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Comment on "Optimizing the Food and Drug Administration's Use of and Processes for Advisory Committees" [Docket No. FDA-2024-N-1809]

August 13, 2024

The Honorable Robert M Califf, MD
Commissioner
US Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf:

Thank you for your and Principal Deputy Commissioner Bumpus's leadership in FDA efforts to improve the functioning of the agency's advisory committees, and for providing an opportunity for the public to submit comments on potential reforms.

I am a PhD economist and Associate Professor of Public Policy at the University of Southern California. I am submitting my comments as a researcher who has studied and published on FDA advisory committees. The views expressed are my professional opinions and do not reflect the position or policy of the University of Southern California or the Sol Price School of Public Policy.

Topic 1: Composition of Advisory Committee Members

If all drug and device applications were supported by high-powered, randomized double-blind placebo-controlled trials with prespecified clinical endpoints, there would hardly be a need to convene FDA advisory committees. The agency could observe whether the estimated effect exceeded, with statistical significance, a prespecified efficacy threshold, and straightforwardly issue its approval decision.

Given the messiness of real-world research, however, the agency is often asked to make decisions based on imperfect studies. There are unanticipated changes and practical compromises made in study design; unexpected adverse events; failures in recruitment; weak clinical outcomes observed alongside strong effects in post hoc subsamples or using surrogate endpoints. In these cases, the agency would be sensible to consult advisory committees that can assist in the interpretation of complicated and conflicting findings.

FDA advisory committees are therefore convened, not to review every single application, but to specifically tackle "hard cases." These hard cases require technical knowledge about the implications and biases that arise from limitations in the study design. Is the effect size from a post hoc subsample likely to be a real signal or a statistical artifact? What sorts and what sizes of bias are likely to arise from deficiencies in the study design?

To what degree can the observed effects be generalized to populations not well-represented in the trial? How can the design limitations be formally taken into account in post-study analyses or in supplemental studies?

Advisory committee members should be selected with an eye to including individuals who can assist in answering these hard questions—to provide information on what can and cannot be inferred from the existing design. For this reason, I recommend that:

- **each meeting include – in addition to the agency's own non-voting statistical reviewer – at least one standing committee member who is a biostatistics specialist, and one temporary member (specializing in the drug class or therapeutic area relevant for that specific meeting) who is a biostatistics or study design specialist.**

Many advisory committee meetings already include two such members, and I would encourage the agency to routinely include these member types as it assembles its advisory committees. Biostatisticians from other health agencies like NIH, CDC, VHA, and CMS would be a particularly useful pool from which to draw, having already been vetted as government employees. The inclusion of these technical experts need not be at the expense of non-technical members like patient representatives, who serve a different function, and may require increasing the size of advisory committees.

A second issue that arises in discussions of the optimal composition of advisory committees is whether individuals who have financial ties to the sponsor should be included in advisory committee meetings. My own research suggests that only some types of financial ties are problematic. In particular, **individuals with exclusive ownership interests (including stocks and bonds) in the sponsor, or who serve on an advisory committee or steering committee for the sponsor, show a particularly strong pro-sponsor bias in their voting.[1, 2] These individuals should be excluded from participating as voting members.** Other types of ties, including receiving research grants from the sponsor, do not appear to bias members towards voting for the sponsor.

Currently, however, **the most problematic financial ties do not appear to be prevalent among members participating in advisory committees**. Our team's analysis of CDER waivers issued since 2012 suggests a low annual rate of waivers (<5%) and, when waivers are issued, a preponderance of financial ties related to competitors rather than sponsors.[3] In previous work, I have shown that members' financial ties to competitors appear to neither advantage nor disadvantage sponsors.[1, 2]

A related concern is the **inclusion of members with past financial ties to the sponsor or financial relationships that create the appearance of a conflict of interest—so-called section 502 conflicts** that do not reach the regulatory threshold of a financial conflict of interest. As you undoubtedly know, FDA analysts have shown that these section 502 conflicts are not associated with pro-sponsor bias.[4] Even so, **periodic media reporting of these types of ties among advisory committee members erodes the credibility of the agency**. Because waivers for these appearance-of-conflict ties are not disclosed to the public, media coverage of these "undisclosed conflicts" are interpreted, inaccurately, as failures in agency screening or intentional obfuscation, diminishing public trust.

To address concerns about the inclusion of members with past sponsor ties or relationships that create the appearance of a conflict of interest, I recommend:

- **public disclosure of section 502 waivers along with the already disclosed section 208 waivers prior to each meeting.**

A **more sweeping structural change** that the FDA might consider would be to:

- **stop issuing waivers for section 208 and section 502 financial conflicts – that is, exclude all individuals with section 208 or section 502 conflicts**
  and
- **create a nonvoting role within the advisory committee that allows for individuals with these conflicts to provide testimony or advise on specific issues.**

Some individuals with financial conflicts of interest or the appearance of financial conflicts will have important expertise from which the agency and the public might benefit. Individuals with these conflicts could be given a newly created nonvoting role in which they would be asked to provide input on a limited number of issues or questions. By constraining both the substantive and the procedural scope of these individuals' participation, the FDA would benefit from these members' expertise while limiting risks from undue influence and potential bias. These individuals need not be Special Government Employees (SGEs) and subject to regulations governing SGEs. The FDA could create a separate conflict-of-interest vetting and disclosure process for these nonvoting participants.

In summary:

- Because FDA advisory committees are tasked to deal with "hard cases" that arise from limitations in real-world study designs, **each meeting should include at least one standing committee member and one temporary member who are biostatisticians who can provide expert advice on inferences that can and cannot be made from suboptimal study designs.**
- To enhance public trust in the FDA, **the agency should publicly disclose section 502 "appearance-of-conflict" waivers along with its disclosure of section 208 waivers prior to each meeting.**
- As an alternative to issuing waivers, **the agency could create a nonvoting role within the advisory committee that allows for individuals with section 208 and section 502 conflicts to provide testimony or advice on specific issues.**

Topic 3: Public Perception and Understanding of Advisory Committees

There appears to be a large gap between agency understanding of the role of FDA advisory committees and public perception of this role. In particular, the agency views itself as the sole decision-maker on medical product authorizations and approvals, with advisory committees occasionally serving a consultative role in complex or controversial cases. The public perceives advisory committee discussions to be the sole basis for product decisions, and even media reporting occasionally confuses advisory committee recommendations with agency decisions.

One reason for this gap in public vs. agency perception could be that advisory committee meetings are the only engagement that the agency has with the general public on product reviews. The public is largely unaware of the many new and supplemental product applications that undergo review without public fanfare because neither product submissions nor the agency's decisions are routinely made public. Although the FDA is constrained in how much information it can disclose about product applications, any summary information that the agency can regularly – i.e., with greater than annual frequency – provide to the public about submissions and approvals might go some way to closing the perception gap.

A second reason for the public vs. agency perception gap might be the climactic vote at the end of advisory committee meetings. Although members are asked to vote on whether they would recommend approval, the up-down vote is confusingly similar to the up-down agency approval decision. Thus, despite the agency's repeated statements that the committee's recommendation is nonbinding and only one of many factors that the agency takes into account,[5] the approval vote at the end of each meeting sends a very different message.

If, in convening advisory committee meetings, the FDA is truly seeking clarity on specific technical issues rather than on members' approval, then the agency should ask solely those technical questions. However, given that the FDA has consistently and historically asked for voting recommendations, the agency apparently also values members' overall evaluations.

As a way of balancing the FDA's need for detailed technical advice and overall assessments, against the confusing signal sent by an end-of-meeting vote, I suggest the following:

- Alternative 1: **The agency could ask for an overall assessment of the benefits, rated on a scale between (say) 1 and 4, and separately, an overall assessment of the risks, also rated on a 1-4 scale, with 1 being lowest and 4 being highest.** Given that "FDA approval of a drug means that… the drug is determined to provide benefits that outweigh its known and potential risks," [6] these separate benefit and risk ratings would provide the two determinative elements of an approval stance. In this way, the agency would have useful and nuanced summary measures that provide an approval recommendation but that do not aggravate existing confusion about the role of advisory committees.
- Alternative 2: **The agency could request a detailed final approval recommendation document that members must submit in writing within 1-2 days of the meeting. The document would include: (1) the approval/non-approval recommendation; (2) explicit justification for the recommendation; (3) a list of remaining issues and areas of concern; and (4) for non-approval recommendations, the requisite additional clinical results, study design, or information – if any – that would lead to an approval recommendation.** Members' recommendation documents would be made available to the public in a timely way. By providing members with time to reflect on their votes, review supporting data and evidence, and submit a detailed assessment, the agency would obtain valuable feedback in addition to a useful overall assessment. The temporal separation created by this procedure would reduce undue time and peer pressures, and foreground the rationales for the recommendations rather than the votes.

The FDA has historically provided an excellent model of thoughtful, well-designed advisory committee functioning, and we members of the public appreciate the agency's efforts in instituting improvements. Thank you for providing this opportunity for public input and engagement in these efforts.

Sincerely,

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Associate Professor
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[1] Pham-Kanter G. Conflicts of Interest in FDA Advisory Committees: The Paradox of Multiple Financial Ties. In: Lynch HF, Cohen IG, eds. FDA in the 21st Century: The Challenges of Regulation of Drugs and New Technologies. New York: Columbia University Press; 2015.

[2] Pham-Kanter G. Revisiting Financial Conflicts of Interest in FDA Advisory Committees. Milbank Quarterly 2014; 92:446-470.

[3] Unpublished work. Available upon request.

[4] 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 Intern Med 2017; 177:1038-1040.

[5] https://www.fda.gov/consumers/consumer-updates/advisory-committees-give-fda-critical-advice-and-public-voice

[6] https://www.fda.gov/drugs/development-approval-process-drugs#:~:text=FDA%20approval%20of%20a%20drug,risks%20for%20the%20intended%20population.