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FINAL

FINANCIAL CONFLICT-OF-INTEREST DISCLOSURE AND VOTING PATTERNS AT FDA ADVISORY COMMITTEE MEETINGS

Submitted to:
Nancy Gieser
Office of Policy, Planning and Preparedness
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Submitted by:
Nyssa Ackerley
John Eyraud
Cal Franz
Brielle Kissel
Dina Metivier
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421
www.erg.com

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ERG

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EXECUTIVE SUMMARY

Under contract to the US Food and Drug Administration, Eastern Research Group, Inc. (ERG) assessed the relationship between financial conflict-of-interest disclosure and voting patterns at FDA advisory committee meetings. The objective of this study is to extend the analysis presented by Peter Lurie et al. in "Financial Conflict-of-interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings." This report presents ERG's study findings covering advisory committee meetings of three FDA centers—the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER)—from 2001 through the first quarter of 2008.

In 2006, the Journal of the American Medical Association (JAMA) published findings regarding the relationship between disclosure of financial conflicts-of-interest and voting behavior among FDA advisory committee members (Lurie et al., 2006). That study found a weak, but statistically significant positive relationship between certain types of financial conflicts-of-interest and voting patterns in two different analyses that assessed the effects of disclosure on individual votes. Nonetheless, Lurie et al. also found that even if voting standing and temporary members with financial conflicts-of-interest had been excluded from voting, the voting outcomes for all 76 product meetings analyzed would have been unchanged.

FDA reviewed the Lurie study and published comments regarding the conclusions on its website. While FDA did not dispute the analysis, the agency suggested some changes in the interpretation of results. Specifically, FDA considered to be flawed the authors' interpretation that all votes in favor of the drug of interest at product meetings (i.e., the index drug) favor the financial interests of pharmaceutical companies and all votes not in favor oppose their interests. FDA also identified an important result that was not highlighted in the original article: Advisory committee standing and temporary members with financial ties to pharmaceutical companies tend to vote against the financial interest of those companies. FDA suggested that votes should be interpreted based on their effects on the financial interest of the relevant pharmaceutical companies. Specifically, if a voter has a financial tie to the sponsoring company, FDA interpreted a vote in favor of the drug as favoring the company; if a voter has a financial tie to a competitor, FDA interpreted a vote not in favor of a drug as favoring the competing company. Rather than asking whether having a financial tie to *any* pharmaceutical company tends to increase votes in support of a drug (a notion inconsistent with conventional interpretations of conflict-of-interest), FDA asked whether having a financial interest tends to increase votes in favor of that interest.

The Lurie study was based on data collected for CDER meetings held between January 2001 and December 2004. ERG obtained these data from Public Citizen and expanded the original dataset to include meetings within CDER, CBER and CDRH held between January 2001 and the first quarter of 2008. Data were compiled from publicly available advisory committee meeting transcripts, agendas, rosters and minutes on the FDA website. For some committee members who were granted waivers, ERG also obtained information from FDA regarding the nature of their financial interests. ERG conducted four meeting-level and two individual level analyses to assess the relationship between financial interests and voting patterns.

ERG found that the expanded dataset produced meeting-level results similar to Lurie's findings. Specifically, ERG found no statistically significant relationship between conflict rates and voting outcomes (α=0.05) when considering financial ties with: the product sponsor ("index conflict"), a competitor of the sponsor ("competitor conflict"), or the product sponsor or a competitor or both ("any conflict"). ERG also found individual-level results similar in direction to Lurie's findings. Overall, ERG found no evidence to suggest that having a financial conflict-of-interest tends to increase votes in favor of that interest.

1. INTRODUCTION

The mission of the U.S. Food and Drug Administration (FDA) is to protect the public health by helping to ensure the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. To that end, FDA established advisory committees to "provide independent expert advice to the agency on scientific, technical, and policy matters related to the development and evaluation of FDA-regulated products" (FDA, 2008). For specific products, advisory committees consider the available evidence and provide scientific and medical advice on safety, efficacy, and appropriate use. Committees might also be relied upon to participate in the agency's decision-making process on broader regulatory and scientific issues. Advisory committee meetings can occur during any stage of a product's review process or, if necessary, as post-marketing issues arise. Committee recommendations remain advisory in nature, as all final decisions on both policy and technical matters are made by FDA.

Over the years, there has been interest in the potential relationship between advisory committee members' financial, professional, or personal stakes in advisory committee recommendations and their voting behavior at such meetings.[1] In particular, a 2006 JAMA article studied the relationship between disclosure of financial conflicts-of-interest and voting behavior among FDA advisory committee members (Lurie et. al., 2006).[2] One significant finding of the study, which was co-authored by Peter Lurie of Public Citizen's Health Research Group,[3] was that even if voting committee members with financial conflicts-of-interest had been excluded from voting, none of the voting outcomes for the 76 product meetings analyzed would have changed.[4] Nevertheless, Lurie found a weak, but statistically significant positive relationship between certain types of conflicts and voting patterns in two different analyses that assessed the effects of disclosure on individual votes.

FDA reviewed the Lurie study and published comments regarding the conclusions on its website. While FDA did not dispute the analysis, they suggested some changes in the interpretation of results. Specifically, FDA considered to be flawed Lurie et al.'s interpretation of "all yes votes on drugs as favoring the financial interests of pharmaceutical companies and all no votes as opposing their interests" (FDA, 2008b). FDA suggested that votes should be interpreted based on their effects on the financial interest of the relevant pharmaceutical companies. Specifically, if a voter has a financial tie to the sponsoring company, FDA interpreted a vote in favor of the drug or device as favoring the company; if a voter has a financial tie to a competitor, FDA interpreted a vote not in favor of a drug or device as favoring the competing company. Rather than asking whether having a financial tie to *any* pharmaceutical company tends to increase votes in support of a drug (a notion inconsistent with conventional interpretations of conflict-of-interest), FDA asked whether having a financial interest tends to increase votes in favor of that interest.

[1] See ERG's previous study, "Measuring Conflict-of-interest and Expertise on FDA Advisory Committees" for more information on this topic.

[2] See Lurie et al., 2006. "Financial Conflict-of-interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings." *JAMA*, 295:1921-1928.

[3] Public Citizen is a national, nonprofit consumer advocacy organization founded in 1971 to represent consumer interests in Congress, the executive branch and the courts. (http://www.citizen.org/about/)

[4] Product meetings were defined as those involving specific products. Non-product meetings involved more general scientific issues that may relate to a class of products.

Reinterpreting Lurie's results, FDA's comments identified "an important result that was not highlighted in the original article: Advisory committee standing and temporary members with financial ties to pharmaceutical companies tend to vote against the financial interest of those companies" (FDA, 2008b). FDA suggests that Lurie's results provide "further evidence against the charge that the financial interests of voters taint committee votes" (FDA, 2008b).

This study examines the relationship between disclosure of financial conflicts-of-interest and voting patterns for advisory committees from three FDA centers—the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER)—from 2001 through the first quarter of 2008. The objective of this study is to extend the analysis presented by Lurie et al. and analyze whether advisory committee members tend to vote in a manner that is relevant to their financial conflicts-of-interest. In order to conduct this analysis, the data used in Lurie et al. were made available to ERG by Public Citizen.

Section 2 of this report provides an overview of FDA advisory committees and how financial conflicts-of-interest are defined. Section 3 of this report outlines the study methodology as described by Lurie et al. and, therefore, as implemented by ERG. An overview of the aggregated data as collected by ERG and Public Citizen is presented in Section 4. Finally, Section 5 describes both the results obtained by Lurie et al. and the analysis of the expanded sample of FDA advisory committee meetings.

2. OVERVIEW OF FDA ADVISORY COMMITTEES

The Federal Advisory Committee Act (Pub. L. 92-463) regulates the establishment of Federal advisory committees, including those that provide advice to FDA. Some FDA advisory committees are established by statute, but many are formed and dissolved at the discretion of the Department of Health and Human Services.

Currently, there are 31 FDA advisory committees (with one committee that consists of 18 sub-panels) serving as independent advisory bodies. These 48 advisory bodies provide advice on topic areas for the FDA Office of the Commissioner and each of the following six FDA centers:

- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Drug Evaluation and Research (CDER)
- Center for Veterinary Medicine (CVM)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- National Center for Toxicological Research (NCTR).

2.1. FDA ADVISORY COMMITTEE MEMBER SELECTION

To provide inclusive representation, there are four different categories of FDA advisory committee membership: academicians/practitioners and consumer, patient, and industry representatives. Committees have on average ten standing members, who serve staggered four-year terms. Although members can serve up to eight years within a twelve-year period, they may not serve consecutive terms.

Standing committee members are selected from qualified candidates with relevant professional, scientific, or academic experience. Like their academic and clinical colleagues, consumer representatives are typically voting members and therefore are required to be "technically and scientifically qualified" to analyze research design and scientific data (FDA Handbook, 1994).[5] Industry representatives are non-voting members. In addition to standing members, temporary members might be appointed to attend a single committee meeting when a quorum is needed or additional expertise is required. Temporary members may or may not be authorized to vote on meeting topics.

FDA posts impending vacancies for advisory committee positions in a Federal Register notice, as well as on an Internet website that shows current vacancies on all of its committees. FDA advisory committee staff members may also recruit members by networking at large events, such as national meetings of relevant professional organizations (FDA Handbook, 1994).

According to the Policy and Guidance Handbook for FDA Advisory Committees, all potential candidates must meet certain general criteria. Specifically, they are required to:

[5] Consumer representatives are not voting members on advisory committees for the Center for Devices and Radiological Health.

- Have the background, education and experience commensurate with the purposes and objectives of the individual committee and the advice they are expected to render. Scientific and technical competence is critical.
- Be at least 21 years of age.
- Preferably be a United States citizen.

Candidates are carefully screened to ensure that they possess expertise relevant to the particular committee or subject matter on which their advice will be sought. In addition, when FDA considers a term appointment to an advisory committee, the agency reviews the financial disclosure report filed pursuant to the Ethics in Government Act of 1978 for each individual under consideration for the appointment, so as to reduce the likelihood that an appointed individual will later require a waiver to participate in a meeting (Section 712(b)(2) of the FDCA).

FDA officials confirm that selecting advisory committee members is not an easy task. Resumes or curriculum vitae of candidates are reviewed for attributes that are suggestive of highly qualified individuals, such as professional titles held, years of experience, board certifications, specialties, and number of publications. Letters of recommendation are also acquired from outside sources. Qualified individuals who meet the current needs of the committee and the function and structure set forth in its Charter are contacted and informed of the responsibilities of membership, including financial conflict-of-interest screening. Should a vacancy exist on a committee, an individual may be officially nominated and considered for final appointment as a standing member on the committee. In some cases, candidates might serve as temporary members of advisory committees before they are invited to serve as standing members.

Finding a balance for advisory committee membership is crucial, in terms of expertise, specialty, and opinion, as well as race/ethnicity, gender, and geography. Such balance is important for impartiality and transparency; it is also specifically mandated under the Federal Advisory Committee Act.

2.2. FDA ADVISORY COMMITTEES AND FINANCIAL CONFLICTS-OF-INTEREST REGULATIONS

Several laws determine how FDA screens individuals for potential financial conflicts-of-interest and whether they can participate in FDA advisory committee meetings: 18 U.S.C. section 208, section 712 of the Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 379d-1, added by the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, sec. 701), and, until replaced in October 2007 by section 712, section 505(n)(4) of the FDCA (21 U.S.C. 355(n)(4)).

Voting and non-voting committee members (except industry representatives) are designated as special Government employees (SGEs) and are subject to laws governing Federal employees. Specifically, 18 U.S.C. 208 prohibits committee members from participating in matters where they—or individuals whose interest is imputed to them—have a disqualifying financial interest, unless the member meets the requirements for a waiver of conflict-of-interest and such a waiver is granted. Section 712(c)(2) of the FDCA also prohibits FDA committee members from participating in matters if the member or her immediate family member has a financial interest that could be affected by the advice given to FDA, unless the member meets the requirements for a waiver of conflict-of-interest and such a waiver is granted. FDA requires that prospective committee member participants disclose any potential financial conflicts-of-interest to the agency prior to appointment and again prior to each advisory committee meeting.

In advance of every meeting, SGEs ordinarily complete FDA Form 3410: Confidential Financial Disclosure Report for Special Government Employees.[6] On this form, participants must disclose current and past financial interests relating to the products, firms, and issues that pertain to the meeting topic (as previously described to the SGE by FDA in a cover memorandum).[7] FDA then reviews the disclosure report and analyzes whether any of the reported interests constitute a potential conflict-of-interest. If an interest is a potential conflict-of-interest, the member may not participate unless she meets the requirements for a waiver under 18 U.S.C. 208(b) and, for meetings held after October 1, 2007, section 712 of the Federal Food, Drug, and Cosmetic Act (FDCA) (where applicable), and such a waiver is granted. Prior to October 1, 2007, members of certain drug and biological product advisory committees were prohibited from voting if the member or his immediate family could gain financially from the advice given to FDA (*see* former section 505(n)(4) of the FDCA). A waiver of the requirement could be granted if the waiver was necessary to afford the advisory committee essential expertise. Waivers under 18 U.S.C. 208 and section 712 of the FDCA can either be full, granting the member voting privileges to fully participate in a meeting, or limited, for example, granting participation in discussions but excluding the individual from voting. Table 2-1 describes the various statutory provisions concerning waivers that may be granted to advisory committee members.

Table 2-1: Waivers Available for Participants of FDA Advisory Committee Meetings

U.S. Statutory Provision	Description
18 U.S.C. § 208(b)(1)	Waiver can be granted if the size of the financial interest is fully disclosed and the agency determines that "the interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such officer or employee."
18 U.S.C. § 208(b)(2)	Certain interests are exempted in regulations as "too remote or too inconsequential to affect the integrity of the services of the Government officer"
18 U.S.C. § 208(b)(3)	Waiver can be granted if "the need for the individual's services outweighs the potential for a conflict-of-interest created by the financial interest involved."
21 U.S.C. § 712(c)(2)(C) (after October 1, 2007)	Committee members are prohibited from participating in FDA advisory committee meetings if the member (or his immediate family member) has a financial interest that could be affected by the meeting outcome. The statute authorizes FDA to grant a waiver of the prohibition if it is necessary to afford the advisory committee essential expertise. The legislation caps the numbers of waivers that FDA may issue in a given year.
21 U.S.C. 355(n)(4) (prior to October 1, 2007)	Waiver to permit voting can be granted if such waiver is necessary to afford the advisory committee essential expertise.

Source: United States Code, 2000 Edition, Supplement 5.

[6] In some cases, FDA may review OGE Form 450 in lieu of FDA Form 3410.

[7] Intellectual conflicts are difficult to quantify or analyze and are not the subject of this study. The word 'conflict' is used throughout this document to represent a financial conflict-of-interest.

2.3. FDA GUIDANCE ON DETERMINING FINANCIAL CONFLICTS-OF-INTEREST

In August 2008, FDA published revised guidance on financial conflicts-of-interest and participation in FDA advisory committee meetings.[8] FDA chose to implement policies regarding eligibility for advisory committee meeting participation that are more stringent than required under current law. This updated guidance uses an eleven-step algorithm to determine when and if waivers will be granted. It differs from the preceding guidance (Waiver Criteria 2000 Guidance[9]) in four major ways:

- Stricter policy regarding waivers for participants whose personal financial interests (and/or those of immediate family members) exceeds certain monetary thresholds.
- The test to determine eligibility for waivers is more stringent than previous guidance and, in some cases, current law.
- FDA will not issue a waiver if the agency has determined that the level of the financial conflict-of-interest is significant.
- The number of waivers granted per year will be limited, in accordance with 21 U.S.C. §712(c)(2)(C) of the Food and Drug Administration Amendments Act of 2007 (FDA, 2008).

The eleven steps included in the algorithm to determine eligibility for participation include:

1. Is the subject matter of the meeting a "particular matter"? (Will the meeting itself or governmental action of which it is a part involve deliberation, decision or action that is focused upon the interest of specific persons, or a discrete and identifiable class of persons?)
2. Will the particular matter have a direct and predictable effect on the financial interest(s) of any organization?
3. Identify potentially affected products/organizations and request that the employee complete the financial disclosure form.
4. Does the employee, or persons/organizations whose interests are imputed to him, have a financial interest in one or more of the potentially affected products and/or organizations?
5. Will the particular matter have a direct and predictable effect on the financial interest of the employee and/or persons/organizations whose interests are imputed to him?

[8] See "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." Available at: http://www.fda.gov/oc/advisory/GuidancePolicyRegs/ACWaiverCriteriaFINALGuidance080408.pdf. (Accessed: October 14, 2008)

[9] Available at: http://www.fda.gov/oc/advisory/conflictofinterest/intro.html. (Accessed: August 15, 2008)

6. After applying applicable regulatory exemptions, does the employee or persons/organizations whose interests are imputed to him have a disqualifying financial interest?

7. Are there disqualifying financial interests for which a waiver would not be considered?

8. Is the combined value of the employee's personal disqualifying financial interests and those of his spouse and minor children $50,000 or less?

9. Is the individual's participation necessary to afford the advisory committee essential expertise?

10. If the individual is a special Government employee, does the need for the individual's services outweigh the potential for a conflict-of-interest created by the financial interest involved?
OR
If the individual is a regular Government employee, is the financial interest not so substantial as to be deemed likely to affect the integrity of the services provided by the individual?

11. Waiver may be recommended if consistent with waiver cap.

Section 712(c)(1) of the FDCA requires public disclosure of certain information associated with financial conflicts-of-interest. In addition, FDA recently published a separate guidance on the transparency of waivers and financial information for advisory committee members.[10] In accordance with this guidance, FDA intends to make publicly available the information related to financial interests that result in waivers. This is done by posting disclosure statements and waivers on the FDA website. In addition, each committee's Designated Federal Officer reads a conflict-of-interest statement at the beginning of every meeting. The statement indicates those members who have been granted waivers, the type of waiver, and the nature of the disqualifying financial interest for which a waiver has been granted.

[10] See: Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers. Available at: http://www.fda.gov/oc/advisory/GuidancePolicyRegs/ACDisclosureFINALGuidance080408.pdf. (Accessed: November 5, 2008).

3. STUDY METHODOLOGY

In the Lurie study, data were collected on a total of 221 CDER meetings from January 2001 through December 2004. ERG obtained these data from Public Citizen's Public Health Research Group in a Microsoft Access database. ERG expanded the original dataset to include meetings within CDER, CBER, and CDRH from January 2001 through the first quarter of 2008.[11] In accordance with Lurie et al., data were collected primarily from advisory committee meeting transcripts as publicly available on the FDA website.[12]

3.1. TYPES OF DATA COLLECTED

ERG collected two types of information: meeting data and participant data. Each of these categories is described immediately below. Data were collected and analyzed in Microsoft Excel 2003, and were later merged with the data collected by Lurie et al. into a comprehensive database using Microsoft Access 2003. Various statistical programs, such as SAS, STATA, and @RISK were used to conduct the statistical analyses.

3.1.1. Meeting Data

For each meeting, ERG recorded the FDA Center, committee name, meeting date, and topic(s). Many FDA advisory committee meetings consist of multiple topics or "particular matters." The Office of Government Ethics regulations define two types of particular matters: "particular matters involving specific parties" (PMISP) and "particular matters of general applicability" (PMGA). For the purposes of ERG's study, each particular matter involving specific parties (PMISP) was considered to be a single meeting. For consistency with the data collected by Lurie et al, these were considered to be "product meetings."[13] Although ERG also collected data on additional "non-product" meetings or topics involving particular matters of general applicability, they are not the subject of this study.

For product meetings (or PMISP) where a dichotomous yes/no vote regarding a drug or device was taken, ERG recorded the question and the overall vote outcome. When a single product meeting had more than one dichotomous yes/no vote, ERG followed the question ranking procedure outlined in Lurie et al. Specifically, "we selected a single question per meeting by first assigning questions to one of three

[11] ERG collected data on any 2008 meetings for which transcripts were available at the time of data collection. Two meetings that took place before the end of the first quarter 2008 did not have transcripts available. Five meetings that took place after the first quarter 2008 did have transcripts available.

[12] As necessary, ERG supplemented data collection with agendas, rosters, minutes and other documents also publicly available on the FDA website. As noted in Section 3.1.2, ERG also obtained from FDA information on the nature of disqualifying financial interests for which 131 waivers had been granted, but for which the transcripts lacked detail.

[13] The 110 "product meetings" in Lurie et al. are consistent with the definition of PMISP with three exceptions: the 12/8/2003 meeting of the Cardiovascular & Renal Drugs Advisory Committee discussing whether aspirin should be recommended for primary prevention of myocardial infarction, the 5/6/2004 joint meeting of the Nonprescription Drugs Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee regarding efficacy and labeling issues for over-the-counter drug products used in the treatment of tinea pedis, and the 9/13/2004 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee on Pediatric SSRI use. These are not included as "product meetings" in the combined dataset.

ranked categories: (1) questions considering whether to recommend approval of a drug, approval of an indication, or withdrawal of a drug (these included questions on whether both safety and efficacy had been established, or if the drug had a favorable risk-benefit profile); (2) questions concerning whether to recommend accelerated approval of a drug; and (3) questions considering whether either safety OR efficacy had been established for a drug" (Lurie et al., 2006). For each meeting, the question with the highest numerical ranking was selected and in meetings with tied rankings, a question was randomly selected using the VassarStats integer randomization program.[14] ERG applied these criteria during the data collection phase and recorded only one question and relevant voting data per meeting.

3.1.2. Participant Data

Participant data included the participant name, participation type (e.g., standing advisory committee member or temporary advisory committee member),[15] disclosed information on recusals or restrictions, individual votes, and disclosed financial conflicts-of-interest for meeting attendees. Only advisory committee standing and temporary members and open public hearing participants were included in the data collection; other participants were excluded, such as FDA or other federal employees, guest speakers, industry representatives, and the Designated Federal Officer of the committee. Also excluded from the data collection were those members whose conflicts were deemed so significant as to preclude their participation, unless such recusals are noted in the transcripts.

Financial conflict-of-interest data were primarily obtained from the conflict-of-interest disclosure statement read into the meeting transcript by the Designated Federal Officer. This disclosure statement provided details on the type, nature, and magnitude of conflicts disclosed by advisory committee standing and temporary members prior to the meeting. The nature of the financial conflict-of-interest refers to the company with which the participant has a financial interest. Conflicts-of-interest involving a financial relationship between a member and the index product's sponsoring company are considered to be "index conflicts." Likewise, conflicts-of-interest involving a financial relationship with a competitor of the index product are considered to be "competitor conflicts." Thus, the nature of the conflict might also be unknown, not specified, or not applicable. Where not otherwise specified, the word 'conflict' is used throughout this document to represent a 'financial conflict-of-interest.'

The level of detail contained in disclosure statements was not consistent across meetings, committees, or centers. In some instances, ERG was unable to identify certain elements regarding a disclosed conflict or a waiver, e.g., the magnitude of the conflict, or whether a conflict involved the product sponsor or a competitor. In these cases, ERG consulted the Nature and Basis Statements of Conflict(s) of Interest, which are also available on the FDA website. If these statements were not available and the information contained within the meeting transcript was vague or incomplete, ERG recorded all available information and categorized the element—or the waiver—as unspecified. Each conflict-of-interest was recorded as a separate entry in our database. Thus, if one person disclosed multiple financial interests, he/she would then have multiple entries in the database, i.e., one for each conflict disclosed.

[14] VassarStats Randomizer program. VassarStats: Web site for Statistical Computation. Available at: http://faculty.vassar.edu/lowry/VassarStats.html. Accessibility verified September 30, 2008.

[15] As noted in Section 2.1, advisory committee members may be appointed as either standing or temporary members. In Lurie et al., the term 'consultants' is used to refer to temporary advisory committee members. Throughout this document, ERG refers to "standing and temporary members" or "members" to include both types of advisory committee members.

The data collected by Lurie et al. included the name of the company with which participants had a conflict-of-interest. The authors found, however, that the 2002 FDA draft guidance on conflict-of-interest disclosure "did not require the competitor company to be named and consequently disclosure of this detail dropped from 54% to 1%" following guidance publication (Lurie et al., 2006:1925). In light of this finding, and the fact that company name was not an integral piece of the subsequent analysis, ERG did not collect information on company name. It might be assumed, however, that that the company name is readily available if a participant disclosed a conflict with the sponsor of the index product.

To the extent that conflicts-of-interest were disclosed by open public hearing participants, those conflicts were also recorded in our database. For the purposes of this study, however, these data were not analyzed and were only collected for informative purposes.

After data collection, ERG identified 138 individuals who were known based on the conflict-of-interest disclosure statement to have been granted waivers, but for whom the transcript contained insufficient information to characterize the nature of the disqualifying financial interest (i.e., 'index' or 'competitor' conflict, or both). ERG was able to obtain from FDA the nature of the financial interests for these individuals for 131 of the waivers granted. FDA was not able to provide the nature of the financial interests for 7 waivers granted to individuals participating in 3 CBER meetings that occurred in 2001. Table 3-1 provides an overview of the supplemental data provided by FDA. Eighty-five percent of the data provided by FDA was for meetings that occurred in 2001.

Table 3-1: Overview of nature of financial conflict data provided by FDA, by Center

Nature of Conflict	Center		
	CDER	CBER	CDRH
Sponsor	24	0	2
Competitor	44	19	24
Sponsor and Competitor	13	0	0
Other	3	0	2
Total	**84**	**19**	**28**
Source: Compiled by ERG from data provided by FDA.			

3.2. ANALYSIS OF VOTING BEHAVIOR

ERG performed the six statistical analyses utilized in Lurie et al. to analyze the relationship between disclosed financial conflicts-of-interest and the voting behavior of advisory committee meeting member participants. These analyses are divided into three general categories of analysis:

- Assessing conflicts as a predictor variable for meeting outcomes to address possible group-level effects on voting due to the participation of individuals with disclosed financial conflicts-of-interest (first and second analysis);
- Evaluating the impact of the exclusion of voters with financial conflicts-of-interest on overall vote outcomes (third and fourth analysis); and
- Determining the effect of financial conflicts-of-interest on individual voters (fifth and sixth analysis).

Each of these categories, and the analyses contained within them, is described in more detail below.

For certain analyses, meetings were also stratified into three conflict type categories—"index conflicts," "competitor conflicts," and "any conflicts"—to reflect the nature of the financial conflicts-of-interest disclosed by advisory committee standing and temporary members present at the meeting (see Table 3-2). Accordingly, meetings where such participants had financial conflicts-of-interest involving the index product's sponsor (such as research funded by the sponsoring company) are included in the category for "index conflicts" and meetings where participants had financial conflicts-of-interest involving a product's competitor(s) are included in the category for "competitor conflicts." Likewise, all meetings where advisory committee members (standing or temporary) had conflicts involving either the product sponsor or a competitor are included in the category for "any conflicts."

Table 3-2: Conflict Type Meeting Stratification

	Conflict Type		
	Index	**Competitor**	**Any**
Includes all meetings in which at least one advisory committee member* had a conflict-of-interest involving:	The index product's sponsoring company.	A competitor(s) to the index product's sponsoring company.	Either the index product's sponsoring company or competitor(s).

* Including all advisory committee members present at the meeting regardless of their vote.

3.2.1. Financial Conflicts-of-Interest as a Predictor Variable for Meeting Outcomes

The first two analyses conducted by Lurie et al. assessed the relationship between the percentage of standing and temporary advisory committee members with financial conflicts-of-interest and the overall vote outcome at meetings. These analyses measure any group-level effects on voting due to attendees with disclosed conflicts-of-interest. These analyses included voter abstentions, where individuals chose not to vote for any number of reasons. Votes were then analyzed both continuously (first analysis) and dichotomously (second analysis).

For these analyses, conflicts (as a predictor variable) are calculated as the percentage of advisory committee members having disclosed conflicts involving either the product's sponsor ("index conflicts"),

the product's competitor ("competitor conflicts"), or either the product sponsor or a competitor ("any conflicts").

In the first analysis, Lurie et al. calculated the dependent variable (vote outcome) continuously, as the "percentage of advisory committee members and voting consultants casting votes favoring the index product" (Lurie et al., 2006:1923). Spearman rho, a non-parametric measure of correlation, was calculated to measure the linear relationship between conflict rate and the vote outcome.[16,17] To calculate Spearman rho, the values for both the predictor variable (conflict rate) and the dependent variable (vote outcome) were sorted and assigned a rank of 1 through *n*. Spearman rho evaluates the association between the assigned ranks for each variable. Values for Spearman's rho range from -1 to +1, where 1 indicates perfect correlation between the rankings, with +1 occurring for identical rankings and -1 occurring for reverse rankings. For this study, a Spearman rho value of 1 would suggest perfect, positive correlation between the rate of individuals with conflicts present at a meeting and the rate of people voting in favor of the index product. This would suggest that the presence of individuals with conflicts might have an impact on the voting behavior of others. If the probability (p-value) of rho is small, then the correlation between the two rankings is statistically significant (i.e., we reject the null hypothesis that there is no linear association between the two rankings).

In the second analysis, Lurie et al. considered vote outcome measured dichotomously, i.e., whether or not the majority cast votes in favor of the index product (Lurie et al., 2006: 1923). In other words, product meetings were grouped into two samples based on the vote outcome (i.e., in favor or not in favor of the index product). Again, the predictor, or independent variable, is the conflict rate, or the percentage of meeting participants with disclosed conflicts. The Wilcoxon rank sum test was calculated to test the null hypothesis that the two independent samples of meetings are from identical continuous distributions with equal medians.[18] For this analysis, a numerical ranking (1 to *n*) is assigned to the predictor variable, i.e., conflict rate, for each meeting in the combined independent samples. The meeting with the highest conflict rate receives the highest ranking, the second highest conflict rate receives the second highest ranking, and so on. In the Wilcoxon rank sum test, if the two independent samples of meetings are from identical continuous distributions then the median rank of the two groups of meetings should be the same. A p-value for the test is calculated based on the sums of the ranks for each independent sample. Here, a small p-value suggests that there is a statistically significant difference between the median ranks of the two groups.

3.2.2. Impact of the Exclusion of Voters with Financial Conflicts-of-Interest

In this category, Lurie et al. conducted two analyses (third and fourth analyses) at the meeting level. The third analysis assessed whether excluding voters with conflicts would have any impact on the absolute vote margin toward the index product. For this analysis, Lurie et al. presents the number of meetings where these exclusions would have made the vote more or less favorable to the index product. The fourth analysis assessed whether excluding these same voters would have changed the overall vote outcome. In both cases, Lurie et al. included meetings with unanimous votes, but excluded meetings with no disclosed conflicts.

[16] Nonparametric statistical methods do not rely on assumptions about the frequency distributions of the variables.

[17] Spearman, C. 1904. The proof and measurement of association between two things. *American Journal of Psychology*, 15:72–101.

[18] Wilcoxon, F. 1945. Individual comparisons by ranking methods. *Biometrics*, 1: 80-83.

3.2.3. Effect of Financial Conflicts-of-Interest on Individual Voters

To assess the effect of conflicts on individual voters, Lurie et al. conducted two additional analyses, a Mantel-Haenszel relative risk or odds ratio analysis and a Monte Carlo simulation. These analyses are described in detail below.

To test whether a voting participant's conflict had an effect on his or her vote, Lurie et al. calculated a relative risk (RR) for each eligible meeting, then combined them according to the Mantel-Haenszel method.[19] Relative risk, a term more commonly used in epidemiological research, is the ratio of the probability of an event occurring in an exposed group versus a non-exposed group. In their analysis, Lurie et al. used a relative risk or odds ratio to refer to the probability that a person with a disclosed conflict-of-interest is more likely to vote a particular way than a person without a conflict-of-interest. Thus, for their analysis, a relative risk of 1.0 means that individuals with conflicts and individuals without conflicts are equally likely to vote in favor of the index product. Rather than assessing the relative risk for each meeting separately, the Mantel-Haenszel method produces a single, weighted RR value across all the meetings within each conflict category, i.e. index, competitor, and any conflicts. A 95 percent confidence interval was calculated. If the 95 percent confidence interval for the RR statistic does not include 1.0, then the likelihood that votes by individuals with conflicts differ from votes by those without conflicts is statistically significant. Meetings with unanimous votes and meetings with no disclosed conflicts were excluded from this analysis.

In the final analysis at the individual level, Lurie et al. used a Monte Carlo simulation to test if voting members and consultants with conflicts exhibit the same voting patterns as members and consultants without conflicts.[20] This analysis tested "whether the votes of panel members with conflicts could be understood as random draws from a pool in which the probability of voting for the index drug was the same as that for members without conflicts (i.e., that holding a conflict had no impact)" (Lurie et al., 2006:1923). The following paragraph describes how the Monte Carlo simulation was conducted:

> …within each meeting, we took the ratio of yes votes to total votes among voters without conflicts as our best estimate of the probability that a "new" voter with a conflict would vote in favor of that particular index drug. For each member with a conflict at a meeting, a random number between 0 and 1 was drawn; if this number was less than the proportion of members without conflicts who voted in favor of the drug in that particular meeting, the member with a conflict was considered to have voted in favor of the drug. This process was repeated for each member with a conflict at each meeting and the total number of yes votes was added up; this process was considered to be one trial. One hundred thousand such trials were run to provide a probability density function for the total number of yes votes by panel members with conflicts across all meetings, from which we determined the 2-tailed 95% confidence interval (CI). If the observed number of yes votes by panel members with conflicts fell outside this CI, the voting behavior of panel members with conflicts was considered statistically significantly different ($P >$ 0.05) from that of members with conflicts. (Lurie et al., 2006:1923-1924)

[19] Mantel, N. 1963. Chi-square tests with one degree of freedom; extensions of the Mantel-Haenszel procedure. *Journal of the American Statistical Association*, 58:690-700.

[20] Additional information about Monte Carlo simulations can be found in: Fishman, G.S. 1995. *Monte Carlo: Concepts, Algorithms, and Applications*, Springer Verlag, New York.

4. OVERVIEW OF COMBINED STUDY DATA

This section describes the data used in ERG's study, which includes a combination of data provided by Public Citizen and additional data collected by ERG. The data from Public Citizen included meeting and participant information for 221 CDER meetings that occurred between January 2001 and December 2004. ERG collected meeting and participant data to expand the dataset to include 611 CDER, CBER, and CDRH meetings that occurred between January 2001 and March 2008. [21]

The combined dataset, henceforth referred to as the expanded sample, consisted of 310 "product meetings" (i.e., "particular matters involving specific parties") held by 32 advisory committees. [22], These advisory committee meetings had an average attendance of 12.4 advisory committee members, including, on average, 7.2 standing members and 5.2 temporary members. Table 4-1 shows meeting attendance statistics by meeting type and FDA center.

Table 4-1: Meeting Attendence Statistics by Meeting Type and FDA Center [a]

Attendee Type	All Product Meetings	FDA Center		
		CDER	CBER	CDRH
Standing Advisory Committee Members				
Average	7.2	8.3	9.1	4.6
Range	1 to 24	1 to 24	5 to 15	1 to 15
Temporary Advisory Committee Members				
Average	5.2	5.0	5.5	5.6
Range	0 to 17	0 to 17	3 to 10	0 to 12
Total Standing and Temporary Members				
Average	12.4	13.3	14.6	10.2
Range	5 to 28	7 to 28	10 to 23	5 to 17

[a] Meeting statistics are based on meeting definitions described in Section 3.1.1, where each 'product meeting' is one particular matter involving specific parties.

All product meetings had at least one standing advisory committee member in attendance, while 300 (97 percent) had at least one temporary member in attendance. In total, there were approximately 1,787 unique individuals who attended meetings during this time period as either a standing or temporary advisory committee member. These individuals accounted for 3,842 person-meetings, defined as "each appearance at a meeting by any attendee" (Lurie et al., 2006:1923).[23]

[21] Including only those meetings for which transcripts were available.

[22] Excludes 3 of Lurie et al.'s "product meetings" that were particular matters of general applicability.

[23] For example, one person that attended three meetings (as defined in Section 3.1.1) would constitute three person-meetings.

4.1. FINANCIAL CONFLICT-OF-INTEREST RATES

Financial conflicts-of-interest were disclosed by at least one standing or temporary advisory committee member at 76 percent of product meetings (2001 through 2008). This number is lower than the 81 percent of product meetings analyzed in the Lurie et al. study (2001-2004). At least one conflict was disclosed by a standing member at 57 percent of product meetings and at least one conflict was disclosed by a temporary member at 54 percent of product meetings. Across FDA centers, fewer CDRH product meetings (62 percent) included at least 1 standing or temporary member with a conflict than CDER product meetings (81 percent) or CBER meetings (91 percent).

Table 4-2 presents statistics on disclosure of financial conflicts-of-interest at product meetings by FDA center. The data are presented both by meeting and by person-meeting. Each person attending a meeting (a person-meeting) can disclose more than one conflict-of-interest at any given meeting, for example, stock in a competitor and consulting for a competitor. Twenty-one percent of all person-meetings for standing and temporary advisory committee members had at least one conflict, with very little difference in this rate between standing and temporary members (20% and 21%, respectively). As indicated in Table 4-2, the conflict rate per person-meeting at product meetings is highest for CDER (22 percent).

Table 4-2: Percentage of Meetings at Which at Least One Financial Conflict-of-Interest Was Reported (n=310) and Percentage of Conflicts by Person-Meetings (n=3,842)

Member Type	CDER		CBER		CDRH		All Product Meetings	
Meetings at Which ≥ 1 Conflict was Reported [a]								
Standing member	124/187	66%	16/22	73%	37/101	37%	177/310	57%
Temporary member	103/178	58%	11/22	50%	49/100	49%	163/300	54%
Standing and temporary members	152/187	81%	20/22	91%	63/101	62%	235/310	76%
Conflicts by Person-Meeting [a]								
Standing member	335/1,560	21%	36/200	18%	85/468	18%	456/2,228	20%
Temporary member	208/926	22%	26/121	21%	113/567	20%	347/1,614	21%
Standing and temporary members	543/2,486	22%	62/321	19%	198/1,035	19%	803/3,842	21%

Source: Compiled by ERG

[a] Meeting and person-meeting counts include only those who attended meetings and, therefore, may not include individuals recused from meetings for financial conflicts of interest or other reasons.

4.2. DETAILS OF FINANCIAL CONFLICTS-OF-INTEREST

Based on publicly available information, ERG recorded 942 disclosed financial conflicts-of-interest among advisory committee members (voting and nonvoting) who attended the product meetings analyzed. For these conflicts, Table 4-3 shows the breakdown of sponsor, competitor and total conflicts by conflict type.

Consulting, investments, grants or contracts and lecturing fees make up the majority of advisory committee member disclosure of financial conflicts-of-interest. Forty-two percent of all conflicts disclosed were for consulting for either the sponsor or a competitor of the index product, while another 26 percent involved investments.

Table 4-3: Detailed Breakdown of Disclosed Financial Conflicts-of Interest

Conflict Type	Number/(%) [a]		
	Sponsor	Competitor	Total [b]
Consulting			
$0-10,000	52 (81)	271 (84)	329 (83)
$10,001-50,000	8 (13)	39 (12)	47 (12)
≥ $50,001	1 (2)	6 (2)	7 (2)
Unknown/other amounts	3 (5)	7 (2)	16 (4)
Investments			
$0-5,000	7 (14)	40 (21)	48 (20)
$5,001-25,000	22 (45)	82 (44)	108 (44)
$25,001-50,000	16 (33)	44 (23)	62 (25)
$50,001-100,000	3 (6)	14 (7)	19 (8)
≥ $100,001	0 (0)	2 (1)	2 (1)
Unknown/other amounts	1 (2)	6 (3)	7 (3)
Grant/contract/CRADAs			
$0-100,000	44 (69)	44 (68)	89 (65)
$100,001-300,000	6 (9)	10 (15)	17 (13)
≥ $300,001	3 (5)	6 (9)	11 (8)
Unknown/other amounts	11 (17)	5 (8)	19 (14)
Lecturing/honoraria			
$0-10,000	15 (65)	59 (72)	80 (69)
≥ $10,001	5 (22)	21 (24)	28 (24)
Unknown/other amounts	3 (13)	3 (4)	8 (7)
Other	10	27	40
Patents/royalties/trademarks	0	4	4
Employment (participant or spouse)	2	3	6
Expert witness	0	2	2
Past financial interests	0	1	1
TOTAL	212	695	950

Source: Compiled by ERG.
Abbreviations: CRADA, Cooperative Research and Development Agreement.
[a] Percentage of conflicts of this type.
[b] Includes sponsor and competitor conflicts, and other conflicts where the conflict affiliation type is unspecified or not applicable.

5. RESULTS - IMPACT OF FINANCIAL CONFLICTS-OF-INTEREST ON VOTING PATTERNS

This section describes the results of replicating the Lurie et al. study using a larger, more recent sample of meetings. For comparison purposes, we first present Lurie's results in Section 5.1. Section 5.2 outlines the results of the analysis using the expanded sample and interprets the results in a manner consistent with Lurie et al. Section 5.3 describes those results according to FDA's preferred interpretation of financial conflicts-of-interest, or whether having a financial interest tends to increase votes in favor of that interest.

5.1. FINANCIAL CONFLICTS-OF-INTEREST AND VOTING PATTERNS –LURIE STUDY RESULTS

A total of 221 CDER meetings from January 2001 through December 2004 were analyzed by Lurie et al. Of these, 110 were product meetings and 76 met the inclusion criteria for the voting pattern analysis.[24] Table 5-1 presents the results of Lurie et al.'s statistical analysis of the relationship between the type of disclosed financial conflicts-of-interest and the voting behavior of advisory committee members (see also Table 4 in Lurie et al.).

Using conflicts as a predictor variable for meeting outcomes (first two analyses), Lurie et al. found that there was not a statistically significant relationship between conflict rates (for "index conflicts," "competitor conflicts," or "any conflicts") and voting patterns. In their analyses of the impact of exclusions on the vote margin and overall vote outcomes (third and fourth analyses), the authors found that excluding those with financial conflicts-of-interest tended to make vote margins overall more favorable to the index drug, but did not change the vote outcome at any meetings.

The authors did find a weak, statistically significant positive relationship between conflict rates and voting patterns for competitor conflicts and any conflicts in the Mantel-Haenszel analysis (fifth analysis). As presented in Table 5-1, the Mantel-Haenszel relative risk for the competitor conflict type and any conflict type are 1.20 (95% CI, 1.12-1.28) and 1.10 (95% CI, 1.03-1.17), respectively. Given a 95 percent probability that the specified CI contains the true RR, Lurie's results suggest that the actual RR is greater than 1.0, (i.e., the 95% CI does not contain 1.0 for either competitor conflict or any conflict types).

Using the Monte Carlo method (sixth analysis), no significant differences were found between the total number of votes favorable to the index drug between members with conflicts and members without conflicts for either index conflict or any conflict types. They did, however, find that members with competitor conflicts were statistically significantly more likely to vote in favor of the index drug than members without conflicts.

The authors suggest several explanations for competitor conflicts being associated with voting for the index drug while index conflicts were not. One possible reason may be that the analyses are underpowered. More specifically, the Lurie analyses suffered from small sample sizes, particularly the number of meetings with index conflicts, i.e., conflicts with the sponsoring company of the index drug at any particular meeting. In statistical analyses, an underpowered study increases the chance that test statistics will not find a statistically significant relationship when there actually might be one.

[24] As discussed in Section 3, a meeting was included in the voting pattern analysis if it was both product-specific (PMISP) and if there was a dichotomous yes/no vote on at least one product question posed during the meeting.

Table 5-1: Analyses of the Relationship between Financial Conflict-of-Interest Type and Voting Behavior by Lurie et al., 2001-2004

Analysis	Conflict Type			Description of Analysis
	Index	Competitor	Any	
Meeting-Level Analyses				
Voting as continuous outcome Spearman rho *P* value	 0.16 0.18	 0.10 0.38	 0.13 0.26	Measure of linear relationship between voting outcome as a percent of individuals voting in favor of the index drug and the percent of individuals having a conflict of type X. Values for Spearman rho range from -1 to +1 where values of 1 indicate perfect correlation.
Majority voting as dichotomous outcome *P* value	 0.31	 0.67	 0.47	Uses the overall vote as a dichotomous outcome (in favor/not in favor of the index drug) to assess whether the percent of individuals having a conflict of type X in 2 independent random samples of meetings have the same distribution. Provides a *P* value for the null hypothesis that the two distributions are the same.
Impact of exclusions on vote margin toward index drug, No. of meetings Less favorable More favorable No change	 14 7 1	 27 5 3	 31 8 4	Shows the impact on the vote margin of excluding from the vote individuals with conflict type X.
Impact of exclusions on overall vote outcome	None	None	None	Shows the impact on the overall vote outcome of excluding from the vote individuals with conflict type X.
Individual-Level Analyses				
Mantel-Haenszel RR/Odds Ratio (95% CI)	0.74 (0.39-1.39)	1.20 (1.12-1.28)*	1.10 (1.03-1.17)*	Calculates the odds that individuals with conflict type X are more likely vote in favor of the index drug than those without conflict type X. Given a 95% probability that the specified CI contains the true RR, a CI that does not contain one is statistically significant.
Monte Carlo, No. of positive votes Observed Expected (95% CI)	 6 8.2 (4.5-10.5)	 36* 29.5 (23.5-34.5)	 40 36.0 (29.5-41.5)	Compares an expected number of votes in favor of the index drug with an observed number between those with and without conflict type X.

Abbreviations: CI, confidence interval; RR, relative risk
Source: Lurie et al., 2006; Table 4. Descriptions added by ERG.
* Statistically significant at $\alpha = 0.05$.

Another explanation for Lurie's paradoxical finding includes the possibility of an FDA screening process that might inherently reduce the number of advisory committee members that have index conflicts being selected for participation. In other words, FDA conflict-of-interest disclosure policies might result in lower participation rates among individuals with index conflicts than individuals with competitor conflicts. Finally, Lurie et al. also proposed the idea of a financial conflict-of-interest as a proxy for an attitude favorable toward industry. As the authors note, it is not possible to "control for the many other potential confounding factors that could have an impact on an advisory committee's vote (secular trends in drug approval rates, forcefulness of the advisory committee chair, press coverage, and the like)" (Lurie et al., 2006:1927).

5.1.1. ERG's replication of the Lurie et al. methodology

In order to ensure that ERG's interpretation of Lurie's methodology was accurate, ERG both discussed the analyses with the lead author and conducted the 6 analyses using only the data analyzed in Lurie et al. (as provided to ERG by Public Citizen). ERG's reproduction of the results outlined in Table 4 of Lurie et al. was largely successful, although in some cases, ERG was not able to produce identical statistics. ERG does not anticipate that these very slight differences affected the analysis.

5.2. RESULTS COMPARISON USING THE EXPANDED SAMPLE

After confirming the methodology and combining the data, ERG repeated the six analyses to determine if the original study findings held true for the expanded sample of advisory committee meetings. Of the additional 203 product meetings for which data was collected by ERG, 98 met our inclusion criteria for the voting analysis.[25] These 98 meetings were combined with 74 meetings[26] analyzed by Lurie et al. for a total of 172 product meetings included in the analyses. Table 5-2 shows the results of the six analyses performed.

In the first analysis of voting behavior at the meeting level, which included all 172 product meetings, ERG found no statistically significant relationship between the conflict rate and voting outcome as a continuous variable for either 'index,' 'competitor,' or 'any' conflict type at the 5 percent significance level. The relationship between conflict rate and voting outcome for 'index conflicts' and 'any conflict' is statistically significant at the 15 percent level (Index conflicts: *P* value = 0.11; Any conflicts: *P* value = 0.14). This differs from Lurie's results, in which there was no statistically significant relationship between conflict rate and voting outcome in any conflict category at the 15 percent level.

Upon further investigation, it was determined that the correlation between index conflict rate and voting outcome at meetings with index conflicts is higher at meetings where the overall vote was unanimous (whether in favor or not in favor of the index product). The higher correlation coefficient at these meetings is a result of the large number of unanimous meetings in which no conflicts were

[25] Excluded from the analyses were 69 CDRH meetings at which the main motion was whether the device was "approvable with conditions." Although the vote was a dichotomous yes/no vote, ERG determined that the nature of a conditional approval might complicate the effect of a conflict-of-interest on voting behavior. In addition, ERG excluded 2 CBER meetings for which supplemental information was not available for those with waivers.

[26] ERG excluded two meetings that were included in Lurie et al.'s analyses. One meeting was not a particular matter involving specific parties. The second meeting involved two different index products and therefore two different sponsors, thus complicating the analysis of conflicts–of-interest at this meeting.

disclosed.[27] Table 5-2 shows the Spearman correlation coefficient separately for meetings where the vote was not unanimous. Among meetings with non-unanimous vote outcomes, there is no statistically significant relationship between conflict rate and voting outcome for any conflict category at the 15 percent significance level.

The second analysis of voting behavior at the meeting level looked at the relationship between the vote outcomes as a dichotomous yes/no vote and the percentage of voters having an index, competitor or any conflict (either sponsor or competitor). This analysis excluded two meetings where the overall vote outcome was a tie. Here, ERG found no relationship between the conflict rate and voting outcome for any conflict type at the 5 percent significance level. These results are consistent with Lurie's results. There is, however, a weak, positive relationship for 'any conflicts' at a higher significance level.

In the third and fourth analyses, ERG assessed the exclusion of advisory committee members with disclosed financial conflicts-of-interest on the absolute vote margin and the overall vote outcome. These analyses included 65 meetings in which the vote was unanimous, but excluded 33 of the 172 product meetings because there were no disclosed conflicts at those meetings. Unanimous meetings accounted for nearly half of the meetings in each conflict category.

Like the results of Lurie et al., the exclusion of individuals with conflicts more often produces absolute vote margins less favorable to the index product in all three conflict categories (third analysis). There is no change in the absolute vote margin for only 12 of the 139 meetings included in this analysis. The median change in the absolute vote margin by excluding individuals with conflicts is 2 votes, with a maximum change of 9 votes.

Given the large number of meetings in which the vote was unanimous, ERG considered the impact of excluding individuals with conflicts only in meetings that did not have unanimous votes. The results of this modified third analysis are also presented in Table 5-2. At meetings where the overall vote was not unanimous, excluding individuals with index conflicts ('index' conflict type) produces vote margins less favorable to the index product almost as often as vote margins that are more favorable to the index product (i.e., in 19 meetings, the resulting vote margin would have been less favorable compared to 18 meetings where the vote would have been more favorable). Excluding individuals with competitor conflicts ('competitor' conflict type) more often produces vote margins less favorable to the index product. Excluding all individuals with sponsor or competitor conflicts ('any' conflict category) also more often produces absolute vote margins less favorable to the index product. The 'any' conflict category result is influenced by the larger number of competitor conflicts than index conflicts among advisory committee members.

[27] Spearman's method assigns the same rank value to all data points of equal value. Thus, for example, all unanimous votes in favor of the index product have the same rank, as do all unanimous votes against the index product. Similarly, all votes with no index conflicts also receive the same rank. Thus there are large blocks of observations with identical ranks that are highly correlated. Furthermore, a review of the meeting transcripts does not support a conclusion that voters with competitor conflicts are convincing non-conflict voters to vote unanimously in favor or against an index product. Therefore, ERG believes these results are an artifact of the statistical method used, and do not represent a significant causal relationship between conflict type and vote outcome.

Table 5-2: Analyses of the Relationship between Financial Conflict-of-Interest Type and Voting Behavior, 2001-2008

Analysis	Conflict Type		
	Index	Competitor	Any
Meeting-Level Analyses			
Voting as continuous outcome (n=172)			
Spearman rho	0.12	0.09	0.11
P value	0.11	0.26	0.14
Voting as continuous outcome (n=93) (excludes unanimous meetings)			
Spearman rho	-0.06	0.09	0.13
P value	0.58	0.38	0.20
Majority voting as dichotomous outcome (n=170) [a]			
P value	0.23	0.22	0.11
Impact of exclusions on vote margin toward index product, No. of meetings (Includes unanimous meetings)	n=74	n=119	n=139
Less favorable	49	80	91
More favorable	19	28	36
No change	6	11	12
Impact of exclusions on vote margin toward index product, No. of meetings (Excludes unanimous meetings)	n=42	n=62	n=74
Less favorable	19	35	38
More favorable	18	19	27
No change	5	8	9
Impact of exclusions on overall vote outcome	Produced 3 outcome changes (1 in favor to tie, 1 not in favor to tie, 1 tie to in favor)	Produced 5 outcome changes (1 tie to not in favor, 1 not in favor to tie, 2 in favor to tie, 1 in favor to not in favor)	Produced 7 outcome changes (1 tie to in favor, 1 tie to not in favor, 2 not in favor to tie, 2 in favor to tie, 1 in favor to not in favor
Individual-Level Analyses			
Mantel-Haenszel Relative Risk/ Odds Ratio (95% CI)	n=39	n=57	n=71
	0.85 (0.66-1.10)	1.13 (0.98-1.29)	1.07 (0.95-1.21)
Monte Carlo, No. of positive votes	n=39	n=59	n=73
Observed	29	95*	116
Expected (95% CI)	34.1 (27.5-40.6)	82.5 (72.1-92.9)	107.1 (95.4-118.8)

Source: Compiled by ERG.
Abbreviations: CI, confidence interval; RR, relative risk
* Statistically significant at $\alpha = 0.05$.
[a] This analysis excludes two meetings in which the vote outcome was a tie.

The results of the fourth analysis show that the exclusion of standing and temporary voting members with conflicts produced 7 vote outcome changes in 139 meetings. This included 2 meetings in which removing individuals with conflicts broke a tie vote. One tie would have resulted in a vote in favor of the index product, while the other would have been not in favor of the index product. In addition, the exclusion of voting standing or temporary members with conflicts would have resulted in tie votes at 4 meetings. Two of the actual votes at these four meetings were votes in favor of an index product, while the other two were votes not in favor of the index product. Finally, there was one meeting in which the outcome of the vote would have changed from in favor to not in favor of the index product.[28] Although Lurie et al. found that no vote outcomes would have changed by excluding individuals with any type of conflict, ERG's results are not inconsistent with findings one might expect from a larger sample of meetings.

As in Lurie et al., unanimous meetings and meetings at which there were no conflicts disclosed were excluded from the fifth and sixth analyses involving individual voting behavior (Mantel-Haenszel and Monte Carlo methods). Removing these meetings results in the following number of eligible meetings for each of the conflict categories: 39 meetings with index conflicts, 59 meetings with competitor conflicts, and 73 meetings with any conflict.[29]

The Mantel-Haenszel analysis resulted in combined relative risks (RRs) of 0.85 (95% CI, 0.66-1.10) for index conflicts, 1.13 (95% CI, 0.98-1.29) for competitor conflicts, and 1.07 (95% CI, 0.95-1.21) for any conflict. As noted earlier, a relative risk of 1.0 suggests that individuals with conflicts are just as likely to vote in favor of the index product as individuals without conflicts. The relative risk calculations suggest, like the Lurie et al. findings, that individuals having index conflicts might be less likely to vote in favor of the index product and individuals with competitor conflicts might be more likely to vote in favor of the index product. The relative risk calculation suggests that those with 'any' conflict are more likely than those without conflicts to vote in favor of the index product (RR = 1.07). Given a 95 percent probability that the specified confidence interval contains the true RR, however, ERG finds that the relative risks are not statistically significant for any conflict type, i.e., the 95 percent CI includes 1.0 in all three conflict categories. This result differs from Lurie et al., which found a statistically significant difference in both the competitor conflict and any conflict cases.

In the final analysis, using the Monte Carlo method, ERG found no statistically significant differences between the expected number of votes and the actual number of votes favorable to the index

[28] This was a 5/17/07 meeting of the Vaccines and Related Biological Products Advisory Committee where the committee voted 9-6 that the safety data demonstrated that the benefits would exceed the risks of FluMist (MedImmune Vaccines, Inc.) for use in the applicant's proposed population, i.e., children age 12-59 months without history of wheeze.

[29] In the Mantel-Haenszel analysis, ERG actually used 39 meetings with index conflicts, 57 with competitor conflicts, and 71 with any conflicts. Lurie et al. note that "for one meeting, in which one of several members with conflicts voted for the drug but no member without conflicts voted for the drug (producing an undefined RR)" the relative risk was calculated based on the method of Jewell. Holford (2002) and others suggest that in these cases, the relative risk estimator is most sensitive to the addition of an arbitrary constant. Since the authors of the original study had only 18 observations for the "competitor conflict" analysis and 23 observations for the "any conflict" analysis, it is understandable that they did not want to lose any observations, and therefore used an adjustment. ERG identified one other meeting with the same characteristics in the expanded dataset. Given the increase in sample size from combining additional years of data to the meeting, ERG chose to follow the recommendation of Holford and drop these two meetings from the analysis (both meetings have competitor conflicts only).

product by voters with conflicts in the 'index' and 'any' conflict categories. Individuals with competitor conflicts, however, were statistically significantly more likely to vote in favor of the index product than those without conflicts [observed: 95; expected: 82.5, 95% CI (72.1-92.9)]. ERG found an observed number of votes in favor of the index product that was less than the number of expected votes for index conflicts and greater than the number of expected votes for competitor conflicts and any conflicts. This result is consistent with Lurie et al., which also found a statistically significant difference between the number of observed votes and the number of actual votes for the index product in the competitor conflict category.

5.3. INTERPRETATION OF THE EXPANDED SAMPLE RESULTS BASED ON CONVENTIONAL INTERPRETATIONS OF CONFLICT-OF-INTEREST

Based on the expanded sample, ERG reinterpreted the results (shown in Table 5-2) for the 'index conflicts' and 'competitor conflicts' categories to consider "whether having a financial interest tends to increase votes in favor of that interest" (FDA, 2008b).[30] The application of this question is straightforward only for the index conflict category. For individuals with index conflicts, a vote in favor of the index product may be interpreted as a vote favoring the individual's interest.

Repeating the findings noted above for index conflicts, ERG found no statistically significant evidence (at a 5 percent significance level) that individuals having conflicts with a sponsoring company have group-level effects on an overall vote in favor of that interest. ERG did, however, find a weak positive relationship between voting outcome and the index conflict rate at the 15 percent level (*P* value = 0.11). This relationship is due to the strong, positive relationship between conflict rate and voting outcome at meetings in which the overall vote was unanimous. Using Spearman's rho, there is no evidence of a relationship between index conflict rate and voting outcome at non-unanimous meetings.

Considering all relevant meetings, ERG found that excluding individuals with index conflicts more often produces vote margins less favorable to the index product. Not including meetings in which the vote was unanimous, however, the exclusion of individuals with index conflicts produces vote margins more favorable to the index product about as often as vote margins less favorable to the index product. The exclusion of individuals with index conflicts would have produced outcome changes in 3 of 74 meetings. At one of these meetings, a vote in favor would have become a tie, at another a vote not in favor would have resulted in a tie, and at the third, a tie would have been broken resulting in a vote in favor of the index product. Based on these results, no conclusive patterns can be drawn regarding whether individuals with index conflicts tend to vote in favor of their financial interest.

In the individual-level analyses, ERG also did not find evidence to suggest that individuals with index conflicts tend to vote in favor of their interest. In the Mantel-Haenszel analysis, ERG calculated a relative risk of 0.85 (less than 1.0), suggesting that those with index conflicts are less likely than those without conflicts to vote in favor of the index product. This finding, however, was not statistically significant at the 5 percent level. In the Monte Carlo simulation, ERG found that the observed number of votes (29) in favor of the index product among members with index conflicts was less than the expected number of votes (34.1). This finding was also not statistically significant (95% CI, 27.5-40.6).

[30] ERG did not attempt to reinterpret the results in the 'any conflict' category, because FDA's interpretation of conflicts-of-interest precludes combining votes in favor of the index drug for those with index conflicts and those with competitor conflicts.

ERG also analyzed the expanded sample results in light of conventional interpretations of conflict-of-interest that a vote not in favor of the index product would tend to favor the competing company. ERG interpreted votes by individuals with competitor conflicts such that a vote 'not in favor' of the index product was considered to be a vote in favor of their financial interest.

Considering the conventional interpretation, the results did not suggest that individuals with competitor conflicts tend to vote in favor of those interests. In the first two meeting-level analyses, ERG found no statistically significant relationship between competitor conflict rate and overall vote outcome as either a continuous or dichotomous dependent variable (i.e., *P* values > 0.15, see Table 5-2). As in meetings with index conflicts, ERG also found that, for all relevant meetings, excluding individuals with competitor conflicts more often makes overall votes less favorable to the index product. Not including meetings in which the vote was unanimous, however, the exclusion of individuals with competitor conflicts again more often produces vote margins less favorable to the index product. Using the conventional interpretation of conflicts-of-interest, this result suggests that some individuals with competitor conflicts voted in a manner that was against their financial interests.

Using the Mantel-Haenszel method, ERG calculated a weighted relative risk of 1.13 (greater than 1.0), suggesting that those with competitor conflicts are more likely than those without conflicts to vote in favor of the index product. This finding, however, was not statistically significant at the 5 percent level. In the Monte Carlo simulation, ERG found that the observed number of votes (95) in favor of the index product among members with competitor conflicts was greater than the expected number of votes (82.5). This finding was statistically significant (95% CI, 72.1-92.9). The finding suggests that members with competitor conflicts are more likely to vote in favor of the index product (against their financial interest) than members without conflicts.

6. CONCLUSIONS

ERG extended the analysis described in the 2006 JAMA article by Lurie et al. to analyze whether standing and temporary advisory committee members tend to vote in a manner consistent with their financial interests. Data used by Lurie, et al. were provided by Public Citizen and combined with data collected by ERG to analyze voting patterns for CDER, CBER, and CDRH advisory committee members for the time period of January 1, 2001 to March 31, 2008. The combined dataset consisted of 310 'product meetings' held by 32 advisory committees. Of these product meetings, 172 were analyzed to assess the relationship between financial conflict-of-interest disclosure and voting patterns.

The study methodology considers two ways in which financial conflicts-of-interest might impact the voting behavior of advisory committee members: the meeting level and the individual level. The meeting-level analyses consider how the extent of financial conflicts-of-interest among meeting participants might influence the voting behavior of even those individuals without conflicts. In comparison, the individual-level analyses consider how the behavior of individual voters might be influenced by their own financial interests.

ERG found that the expanded dataset produced overall results closely similar to the results presented by Lurie et al. Using a 5 percent significance level, ERG found no statistically significant relationship between disclosed conflict rates and voting outcome. At a higher significance level (α =0.15), there is evidence of a weak, positive relationship between the 'index' conflict rate and voting in favor of the index product. For index conflicts, this relationship is believed to be influenced by the large number of unanimous meetings in the dataset in which there were no index conflicts disclosed. There is no evidence of a relationship between index conflict rate and voting outcome at meetings where the vote was not unanimous.

ERG also found, as in Lurie et al., that the exclusion of individuals with conflicts from all relevant advisory committee meetings generally produced overall vote margins less favorable to the index product. Not including unanimous vote meetings, however, ERG found that excluding individuals with index conflicts produced vote margins more favorable to the index product just as often as vote margins less favorable to the index product. Excluding individuals with competitor conflicts more often produced vote margins less favorable to the index product.

In assessing the effects of disclosure on individual votes, Lurie et al. identified statistically significant relationships between certain conflict types and voting behavior. Specifically, "competitor conflict was associated with voting for the index product in both analyses (Mantel-Haenszel RR and Monte Carlo simulation), and any conflict was so associated in the Mantel-Haenszel analysis only" (Lurie et al., 2006:1927). ERG found that using the expanded dataset produced individual-level results similar in direction to Lurie's findings for all conflict types. In particular, ERG's findings also suggested that individuals with index conflicts are less likely to vote in favor of the index product than individuals without index conflicts and that individuals with competitor conflicts are more likely to vote in favor of the index product than individuals without competitor conflicts. Unlike Lurie et al., however, ERG did not find these relationships between conflicts and voting behavior to be statistically significant for any conflict type (i.e., index conflict, competitor conflict, or any conflict) in the Mantel-Haenszel relative risk analysis. Consistent with Lurie et al.'s Monte Carlo analysis, ERG found that members with competitor conflicts were statistically significantly more likely to vote in favor of the index product than those without conflicts.

In regards to FDA advisory committees, conflicts-of-interest raise the concern about whether having a financial interest tends to increase votes in favor of that interest. It is important, however, to note

the impact of FDA's interpretation of conflict-of-interest in replicating the Lurie et al. study exactly. Rather than asking whether having a financial tie to *any* pharmaceutical company tends to increase votes in support of a drug, a notion inconsistent with conventional interpretations of conflict of interest, FDA asks whether having a financial interest tends to increase votes in favor of that interest. As noted, this interpretation precludes combining the votes of individuals who have sponsor conflicts with the votes of individuals who have competitor conflicts. For index and competitor conflicts, ERG's findings suggested evidence among advisory committee standing and temporary members of voting against one's financial interests.

The reader should note certain study limitations regarding the methodology for assessing the impact of conflict-of-interest on voting patterns. In particular, the study data is based on conflicts-of-interest disclosed during the conflict-of-interest disclosure statement read into the record at the beginning of each FDA advisory committee meeting. In general, these statements cover the disqualifying financial interests for which individuals have been granted waivers (in accordance with federal conflict-of-interest regulations and FDA policy). However, in some cases, statements included *de minimis* financial interests that would not be disqualifying nor require a waiver but instead are exempted under federal regulations. Where the disclosure statements included such *de minimis* interests, they are included in the data set as "conflicts-of-interest." We also note that the conflict-of-interest disclosure statement is based on information that is self-reported by each advisory committee member meeting participant and thus, could be limited to the extent that individuals underreport relevant financial interests.[31] Also excluded from the analysis were members whose conflicts were deemed to be so significant as to preclude their participation in a meeting.

In addition, the study methodology treats all financial interests equally. It does not, therefore, attempt to account for any distinct effects on voting behavior by conflict type (i.e., consulting, grants, etc), magnitude, or whether the interest is direct (i.e., personal income from a consulting contract) or imputed to the individual (i.e., a research contract with an individual's employer for which the individual has no involvement).

In this study, we perform two analyses of the correlation between conflicts-of-interest and vote outcomes (Spearman's rho and the Wilcoxon rank-sum). These tests are limited in that only one type of conflict-of-interest can be analyzed at one time, which ignores the effect on the vote of attendees with different types of conflicts. Both types of conflicts are often present at meetings. Therefore, the correlation between, for example, index conflicts and vote outcome ignores the influence of other voters with competitor conflicts at the same meeting. Further, in some meetings, there are advisory committee members who have disclosed financial conflicts with both a sponsor and a competitor of the index drug. For these individuals, it cannot be determined what constitutes voting in favor of one's financial interest. Therefore, although these individuals are included in the analyses for both conflict types separately, it is not possible to consider the impact on voting behavior of both types of conflicts simultaneously. Subsequent research should be considered to more completely explore the relationship between different types of conflicts and voting behavior at any particular meeting.

Lastly, there is no way to accurately account for all of the factors that might influence the votes of FDA advisory committee members. As Lurie et al. suggest, those factors may include "trends in drug

[31] It is important to note, however, that advisory committee members, as special government employees or regular government employees, are required under criminal law to report their financial interests and face criminal sanctions if they fail to report relevant information.

approval rates," the "forcefulness of the advisory committee chair," "press coverage," and any number of other things including, perhaps most importantly, their personal experience and professional expertise. The weakness of disclosed financial interests as an explanatory variable for voting behavior suggests that disclosed financial interests (to the extent they are measurable through the system for evaluating conflicts) do not exert any discernible impacts or exert only minimal impacts on committee member voting behavior. Using the methodology described in Lurie et al., ERG finds no evidence to suggest that the existence of disclosed financial interests in a sponsor or competitor company among FDA standing and temporary advisory committee members tends to increase votes in support of those interests.

7. REFERENCES

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