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Original Article

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Financial conflicts of interest during meetings of the cardiovascular and renal drugs advisory committee

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Abstract

Context: The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration (FDA) reviews safety and efficacy data for cardiovascular and renal drugs, ultimately making recommendations to the Commissioner of Food and Drugs for approval. The Open Public Hearing segment of these meetings allows for patients, advocates, healthcare professionals, clinical trialists, and members of the public to provide testimony, which often results in expressing their preference for, or against, drug approval. Prior to providing testimony, the public speakers are highly encouraged to disclose any financial conflicts of interest (FCOIs) with the sponsor or other groups. Given the potential influence of these speakers on drug approval recommendations, we investigated the industry associations disclosed by public speakers in the Open Public Hearing section of the CRDAC meetings. Previous studies, such as one done by Lurie et al. indicated that positive testimony is tied to a higher likelihood of drug approval, and because drug companies provide financial compensation for speakers to provide testimony in general, we wanted to determine the likelihood with which speakers who have an FCOI provided a positive testimony vs. those without any FCOI.

Objectives: The purpose is to evaluate whether public speakers with an FCOI are more likely to provide positive testimony regarding the drug in question during the CRDAC of the FDA between February 2009 and December 2019 through the use of publicly available transcripts.

Methods: Independent researchers investigated public transcripts and minutes of the CRDAC meetings with public speakers (n=20). We identified all speakers, along with characteristics such as an FCOI, and classified statements utilizing a pilot-tested Google form. The data collected were analyzed utilizing Stata. The speaker's testimony was then compared with their FCOI. An ordered logistic regression was performed utilizing the speaker's testimony regarding the drug as the dependent variable.

Results: Of the 88 speakers represented in our sample, 35 (35/88, 39.8%) disclosed an FCOI, most commonly regarding travel cost. Among speakers with an FCOI, 30 (30/35, 85.7%) spoke positively. Speakers with an FCOI were 4.96 times more likely to provide positive testimony (OR=4.96, 95% CI 1.67–14.78). Speakers with the disease were also more likely to provide positive testimony (OR=13.05, 95% CI 2.84–59.93).

Conclusions: Public speakers often play a role during meetings, and they may also have an FCOI, most commonly related to travel expenses. Our study shows that speakers with an FCOI are more likely to provide positive testimony. Stipulations, such as requiring disclosure of FCOI and randomizing the selection process of speakers, can help ensure the integrity of the drug approval process.

Keywords: cardiovascular; pharmacology; systematic review.

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The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration (FDA) reviews safety and efficacy data for cardiovascular and renal drugs, ultimately making recommendations to the Commissioner of Food and Drugs for ultimate approval [1].

The core committee for CRDAC consists of 11 key voting members who are experts in the fields of hypertension, cardiology, arrhythmias, angina, congestive heart failure, and diuresis [1]. Additionally, the committee offers an opportunity for the public to weigh in on the pharmaceuticals in question. The Open Public Hearing segment of these meetings allows for patients, advocates, healthcare professionals, clinical trialists, and members of the public to provide a testimony, which often results in expressing their preference for, or against, drug approval. Currently, the FDA does not require any financial conflict of interest (FCOI) disclosure for speakers at open public hearings [2].

Previous studies by Lurie [3] and Pham-Kanter [4] evaluated the voting behaviors of FDA committee members at these meetings. Although the study by Lurie [3] does not specify the number of committee members investigated, the study by Pham-Kanter [4] looked at over 1,300 committee members (n=1,379) and the effect that public speaker influence has on the committee. They have shown that positive statements made about drugs under consideration for approval by FDA committees are associated with a significantly higher approval percentage when compared with drugs lacking these subjective voices. Perhaps this association does not indicate that these positive testimonies directly correlate to drug approval, but the evidence suggests that a correlation is mounting [5].

An important example of this potential voter influence are two meetings to evaluate the drug Northera (droxidopa), which was submitted for approval by Chelsea Therapeutics. At the first meeting of the CRDAC in 2012, the drug was approved; however, approval was accompanied by a strong suggestion that a postapproval study be conducted for further evaluation of its efficacy and safety. Although it is not abnormal for a postapproval study to be performed, such as a phase 4 trial, this request was followed by a reconvening of the CRDAC in 2014 to review the results of the trial and ultimately lead to swift approval. Of significant note, there was a substantial uptick in the number of public hearing speakers present at the 2014 meeting, where over twice as many speakers offered positive support of the drug in question compared to the meeting prior (n=6 to n=13). Various studies have demonstrated therapies that were previously not recommended for approval and then re-evaluated at a later FDA meeting with a large increase in public speakers from the first to second meeting, have a much higher rate of approval [6–8]. Although the Northera (droxidopa) example does not explicitly follow the same pattern of rejection followed by later approval, the increase of public speakers with an FCOI from six at the 2012 meeting to 13 at the 2014 meeting, and all providing positive testimony, does warrant elucidation.

Previous studies from our research team in urology, neurology, and anesthesia have noted that drugs with objectively low efficacy, with objections from their respective FDA representatives, have been voted for positively after hearing several speakers voice their approval of said drug [6–8]. Because previous studies, such as the one done by Lurie et al. [5] indicated that positive testimony is tied to a higher likelihood of drug approval, and because drug companies provide financial compensation for speakers to provide testimony in general, we wanted to determine the likelihood with which speakers who have an FCOI provided a positive testimony vs. those without any FCOI. A similar investigation has not been conducted to examine the potential influence that public speakers with an FCOI have in CRDAC meetings, and this study builds upon previous studies by further investigating whether having even a single speaker with an FCOI present at these meetings may influence outcome, and also whether having any speakers present led to any increase in drug approval.

Methods

We derived our study methodology from previous work in other fields of medicine, which involved utilizing publicly accessible transcripts from the FDA to explore the prevalence of an FCOI in CRDAC meetings over a 10-year span [6–10]. Our research did not utilize human subjects, therefore this was not subject to oversight by the Institutional Review Board. Between June 2018 and March 2021, we investigated the publicly available transcripts, and meeting minutes, of all CRDAC meetings (n=31) that occurred between February 2009 and December 2019 (January 2009 was not included because there were no publicly available transcripts archived). We excluded meetings that did not have any public speakers present (n=11). From the meeting minutes, we identified all public speakers and the organizations they represented. We then recorded the following information from each transcript utilizing a pilot-tested Google form: speakers' names, the organization they represented, whether the speaker reported having the condition for which the drug was indicated, whether the speaker had taken the drug in question, whether the speakers reported an FCOI, and if so, the company name that provided the payments. For speakers with an FCOI, we recorded the type of COI they incurred (Table 1). We then classified the speaker's statement as positive, neutral, or negative regarding drug approval. Three researchers (CC, HG, NK) extracted this data and classified the statements in an independent, blinded fashion. Consensus meetings were held to resolve any differences found within the data. A third author (MV) was available for third party adjudication but was not needed.

The speaker's statement regarding each drug was then compared with their reported FCOI or lack thereof. This data set was further stratified by analysis of whether each speaker had the illness that each drug was intended to treat and whether they had received said drug. This study utilized odds ratios, 95% confidence intervals, and

Table 1: Characteristics of speakers at CRDAC meetings from February 2009 to December 2019.

Number of speakers (n=88), their characteristics, and types of FCOI	
Speakers who disclosed a non-FCOI	
Speakers with condition in question	31 (35.2%)
Speakers taking drug in question	15 (17.0%)
*Speakers who disclosed an FCOI (n=35)	
Travel and/or lodging	22 (62.8%)
Paid consultant or employee of pharmaceutical company	5 (14.3%)
Organization represented receives funding/grants from pharmaceutical company	5 (14.3%)
Owns stock in the company	2 (5.7%)
Other or unspecified	5 (14.3%)
Speaker's position on drug approval	
Positive	59 (67%)
Negative	13 (14.8%)
Neutral	16 (18.2%)

*Some speakers had more than one financial conflict of interest present. FCOI, financial conflict of interest.

significance levels to interpret this information. The data were placed into a Google sheet for gathering, and Stata was utilized for the statistical analysis, utilizing odds ratios to determine significance. An ordered logistic regression was performed utilizing the speaker's testimony regarding the drug (positive, negative, or neutral) as the dependent variable. The independent variables analyzed include: conflict of interest, whether the speaker has ever taken the drug in question, the number of speakers present at the meeting, meetings with a conflicted speaker present, and whether the speaker had the disease the drug is targeted to treat. Because there was a limited number of neutral responses (n=16), neutral answers were included as "no" answers. Because all speakers who took the drug in question provided positive testimony, we chose to exclude this independent variable from our analysis. In addition, there were no speakers who had taken the drug that did not have the disease, so these two questions were combined into "drug or disease." All responses were included, even those who reviewed multiple drugs. This was done in part due to the limited sample size, and speakers with multiple testimonies provided variable answers during these meetings.

Lastly, we took a closer look at two specific drugs, Northera (droxidopa) and Kengreal (cangrelor), which both followed the pattern of approval following a second FDA committee review and had an increase in the number of speakers with FCOI present at the second meeting. For these examples, the number of speakers present at both meetings were recorded, along with the number of speakers with an FCOI, and the final committee voting results.

Results

After excluding those meetings with no public speakers, our final sample included 20 CRDAC meetings. There were 88 public speakers during these CRDAC Open Public Hearing sessions held between February 2009 and December 2019, with a mean of 4.4 speakers per meeting (Table 2). Of the 88 speakers represented in our sample, 35 (35/88, 39.8%) disclosed an FCOI (Table 1). The most commonly disclosed FCOI was travel cost associated with attendance at the meetings, which were paid for by either the sponsor or another company (22/35, 62.9%). Furthermore, among the public speakers with an FCOI, 30 (30/35, 85.7%) made positive comments regarding the drug in question, whereas only two (2/35, 5.7%) provided negative testimony. By contrast, only 54.7% (29/53) of public speakers without an FCOI gave positive testimony. Thirty-one speakers (31/88, 35.2%) reported having the condition for which the drug was indicated, and 15 of those with the condition (15/31, 48.4%) reported taking the medication or intervention under review. Among those with the disease, 15 speakers (15/31, 48.4%) reported an FCOI. Of those taking the medication, 15 (15/15, 100%) indicated a positive review of the drug and recommended it for approval. Speakers who indicated having the condition for which the drug was intended to treat overwhelmingly provided a positive recommendation, with 29 (29/31, 93.5%) recommending approval, one (1/31, 3.2%) recommending against approval, and one (1/31, 3.2%) providing a neutral statement.

Speakers who divulged an FCOI were found to be nearly five times more likely to give a positive statement than those who did not disclose an FCOI (OR=5.0, 95% CI 1.7–14.8, p<0.004). In addition, those speakers who had the disease, or had taken the drug, were also more likely to provide a positive testimony (OR=13.1, 95% CI 2.8–59.9, p=0.001), which is consistent with previous work investigating FDA committee meetings (Table 3) [9]. There was no association found between the meeting having a single conflicted speaker present and approval of the drug (OR=2.1, 95% CI 0.3–13.8, p=0.4), or between having multiple speakers present at the meeting and drug approval (OR=1.5, 95% CI 0.2–14.4, p=0.7) (Table 4). An odds ratio could not be performed for comparing the likelihood of providing a positive statement in those who took the drug, vs. those who did not, as all who took the drug provided a positive recommendation.

Of the 20 included CRDAC meetings between February 2009 and December 2019, 11 drugs (11/20, 55.0%) were granted approval of at least some form of recommendation. Of the 11 approved drugs during this time, eight (8/11, 72.7%) had at least one speaker with an FCOI, and seven of those meetings with a speaker having an FCOI (7/8, 87.5%) also had at least one speaker with an FCOI and positive testimony (Table 2). The meetings for drugs such as telmisartan, rivaroxaban, and Northera (droxidopa) had 100% of all speakers with an FCOI provide positive testimony, and garnered approval (Table 2).

Table 2: Voting outcomes among speakers at CRDAC meetings from february 2009 to december 2019.

Drug	Pharmaceutical company	Date of meeting	Number of speakers (n=88)	Speakers with reported FCOI (n=35)	Speakers with positive recommendation (n=62)	Voting outcome
Gadolinium-based contrast agents	Bayer, GE healthcare, covidien pharmaceuticals	December 8, 2009	6	2 (33%)	1 (17%)	No formal vote
Prasugrel	Eli lilly and company	February 3, 2009	2	1 (50%)	0 (0%)	Approval
Telmisartan	Boehringer Ingelheim pharmaceuticals, Inc.	July 29, 2009	1	1 (100%)	1 (100%)	Approval
Dronedarone	Sanofi aventis	March 18, 2009	3	1 (33%)	2 (67%)	Approval
Rivaroxaban	Johnson & Johnson pharmaceutical research & development, LLC.	March 19, 2009	1	0 (0%)	1 (100%)	Approval
Ticagrelor	AstraZeneca LP	July 28, 2010	2	0 (0%)	1 (50%)	Approval
Revatio (sildenafil)	Pfizer	July 29, 2010	2	1 (50%)	0 (0%)	Tabled
*Aranesp (darbepoetin alfa)	Amgen, Inc	October 18, 2010	14	3 (21%)	7 (50%)	Disapproval
Ultrasound contrast agents	Lantheus medical Imaging, Inc, GE healthcare, Bracco diagnostics, Inc	May 2, 2011	3	0 (0%)	3 (100%)	Tabled
Northera (droxidopa)	Chelsea therapeutics	February 23, 2012	10	6 (60%)	10 (100%)	Approval (with post approval trial necessitated)
Lixivaptan	Cardiokine biopharma, LLC	September 13, 2012	2	2 (100%)	2 (100%)	Disapproval
Tolvaptan	Otsuka pharmaceutical company	August 5, 2013	10	1 (10%)	9 (90%)	Disapproval
Adempas (riociguat)	Bayer HealthCare pharmaceuticals Inc	August 6, 2013	2	0 (0%)	2 (50%)	Approval
Cangrelor	The medicines company	February 12, 2014	2	0 (0%)	0 (0%)	Disapproval
Northera (droxidopa)	Chelsea therapeutics	January 14, 2014	18	13 (72%)	17 (94%)	Approval
Serelaxin	Novartis pharmaceuticals corp.	March 27, 2014	2	0 (0%)	0 (0%)	Disapproval
Nebivolol/Valsartan	Forest laboratories, Inc.	September 9, 2014	1	0 (0%)	0 (0%)	Disapproval
Fixed-combination anti-hypertensive drug, aspirin, and statin	N/A	September 10, 2014	3	2 (66%)	2 (67%)	No formal vote
Cangrelor	The medicines company	April 15, 2015	2	1 (50%)	2 (50%)	Approval
Vernakalant	Correvio International sarl	December 10, 2019	2	1 (50%)	2 (50%)	Disapproval

*Aranesp had a vote to be withdrawn from market, and this notion was disapproved. FCOI, financial conflict of interest; GE, General Electric; LLC, limited liability corporation; LP, limited partnership.

In addition, among the drugs under consideration for approval during this time, Northera (droxidopa) and Kengreal (cangrelor) were brought up twice, with approval being granted after the second committee meeting. At the initial meeting for Northera (droxidopa capsules), six (6/10, 60.0%) of speakers had an FCOI, and 100% of the speakers with an FCOI provided positive testimony. The drug was granted conditional approval with 7/13 yes votes. After further studies, Northera (droxidopa) was then brought in front of the CRDAC committee once more, this time with more than twice the number of speakers having an FCOI (13), all 13 of whom provided a positive testimony. This time, the committee voted 16–1 in favor of approval of Northera (droxidopa,

Table 3: Associations of speaker characteristics with positive testimony.

Characteristic	Positive statement	Negative statement	Statistical analysis
Conflict of interest present (n=35)	30	5	OR=4.9655, 95% CI 1.6689–14.7743, p=0.0040
No conflict of interest (n=53)	29	24	
Had disease or taken drug? (n=31)	29	2	OR=13.05, 95% CI 2.8418–59.9269, p=0.0010
Did not have disease or taken drug? (n=57)	30	27	

Table 4: Associations of speaker characteristics with drug approval.

Characteristic	Drug approval	No approval	Statistical analysis
Had FCOI speaker at meeting (n=13)	8	5	OR=2.1333, 95% CI 0.3295–13.8142, p=0.4266
No conflicted speaker (n=7)	3	4	
Meetings with >1 speaker with FCOI (n=6)	4	2	OR=1.5, 95% CI 0.1560–14.4209, p=0.7255
Meetings with 1 or fewer speakers with FCOI (n=7)	4	3	

FCOI, financial conflict of interest.

Appendix A). Other drugs, like Kengreal (cangrelor), also were brought before the CRDAC committee on more than one occasion. The first meeting had no speakers with an FCOI (n=2 speakers), and the committee voted 0–9 for disapproval of the drug. At the second meeting, a speaker with an FCOI was present and provided positive testimony. This time, Kengreal (cangrelor) was approved with nine votes in favor, two votes against, and one vote abstaining.

Discussion

After systematically analyzing CRDAC meetings that occurred between February 2009 and December 2019, our investigation demonstrated that those with reported FCOIs are nearly five times more likely to provide positive testimony about drugs presented at the CRDAC meetings. Such a substantial variance in positive testimony in those with an FCOI vs. those without becomes particularly vital in circumstances where drugs are garnering approval through a second meeting in which there is an increase in speakers with an FCOI. Most strikingly, our data shows that 85.7% of speakers with an FCOI provided positive testimony, in contrast to just 54.7% of speakers without an FCOI. Likewise, studies in the Oncology Drug Advisory Committee (ODAC), Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC), Pulmonary-Allergy Drugs Advisory Committee (PADAC), and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) have shown this relationship to be consistent [6–9, 11, 12]

In addition, even though speakers with an FCOI were found to be nearly five times more likely to provide positive testimony, there was no association found between having a certain number of speakers present at a meeting and drug approval (Appendix B). However, this association becomes a gray area when considering drugs where the committee decision may not be unanimous. By including speakers who may receive financial compensation by virtue of travel reimbursement, grants, or other ways, pharmaceutical companies were much more likely in this study to receive a positive testimony on their behalf. By coupling this with the fact that all speakers who took the drug in question and had an FCOI provided a positive testimony (15/15), public speakers with an FCOI play to the benefit of the drug companies that recruited these speakers (Table 1). This voting behavior particularly plays a role in meetings for drugs with limited evidence or drugs in which 100% of all speakers providing testimony disclose an FCOI.

Overall, more than one-third of public speakers at the CRDAC sessions had an FCOI involving the sponsor of the drug. These individuals with an FCOI were far more likely to support drug approval, and in some instances like Northera (droxidopa), all speakers with an FCOI provided positive testimony. Open Public Hearing speakers provide an important and unique perspective on the drugs or devices in question. However, these valuable perspectives can potentially be compromised by the presence of conflicts of interest. Currently, the FDA does not require an FCOI disclosure for speakers at open public hearings, such as funding for travel, lodging, and meals, along with financial interests in each company such as stock and employment [2, 5]. Drugs such as Northera (droxidopa) and Kengreal (cangrelor) had an increase in speakers with an FCOI in comparison to the first meeting, and there was a drastic sway in the number of committee members voting for approval.

We suggest that CRDAC should require full disclosure of an FCOI instead of simply encouraging it, because this requirement would allow the committee members to consider the possible influence of an FCOI on public speakers' testimonies, as well as allowing the committee

members to focus on the safety and efficacy of the drug in question, instead of the potential bias in testimonies [9]. Although the data available in the public transcripts do not indicate the extent of transparency among public speakers regarding their disclosure, such a requirement as this may help ensure that speakers are more transparent regarding their FCOI and testimonies. We also recommend a randomization to the selection process, such as randomly picked video diaries, in an attempt to limit the amount of influence that these conflicts have on the approval of drugs during the CRDAC meetings, as mentioned by Roberts et al. [10]. Similarly, if speakers decline to disclose their FCOI, there should be limitations on whether they should be allowed to give statements, which have been shown in previous studies examining 379 and 385 meetings, respectively, to have the potential to sway the outcome of drug approval voting [4, 13]. In addition, committee members may also have conflicting interests. A study by Pham-Kanter [4] found that between 1997 and 2011, committee members with an FCOI, with sole interests in the drug or device companies and with products up for vote, were more likely to vote in favor of approval than those with no financial ties (OR=1.5, p=0.03).

Beyond public speaker influence on voting outcomes, previous studies have shown that committee voting members also often have an FCOI with industry [7, 9–12]. Lurie et al. [5] found in their 2006 study that of the 221 meetings by 16 FDA advisory committees between 2001 and 2004, one or more committee members in over 70% of the meetings (73.0%) disclosed an FCOI. Among those advisory members who disclosed an FCOI, only 1% were asked not to vote or chose to abstain. Among the disclosed conflicts, the most common included consulting, grants or contracts, and personal investments. They found that 19% of consulting conflicts were valued over $10,000, 23% of grants and contracts were for more than $100,000, and 30% of the investments exceeded $25,000 [3, 5].

Furthermore, an analysis by Herder [14] in 2019 noted a trend toward the above management of the drug approval process, in which pharmaceutical companies were provided initial approval of drugs, with the stipulation of additional postmarketing requirements. Herder [14] noted that these postmarketing requirements frequently lack transparency and ultimately may fail to address the questions of most clinical significance [14]. This becomes important when one considers that, despite the flaws noted in the postmarketing requirement process, drugs are often approved when coupled with the trend of increased positive, public testimony at the second hearing. These studies provide further evidence that a more robust process is needed for evaluating the relationships among committee and voting members and their potential conflicts. Transparency and objectivity are paramount when making decisions to recommend approval of new therapies for the public, and such action is needed to address this, and the other concerns, that we have raised in our study.

Strengths and limitations

This study has several key strengths and limitations. One of the important strengths of this study is that we were able to successfully show significance, utilizing an odds ratio, that speakers with an FCOI were five times more likely to provide positive testimony than those without an FCOI. This study also looked at a large time span from 2009 to 2019, which helps ensure the accuracy of the results.

With regard to limitations, one of the limitations of this study was not being able to include those who did not disclose an FCOI in our data regarding speakers with an FCOI providing a positive testimony, which would have ensured a larger sample size. Even though our study reviewed a 10-year span of data from 2009 to 2019, our sample size remained limited at n=88. Also, our data extraction was limited to publicly available transcripts only, therefore there may be additional confounding variables to consider. Further research needs to be conducted regarding whether those who did not disclose an FCOI were more likely, or less likely, to provide a positive testimony regarding the drug in question.

Likewise, this study seeks to explore the potential influence of speakers with an FCOI and does not take into account some of the considerations surrounding the disease in question, such as how rare the disease is, how debilitating it is, or the current treatment options available for the disease in question. The impact of the diseases that these drugs are utilized to treat have been considered but are not the primary focus of this paper. Further research regarding FCOIs and speakers' votes regarding rare or difficult-to-manage diseases should be considered.

Conclusions

The process of drug approval through the FDA is highly regulated and specialized into subcommittees based on specific fields of medicine. The CRDAC specifically reviews the safety and efficacy data for cardiovascular and renal drugs. This team of 11 expert, core committee members ultimately will vote for, or against, approval after hearing recommendations from public speakers [1]. Sometimes, additional

voting members will also be present. The CRDAC then makes recommendations for approval or disapproval to the Commissioner of Food and Drugs. Public speakers often play a role during these approval meetings, and they may also have an FCOI, with the most common FCOI being related to travel expenses. Our study has shown that speakers with an FCOI are also more likely to provide a positive testimony regarding the drug. Having an FCOI does not prevent these speakers from providing testimony, which may sway voters in favor of approval for a drug that may not have otherwise been approved, due to factors such as limited efficacy or trial data [15]. This research is particularly important for scenarios in which drug evidence may not be as clear or as beneficial. In addition, a large percentage of speakers do not disclose their conflict of interest, and more transparency in the drug approval process will help to ensure that only drugs meeting the correct guidelines will be approved. Although our data showed that there was no statistically significant association found between the meeting having a single conflicted speaker present and approval of the drug, the overwhelmingly positive testimonies given by speakers with an FCOI has the potential to influence committee members' objectivity. FDA committee members ultimately make independent decisions in spite of situations with overwhelmingly positive testimony; however, an adjustment made to counter the proportion of speakers present at meetings with an FCOI and positive testimonies might help eliminate a confounding variable and prevent excess subjectivity. Further stipulations, such as requiring the disclosure of an FCOI and randomizing the process of selection for speakers, can help to ensure that the integrity of the drug approval process is maintained.

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Competing interests: None reported.

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