies (REMS) database, general internet search for FDA press releases, industry publications, and company press releases.

Results

Frequency

FDA's use of advisory committees declined substantially from 2010 to 2021. From 2010 to 2012, over 40 meetings were convened each year to advise on issues relating to human drugs. In 2020 and 2021, only 18 were convened—a decline of 64 percent from its peak of 50 in 2012 (Figure 1). This decline occurred largely in the two biggest categories—meetings considering new drug approvals, and meetings in which the committee did not vote on a regulatory action. Initial approvals (new drug approvals) made up 54 percent of all meetings, supplemental indications 14 percent, safety actions 7 percent, withdrawals of a drug or indication granted accelerated approval 2 percent, different regulatory actions 3 percent, and no regulatory action 20 percent.

Figure 1. Topics Covered by FDA Drug Advisory Committee Meetings, 2010-2021

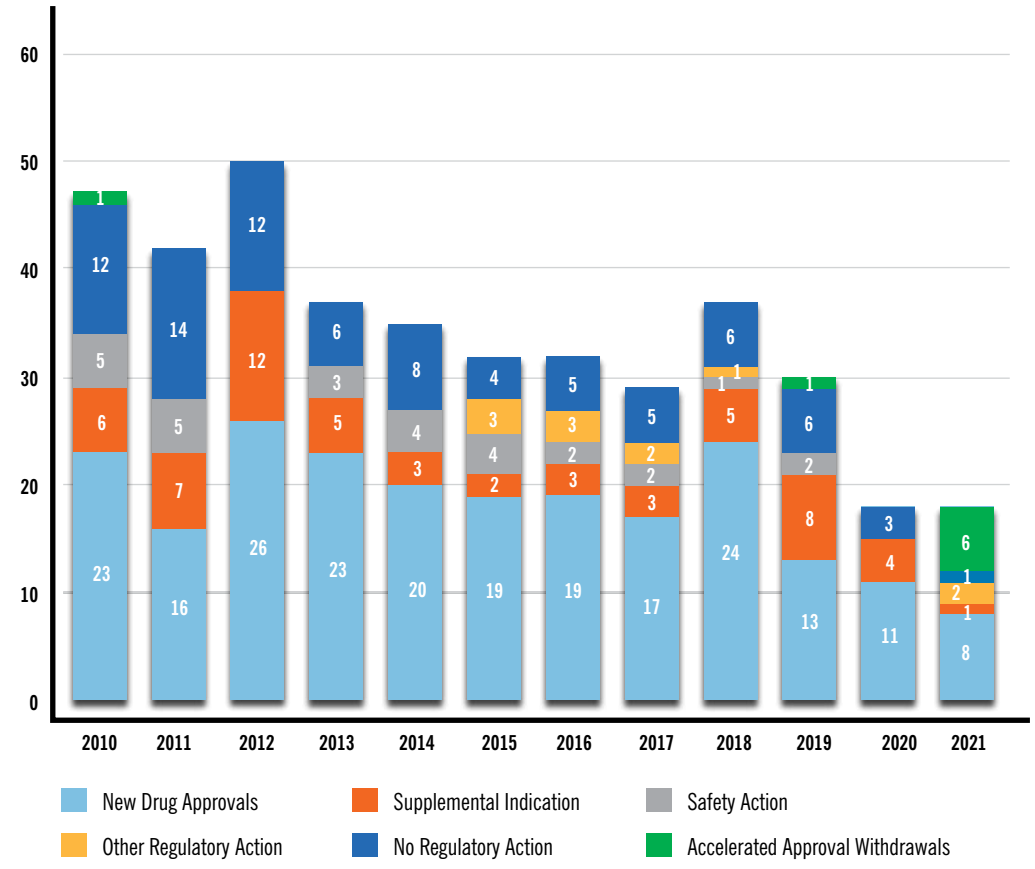
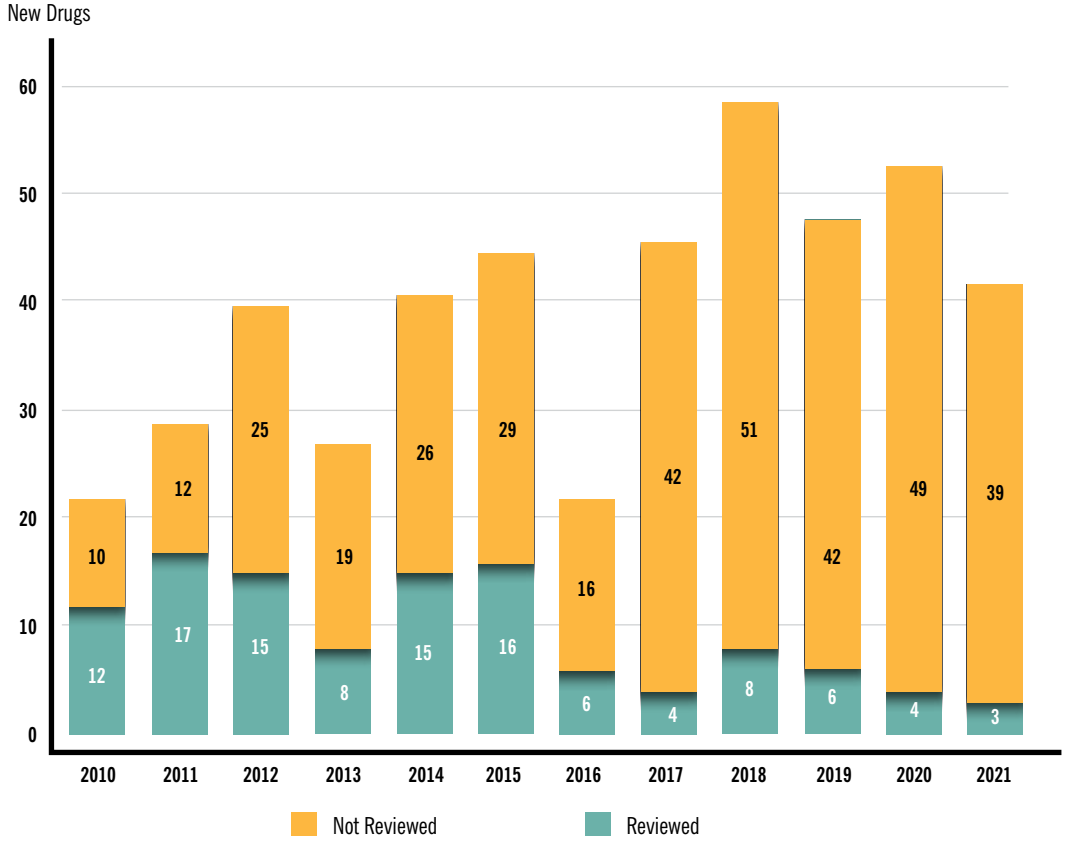


Figure legend: Adapted from JAMA Health Forum. 2023;4(7):e231718. doi:10.1001/jamahealthforum.2023.1718

From 2010-2021, drugs reviewed by an advisory committee made up a declining portion of all new drug approvals (Figure 2). In the early 2010s, about half of new drugs were reviewed by an advisory committee before approval. By 2021, that portion had dropped to 6 percent (three meetings), from a high of 59 percent (17 meetings) in 2011.

Figure 2. Number of New Drugs Reviewed or Not by an FDA Advisory Committee, 2010-2021



Source: Drugs@FDA, ***Notes:*** FDA-approved drugs by year of approval. "Reviewed" is the portion of drugs each year subject to advisory committee review before approval.

Figure legend: Adapted from Daval et al. Unwanted Advice, Health Affairs. 10.1377/hlthaff.2021.01927 HEALTH AFFAIRS 41, NO. 5 (2022): 713–721

Alignment and Timing

Recommendations, measured by the outcomes of advisory votes on regulatory questions, were closely associated with corresponding FDA actions. FDA actions aligned with votes in 88 percent of initial approvals (182/207), 89 percent of supplemental approvals (51/57), 88 percent of safety actions (23/36), and 75 percent of accelerated approval withdrawals (6/8), leading to overall alignment of 88 percent for regulatory actions. Alignment also stayed relatively consistent over time, with a low of 73 percent alignment between recommendations and FDA actions in 2014 (see Figure 3).

Voting outcomes were closely associated with the likelihood and timing of approvals, with a positive recommendation making it far more likely that a drug or indication would receive an approval, and far more quickly, than a negative vote. Positive votes on initial approvals were followed by approval 97 percent (142/147) of the time, with a median of 75 days between the vote and approval. FDA declined to approve 67 percent (40/60) of products with negative

votes on initial approvals, and, if approved, drugs with negative recommendations received the approval 700 days after the advisory committee vote. Positive votes on supplemental indications were followed by approval in 92 percent (33/36) of cases, and negative votes were followed by non-approval in 86 percent (18/21) of cases.

Figure 3. Alignment between FDA Action and Advisory Committee Votes

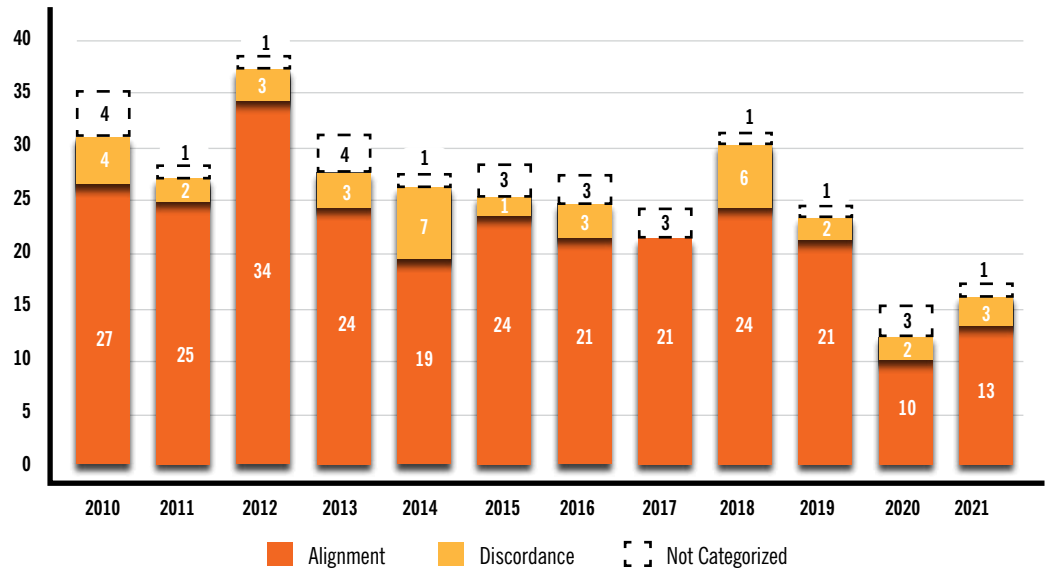


Figure legend: Adapted from JAMA Health Forum. 2023;4(7):e231718. doi:10.1001/jamahealthforum.2023.1718

From 2010-2021, FDA approved a new drug about once a year that an advisory committee voted should not receive approval. These included some drug approvals that became the subject of substantial public controversy, including aducanumab, eteplirsen, and flibanserin.

Measuring from a year after the votes on initial approval, FDA alignment with advisory recommendations was 86 percent, including approval of 85 percent (127/149) of the drugs that received a positive vote, and non-approval of 88 percent (58/66) of those that received a negative vote. As of 2022, FDA had approved 20 initial approvals that had received a negative vote, as well as six that later received a second, positive vote before approval. For the 20 with only a negative vote, FDA declined to reconvene another advisory committee before approval. It had also declined to approve five drugs that received a positive vote. Table 2 identifies examples of drugs approved following a negative advisory committee recommendation.

Table 2: Notable Votes Featuring Discordance Between FDA Advisory Committee and Subsequent FDA Decision

Product	Key Voting Question(s)	Outcome	FDA Action
Eteplirsen (Exondys 51)	Question 1: Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit? Question 2: Do the clinical results of the single historically controlled study (Study 201/202) provide substantial evidence (that is, evidence from adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy) that eteplirsen is effective for the treatment of [Duchenne muscular dystrophy]?	Question 1: Yes: 5 No: 8 Question 2: Yes: 3 No: 7 Abstained: 3	Approved 2016
Aducanumab (Aduhelm)	In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?	Yes: 0 No: 10 Uncertain: 1	Approved 2021
Flibanserin (Addyi)	Considering the available data on efficacy and safety, has the Applicant demonstrated that the overall risk/benefit profile of flibanserin for the treatment of [hypoactive sexual desire disorder] in premenopausal women is acceptable?	Yes: 0 No: 11	Approved 2015
Hydrocodone extended release (Zohydro ER)	Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?	Yes: 2 No: 11 Abstained: 1	Approved 2013
Olaparib (Lynparza)	Do the safety and efficacy results from Study 19 in the gBRCAm population support and accelerated approval, or should marketing approval consideration be delayed until the results from SOLO-2 are available?	Yes: 2 No: 11	Approved 2014

Voting Questions

The majority (80 percent) of meetings included voting questions that asked the advisors to offer recommendations directly on the regulatory question at hand. Voting questions posed by FDA to the advisory committees exhibit wide variation in their wording and substance.

Summary

This empirical review of FDA's use of human drug advisory committees suggests that FDA has leaned away from advisory committee review since the early 2010s, even as the agency continues to follow advisory recommendations closely. The vast majority of new drug approvals in recent years have not been reviewed by advisory committees, and FDA's use of advisory committees has dropped steadily over the past decade. FDA's regulatory decisions aligned closely with advisory committee recommendations across years, regulatory areas, and committees. The fact that discordance was consistently low, and not concentrated in any particular place, speaks to the key role that advisors play in decision making across the areas of drug regulation at FDA.

One possible explanation for the decrease in advisory committees in 2020 and 2021 is the COVID-19 pandemic. This explanation is limited by the fact that the COVID-19 pandemic was accompanied by a shift to virtual, rather than in person meetings, which are in important ways logistically simpler to convene.

How Do Other Expert Agencies Use Advisory Committees?

This section considers common and disparate features of three advisory committees used by other expert agencies to inform technical decision making, reviewing the characteristics, sources of authority, and regulatory structures of outside advisory committees based in the Environmental Protection Agency (EPA), Centers for Medicare and Medicaid Services (CMS), and Centers for Disease Control and Prevention (CDC). The features of these committees suggest useful practices for scientific agencies receiving expert advice, while also informing the recommendations for FDA in the subsequent section.

These three advisory committees provide case studies of scientific policymakers regularly consulting with outside experts when considering consequential decisions affecting public health and safety, which depend on technical assessments of complex questions. The committees represent only three of many used by these agencies, although they are particularly prominent examples. While the missions and structure of these agencies and their advisors may present contexts that differ meaningfully from FDA's, and while these agencies' committees sometimes also generate controversy, they can nonetheless provide valuable grounding for a discussion on reforming FDA and other scientific agency advisory committees, including the creation for clear standards and procedures for when to convene advisors, how to ask consistent and useful questions, and how to address disagreement.

Clean Air Scientific Advisory Committee (EPA)

Under the Clean Air Act, the EPA reviews national ambient air quality standards every five years. Under federal law, the EPA must consult the Clean Air Scientific Advisory Committee (CASAC) for each updated rule, which it does at multiple points in the review process. CASAC, comprised of experts in climate and public health based outside the EPA, reviews evidence and routinely recommends specific air standards for EPA to promulgate as a final rule, which EPA frequently, but not always, accepts.[80] As outlined in the EPA's enacting legislation, EPA's proposed final rule must identify a) the key elements of the CASAC recommendations, b) any divergence from the recommendations, and c) the basis for that divergence.

The recommendations take the form of lengthy reports which, in addition to offering advice on what the air standards should be, offer consensus responses to questions posed by EPA about how to interpret the results and methodologies of studies. This open-ended format creates opportunities for advisors to offer dissents and rebuttals when they disagree with one another.[81]

Medicare Evidence Development & Coverage Advisory Committee (CMS)

Under Medicare Parts A and B, CMS must only reimburse items or services that are "reasonable and necessary" for a medical or research purpose. To aid in its assessment of whether to cover a product or procedure nationally, CMS seeks advice from the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), which engages in a thorough review of the available evidence to determine the appropriateness of coverage for the population of Medicare beneficiaries.

80. There is, to our knowledge, no empirical review of how frequently and to what degree EPA diverges from CASAC's recommendations. For a review of litigation on CASAC at EPA, see Fisher, Elizabeth, Pasky Pascual, and Wendy Wagner. Rethinking Judicial Review of Expert Agencies, *Texas Law Review*, 2015;93:1681, at 1703-04.
81. See, e.g., Letter from CASAC to EPA Administrator Michael Regan, CASAC Review of the EPA's Policy Assessment (PA) for the Reconsideration of the Ozone National Ambient Air Quality Standards (External Review Draft Version 2) (June 9, 2023).

CMS issued a guidance document in 2006 describing the instances in which a technology's referral to MEDCAC is appropriate.[82] These criteria include:

- "There is significant controversy among experts."
- "The existing published studies contain potentially significant methodological flaws."
- "The available research has not addressed policy relevant questions."
- "The existing published studies show conflicting results."

The latter half of the MEDCAC meeting is reserved for the members to "deliberate openly on the issue." Questions are posed to the committee by CMS, and the members vote using a five-point scale, with the instruction: "For the voting questions, use the following scale identifying level of confidence—with 1 being the lowest or no confidence and 5 representing a high level of confidence." For example, in a 2018 meeting on Transcatheter Aortic Valve Replacement (TAVR), CMS asked, "How confident are you that there is sufficient evidence that a certain threshold of [Surgical Aortic Valve Replacement] procedural volumes must be required for hospitals without previous TAVR experience to begin TAVR programs?" The voting member average was 3.78 (range: 1-5).

Advisory Committee on Immunization Practices (CDC)

The CDC sets national recommendations for pediatric and adult vaccines with the aid of its Advisory Committee on Immunization Practices (ACIP). ACIP meets at least three times a year and votes on recommendations for all new FDA-approved or authorized vaccines as a matter of course, although this is not required by statute.[83]

ACIP's procedures for voting on vaccine recommendations provide a potential model for FDA advisors voting on indications. Rather than asking the committee a voting question, advisors are asked to favor or oppose the wording of resolutions such as recommendation statements or vaccine schedules (sometimes in the form of tables). For example, when voting in 2021 on a dengue vaccine (Dengvaxia), a CDC official "presented the following proposed wording for an ACIP vote: *ACIP recommends three doses of Dengvaxia administered six months apart at months 0, 6, and 12, in persons 9-16 years of age with a laboratory confirmation of previous dengue infection and living in endemic areas*."[84] After which, "[ACIP advisor] Dr. Sanchez made a motion to approve the proposed language for an ACIP vote on Dengvaxia as presented. [ACIP advisor] Dr. Lee seconded the motion." (The vote was 14 in favor, 0 opposed).[85]

82. Guidance for the public, industry, and CMS staff: Factors CMS considers in referring topics to the Medicare evidence development & coverage advisory committee. (Dec 2006) Accessed Dec 6, 2023. https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=10.
83. "Upon the licensure of any vaccine or any new indication for a vaccine, the Committee shall, as appropriate, consider the use of the vaccine at its next regularly scheduled meeting." Page 1, ACIP Charter; ACIP Practices Policies and Procedures, June 2022. Accessed Dec 6, 2023. https://www.cdc.gov/vaccines/acip/committee/downloads/Policies-Procedures-508.pdf [hereinafter "ACIP Practices"].
84. ACIP meeting summary, June 24-25, 2021, at page 22.
85. Id.

CDC has published nonbinding procedures explaining how it handles disagreement with ACIP,[86] although it is worth noting that it is very rare for CDC to overrule ACIP and that CDC did not acknowledge or explain in the Federal Register when disagreement occurred over the COVID-19 booster recommendation in 2021.[87] CDC guidance states, "If the CDC Director disagrees with one or more of the ACIP recommendations" then the basis for the disagreement is conveyed in a memo to ACIP, which has a chance to either change its recommendations or further explain the basis for its recommendation. If at that point "the Director still disagrees with ACIP recommendations," then CDC staff "drafts and publishes a Federal Register Notice with opportunity for 30 days public comment that articulates the Director's views and proposed decision."[88]

Summary of Effective Practices

Reviewing other U.S. federal scientific agencies and their associated advisory committees reveals some consistent useful features (see Table 3). First, many agencies have *consultation requirements*, or clear expectations for when leaders will convene advisors. These commitments may be set in federal law by Congress, as with the CASAC; may be made by the agency itself through notice-and-comment rulemaking, as with OSHA's Advisory Committee on Construction Safety & Health;[89] or may be made through informal guidance, as with ACIP. Other advisory committees with consultation requirements include the Advisory Committee on Reactor Safeguards (NRC),[90] and the National Committee on Vital and Health Statistics (HHS).

Another characteristic shared by some advisory committees is a *disagreement process* outlining how to proceed if the agency does not want to follow the committee's recommendations. These explanations for departing from recommendations are sometimes required by law, as with CASAC, and at other times are procedures developed internally by agencies, such as at ACIP. Another advisory committee with a statutory response requirement is the National Agricultural Research, Extension, Education, and Economic Advisory Board at the USDA.

Finally, some advisory committees had *consistent procedures* for soliciting and offering advice, although the recommendations took a range of forms. ACIP, for example, consistently takes up-or-down votes on the wording of specific vaccine recommendations.

86. ACIP Practices at 8.
87. Mandavilli, Apoorva, and Benjamin Mueller. CDC Chief Overrules Agency Panel and Recommends Pfizer-BioNTech Boosters for Workers at Risk. *New York Times*. (Oct 21, 2021). Accessed Dec 6, 2023. https://www.nytimes.com/2021/09/24/world/covid-boosters-vaccine-cdc-director.html. A search of the HHS federal register within the timeframe of the announcement did not yield a Federal Register Notice.
88. ACIP Practices.
89. 29 CFR § 1912.3(a).
90. 42 U.S.C. § 2039. 10 C.F.R. §§ 52.23, 52.87, 52.53, and 54.25.

Table 3. Purpose and Features of Three Prominent Expert Advisory Committees

Committee	Purpose	Features
CASAC (EPA)	To advise on National Ambient Air Quality Standards EPA must promulgate every five years under the Clean Air Act	• Statutory consultation requirement • Statutory response requirement with explanation for disagreement[91] • Advice in the form of lengthy written reports summarizing the basis for recommendations
ACIP (CDC)	To develop recommendations on the use of vaccines, subject to approval by the CDC Director	• Regular consultation outlined in charter, including recommendations on all new vaccines • Guidance outlines procedures, including a required explanation, in case of disagreement[92] • Votes taken on specific wording of recommendation
MEDCAC (CMS)	To evaluate available evidence for a medical technology or procedure and make recommendations as to the appropriateness of Medicare coverage	• Criteria for consultation outlined in guidance • Votes taken on a scale of 1-5

91. 42 USC § 7409 (d).
92. ACIP Practices.

Recommendations

In this section, we identify actionable areas for reform to improve the usefulness of advisory committees to agency decision makers and their ability to promote public trust in agency decisions. While these recommendations have been developed to improve the operations of advisory committees at FDA (with a focus on medical products like prescription drugs), they offer lessons to policymakers at other agencies as well.

Establish Consistency in Advisory Committee Referrals

Consistency and reliability are essential to ensuring that advisory committees support FDA credibility. If committees are convened entirely ad hoc, or too infrequently, patients and physicians may lack the assurance that FDA's decisions on critical regulatory questions are benefitting from the recommendations of independent experts.

The substantial decline in advisory committee referrals since 2010 in the context of drug regulation threatens to erode the trust of patients and medical providers in FDA decisions. This is especially true in the context of new drug approvals, as advisory committee review of approved drugs dropped from over 50 percent of new drugs to under 10 percent from 2010 to 2021. When FDA declines to convene an advisory committee for a decision that is high-profile, particularly consequential, or a "close" call—such as for the accelerated approval of the Alzheimer's disease drug lecanemab—it misses an opportunity to receive useful input on the decision and risks eroding the trust of the medical community and the public.

Because advisory committees are not necessary for all regulatory decisions, establishing consistent referral practices requires developing public-facing criteria for FDA to refer to when it makes a decision on whether to refer a question or product to advisors for review. These criteria could take the form of a guidance document from FDA, legislation from Congress, or an executive order from the White House.

Two sources of law and policy provide valuable starting points for developing these criteria. The first is the FDA regulation from 1979 identifying "high priority" characteristics of new drug and biologic applications that FDA will refer to advisory committees, including "potential therapeutic advances," "narrow benefit-risk considerations," and drugs implicating "major scientific or public controversy." These and other categories should be more thoroughly and prospectively defined, and could provide the basis for referral criteria that would improve consistency in the advisory process.

The second starting point is section 21 USC 355(s) of FDCA, which requires FDA to refer all new drug and biologic products that are new molecular entities to an advisory committee before approval by default, or otherwise provide an explanation why it did not. This provision of the Act reflects an understanding by Congress that review of new molecular entities by FDA advisors would be the norm, with any deviation from that norm requiring an explanation. FDA has relied heavily on these explanations as it refers fewer new product to advisory committees. However, these explanations are often only a single sentence, and are sometimes inadequate given the context of the product at issue. For example, for the recently approved Alzheimer's drug lecanemab (Leqembi)—the subject of major controversy within the medical community due to its low demonstrated efficacy and substantial safety risks—FDA stated in its letter authorizing accelerated approval in January 2023 only the following: "Your application for Leqembi was not referred to an FDA advisory committee because this biologic did not raise new or unexpected safety or efficacy issues for a drug of this class." Notably, in this case, after some public criticism, the FDA did organize an advisory committee in June 2023 as the drug was being considered for conversion from accelerated to traditional approval.

As currently used by FDA, its 1979 advisory committee regulations are insufficient to address the concerns about unexplained variation in when advisory committees are convened because they are subjective and functionally nonbinding. However, they serve as important statements of basic principles about the kinds of decisions that warrant advisory review, as well as an expectation that most approval decisions will be reviewed by advisors.

In addition to a statement of criteria for referral, FDA could reestablish a default assumption that certain approval decisions, such as approval of new molecular entities, will be reviewed by advisory committees. This would benefit FDA decision makers, advisors, product sponsors, and the public by increasing the predictability of advisory committee review for decisions more likely to be particularly consequential. One option would be for Congress to amend the FDCA, requiring FDA to consult advisory committees before making certain decisions, like accelerated approvals.

Restructure Meetings to Expand Time for Committee Discussion

Although advisory committee meetings often span five hours or more, FDA advisors typically have no more than an hour and a half to ask questions, deliberate, and vote. Given the complexity of the issues at hand, this time often does not allow for the full benefit of the convening. While the specifics vary, the primary items on most meeting agendas in addition to the committee discussion and vote include the FDA presentations, the sponsor presentation, and the open public hearing.

To allow more time for discussion, FDA could limit, or eliminate, sponsor presentations and expand the committee discussion (which could include questions to the sponsor). Product sponsors frequently provide long presentations to the advisors making the case for the regulatory outcome they favor, and are generally presented to maximize the probability of approval. These sponsor presentations, which take up much of the morning session, are largely duplicative of the briefing materials, including materials from the sponsors, which are sent to the advisors in advance of the meeting. They also often duplicate presentations made by FDA providing background on the available clinical data on safety and effectiveness, characteristics of the patient population, and other relevant factors. They can therefore be substantially shortened to allow committee members more time for thorough, open deliberations on the regulatory decision at hand.

Limiting the sponsor presentation would align FDA's advisory committee procedures more closely with other comparable advisory committees at expert agencies. At CMS's MEDCAC, half of the meeting is dedicated to deliberative discussion between the advisors, and none of it dedicated specifically to representatives of the industries that would benefit from a favorable coverage decision, although industry representatives still may comment in the public session.[93]

There is no legal requirement that a manufacturer be allowed a special presentation to advisory committees, either in the FDCA, FACA, or FDA regulations. Instead, manufacturers are free to challenge FDA's final regulatory action, and there is a public hearing portion (usually an hour, but up to as many as 4-5 hours in rare cases) during which time speakers, including manufacturers, can provide views.

93. Guidance for the public, industry, and CMS staff: Factors CMS considers in referring topics to the Medicare evidence development & coverage advisory committee. (Dec 2006) Accessed Dec 6, 2023. https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=10.

Bolster Voting Procedures to Ensure the Integrity of Recommendations

Much of the controversy and confusion surrounding FDA's use of advisory committees relates to the wording, timing, and response to voting questions posed to the committee.

Wording of Voting Questions

FDA should develop a consistent wording template for voting questions, including a consistent up-or-down approval question for all meetings contemplating approval or withdrawal of a product or indication, in addition to any other questions FDA wants to ask. At least one voting question should reflect the relevant regulatory standard FDA faces for that particular product.

For example, for regular approvals and supplemental indications, the question might ask: "Do well-controlled investigations provide substantial evidence that [the product] is safe and effective for the following use: [insert proposed indication]" [Yes/No]. Voting questions for the approval or withdrawal of an accelerated approval drug might ask whether the surrogate measure serving as the outcome in the pivotal clinical trial is "reasonably likely to predict clinical benefit for the following use" as required by statute, or whether the results of confirmatory trials "demonstrate that the drug is safe and effective for the following use."

Another option, modeled after ACIP's voting procedures, would be to ask advisors to vote on the labeling language itself, such as the scope of the indication or which material is best placed in a boxed warning. Under this model, FDA would present the potential language of the indication (in the case of a new drug approval), and the advisors would be asked to vote on the appropriateness of that wording based on the available evidence. In addition to the up-or-down voting question, FDA could incorporate a 1-5 scale voting question, as MEDCAC does, for advisors to indicate answers to questions such as their degree of confidence in the effectiveness of the product.

These question types can be combined for greater clarity. For example, a template for a new drug approval might ask:

> Is there substantial evidence to approve [drug] as safe and effective for [indication]? *Vote [Yes/No].*
>
> Please rate your confidence that [drug] is safe and effective for [indication] on a scale of 1 to 5, with 1 being low or no confidence, and 5 being high confidence. *Vote. [1-5].*

A template for an accelerated approval might ask:

> Is [surrogate measure] reasonably likely to predict clinical benefit for [indication]? *Vote [Yes/No].*
>
> Please rate your confidence that [surrogate measure] is likely to predict clinical benefit for [indication] on a scale of 1 to 5, with 1 being low or no confidence, and 5 being high confidence. *Vote. [1-5].*

It is critical to the integrity of advisory committees that vote on discrete regulatory decisions that at least one voting question be a "confirmable" vote on the regulatory decision at issue, phrased in such a way that it must be either followed or not followed. FDA's current use of confirmable voting questions provides for a clear recommendation that can support the agency's credibility. For example, "Should the drug be approved?" is a confirmable voting question. Either FDA follows the recommendation and benefits from the unambiguous support of its advisors, or does not, and the public benefits from a transparent view of any discordance. By contrast, a question such as "What actions could be taken by industry or the FDA to facilitate patient access to medical devices designed to be safe and effective outside the clinic setting?"[94] is not confirmable, because the response neither supports a discrete regulatory decision nor draws attention to FDA's divergence from a recommendation.

To be sure, such non-confirmable questions may frequently be useful and appropriate, allowing FDA to better facilitate conversation and recommendations. However, they do not substitute for clear up-or-down votes, which support transparency, accountability, and credibility due to their simplicity and legibility to the expert and nonexpert public, as well as Congress. Without a clear recommendation, advisory committees cannot meaningfully "support" an FDA action, and thus cannot bolster trust in its decisions.

Disagreement Procedures

We recommend that FDA establish clear procedures for what to do in the event of disagreement, including a thorough explanation of the advisors' recommendation and FDA's reasoning for the discordant action. While FDA drug approval documents associated with discordant approvals sometimes mention the advisory committee's recommendation in the context of a broader explanation of the basis for the approval, they do not consistently include a section summarizing the advisory committee's position and providing reasons for not following the committee's recommendation. And other regulatory actions do not include an analogous format for explanation.

EPA's CASAC provides a model for how to do this, as EPA is required by law to address and explain any disagreement with CASAC in the explanation for its final rule published in the Federal Register. For FDA, this might look like an opportunity for advisors to offer written responses before the regulatory action is taken, including dissenting opinions. FDA could then respond directly, as CASAC does, to the points made by the advisors at the time of the regulatory decision.

94. Summary Minutes, Center for Devices and Radiological Health Patient Engagement Advisory Committee (Sept 6, 2023). Accessed Dec 6, 2023. https://www.fda.gov/media/173358/download.

CONCLUSION

Advisory committees are a key component of FDA's regulatory decision making, enhancing the agency's capabilities and building trust among the medical community, patients, and the broader public. FDA's use of advisory committees in the context of drug regulation has changed substantially from 2010 to 2021, with FDA convening fewer committees in advance of major decisions, including new drug approvals. By looking to other examples of expert agencies that use advisory committees, FDA can take steps towards engaging independent experts in a more consistent and rigorous way. Such efforts would help build and strengthen the public trust upon which FDA's authority, and the authority of all expert agencies, ultimately rests.

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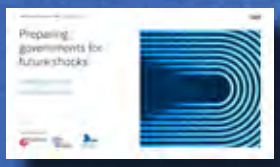

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