

The Potential Effects of Financial Conflicts of Interest of Speakers at the US Food and Drug Administration's Pulmonary-Allergy Drug Advisory Committee Meetings

To the Editor:

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) evaluates the safety and efficacy of new drugs used in the treatment of pulmonary, allergic, and immunologic diseases.¹ Previous studies have shown that positive recommendations from advisory committees are associated with drug approval by the Food and Drug Administration (FDA).² Our previous

studies also showed that speakers with financial conflicts of interest (FCOI) were more likely to speak positively about the drug in question.^{3,4} Our study of the Bone, Reproductive, and Urologic Drugs Advisory Committee also showed that a drug that was rejected had an increase of 233% in the number of public speakers when the drug was resubmitted.⁵ Other studies outside of our research team have shown that public speakers with an FCOI are 6.07 times more likely to speak positively about the drug in question.⁷ We are concerned that pharmaceutical companies may increase the number of public speakers when resubmitting rejected drugs to increase their chances of getting a positive recommendation for approval, and this raises questions as to whether this strategy may be used on initial submission in the event that the drug company has concerns about approval because of a drug's marginal efficacy or safety evidence.

Methods

We included the testimonies of all public speakers at the PADAC meetings from November 2009 to May 2019, using all available transcripts on the FDA website. We used a pilot-tested Google form to perform blinded, independent data extraction for each speaker. Our primary outcome was the association between the nature of public speakers' testimonies and whether these speakers disclosed FCOI. The following data points were extracted from each transcript: organization represented, drug discussed, whether the speaker had taken the drug, whether the speaker had the disorder the drug was intended to treat, whether the speaker disclosed an FCOI (negative if undisclosed or disclosed no conflict), the nature of the FCOI (eg, travel, lodging, employment), and whether the speaker made a positive, negative, or neutral recommendation for drug approval. After data

extraction, the authors came together to settle discrepancies with the extracted data and testimony interpretations. We also obtained data from the FDA website regarding drug approval status.

A binary logistic regression was performed with each speaker's overall statement about the drug—positive and not positive—serving as the dependent variable. Independent variables included whether the speaker was taking the drug in question, whether the speaker had the disorder treated by the drug, and whether the speaker disclosed an FCOI. Standard errors were clustered at the drug level to account for some drugs that were presented at multiple meetings, using the bootstrapping method with 500 replications. Analyses regarding the effect of number of speakers and the presence of conflicted speakers on drug approval status were conducted at the meeting level. Stata 15.1 was used for all analyses.

Results

From 16 PADAC meetings, we extracted data for 127 speakers. Table 1 represents the number of speakers for each drug and the number of speakers that disclosed an FCOI. Forty-nine (of 127 [38.6%]) speakers disclosed an FCOI, and of those speakers that disclosed an FCOI, 43 (87.7%) also made positive statements. Fifty-one (of 127 [40.2%]) speakers had the disorder for which the drug was being evaluated. Only 15 (of 51 [30%]) speakers who had the disorder disclosed an FCOI. Of the patients who had the disorder, 48 (of 51 [94%]) made positive statements.

Our binary logistic regression model found that speakers who disclosed an FCOI were 4.470 times more likely to give a positive testimony than those who did not (OR = 4.470; 95% CI = 1.366-14.634, $P = .013$) and that speakers who had the disorder for which the drug was taken were 4.919 times more likely to provide positive testimony than speakers who did not have the disorder (OR = 4.919; 95% CI = 1.674-14.456; $P = .004$). Speakers who took the medication in question were not more likely to provide a positive testimony than those who did not (OR = 3.431; 95% CI = 1.081-10.891; $P = .036$). The width of these CIs, however, limits the

TABLE 1] Number of Speakers and Number of Speakers With FCOI With Percent Total for Each Drug and Its Sponsoring Drug Company

Drug Name Presented at Hearing and Meeting Date	Drug Company	No. of Speakers ^a	No. of Speakers With Disclosed Financial Conflicts of Interest ^b	Meeting Vote: Approval, Disapproval, Tabled
Bronchitol; May 8, 2019	Chiesi	20 (15.75%)	12 (24.49%)	Approval
Long-acting beta-2 agonist; March 11, 2010	Merck	4 (3.15%)	2 (4.08%)	Tabled/no formal vote
Xolair; November 18, 2009	Genentech and Novartis	3 (2.36%)	2 (4.08%)	Disapproval
Umeclidinium/vilanterol; September 10, 2013	GlaxoSmithKline (GSK)	3 (2.36%)	1 (2.04%)	Approval
Tiotropium bromide; August 14, 2014	Boehringer Ingelheim Pharmaceuticals	1 (0.79%)	0 (0%)	Approval
Pirfenidone; March 9, 2010	InterMune	18 (14.17%)	4 (8.16%)	Approval
Olodaterol; January 29, 2013	Boehringer Ingelheim Pharmaceuticals	1 (0.79%)	0 (0%)	Approval
Mannitol inhalation powder (2013 Bronchitol); January 30, 2013	Pharmaxis	9 (7.09%)	3 (6.12%)	Disapproval
Mannitol challenge; November 20, 2009	Pharmaxis	8 (6.30%)	7 (14.29%)	Approval
Lumacaftor/ivacaftor; May 12, 2015	Vertex	20 (15.75%)	4 (8.16%)	Approval
Ivacaftor; October 21, 2014	Vertex	10 (7.87%)	2 (4.08%)	Approval
Indacaterol; March 8, 2011	Novartis	3 (2.36%)	1 (2.04%)	Approval
Icatibant; June 23, 2011	Jerini US, Inc.	5 (3.94%)	5 (10.20%)	Approval
Fluticasone Furoate/vilanterol (2013); April 17, 2013	GlaxoSmithKline (GSK)	3(2.36%)	0 (0%)	Approval
Fluticasone Furoate/vilanterol (2015); March 19, 2015	GlaxoSmithKline (GSK)	2 (1.57%)	0 (0%)	Approval for adults 18 years and older, Disapproval for children 12-17
Epinephrine inhalation OTC; February 25, 2014	Armstrong Pharmaceuticals, Inc.	7 (5.51%)	0	Disapproval
Ecallantide; February 4, 2009	Dyax	6 (4.72%)	6 (12.24%)	Approval
Codeine; December 10, 2015	N/A	3 (2.36%)	0 (0%)	Approval to remove codeine for use in children younger than 18
Aclidinium bromide; February 23, 2012	Forest Laboratories, Inc.	1 (0.79%)	0 (0%)	Approval

^aPercentage from total number of speakers (n = 127).^bPercentage from total number of speakers with financial conflicts of interest (n = 49).

TABLE 2] Binary Logistic Regression Results of Public Speaker Characteristics and the Nature of Their Statements

Covariables	OR	SE	95% CI	
Speaker disclosed FCOI	4.470	2.705	1.366	14.634
Speaker had disease	4.919	2.705	1.674	14.456
Speaker had taken drug	4.431	2.022	1.081	10.891

FCOI = financial conflicts of interest.

certainty of these findings. Finally, we evaluated whether meetings with conflicted speakers and the number of speakers per meeting were associated with FDA drug approval. Our results suggest that neither conflicted speakers (OR = 0.55; 95% CI = 0.05-6.53; $P = .63$) nor the number of speakers (OR = 1.12; 95% CI = 0.87-1.45; $P = .38$) was related to ultimate approval of the drug.

Discussion

This study and others indicate that public speakers compensated by drug companies are more likely to make positive statements about the drug in question, and this study also shows that speakers that have the disorder treated by the drug in question frequently make positive statements. Possibly drug companies are seeking out ideal patients who responded well to the drug and experienced minimal adverse events to present at these meetings. However, these patients may not be representative of all patients who take the drug. Thus, better selection methods should be discussed by Drug Advisory Committees to minimize the potential for selection bias and to retain focus on drug efficacy and safety. Although findings from our study do not suggest that meetings with conflicted speakers or the number of speakers were significantly associated with drug approval, we speculate that the nature of the evidence supporting drug approval may play an important role. In cases in which large trials present clear evidence of clinical efficacy, the decision made by the committee would likely be appropriate, and public speakers would have less of an impact. However, in cases in which there is unclear clinical benefit, or cases in which no current treatment exists, public speakers may play an important role in influencing voting behaviors. Our data do not lend themselves to such an inquiry, but it would be an interesting avenue for future research. Our data are limited by a small sample size, and we would suggest

future research looking at multiple drug advisory committees to determine whether a relationship existed between speaker FCOI and drug approval.

Unicted Table

Table 2

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FINANCIAL/NONFINANCIAL DISCLOSURES: None declared. The findings in this research have been presented at the 2020 Oklahoma Research Day and the 2020 OSU-CHS Research Day.

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DOI: <https://doi.org/10.1016/j.chest.2020.10.073>

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