Public Speaker Characteristics at Meetings of the Dermatologic and Ophthalmic Drug Advisory Committee and the Ophthalmic Devices Panel

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• PURPOSE: **We investigated meetings of the Dermatologic and Ophthalmic Drug Advisory Committee (DODAC) and the Ophthalmic Devices Panel (ODP) of the Food and Drug Administration (FDA) to determine whether a relationship exists between receipt of industry payments by speakers of the Open Public Hearing (OPH) portion and the nature of their recommendations regarding treatment approval.**

• DESIGN: **Cross-sectional study.**

• METHODS: **We reviewed publicly available transcripts of all DODAC and ODP meetings from February 2009 to December 2019. For each meeting, information about each public speaker including presence of conflict of interest (COI) and whether their testimony regarding the drug or device was positive, negative, or neutral toward treatment approval was extracted in a blinded fashion using a pilot-tested Google Form.**

• RESULTS: **Of the 86 speakers, 66 (76.7%) included a COI disclosure statement and 41 (47.7%) disclosed a COI. Regarding classification of the speakers' testimonies, 70 (81.4%) of 86 were positive, 9 (10.5%) of 86 were negative, and 7 (8.1%) of 86 were neutral. Each one of the 41 speakers with a COI gave a positive testimony. Speakers who disclosed a COI were significantly more likely to give a positive testimony than speakers who did not ($P < .001$).**

• CONCLUSION: **We recommend the DODAC and ODP require full disclosure of COI information and introduce stricter policies to manage COIs, allowing the committee to fully understand the context of the public speakers' comments, including the possible influence of COI on these comments. (Am J Ophthalmol 2021;223: 28–32. © 2020 Elsevier Inc. All rights reserved.)**

THE FOOD AND DRUG ADMINISTRATION (FDA) IS responsible for "protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices."[1] As part of its mission, the FDA evaluates specific drugs and medical devices for safety and efficacy through meetings of special advisory committees such as the Dermatologic and Ophthalmic Drug Advisory Committee (DODAC) and the Ophthalmic Devices Panel (ODP). Included in these meetings is an Open Public Hearing (OPH) portion, during which patients, physicians, drug representatives, advocacy groups, and other parties are allowed to present opinions on the drug or device. At the start of the OPH, the meeting moderator provides a statement encouraging speakers to advise the committee of any financial relationships they may have with the meeting sponsor, its product, or any of its competitors in an effort to ensure transparency and allow the committee members to understand the context of an individual's presentation. Speakers with no such financial relationships are likewise encouraged to disclose that to committee members. The moderator then states that those who choose not to address the subject of financial relationships are not precluded from speaking, leaving speakers with the option of foregoing this statement altogether. It has recently been called into question whether COI may sway a speaker's argument toward approval of a drug or device.[2–5] It has been demonstrated that even "small gifts" can be surprisingly influential.[6,7]

Public speakers can play an active role during committee meetings. For example, consider the February 2015 joint meeting of the FDA's DODAC and ODP to discuss a new KXL combination device-drug technology used to treat progressive keratoconus and corneal ectasia following LASIK. During the open public hearing portion of the meeting, several of the 14 public speakers voiced concern about the sponsor and its chief executive officer who they stated had allegedly earned $18 million for marketing the first FDA-approved lasers for LASIK.[8] They also spoke about payments made from the sponsor to influential politicians in efforts to bring the laser to market. Despite speakers attempting to point out gaps and lack of detail in the sponsor's clinical data, the absence of any performance data from the KXL machine itself, and the sponsor's failure to provide patient satisfaction assessments, the panel voted 10-4 with 1 abstention to recommend approval of the progressive keratoconus indication and 6-4 with 4 abstentions for the ectasia following refractive surgery (LASIK) indication. Although FDA approval was ultimately granted for this therapy—despite the testimony of the

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public speakers—other cases, such as eteplirsen for Duchenne Muscular Dystrophy[4] and flibanserin for female hypoactive sexual desire disorder[9] highlight examples where public speakers may have played a pivotal role in drug approval despite limited clinical efficacy data. In the case of flibanserin, prior to its approval in 2015, the FDA had rejected approval twice, citing concerns about possible adverse effects of central nervous system depression. In preparing for its third attempt at approval, the new sponsor of flibanserin hired a public relations firm, formed a patient advocacy group, and paid members of this group to speak positively about the drug at the third meeting for approval.[10,11] The drug was approved, with members voting in favor of approval despite noting that it had "small treatment effects and substantial safety concerns."[9] Since approval, studies have demonstrated the drug's mild efficacy and concerning adverse effects.[12]

Efforts must be made to approve therapies that provide meaningful benefits to patients. Talati and associates[13] found that although recalls of ophthalmic devices are rare, they have a disproportionate impact on public health because of the sheer volume of devices per recall event. Our study investigated the financial conflicts of interest of open public hearing speakers at meetings of the Dermatologic and Ophthalmic Drug Advisory Committee and the Ophthalmic Devices Panel to determine whether a relationship exists between receipt of payments by public speakers and the nature of their recommendations regarding approval for the therapy. To our knowledge, this is the first study of its kind in the field of ophthalmology.

METHODS

• **STUDY DESIGN:** Our methods are based on previous studies.[2–5] Our study used publicly accessible data of FDA transcripts and did not involve human subjects; therefore, it did not qualify as human subject research as defined in 45 CFR 46.102(d) and (f) and was not subject to further oversight by the OSU-CHS IRB. Our study adhered to the Declaration of Helsinki and all federal and state laws in our country. We searched the FDA website for published transcripts from the DODAC and ODP meetings from February 2009 to December 2019 (n=25) and reviewed these transcripts.[14,15] The transcript for the DODAC meeting of December 2019 was not publicly available at the time of data collection, so that meeting was excluded. For the purpose of this study, meetings without public speakers were excluded (n=5), as well as meetings without an industry sponsor that discussed general topics rather than a specific product or intervention (n=6). Our review of the remaining 13 meetings concluded on December 23, 2019.

• **DATA EXTRACTION:** Two investigators (MK and MW) used a pilot-tested Google Form to perform blinded, independent data extraction. Google Forms is a survey platform that has previously been effectively used in systematic reviews for data extraction. Each of the prespecified variables from our study was included in the Google Form, allowing the investigators to record their responses for each meeting. The data were then extracted into a Google spreadsheet for further statistical analysis. The form was pilot-tested for the first meeting to account for any necessary adjustments before it was launched for the rest of the study. For each meeting, the investigators recorded public speakers' names, the organizations they represented, whether they were affected by the disease for which the drug or device was indicated, whether they were treated with the drug or device, and whether the speaker reported any COI. We categorized the speakers into the following categories: patient, relative of a patient, patient advocate, medical organization representative (eg, professional society or medical school), industry representative, nonprofit, and general public (ie, unrelated to a patient or organization). Finally, we classified each testimony regarding the drug or device as positive, negative, or neutral toward approval. Positive testimonies were identified as those containing statements such as "I strongly urge you to consider passing this and labeling it." Negative testimonies were identified as those containing statements such as "the evidence indicates this treatment would do more harm than good." Neutral testimonies were identified as those containing statements such as "I suggest that the panel recommend limiting the product to cases with active progression and include all applicable risks." Each testimony was classified based on the respective speaker's final suggestion regarding drug or device approval, and thus no situation arose where there was a testimony being classified as a combination of positive, negative, and neutral. All testimonies were reviewed and categorized in a dual, blinded, and independent process. After completion of the review, the 2 investigators (MK and MW) resolved any discrepancies by consensus. A third-party investigator (CC) was available for further discrepancy resolution; however, this mitigation process was not needed.

• **DATA ANALYSES:** With the classification of each testimony (positive vs not positive [negative or neutral]) as our dependent variable, we performed an ordered logistic regression. Our independent variables included whether speakers were affected by the disease for which the drug or device was indicated, whether they were treated with the drug or device, and whether the speaker reported any COI. All responses, including those from speakers who reviewed multiple drugs or devices from different meetings, were used. All analyses were conducted using Stata, version 15.1.

RESULTS

WE IDENTIFIED 86 SPEAKERS FROM THE 13 DODAC AND ODP meetings included in our study with a mean of 6.6 (SD =

TABLE 1. Characteristics of Meetings of the Dermatologic and Ophthalmic Drug Advisory Committee and Ophthalmic Devices Panel

Advisory Committee	Drug/Device Name	Pharmaceutical Company	Total no. of Speakers	No. of Speakers With COIs	No. of Speakers Without COIs	No. of Speakers Without Disclosure Statement
ODP	Implantable Miniature Telescope	VisionCare Technologies Inc.	7	4	2	1
DODAC	Elyea (Aflibercept ophthalmic solution)	Regeneron Pharmaceuticals, Inc.	2	1	1	0
DODAC	Lucentis (Ranibizumab injection)	Genentech Inc.	13	3	3	7
DODAC	Jetrea (Ocriplasmin intravitreal injection)	ThromboGenics, Inc.	5	2	2	1
ODP	Argus II Retinal Prosthesis System	Second Sight Medical Products, Inc.	9	2	4	3
ODP	Trulign Toric Accommodating Posterior Chamber Intraocular Lens	Bausch & Lomb	2	1	1	0
ODP	Visian Toric Implantable Collamer Lens	STAAR Surgical Company	7	5	2	0
ODP	Kamra Inlay	AcuFocus, Inc.	4	4	0	0
DODAC	Secukinumab	Novartis	3	3	0	0
ODP	AcrySof IQ ReSTOR Multifocal Toric Posterior Chamber Intraocular Lens	Alcon Inc	8	5	0	3
DODAC and ODP	Riboflavin ophthalmic solutions with UV-A irradiation	Avedro Inc	14	1	8	5
DODAC	Deoxycholic acid injection	Kythera Biopharmaceuticals	11	9	2	0
DODAC	Brodalumab injection	Valeant Pharmaceuticals Luxembourg S.a.r.l.	1	1	0	0

COI = conflicts of interest, DODAC = Dermatologic and Ophthalmic Drug Advisory Committee, ODP = Ophthalmic Devices Panel.

4.27) speakers per meeting. Table 1 lists the FDA committee holding each meeting, the name of the device or drug, the respective pharmaceutical company, the total number of speakers, the number of speakers with a COI, the number of speakers without a COI, and the number of speakers who did not make a disclosure statement. Prior to resolving discrepancies, inter-rater reliability was within acceptable ranges (Gwet's AC1 0.85, 95% CI 0.76-0.95). Of the 86 speakers of DODAC and ODP meetings, 33 (38.4%) were patients, 14 (16.3%) were industry representatives, 11 (12.8%) were members of the general public, 11 (12.8%) were nonprofit organization representatives, 9 (10.5%) were medical organization representatives, 4 (4.7%) were relatives of a patient, and 4 (4.7%) were patient advocates. Of the 86 speakers, 66 (76.7%) included a COI disclosure statement and 41 (47.7%) disclosed a COI. Regarding classification of the speakers' 86 testimonies, 70 (81.4%) were positive, 9 (10.5%) were negative, and 7 (8.1%) were neutral.

Of the 41 speakers with COIs, 24 (58.5%) only reported being supported through travel compensation and 16 (39.0%) were supported by, previously funded by, or represented patient groups that were funded by the drug sponsors. Among the speakers who reported a COI, all 41 gave a positive testimony. Among the 45 speakers who did not disclose a COI, only 29 (64.4%) gave a positive testimony. Speakers affected by the disease for which the device or drug was indicated gave a positive testimony in 33 (91.7%) of 36 instances, whereas speakers who were treated with the device or drug in question gave positive testimonies in 30 (96.8%) of 31 instances. Of the 66 speakers who included a COI disclosure statement, 55 (83.3%) gave a positive testimony. Of the 20 speakers who did not include a COI disclosure statement, 15 (75%) gave a positive statement. Fisher exact analysis revealed no significant difference in the likelihood of giving a positive statement between speakers who included a COI disclosure statement and speakers who did not ($P > .5$).

We examined both unadjusted and adjusted associations. Regarding the unadjusted associations, both speakers who disclosed a COI (OR 5.26, 95% CI 2.17-12.75; $P < .001$) and speakers who had the disease (OR 3.99, 95% CI 1.05-15.20; $P = .043$) were significantly associated with speakers giving a positive testimony vs a nonpositive testimony (negative or neutral). Our ordered logistic regression model, in which both predictors were entered into the regression model, found that speakers who disclosed a COI were significantly more likely to give a positive testimony than speakers who did not (OR 4.63, 95% CI 1.95-10.96, $P < .001$), although speakers who were affected by the disease for which the drug or device was indicated were not found to be more likely to give a positive testimony than those who were not affected (OR 2.79, 95% CI 0.66-11.83, $P = .17$). Owing to the high degree of collinearity between those who were affected by the disease in question and those who were treated with the drug or

TABLE 2. Two-Way Tables Demonstrating the Results of Our Ordered Logistic Regression

Speaker Testimony by Characteristic	COI	No COI	Did Not Disclose
Speaker had condition			
Positive statement	18	3	12
Negative/neutral statement	0	2	1
Speaker took drug			
Positive statement	16	2	12
Negative/neutral statement	0	1	0
Speaker did not have condition or take drug			
Positive statement	23	11	3
Negative/neutral statement	0	9	4

COI = conflicts of interest.

The nature of the testimony of speakers is compared based on COI status for speakers who suffered from the disease in question, speakers who were treated with the respective therapy, and speakers who did not suffer from the disease and were not treated, respectively.

device, we only included the disease variable in our model. Table 2 demonstrates the results of each of the variables from our ordered logistic regression.

DISCUSSION

WE INVESTIGATED DODAC AND ODP MEETINGS TO EVALuate the association between financial conflicts of interest and the likelihood that speakers would give a positive testimony regarding a drug/device. Nearly one-half of the 86 Open Public Hearing speakers in our study had COIs involving the drug or device sponsor, with payments for travel being the most common. All of these speakers gave positive testimonies. Our results showed that speakers with a COI were 4.63 times more likely to speak positively regarding the drug/device. This finding is similar to those reported in other FDA Advisory Committee meetings. In meetings of the Anesthetic and Analgesic Drug Products Advisory Committee (AADAC), McCoy and associates[5] found speakers who disclosed a COI to be 6.07 times more likely to speak positively about the drug in question. Arthur and associates[4] investigated meetings of the Peripheral and Central Nervous System Drug Advisory Committee (PCNSDAC) and found that 126 of 129 speakers had a COI, and those with a COI were 5.59 times more likely to give a positive testimony in regard to the drug in question. Abola and Prasad[3] investigated meetings of the Oncologic Drug Advisory Committee (ODAC) and found that 31 of 103 public speakers reported financial COIs, all of which gave positive testimonies in regard to the drug in question.

Regarding those affected by the disease process in question and those who were treated with the associated drug or device, our study did not find either of these groups to be statistically significantly more likely to speak positively about the drug or device.

More than 23% of the speakers in our study failed to mention COIs in their testimonies. This finding is similar to that of AADAC meetings,[5] where nearly 20% of speakers were found to have undisclosed COIs. Conflicts of interest are seriously considered for those serving on Advisory Committees for the FDA. Specific legislative guidance in 18 USC 208(a) "prohibits all employees, including Special Government Employees (SGEs) serving on advisory committees, from participating in any particular Government matter that will have a "direct and predictable effect" on their financial interests."[5] These guidelines, however, are only applicable to those participating in the committee and not to the speakers participating in the OPH, allowing for the possibility of COIs to go unreported. It has been previously argued that industry relationships are prevalent in the medical community[16] and that small industry gifts can be surprisingly influential in the medical field.[6,7,17] When viewed in the context of this study, if physicians' drug-prescribing behaviors can be influenced by small gifts such as meals, we question the likelihood of industry COIs having an influence on members of the general public's testimonies regarding drug or device approval. We argue that the likelihood is significant enough to merit additional research into its effects as well as stricter guidelines by the FDA.

It has been demonstrated in our study and previous studies that speakers with financial COIs are more likely to speak positively regarding drug or device approval. A study investigating Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) meetings found a 233% increase in the number of public speakers for the resubmission of a drug that was previously rejected. This is a tactic that can potentially be used by pharmaceutical companies when resubmitting a drug for approval or even in an initial submission. For drugs in which large-scale randomized controlled trials demonstrate clear evidence of clinical efficacy and safety, the impact of public speakers is likely not as prominent. It is in the case of drugs such as flibanserin,[9] in which the sponsor has doubts of market approval because of limited efficacy or safety concerns, that public speakers may be used to sway voters. We recommend a standardized approach to public speaker selection. This may include, for example, a limit on the number of public speakers allowed to speak per meeting or preselecting random patients participating in a drug's clinical trial to record video diaries and having those videos played at drug approval meetings, rather than having patients handpicked by the pharmaceutical company attend the meetings. In the case of public speakers who are health care providers, we recommend the FDA utilize the Physician Payments Sunshine Act[18] to provide committee members with information regarding financial relationships of the speakers with medical product manufacturers. The

Sunshine Act, however, only applies to the few public speakers who are health care providers; therefore, we recommend the FDA require other public speakers to disclose any financial relationships in a similar manner. Although this full disclosure would increase transparency, we realize that it may not be sufficient in mitigating bias. Therefore, we agree with recommendations made by McCoy and Emmanuel[19] to implement additional procedures such as stricter management of COIs or prohibition. Stricter management of COIs may include a limit on the number of speakers with a COI allowed to speak at each meeting, whereas prohibition would prevent all speakers with a COI from speaking altogether. Such requirements would assist in maximizing transparency and the likelihood of therapies being approved based on objective findings, therefore minimizing the risk of bias and the potential effect of industry payments on drug or device approval.

Regarding limitations of this study, we acknowledge the subjective nature of classifying speakers' statements as positive, negative, or neutral. To mitigate this subjectivity, we used speakers' final recommendation regarding drug or device approval when present. As a secondary limitation, there were a number of speakers who did not include a COI disclosure statement in their testimonies. These speakers were included in our data as speakers without a COI; however, it is possible that they had an undisclosed COI.

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