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## FDA ADVISORY COMMITTEES: An Empirical Examination of Conflicts of Interest

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Searle Civil Justice Institute

FDA ADVISORY COMMITTEES:  
AN EMPIRICAL EXAMINATION OF CONFLICTS OF INTEREST

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# EXECUTIVE SUMMARY

## ***Background***

The Food and Drug Administration (FDA) implements a rigorous review process to determine whether drugs and medical devices are sufficiently safe and effective for use by consumers. Although the FDA relies solely on the advice of its own staff of technical experts for about half of the drugs it reviews, the FDA uses external experts on Advisory Committees (ACs) when making approval decisions with respect to drugs that may require highly specialized knowledge.<sup>1</sup> The same qualifications that tend to make these experts attractive candidates to sit on ACs, however, often create financial ties between experts and drug companies. Congress and the public have expressed concern that these financial ties will bias experts' votes in favor of drug approvals, leading to unsafe and ineffective drugs on the market. Commentators both within and outside the FDA, however, have pointed out that stringent rules limiting conflicted members from serving on ACs risks reducing the efficacy of FDA decision-making.

## ***Searle Civil Justice Institute Task Force on FDA Advisory Committees***

The SCJI established the FDA Advisory Committee Task Force to examine how financial conflicts and other factors may affect AC member voting. This Report is the first phase of a two-phase project that will provide empirical evidence to policy makers. This Report describes the results from the first phase of this project, which involved collecting data on individual votes and examining the relationship between the presence of financial conflicts and voting decisions. The second phase of the FDA project will compare AC member voting to proxies for an unbiased benchmark of "correct" voting.

## ***Data and Methodology***

The unit of analysis for this study is an AC member's vote on a particular drug or biologic at a particular meeting. The Task Force used raw filings of the AC meetings from 1997 to 2012 to build the data set for this study.<sup>2</sup> For each meeting of interest in the study, first- and second-year law students accessed meeting documents (announcements, transcripts, committee rosters, minutes, and statements of conflicts of

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<sup>1</sup> And for all new drugs, FDA division or office directors make the final approval decision, based solely on FDA employee work or FDA employee work combined with that of an AC. Although FDA usually follows the ACs' recommendations, the common perception is that they almost always do. See Diana Zuckerman, *FDA Advisory Committees: Does Approval Mean Safe?*, Washington, D.C.: National Research Center for Women and Families (2006), available at <http://center4research.org/nrc-in-the-news/press-releases/fda-advisory-committee-does-approval-mean-safety/> (last visited May 14, 2013).

<sup>2</sup> Filings for committee meetings held from 1997 through 2009, were found at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>. Filings for 2010 through 2011 were found at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm>. Both links were accessed and data was extracted between January and September 2012.

interest) posted on the FDA website.<sup>3</sup> From these documents, students filtered out and compiled the following meeting and member data:

- Notice of meeting date and meeting start date;
- Advisory committee name;
- Trade and technical drug names;
- Drug company;
- Member names, roles, standing, degrees, and expertise; and
- Number, size, type, and company for each conflict of interest in the meeting.

The final sample includes a total of 5,719 votes placed by individual AC members and covers a total of 316 party matter meetings concerning 416 new or previously approved drugs and biologics.

### ***Key Findings***

- **Experts comprise the majority of conflicted members, although both consumer and patient representatives also have conflicts:**
  - 94 percent of conflicts in the sample are associated with experts.
  - 4 percent of conflicts in the sample are associated with consumer representatives.
  - 2 percent of the conflicts in the sample are associated with patient representatives.
- **There is no statistically significant difference in drug approval voting rates between conflicted and non-conflicted expert members of ACs:**
  - 64.2% conflicted vs. 62.6% non-conflicted, ( $p$ -value = .22)
- **Conflicted consumer and patient representatives vote for drug approval at higher rates than conflicted experts:**
  - 69.0% (consumer) vs. 64.2% (expert), ( $p$ -value = .30)
  - 85.7% (patient) vs. 64.2% (expert), ( $p$ -value .05)

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<sup>3</sup> These documents include mainly the meeting transcript, but also, based upon availability, the Federal Register Notice of Meeting announcement, committee and meeting rosters, minutes, and statements of conflicts of interest.

- **There are statistically significant differences in approval voting rates between conflicted and non-conflicted consumer representatives and patient representatives:**
  - consumer representatives: 69.0% conflicted vs. 55.9% non-conflicted, ( $p$ -value = .08)
  - patient representatives: 85.7% conflicted vs. 68.2% non-conflicted, ( $p$ -value = .08)
- **From 2002–2012, 89.1 percent of conflicts involved a competitor drug company, and only 24.5 percent of conflicts involved the drug sponsor.<sup>4</sup>**
- **AC members with sponsor conflicts vote for drug approval at the same rate as those with competitor conflicts (65%).**
- **There is no statistically significant difference in approval voting rates between conflicted and non-conflicted members with either sponsor or competitor conflicts.**
- **Multivariate logit regression analysis finds no statistically significant relationship between the presence of a conflict and the odds of voting for drug approval.**
  - Consumer representatives are 22 percent less likely than experts to vote for approval, and patient representatives are 34 percent more likely than experts to vote for drug approval.
  - AC member standing — permanent, temporary, or chairman — appears to have no effect on voting propensities.
  - The 2007 FDA Improvement Act and subsequent FDA policies limiting the ability of conflicted potential AC members to receive waivers appears to have had no effect on approval voting rates of conflicted members that are allowed to serve on ACs under the more stringent standard.

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<sup>4</sup> The sum of the two types of conflicts exceeds 100 percent because some members have both sponsor and competitor conflicts.

- **Meeting-level analysis finds no statistically significant correlation between AC approval voting rates and the proportion of conflicted members.**
- **Removing conflicted members from ACs would have had only a trivial effect on AC approval decisions, and in no systematic direction:**
  - Excluding all votes of AC members with sponsor conflicts results in no change in approval decisions.
  - Excluding all votes of AC members with competitor conflicts results in one change in recommendation from rejection to approval.
  - Excluding votes of all conflicted AC members from the sample results in five vote changes: two from a tie to reject, one from a tie to approve, one from reject to tie, and one from reject to approve.

## ACKNOWLEDGEMENTS

We would like to thank the Searle Civil Justice Institute for financial and other support for this project. We are also grateful for the helpful comments from members of the SCJI Board of Overseers, participants in the SCJI research workshop at George Mason University School of Law, and two anonymous referees. William Bang, Louisa Brooks, Wei Fan, Will Freeland, Timothy Fox, Emily Gardner, Daniel Mixton, Sam Schmitt, and Cynthia Thaxton provided outstanding research assistance in collecting and compiling data for this project. Finally, we thank Michael Wilt for his excellent editorial work in finalizing this Report.

***In Memoriam:*** Our colleague John Vernon died unexpectedly on June 19, 2012 during the initial stages of this research. John was internationally known for his research on the economics of pharmaceuticals and biologics. His enthusiasm for research and his intellectual curiosity, creativity, and good nature will be missed.

Joseph H. Golec  
FDA Advisory Committee Task Force Chair

# FDA ADVISORY COMMITTEES: AN EMPIRICAL EXAMINATION OF CONFLICTS OF INTEREST

## 1. INTRODUCTION

The Food and Drug Administration (FDA) implements a rigorous review process to determine whether drugs, biologics, and medical devices are sufficiently safe and effective for use by consumers. The FDA relies solely on the advice of its own staff of technical experts for about half of the drugs it reviews.<sup>1</sup> For the other half of new drugs—typically those that are relatively specialized or require accelerated review—the FDA obtains the advice of outside experts or special government employees (SGEs).<sup>2</sup> These experts participate on advisory committees (AC), which make recommendations to the FDA on the safety and effectiveness of drugs under review.

The composition of these ACs, however, is not without controversy. The same specialized education and scientific experience that makes these experts attractive candidates to serve on ACs also puts them in contact with drug companies. The root of the conflict-of-interest issue lies in the fact that most governments do not believe that consumers are competent to judge the safety and effectiveness of many biopharmaceutical products. Instead, medical experts make the decisions for them: FDA staff and AC members at the point of market entry, and physicians at the point of prescription. Conflicts arise because biopharmaceutical firms often employ or contact these same expert physicians, researchers, and clinicians to help them develop and market their products. For instance, companies seek out these experts to monitor or run their clinical trials, speak at various company-sponsored meetings, consult, write, or serve on review boards. Drug companies, moreover, fund research studies at universities and research institutes that employ these experts. Finally, these experts may be able to assess companies' scientific promise and invest in the stocks of those with superior prospects.

Congress and the public have expressed concerns that financial ties between experts and drug companies may bias their recommendations in favor of drug approval,

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<sup>1</sup> And for all new drugs, FDA division or office directors make the final approval decision, based solely on FDA employee work or FDA employee work combined with that of an AC. Although FDA usually follows the ACs' recommendations, the common perception is that they almost always do. See Diana Zuckerman, *FDA Advisory Committees: Does Approval Mean Safe?*, Aug. 28, 2006, National Research Center for Women and Families, *available at* <http://center4research.org/newsite/wp-content/uploads/2006/09/FDA-Report-v7.pdf> (last visited May 14, 2013).

<sup>2</sup> See Susan L. Moffitt, *The Policy Impact of Public Advice: The Effects of Advisory Committee Transparency on Regulatory Performance*, Ch. 9 in *REGULATORY BREAKDOWN: THE CRISIS OF CONFIDENCE IN U.S. REGULATION*, (C. Coglianese, ed., Univ. of Penn. Press, 2012). The 50 percent rate is biased up because it includes only approved drugs.

ultimately harming the public through exposure to unsafe or ineffective drugs.<sup>3</sup> Heavy publicity surrounding certain drugs recalled for safety concerns has reinforced this impression. After Merck's Vioxx was removed from the market in 2004, for example, the FDA was criticized for issuing conflict waivers to four of the six members on the committee that originally voted to recommend approval of Vioxx in 1999.<sup>4</sup> Some commentators have suggested that even small financial interests can seriously bias those decisions; consequently, they recommend prohibiting most financial conflicts.<sup>5</sup> For example, a well-publicized study from the *Journal of the American Medical Association (JAMA)* found that 73 percent of AC meetings between 2001 and 2004 involved at least one member with a conflict, and well over 60 percent of the conflicts consisted of members owning drug company stocks or receiving consulting fees from drug companies.<sup>6</sup> The study presented evidence that conflicted members voted in favor of drug approvals more frequently than non-conflicted members, which the authors contend threatens to undermine the integrity of the FDA regulatory process.<sup>7</sup>

In response to such criticisms, legislation was proposed in 2005 in the U.S. House of Representatives and backed by consumer interest groups to prohibit conflicted members from serving on ACs.<sup>8</sup> Although this outright ban on conflicted members did not pass, Congress passed a law in 2007 limiting the number of members with conflicts of interest who can serve on ACs and reducing the maximum size of conflicts eligible for waivers.<sup>9</sup> Further, beginning in 2009, the Obama administration began to take additional steps to further limit the prevalence of conflicted members serving on ACs.

Limiting the number of conflicted experts who can serve on ACs, however, is not free; this policy raises costs associated with finding qualified, non-conflicted members and appointing less qualified AC members. Because the FDA appoints ACs for more important, technical, and specialized drug applications, it must draw from a small pool of

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<sup>3</sup> See, e.g., 151 CONG. REC. H4245 (daily ed. Jun. 8, 2005) (statement of Rep. Hinchey). See also *Editorial, Experts, Conflicts, and the F.D.A.*, N.Y. TIMES, May 4, 2010, at A30, available at [http://www.nytimes.com/2010/05/05/opinion/05wed3.html?\\_r=1&](http://www.nytimes.com/2010/05/05/opinion/05wed3.html?_r=1&).

<sup>4</sup> *Editorial, Experts and the Drug Industry*, N.Y. TIMES, Mar. 4, 2005, available at <http://select.nytimes.com/gst/abstract.html?res=FB0F12F73B590C778CDDAA0894DD404482>.

<sup>5</sup> Troyen A. Brennan, et al., *Health Industry Practices that Create Conflicts of Interest*, 295 JAMA 429, 429-33 (Jan. 25, 2006), available at <http://jama.jamanetwork.com/article.aspx?articleid=202261> (last visited May 10, 2013).

<sup>6</sup> Peter Lurie, et al., *Financial Conflicts of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 JAMA 1921, 1921-28 (Apr. 26, 2006), available at [http://www.people.fas.harvard.edu/~stine/Files/Lurie\\_Almeida\\_Stine\\_Stine\\_Wolfe\\_2006\\_Financial%20conflict%20of%20interest%20disclosure%20and%20voting%20patterns%20at%20food%20and%20drug%20administration%20drug%20advisory%20committee%20meetings.pdf](http://www.people.fas.harvard.edu/~stine/Files/Lurie_Almeida_Stine_Stine_Wolfe_2006_Financial%20conflict%20of%20interest%20disclosure%20and%20voting%20patterns%20at%20food%20and%20drug%20administration%20drug%20advisory%20committee%20meetings.pdf) (last visited May 10, 2013).

<sup>7</sup> *Id.*

<sup>8</sup> Jeanne Lenzer, *New Law Aims to Distance the FDA from the Drug Industry*, 330 BRITISH MED. J. 1106, 1106 (May 14, 2005), available at <http://www.bmj.com/content/330/7500/1106.2> (last visited May 10, 2013).

<sup>9</sup> FDA Amendments Act of 2007, Pub. L. No. 110-85, Sec. 701 (codified as amended in scattered sections of 21 U.S.C.).

experts experienced with the new drug's science.<sup>10</sup> Moreover, because drug companies often fund much of the new research, these experts are more likely to have substantial financial interests connected to the firms working on these specialized drugs.<sup>11</sup> For example, a survey of academic medical researchers discovered that about 60 percent felt industry involvement contributed to their most important scientific work. The survey also found that faculty with industry relationships published more top research articles. Under a strict no-conflict rule, consequently, filling AC committees with many of the top researchers could prove difficult.<sup>12</sup>

The FDA's director of the Center for Drug Evaluation and Research has made it clear that the current near prohibition of conflicted members since 2007 has made it difficult to fill AC vacancies with individuals experienced in a highly technical drug science.<sup>13</sup> Similarly, a coalition of 80 patient groups representing those who will benefit or suffer most from the approval of new drugs have lobbied Congress to revert back to a more balanced approach to appointing AC members. They argue that imposing a near complete prohibition slows the evaluation process, unnecessarily restricts the flow of top expertise to inform the FDA's decisions, and inhibits innovation.<sup>14</sup>

If financial ties between experts and drug companies leads to FDA approval of unsafe or ineffective drugs, the costs associated with policies limiting the ability of conflicted experts to serve on ACs may be justified. If financial ties have no impact on drug approval decisions, however, such policies are likely to impose net costs on society.

The Searle Civil Justice Institute established the FDA Advisory Committee Task Force to examine this important empirical question. This Report, which is the first phase of a two-phase research project, expands on prior empirical work to examine the extent to which financial conflicts of interest affect AC member voting behavior. The Task Force gathered data on 774 non-voting AC members and data on over 5,700 individual votes by 1,483 voting AC members representing 316 AC meetings on 416 pharmaceutical and biologic drug evaluations. Following earlier studies of AC voting, this Report defines a conflict of interest as a financial interest of a voting AC member

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<sup>10</sup> Comments of Eastern Research Group, Inc. to the Food and Drug Administration, *Measuring Conflict of Interest and Expertise on FDA Advisory Committees*, (Oct. 26, 2007), available at <http://www.fda.gov/downloads/AdvisoryCommittees/AboutAdvisoryCommittees/UCM165332.pdf> (last visited May 10, 2013).

<sup>11</sup> Thomas Sullivan, *Patient Groups Encourage Congress to Remove Burdensome FDA Rules*, Oct. 31, 2011, POLICY AND MEDICINE, available at <http://www.policymed.com/2011/10/patient-groups-encourage-congress-to-remove-burdensome-fda-rules.html> (last visited May 10, 2013).

<sup>12</sup> See, e.g., Darren E. Zinner, et al., Participation of Academic Scientists in Relationships with Industry, HEALTH AFFAIRS, 28: 1814-1825 (Nov./Dec. 2009), available at <http://www.ncbi.nlm.nih.gov/pubmed/19887423> (last visited May 10, 2013); Lisa Richwine, *FDA Official Sees Drug Approvals Rising*, May 9, 2011, REUTERS, available at <http://www.reuters.com/article/2011/05/09/us-summit-fda-approvals-idUSTRE7485B120110509> (last visited May 10, 2013).

<sup>13</sup> Richwine, *supra* note 12.

<sup>14</sup> Sullivan, *supra* note 11.

associated with the company sponsoring the new drug or a company that produces a competitor drug.<sup>15</sup> This Report improves on earlier work by using a larger sample period and considering new variables to explain member voting.<sup>16</sup> It examines several important empirical questions such as

- **Conflicts of Interest over Time:** Are AC member conflicts more common in particular years between 1997 and 2012?
- **Characteristics of Conflicted Members:** Do conflicts vary with the committee member's role (expert, industry rep, consumer rep) or standing (chairman, permanent, temporary)?
- **Characteristics of Conflicts:** What are the most common types of financial interests? What is the typical size of a conflicted member's financial interest? Are conflicts mostly associated with the drug sponsor firms or with competitor firms?
- **Impact of Conflicts on Voting:** Do conflicted members vote for drug approval more frequently than non-conflicted members?
- **Voting Behavior across Member Type, Conflict Type, and by Conflict Company:** How do "yes" voting rates vary across member types and across conflict types? How do "yes" voting rates differ between sponsor-company conflicts and competitor-company conflicts?
- **Impact of Conflicts on Meeting Outcomes:** Does the presence of conflicted members affect AC approval recommendations?

The results suggest a small and statistically insignificant positive relationship between conflicts—defined to include both competitor and sponsor interests—and “yes” votes, but find no difference between competitor and sponsor interests when examined separately. The Report finds that member type—expert, consumer representative, or patient representative—is the only significant predictor of voting patterns. Compared to experts, on average, AC members representing consumer interests vote “yes” less frequently, and AC members representing patient interests vote “yes” more frequently. Further, data suggest that conflicted consumer and patient representatives vote more frequently in favor of drug approval than their non-conflicted counterparts or conflicted experts.

This Report proceeds as follows. Section 2 provides a general background on ACs and their processes—meeting preparations, member selection, and the review

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<sup>15</sup> The FDA must provide a waiver for the conflicted member to participate and vote at a meeting. Other non-monetary interests that the FDA feels could appear to compromise the member's impartiality would have to be disclosed or could be enough to disqualify the member. These cases are relatively rare and their magnitudes are difficult to measure, hence, we do not consider them. For example, an AC member who has already written favorable or unfavorable opinions on a proposed new drug, before viewing the clinical data that will be presented at the AC meeting, could be considered biased and be disqualified.

<sup>16</sup> Our sample and those of earlier papers will not exactly match, so we do not try to reproduce their results for their smaller samples. Nevertheless, our basic results are consistent with theirs.

process for potential conflicts of interest. We also briefly compare advisory committees among selected countries to illustrate how other countries assess new drugs and deal with conflicts of interest. Section 3 provides a brief review of the relevant literature. Section 4 discusses data sources and collection, and it also provides some descriptive statistics and trends. Section 5 presents the main empirical results, examining the relationship between voting and conflict of interests with both univariate statistics and multivariate logit analysis. Section 6 concludes with policy recommendations and proposals based on the empirical analyses, and it also describes future empirical work on this project.

## 2. BACKGROUND

### 2.1. FDA Advisory Committees

The Federal Advisory Committee Act (FACA) sets out the law governing ACs.<sup>17</sup> ACs must follow regulations set by the Act, which apply whenever executive branch officers and agencies seek advice from a committee with at least one member who is not a permanent federal employee. The FACA requires all committee members to be screened for potential conflicts of interest.

Each AC defines its scope, the number of members, and the qualifications of its members in a charter that requires periodic reauthorization. AC meetings are pre-announced, recorded, and open to the public, except for the parts during which confidential (e.g. proprietary) information is discussed. The AC's recommendations are not binding; a government official or agency makes the final decisions.

ACs are categorized in line with FDA's eleven general divisions: biologics, drugs, food, medical devices, pediatric, radiation-emitting products, risk communication, science board, toxicological research, veterinary, and tobacco. Each category is composed of one or more ACs organized along specific product lines. For example, the Arthritis AC is one of seventeen ACs in the drug division. In 2011, a total of 1,364 members<sup>18</sup> participated in fifty ACs. The two product groups of interest in this report—drugs and biologics—have a combined number of twenty-three ACs. Each committee can be as small as nine or as large as twenty-six members, but most consist of eleven to thirteen members.

#### 2.1.1 Meeting Preparation Process

Selecting members, organizing the meeting, and managing the information presented at and obtained from a meeting is a formidable yet ongoing task for the FDA.

Figure 1 illustrates the timing of the information preparation process for one AC meeting. The FDA and committee members work under substantial time pressure: the FDA schedules a meeting about two months before the meeting date and posts any conflict waivers two to three weeks before the meeting. Therefore, the FDA has a little over a month in which to contact committee members, request conflict of interest statements, analyze the statements, exclude members or request waivers, approve the waivers, and fill the vacancies of excluded members.

In addition, the FDA staff and committee members must prepare for the presentations and analyses of information at the meeting. Approximately one month before the meeting, the FDA receives the drug sponsor's brief and then sends its own

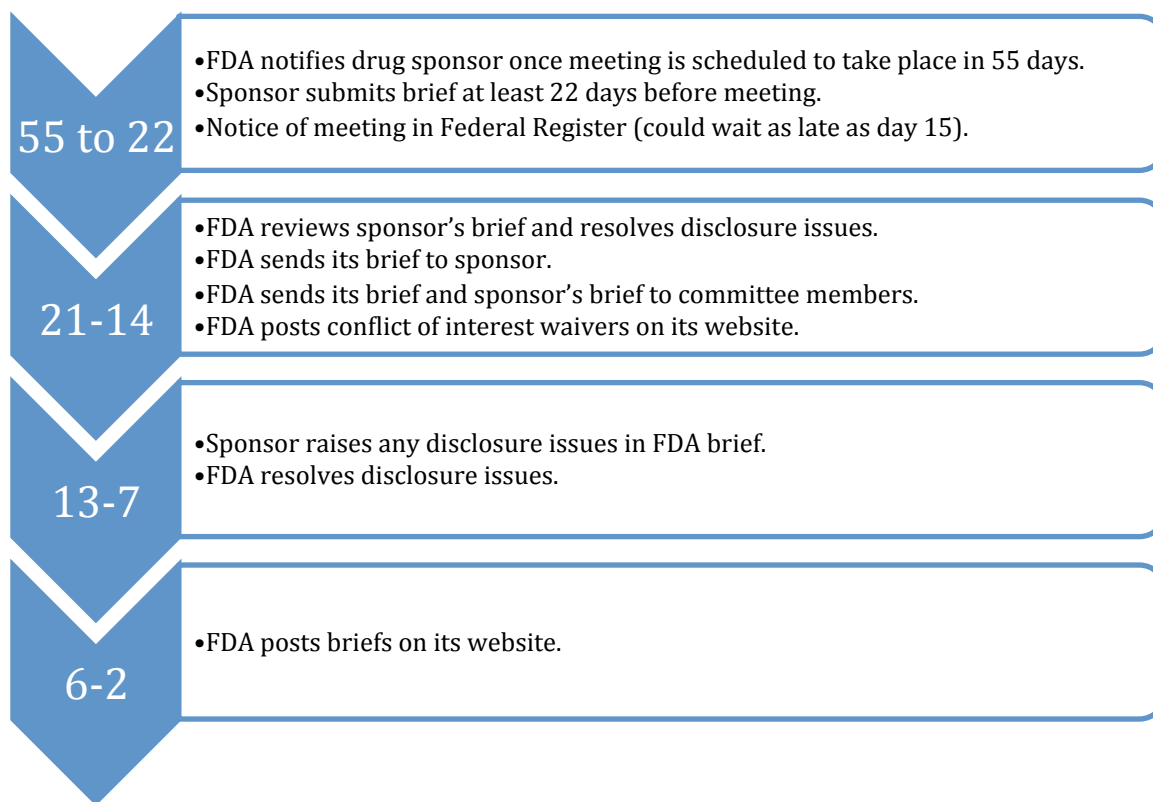
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<sup>17</sup> 5 U.S.C. App. 2, §§ 1-16.

<sup>18</sup> FDA-TRACK Advisory Committees Quarterly Briefing Summary, Jan. 9, 2012, *available at* <http://www.fda.gov/AboutFDA/Transparency/track/ucm289615.htm> (last visited May 10, 2013).

brief to the sponsor. These briefs are used by the sponsor and FDA staff to support their presentations at the AC meeting and contain detailed technical statistics and clinical results of the drug under review—each representing, respectively, the sponsor’s and FDA’s analysis of the proposed new drug. The Committee members have two to three weeks to analyze the briefs.

FIGURE 1  
PREPARATION FOR FDA AC MEETINGS  
(DAYS PRECEDING THE MEETING)



### 2.1.2 Member Selection

Each AC has FDA staff devoted to managing its membership, with each consisting of permanent members serving four-year terms and temporary members serving for one meeting. In general, permanent members include a consumer representative, a patient representative, an industry representative (non-voting and not associated with the drug sponsor), and at least two highly qualified experts who specialize in the specific disease or drug category. Temporary members fill in for absent permanent members or provide specialized expertise that the FDA feels is necessary to evaluate a particular new drug.

Permanent member candidates and a pool of temporary member candidates undergo a rigorous multi-step process beginning with a request for nominations from FDA that appears in the Federal Register, on the FDA's website, or similar locations. Professional societies, advocacy groups, current members, and aspiring members each can make nominations for openings. In the event of a vacancy or special need, the staff prescreens the nominee's *vitae* and disclosed potential conflicts. Potential members must disclose all of their financial interests related to any drug or biologic company. The staff member can reject nominees deemed technically unqualified or compromised by too many potential conflicts.

Expert members must possess sufficient scientific or clinical training to analyze clinical data, research trial designs, weigh drug risks and benefits, and evaluate drug safety and efficacy. Thus, they face a higher standard of competency along these margins than consumer, patient, and industry representatives. The committee chairman is typically the most highly qualified permanent committee member. Consumer, patient, and industry representatives provide balance to the committee by representing a constituency as well as possessing some technical qualifications. The FDA staff selects the representatives in consultation with advocacy groups.<sup>19</sup>

Finally, division-level committee management staff and the FDA's general Advisory Committee Oversight Management staff rescreen all AC selections to finalize the members. They review the range of financial interests disclosed by the potential members for any conflicts of interest.

### 2.1.3 *Conflicts of Interest*

Once the FDA staff has chosen a member for a specific AC within a division (drug, biologic, etc.), the staff must rescreen the member for conflicts of interest and expertise with respect to the specific drug to be evaluated at a particular meeting. Federal law requires committee members who are regular government employees, or more commonly, special government employees, to disclose all conflicts of interests relevant to the topics to be discussed at an AC meeting.<sup>20</sup> Rescreening of AC members takes into account any changes in their financial interests between their initial screening when appointed, and the AC meeting.

The law considers a member's financial interest to be a potential conflict of interest if the discussions and potential outcomes of the AC meeting will have a direct

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<sup>19</sup> Norman J. Levinsky, *Respect for Patients' Autonomy is Now Considered Fundamental to the Practice of Medicine*, NEW ENG. J. OF MED. (Feb. 22, 1996), available at <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/PatientInvolvement/ucm123861.htm> (last visited May 10, 2013).

<sup>20</sup> Ethics in Government Act of 1978, Title I Pub. L. 95-521, 92 Stat. 1824 (codified at 5 U.S.C. App. § 101(f)(3)) ("each officer or employee in the executive branch, including a special government employee . . .").

and predictable effect on the member's financial interests.<sup>21</sup> AC members' financial interests include stock, consulting fees, speaking fees, grants, wages and other monetary and non-monetary ties related to the company sponsoring the new drug, or currently marketed drugs of competitors to the potential new drug. In addition, individuals must report financial interests imputed to them through their spouses, minor children, employers, prospective employers, general partners, and organizations in which they serve as an officer, director, trustee, or general partner. The conflict net is cast wide; for example, an oncology researcher serving on the oncologic AC is "conflicted" if the university where she works received funds from the sponsor drug company, even if none of it funded general oncology research or her specific research. In this case, the benefit to her employer (the university) is imputed to her.

Division-level staff can exclude a conflicted member, or propose a waiver of the conflict if the member offers substantial expertise and the conflict is small or moderate. A proposed waiver that allows a conflicted member to participate in a meeting must be reviewed by the FDA's Ethics and Integrity staff (and Health and Human Services general counsel or the Office of Government Ethics in special cases). Based upon the ethics opinion, Advisory Committee Oversight Management staff may send the waiver to the Senior Associate Commissioner of Policy and Planning, who can approve the waiver if he or she judges that the member's expert contribution to the meeting outweighs the potential conflict of interest.<sup>22</sup>

The FDA Amendments Act of 2007 placed additional restrictions on ACs with respect to conflicts of interest, requiring that by 2012, no more than thirteen percent of member participants per year could receive waivers.<sup>23</sup> Furthermore, the FDA reduced the maximum size of financial interests eligible for waivers from a combined financial interest of up to \$100,000, to a maximum to \$50,000. Less than a year after taking office, moreover, President Obama's FDA Commissioner, Margaret Hamburg, made it clear that she was endorsing a very high standard for waived conflicts: "In my view, it is clearly better for the agency in fulfilling its public health mission when advisors have no conflicts of interest. FDA staff should search far and wide for experts who have the requisite knowledge without conflicts of interest."<sup>24</sup>

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<sup>21</sup> 18 U.S.C. § 208; 21 U.S.C. § 379d-1 (amended by the FDA Amendments Act of 2007, Pub. L. No. 110-85, Sec. 701).

<sup>22</sup> This is a somewhat simplified view of the process. See Appendix A, *infra*, which reproduces FDA's flowchart of the process that appears in *Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflicts of Interest and Eligibility for Participation in FDA Advisory Committees*, Aug. 2008, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf> (last visited May 10, 2013).

<sup>23</sup> FDA Amendments Act of 2007, *supra* note 9.

<sup>24</sup> Margaret A. Hamburg, *Comm'r's Letter to FDA Staff on Disclosure of Financial Conflicts of Interest*, Apr. 21, 2010, available at <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm209001.htm> (last visited May 10, 2013).

Commissioner Hamburg also proposed three criteria for staff to use in deciding whether to grant a waiver. First, tangential conflicts, such as a researcher whose organization receives a grant not directly tied to the researcher, should be considered less serious. Second, conflicts for members voting on specific drug approvals (party matters) as opposed to general drug-related recommendations should be considered more serious. Third, if a waiver is requested, the staff member should describe the search process used to identify the conflicted member and explain why an equally qualified expert without conflicts was not identified.

## 2.2 International Comparison of Drug Advisory Committees

The United States is not alone in utilizing administrative committees to evaluate new pharmaceutical drugs. To get an idea of alternative structures for expert drug advisory committees, we gathered information on the structure of comparable drug advisory committees in similarly situated foreign nations.<sup>25</sup> Table 1 compares the characteristics of the U.S. FDA drug advisory committees with those of foreign countries. We considered the following eight countries (region in the case of the EU) and their associated drug evaluation agencies or committees.

Australia (AU): Therapeutic Goods Administration  
Canada (CA): Canadian Drug Expert Committee  
New Zealand (NZ): Pharmacology and Therapeutics Advisory Committee  
United Kingdom (UK): Technology Appraisals Committee  
European Union (EU): Committee for Medicinal Products  
China (CH): Center for Drug Evaluation  
Japan (JP): Pharmaceutical and Medical Device Agency  
India (IN): New Drug Advisory Committee

The abbreviated country name appears across the top of the table and the comparison characteristic is listed in the first column. A “yes” indicates that the

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<sup>25</sup> See the following references and websites for details: Steven C. Morgan, et al., *Centralized Drug Review Processes in Australia, Canada, New Zealand, and the United Kingdom*, HEALTH AFFAIRS, 25: 337-347 (Mar./Apr. 2006), available at <http://www.ncbi.nlm.nih.gov/pubmed/16522575> (last visited May 10, 2013); U.S. General Accounting Office, *European Union Drug Approval*, GAO/HEHS-96-71 (April 2006); Dong Lu & Wenlong Huang, *Overview of Drug Evaluation System in China*, SCIENTIFIC RESEARCH & ESSAYS 5: 514-518 (Mar. 2010), available at <http://www.academicjournals.org/sre/pdf/pdf2010/18Mar/Lu%20and%20Huang.pdf> (last visited May 10, 2013). The following websites for the various countries' committees were all last visited on May 8, 2012: Australia, <http://www.tga.gov.au/>; Canada, <http://cadth.ca/en/products/cdr/committees/canadian-drug-expert-committee>; New Zealand, <http://www.pharmac.govt.nz/PTAC>; United Kingdom, [http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalcommittee/technology\\_appraisal\\_committee.jsp](http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalcommittee/technology_appraisal_committee.jsp); European Union, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000094.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp); China, [http://former.sfda.gov.cn/cmsweb/webportal/W43879537/index.html?UID=DWV1\\_WOUID\\_URL\\_43879537](http://former.sfda.gov.cn/cmsweb/webportal/W43879537/index.html?UID=DWV1_WOUID_URL_43879537); Japan, <http://www.pmda.go.jp/Eng.ish/index.html>, <http://www.cdsco.nic.in/>.

country's committee possesses the particular characteristic; a "no" cell indicates the country's committee does not possess the characteristic. For example, six of the nine countries have a single central committee to evaluate new drugs. Only the U.S., Australia, and India have separate committees, each handling a particular group of drugs defined by therapeutic use.

Even among countries with separate committees, however, the U.S. has more specialized committees than any other country. This type of structure may provide the FDA with more specialized information but at a cost of having to manage more committees, more committee members, and more conflicts.

TABLE 1  
COMPARISON OF DRUG ADVISORY COMMITTEES ACROSS COUNTRIES

Country	US	AU	CA	NZ	UK	EU	CH	JP	IN
Single Central Committee?	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Committee Weighs Cost Effectiveness of Drug?	No	Yes	Yes	No	Yes	No	No	No	No
Committee's Decision Binding?	No	No	No	No	No	Yes	No	No	No
Sponsor Can Contest Committee Decision?	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Technical Details and Transcript on Web?	Yes	Yes	No	No	Yes	No	No	Yes	No
Blinded Experts Used?	No	No	Yes	Yes	Yes	No	Yes	Yes	No
Conflict Waivers Allowed?	Yes	Yes	Yes	Yes	No	No	No	No	No
Who Approves the Waiver?	Admin	Rest of Comm	Chair + Admin	Chair + Admin	n/a	n/a	n/a	n/a	n/a
Conflicts Recorded in Transcript?	Yes	Yes	Yes	Yes	n/a	n/a	n/a	n/a	n/a

Most countries' drug committees evaluate only the safety and efficacy of new drugs. Nevertheless, AU, CA, and UK include economists or business experts on their committees to help decide whether the additional therapeutic benefit to the patient is worth the proposed price of the new drug. If a committee decides that the price is not worth the benefit, it may recommend rejection. Still, the recommendations of all of the committees, except for the EU's, are only that—recommendations—and not final decisions. Final decisions ultimately lie in the hands of government agencies or

officials. Even in the EU, where committee approval technically means that the drug can be sold in any EU country, member countries can decide whether or not to publicly fund the approved drug, substantially limiting its market.

About half of the countries allow a drug's sponsor company to contest the committee's recommendation. For the other half, the company must file a new case with additional clinical information or analysis in order to have its drug reevaluated.

About half of the countries allow blinded experts to evaluate new drugs and provide the evaluations to all committee members to help them decide whether to recommend approval or rejection. These experts may be committee members themselves or external experts. The point is that the identity of the experts is not made public. Note that all of these countries, except for the EU, also have a single central committee. These central committees may not be large enough to have the appropriate expertise for each new drug candidate; hence, some obtain expert analysis from external blinded experts.

Instead of a blind review, the FDA constructs specialized committees, each containing specialized experts. When an FDA committee lacks some unusual expertise required for a particular meeting, they may appoint a temporary member with the necessary expertise. The identities of the experts and what they say at a meeting, however, are recorded and publicly disclosed. Indeed, the FDA recently started posting video recordings of AC meetings on its website.<sup>26</sup>

The UK, EU, CH, JP, and IN do not allow conflicted committee members to participate in the drug evaluation process. The US, AU, CA, and NZ may waive conflict of interest concerns under certain circumstances, typically when they determine that the conflict is small or moderate and the member's expertise is important to the committee's evaluation.

In AU, the rest of the committee must decide whether conflicted members can participate. In CA and NZ, the committee chairman, along with an agency official, make the decision. Those countries that allow conflict waivers also record conflicts in the meeting transcripts. About half of the countries provide public access to the technical details of the drug evaluation and the committee meeting transcripts.

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<sup>26</sup> See, e.g., FDA.gov, *Hearing on Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab*, Jun. 28, 2011, available at <http://www.fda.gov/newsevents/meetingsconferencesworkshops/ucm255874.htm> (last visited May 10, 2013).

### 3. LITERATURE REVIEW

Not surprisingly, financial conflicts of interest within the healthcare industry in general, and between biopharmaceutical firms and medical researchers, clinicians, and healthcare providers in particular, have attracted much attention in the popular press and some academic journals. Interest in the importance of AC conflicts of interest jumped following the withdrawal of Merck's Vioxx in 2004, and the finding that the AC that approved Vioxx in 1999 had several conflicted members.<sup>27</sup> Most of this published work, however, is anecdotal, editorial, or based on survey data.<sup>28</sup>

Only a few earlier studies bring substantial data to bear on these questions. Most find a weak association between AC member conflict of interest and “yes” voting, and that exclusion of conflicted AC members would not have changed the ultimate AC

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<sup>27</sup> Editorial, *Experts and the Drug Industry*, N.Y. TIMES, Mar. 4, 2005, available at <http://select.nytimes.com/gst/abstract.html?res=FB0F12F73B590C778CDDAA0894DD404482>.

<sup>28</sup> The following is a sample of articles covering a wide range of these conflicts. Marcia Angell, *Is Academic Medicine for Sale?*, 342 N. ENG. J. MED. 1516, 1516-18 (2000); J.P. Kassirer, *A Piece of My Mind: Financial Indigestion*, 284 JAMA 2156, 2156-57 (2000); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just A Gift?*, 283 JAMA 373, 373-80 (2000); Dennis Cauchon, *FDA Advisers Tied To Industry*, USA TODAY, Sept. 25, 2000, at 1A; Dennis Cauchon, *Number of Drug Experts Available is Limited*, USA TODAY, Sept. 24, 2000, at 1A; Stolberg, S. G., *Financial ties in biomedicine get a closer look*, N.Y. TIMES, Feb. 20, 2000, at A1; David Korn, *Conflicts of Interest in Biomedical Research*, 284 JAMA 2234, 2234-37 (2000); Thomas Bodenheimer, *Uneasy Alliance -- Clinical Investigators and the Pharmaceutical Industry*, 342 N. ENG. J. MED., 1539, 1539-44 (2000); Hamilton Moses, et al., *Collaborating with Industry – Choices for the Academic Medical Center*, 347 N. ENG. J. MED. 1371, 1371-75 (2002); Catherine D. DeAngelis, *Conflict of Interest and the Public Trust*, 284 JAMA 2237, 2237 (2002); Karine Morin, et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 JAMA 78, 78-84 (2002); Geeta Anand & Randall Smith, *Trial Heat: Biotech Analysts Strive to Peek Inside Clinical Tests of Drugs*, WALL ST. J., Aug. 8, 2002, at A1; David Blumenthal, *Academic-Industrial Relationships in the Life Sciences*, 349 N. ENG. J. MED. 2452, 2452-58 (2003); Daniel Carlat, *Diagnosis: conflict of interest*, N.Y. TIMES, June 13, 2004, at A1, A21; Gregory Zuckerman & Geeta Anand, *The Doctor Is In And, Increasingly, Advising Investors*, WALL ST. J., Dec. 3, 2004, at C1; David Blumenthal, *Doctors and Drug Companies*, 351 N. ENG. J. MED. 1885, 1885-89 (2004); David M. Studdert, Michelle Mello, & Troyen Brennan, *Financial Conflicts of Interest in Physicians' Relationships with the Pharmaceutical Industry—Self-Regulation in the Shadow of Federal Prosecution*, 351 N. ENG. J. MED. 1891, 1891-1900 (2004); Alex Berenson, *Evidence in Vioxx Suits Shows Intervention by Merck Officials*, N.Y. TIMES, April 24, 2005, at A1; Gardiner Harris, & Alex Berenson, *10 Voters on Panel Backing Pain Pills Had Industry Ties*, N.Y. TIMES, Feb. 25, 2005, at A1; Rosie Taylor & Jim Giles, *Cash interests taint drug advice*, 437 NATURE 1070, 1070-71 (2005); Stephanie Saul, & Jenny Anderson, *Doctors' Links With Investors Raise Concerns*, N.Y. TIMES, Aug. 16, 2005, at A1; Robert Steinbrook, *Wall Street and Clinical Trials*, 353 N. ENG. J. MED. 1091, 1091-93, (2005); Robert Steinbrook, *Financial Conflicts of Interest and the Food and Drug Administration's Advisory Committees*, 353 N. ENG. J. MED. 116, 116-18 (2005); Lindsay Hampson, et al., *Patients' Views on Financial Conflicts of Interest in Cancer Research Trials*, 355 N. ENG. J. MED. 2330, 2330-37 (2006); Eric G. Campbell, et al., *Financial Relationships Between Institutional Review Board Members and Industry*, 355 N. ENG. J. MED. 2321, 2321-29 (2006); Troyen Brennan, et al., *Health industry practices that create conflicts of interest: a policy proposal for academic medical centers*, 295 JAMA 429, 429-33 (2006); Eric G. Campbell, et al., *Institutional Academic Industry Relationships*, 298 JAMA 1779, 1779-86 (2007); Robert Steinbrook, *Guidance for Guidelines*, 356 N. ENG. J. MED. 331, 331-33 (2007); Elizabeth Williamson, & Christopher Lee, *Conflict Alleged In Drug Firms' Education Role*, WASH. POST, June 27, 2007, at A3; Gardiner Harris & Benedict Carey, *Researchers Fail to Reveal Full Drug Pay*, N.Y. TIMES, June 8, 2008, at A1.

recommendation. The most widely cited and closest study to this Report found a positive, but in most tests, insignificant, association between AC member conflicts and votes in favor of drug approval.<sup>29</sup> Another study considered an even smaller sample of AC meetings from 1998 through 2005.<sup>30</sup> It constructs a random sample of both drug and device AC meetings and finds that rates of drug and device approval are surprisingly high given that ACs were supposedly used for the most controversial products, and where the data were not clear cut. Votes were often unanimous even when some members voiced safety and efficacy concerns.

The U.S. Government Accountability Office (GAO) was asked by the U.S. Senate Committee on Health, Education, Labor, and Pensions to evaluate the FDA's AC process in light of criticism from the public and Congress.<sup>31</sup> The GAO examined AC meetings held between 2004 and 2006, and found that conflicts were relatively frequent among AC members. Although the GAO acknowledged that the FDA faced barriers to recruiting qualified AC candidates with no conflicts of interest, it suggested that the FDA could find qualified candidates with no conflicts by using better recruitment methods.

The FDA itself commissioned two studies related to AC conflicts of interest. The first study assessed the relation between conflicts of interest and AC member expertise using a small sample covering December 2005 through October 2006. The study discovered that AC members with greater expertise were more likely to have been granted waivers for financial conflicts of interest. They also found that many comparable alternative AC candidates would also require waivers or may not be available to serve on an AC.<sup>32</sup> The second study examined the relation between conflicts of interest and AC member voting using a larger sample covering January 2001 through March 2008.<sup>33</sup> The study found no statistically significant evidence that conflicted AC members vote in line with their financial interests.

Finally, one study attempts to assess the quality of AC decision making in the presence of conflicts by using FDA filings for new molecular entities (NMEs) between 1986 and 2009, some of which were evaluated by an AC while the others were not.<sup>34</sup> It found that those NMEs that were first evaluated by an AC before the FDA made its approval decision were less likely to experience post-marketing drug safety problems (black box warning label or safety alert). But for the subsample of meetings that involved conflicted AC members, post-marketing safety problems were more likely.

This Report contributes significantly to the existing literature by focusing on a larger sample of product-specific AC meetings from 1997–2012. In addition to duplicating many of the statistical tests found in the extant literature with a larger data

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<sup>29</sup> Lurie, *supra* note 6.

<sup>30</sup> Zuckerman, *supra* note 1.

<sup>31</sup> U.S. Gov. Accountability Office, GAO-08-640, *FDA Advisory Committees: Process for Recruiting Members and Evaluating Potential Conflicts of Interest* (2008).

<sup>32</sup> Eastern Research Group, *supra* note 10.

<sup>33</sup> *Id.*

<sup>34</sup> Moffitt, *supra* note 2.

set, this is the only study to examine voting patterns along dimensions other than conflict status or to use multivariate techniques that simultaneously control for member characteristics and drug effects.

## 4. DATA

### 4.1 Collection Methodology & Overview of Sample

This Report focuses on member votes for the drug (Center for Drug Evaluation and Research, or CDER) and biologic (Center for Biologics Evaluation and Research, or CBER) advisory committee meetings between January 1997 and December 2012. As mentioned above, CDER encompasses seventeen different advisory committees and CBER includes six different ACs. Each of these ACs conducts up to five meetings or so per year for a total of around 30 to 40 CBER and CDER meetings each year. ACs meet to consider 1) *general* matters such as the appropriate size and design of clinical trials, and 2) *party*, or drug-specific, matters.

We limit our analysis to party matters that involve a vote. Party matters generally involve a vote on whether to approve a new drug or biologic; however, they also discuss related matters such as 1) whether to keep a drug on the market based on a risk assessment, or 2) whether to approve a supplementary application for an approved drug (new indication, labeling revisions, efficacy supplement, patient population expansion, or a switch to over-the-counter status).

The unit of analysis for this study is an AC member's vote on a particular drug or biologic at a particular meeting. Party matter meetings can bring up a voting question in two ways: a single vote on approval to market a new drug or biologic; or a two-part vote, in which the AC first decides whether the drug's clinical evidence establishes the drug as safe enough for marketing, and then determines whether the drug is effective in treating the targeted illness. The FDA makes its final decision based on both criteria, and in its judgment, a drug must attain a reasonable level of safety while providing significant improvement in the targeted health outcome. In meetings involving these two-part votes, we define a member's vote as "yes" if the member votes yes on both, and "no" if the member votes no on either safety or efficacy.

Sometimes an AC meets more than once on the same day to evaluate more than one new drug candidate. In this case, individual members place more than one vote per meeting. Similarly, a meeting on a single new drug held over multiple days only provides one vote from each member. Because some meetings involve votes on more than one drug, the distribution of votes can differ slightly from the number of meetings over a year, but the two are highly correlated.

The FDA does not make public any summary data sets of meeting, drug, and AC members' information, but the raw filings of the AC meetings (announcements, transcripts, committee rosters, minutes, and statements of conflicts of interest) from 1997 to 2012 are posted on the FDA website. We used these filings to build the data set for this study.<sup>39</sup> For each meeting of interest in the study, first- and second-year law

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<sup>39</sup> Filings for committee meetings held from 1997 through 2009, were found at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>. Filings for 2010 through 2011 were found at

students accessed meeting documents—mainly the meeting transcript—but also, based upon availability, the Federal Register Notice of Meeting announcement, committee and meeting rosters, minutes, and statements of conflicts of interest. From the documents, students filtered out and compiled the following meeting and member data:

- Notice of meeting date and meeting start date.
- Advisory committee name.
- Trade and technical drug names.
- Drug company.
- Member names, roles, standing, degrees, and expertise.
- Number, size, type, and company for each conflict of interest in the meeting.

In the cases of earlier years where only the meeting transcripts are posted, specific characteristics of members (degrees, expertise, employer) and conflicts (type, size and nature of conflict) are typically missing, but the conflicted AC members are identified. We did not count a “reported interest” or the “appearance of a conflict” as a conflict of interest; only those conflicts that were disclosed because they required conflict waivers. Following compilation, the data set was thoroughly reviewed to ensure that each voting member present was included in the data set and that any data on conflicts of interest were entered accurately as well.

The sample includes a total of 5,719 votes placed by individual AC members. To be included, a vote had to be either a “yes” or a “no.” Occasionally, a member leaves a meeting before the vote or decides to abstain from voting. These votes represent about two percent of votes and are excluded. A total of 316 party matter meetings discussing a total of 416 new or previously approved drugs and biologics took place during our sample period. The vote total is somewhat over-weighted toward 2008, 2009, and 2010, with 725, 658, and 547 votes, respectively. Each of these vote totals represents about twice as many votes as the average number of votes in other years.

## 4.2 Overview of Trends

A total of 316 party matter meetings discussing a total of 416 new or previously approved drugs and biologics took place during our sample period. Figure 2 shows the number of meetings varying by year with an average of about 20 per year, but relatively more in 2008, 2009, and 2010.

FIGURE 2  
FDA ADVISORY COMMITTEE MEETINGS: 1997–2012

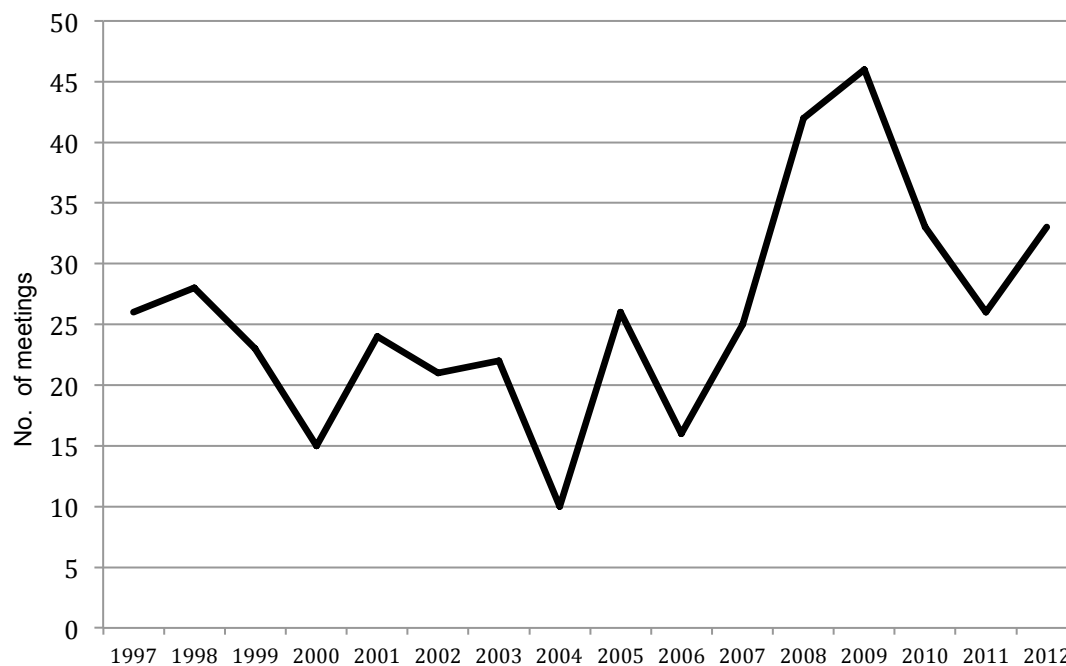
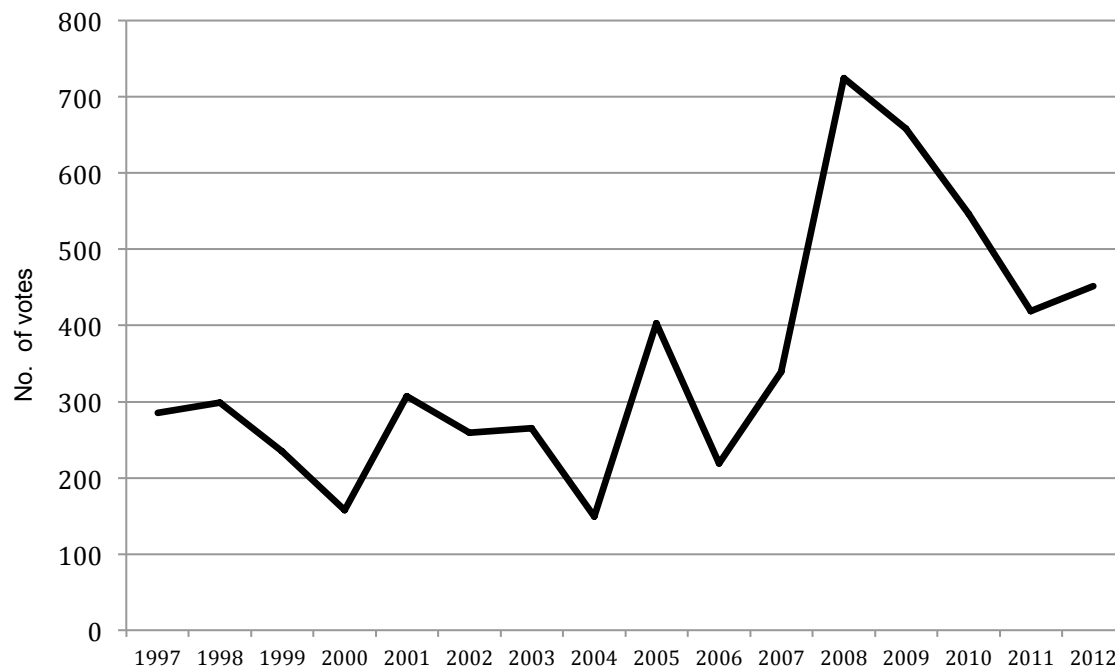


Figure 3 shows a pattern similar to Figure 2 but for the number of votes in each sample year. The number of votes for a particular year is the total number of votes placed by AC members at party matter meetings in that year. The substantial increase in meetings and votes could be due to the fact that the FDA Amendments Act of 2007 requires any drug with a new active ingredient to be evaluated by an AC, unless the Secretary of Health and Human Services provides a letter stating why it was not referred to an AC.<sup>40</sup> Therefore, prior to 2008, the FDA could choose not to use an AC to evaluate drugs with a new active ingredient, reducing the number of AC meetings and votes.

FIGURE 3  
TOTAL NUMBER OF VOTES BY AC MEMBERS: 1997-2012



<sup>40</sup> See FDA Amendments Act of 2007, Sec. 918.

Figure 4 maps the change in the proportion of AC meetings in each year in which at least one voting member of the committee had a conflict of interest over time. First, note that it was quite common up until 2008 for at least one AC member to have a conflict of interest in meetings involving votes to recommend approval or rejection of particular drugs. The proportion varies between 70 percent and 90 percent until 2008, when it drops drastically to 29 percent, and falls even further to a low of 3 percent in 2010.

FIGURE 4  
PERCENTAGE OF AC MEETINGS WITH AT LEAST ONE CONFLICT: 1997-2012

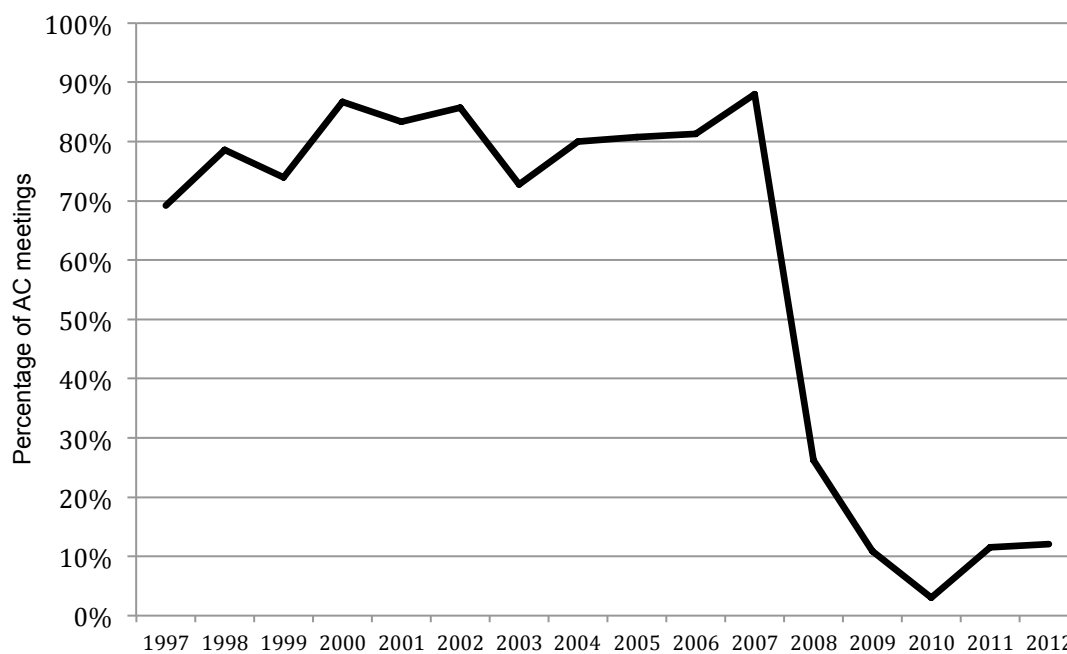


FIGURE 5  
PERCENTAGE OF AC MEMBERS WITH CONFLICTS: 1997–2012

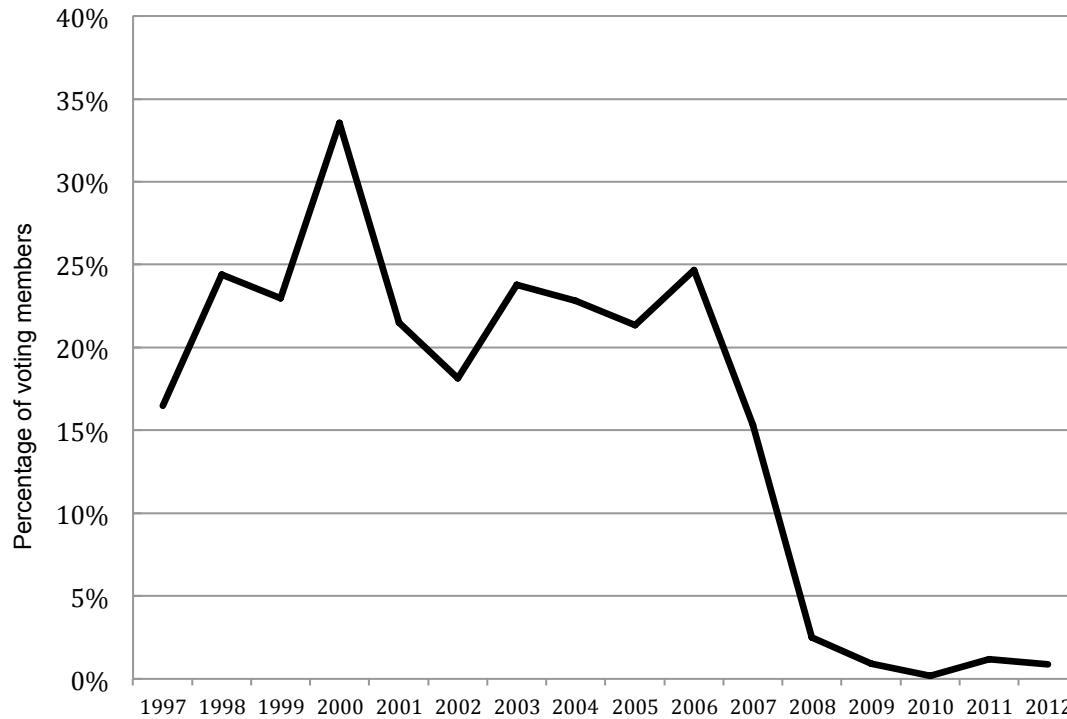


Figure 5 plots the percentage of AC members with conflicts by year and shows a pattern similar to that found in Figure 4. Until 2008, between 15 and 35 percent of voting members received conflict waivers, with an average of about 23 percent. The year 2000 stands out because about a third of all voting members had conflicts. The dramatic reduction in the proportion of meetings with conflicted members beginning in 2008 is almost certainly due to the FDA Amendments Act of 2007 and the Obama administration's new policy regarding conflicts.

### 4.3 Characteristics of Conflicted Members

Table 2 reports the distribution of conflicted members across various member characteristics. Most AC members are experts whose primary role is to evaluate the clinical and statistical evidence presented by the sponsor company to support their drug candidate. Each AC, however, typically includes one consumer representative and one patient representative, although occasionally a committee has either none or two of them. Table 2 shows that conflicts are not evenly distributed across these groups.

TABLE 2  
THE RATE OF CONFLICTS FOR MEMBERS GROUPED BY CHARACTERISTIC

Member Groups	Grouped by Expertise			Grouped by Committee Standing		
	Expert	Consumer Rep	Patient Rep	Permanent Member	Temporary Member	Chairman
% of Sample	89%	7%	4%	50%	43%	7%
% of Conflicted	94%	4%	2%	57%	30%	12%

About 89 percent of all committee members are experts; however, they represent about 94 percent of the conflicted members. Consumer representatives make up about 7 percent of committee members, but only about 4 percent of conflicted members. Patient representatives comprise 4 percent of committee members but only 2 percent of conflicted members. Clearly, experts are overrepresented in the group of conflicted members, which is not surprising considering that the FDA seeks specialized advice from AC experts that its own staff may not possess. Those experts are also more likely to be financially connected to drug companies who value their clinical study and consulting skills. Experts also may be more likely to use their expertise to evaluate promising new drugs and to purchase the stocks of the associated companies. But Table 2 makes clear that even consumer and patient representatives have some conflicts.

Members also can be characterized as permanent or temporary. A temporary member fills in for an absent (or excluded) permanent member or is appointed to the AC temporarily because the FDA seeks the temporary member's special expertise. Temporary members usually serve for a single meeting. Committee chairmen are permanent members, but we consider them as a separate group because they often possess the greatest expertise among permanent members, and because they control the AC meeting dialog.

Table 2 shows that permanent members make up 50 percent of committee members but 57 percent of the conflicted members. Temporary members comprise 43

percent of all members but only 30 percent of all conflicted members. Finally, chairmen represent 7 percent of all members but 13 percent of conflicted members.

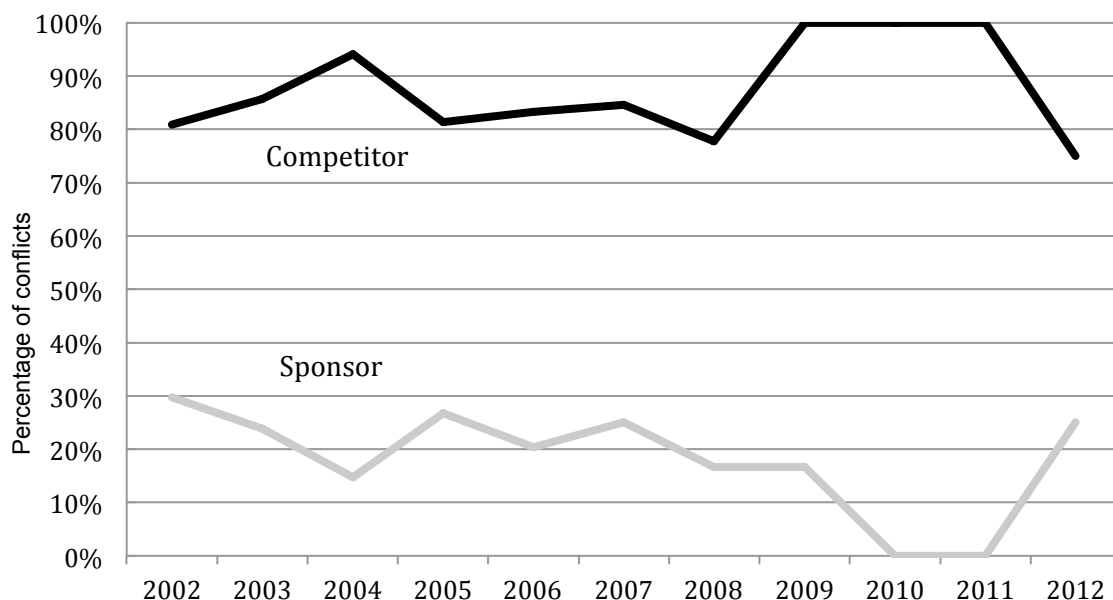
The substantial over-representation of permanent members and chairmen in the conflicted group is likely due, in part, to the AC selection process. Oftentimes, a temporary member is selected to replace a permanent member who has a company-specific financial conflict that is substantial enough that the FDA staff excludes the member from a particular meeting. He or she is replaced with someone who is more likely to have no conflict. Therefore, temporary members are less likely to be conflicted, while permanent members are more likely to be conflicted.

For the chairman, on the other hand, the FDA may be more willing to request a conflict waiver. The FDA may place relatively more value on the chairman's expertise and be more reluctant to exclude him or her. This is especially true if the FDA has some defined or implied limit on the number of waivers, like the 13 percent annual limit required by Congress after 2012. If only so many waivers will be granted, then FDA staff may reserve some for the chairmen. This could explain why their rate of conflicts is much higher than that of other members.

#### 4.4 Characteristics of Conflicts of Interest

Figure 6 shows that most, if not all, conflicts are associated with competitor companies as opposed to the sponsor company. The sample period for this figure starts in 2002 because specific details on the conflicts were not reported on the FDA website for the years before 2002. Competitor-related conflicts are relatively more common than sponsor-related conflicts. Over the sample period for which there is information about type of conflict (2002–2012), 89.1 percent of conflicts are related to competitor firms and 24.5 percent are related to the drug sponsor. This difference could be because the FDA believes that sponsor conflicts are potentially more serious and waive them less frequently, or because there is (usually) only one sponsor but potentially many more competitors.

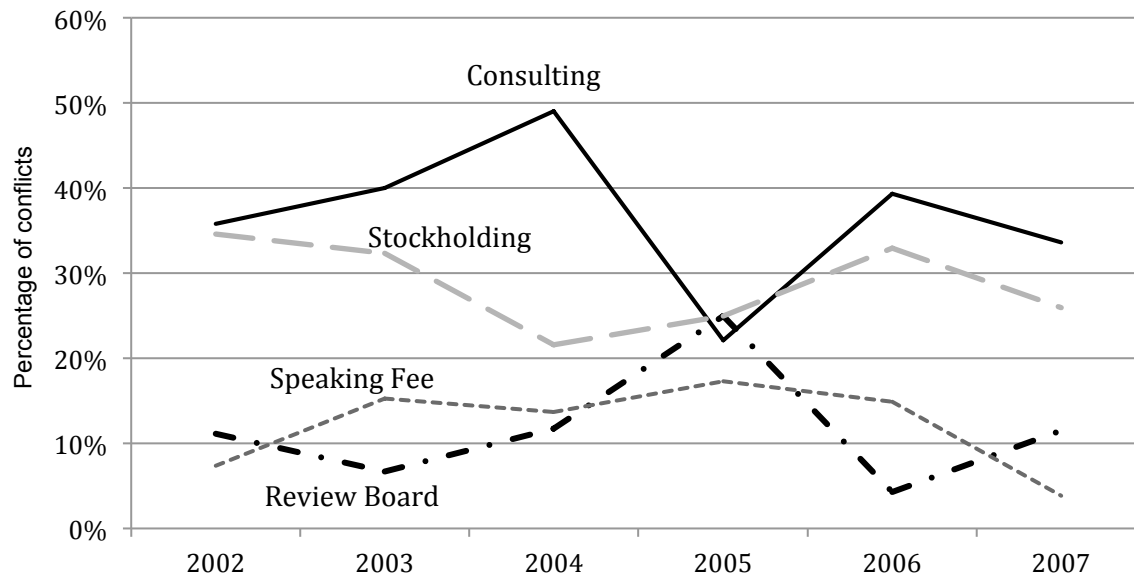
FIGURE 6  
CONFLICTS BY SPONSOR VS. COMPETITOR: 2002–2012



Until 2009, about 80 percent of the conflicts were associated with competitor companies. The proportion of conflicts associated with the drug's sponsor is much less, usually about 20 percent. Because a conflicted member could have financial conflicts related to both the sponsor and to competitors, the combined percentages in some years exceed 100 percent. Since there are fewer conflicted members after 2007, proportions can change substantially due to a single conflict landing in one group versus the other. For example, among four total conflicted members in 2012, only one had a sponsor-related conflict, but this produces a 25 percent sponsor conflict rate, and a large change from a zero sponsor rate in 2011.

Figure 7 displays the different types of conflicts by type of financial interest. Note that the types of conflicts were not disclosed on the FDA website before 2002; and after 2007, there were very few total conflicts in each year so that the proportions of conflicts after 2007 fluctuate wildly. Therefore, the sample period used for Figure 7 is constrained to cover 2002 through 2007.

FIGURE 7  
CONFLICTS BY FINANCIAL INTEREST: 2002–2007



There were seventeen different types of financial interests reported by conflicted AC members, but the top four types combined represent at least 85 percent of all conflicts in each year. No other conflict type represents more than six percent of the conflicts in any one year. The sum total of the other thirteen conflicts, such as patents, royalties, and expert witness, never amounts to more than fifteen percent of the conflicts in any one year.

Table 3 reports the frequencies and sizes of the top four conflict types. Overall, consulting represents the most common conflict (about 39%), followed by stockholding (28%), speaking fee (11%) and review board (11%).<sup>41</sup>

TABLE 3  
FREQUENCIES AND SIZES OF THE TOP FOUR CONFLICT TYPES

	Consult	Stock	Speaking Fees	Review Board
% of Conflicts	39%	28%	11%	11%
Average	\$10,759	\$24,845	\$11,947	\$6,705
Median	\$5,000	\$15,000	\$5,000	\$5,000

When members report the sizes of their conflicts, they disclose a dollar range as opposed to a specific dollar figure. This makes it difficult to gauge the exact size of the conflicts; however, we took the midpoint of the ranges for each reported conflict and computed the means and medians of these midpoints. For example, the midpoint for a dollar range of \$0–\$5,000 is \$2,500. The mean and median conflict levels for the four main conflict types are shown in the second and third rows of Table 3.

The relatively large size of the stockholding conflicts (average \$24,845 and median \$15,000) is somewhat misleading because it is the dollar value of the stock. The expected gain from a stock conflict would be the additional return on a stock one might expect to receive by voting for approval when voting against approval is appropriate, with this vote being the deciding vote for the AC recommendation. Of course, the FDA would also have to follow the recommendation. Therefore, the expected size of the gain, and hence the conflict size, is rather nebulous and certainly smaller than the dollar value of the stock. This contrasts with, for example, a \$10,000 consulting fee where the dollar value of the benefit is clear.

Overall, the sizes of the conflicts in relation to the conflicted experts' likely compensation from their full-time jobs are not large.<sup>42</sup> Using the midpoints of the reported ranges could mean that the figures are underestimated if most of the conflicts' actual dollar values are above the midpoint. Furthermore, we have averaged the conflict sizes, so some particular conflict sizes are greater than the group mean.

<sup>41</sup> Review board refers to boards of experts who monitor clinical trials. Drug companies fund clinical trials and compensate experts, so if an AC member was on a review board for one of the sponsor's or competitor's past drug candidates, it is considered a conflict of interest.

<sup>42</sup> But again, there is some evidence that even small financial incentives influence physicians' prescribing habits. See Brennan, *supra* note 5.

Infrequently reported conflicts like grants, research study funding, and contracts range between \$100,000 and \$200,000 on average. But these typically represent multi-year arrangements with the member's employer, such as a grant to a professor's university or a contract to a clinician's hospital. Accordingly, the potential gain to the professor or clinician could be small. FDA staff imputes some annual value for the conflicted member but does not report this amount.

## 5. EMPIRICAL RESULTS

This section presents the main empirical results of the Report. Part 5.1 presents univariate analysis that examines the relationship between voting propensities and the presence of conflicts and other AC member attributes. Part 5.2 presents the results from multivariate logit estimates of voting propensities conditioned on conflicts, other member characteristics, and drug-specific effects. Finally, Part 5.3 explores the relationship between meeting-level voting outcomes and the presence of conflicts.

### 5.1 Univariate Analysis

Although it is reasonable to assume that conflicted members act in their own financial interests when voting to approve a drug, there are several reasons why conflicts might not affect voting behavior or bias their votes in favor of approving drugs whose safety and efficacy do not merit an approval recommendation.

First, the FDA limits the size of a conflict that is eligible for a waiver, which means the average size of a waived conflict is not large in relation to the likely income levels of committee members. Second, anecdotal evidence from FDA staff suggests they have avoided proposing waivers when a conflict is associated with a firm sponsoring a new drug. This means that in an effort to avoid the appearance of direct conflicts, FDA staff may be more inclined to waive conflicts associated with competitor firms. Based on pure economic incentives, this would seem to argue for a bias against approval because if the drug is rejected, competitor companies generally stand to benefit.

Finally, assuming a bias toward approval implies that conflicted members are willing to vote in favor of drugs that are either unsafe or ineffective to reap a moderate-sized personal gain.<sup>43</sup> It seems equally plausible, however, that a conflicted member, especially one with a competitor-related conflict, could rationalize his or her skepticism (risk aversion) about approving a new drug. When he votes against a relatively safe and effective new drug, no patient receives anything worse than the current treatment. Conversely, if he knowingly pushes for approval of a dangerous one, his vote can cause serious harm.<sup>44</sup>

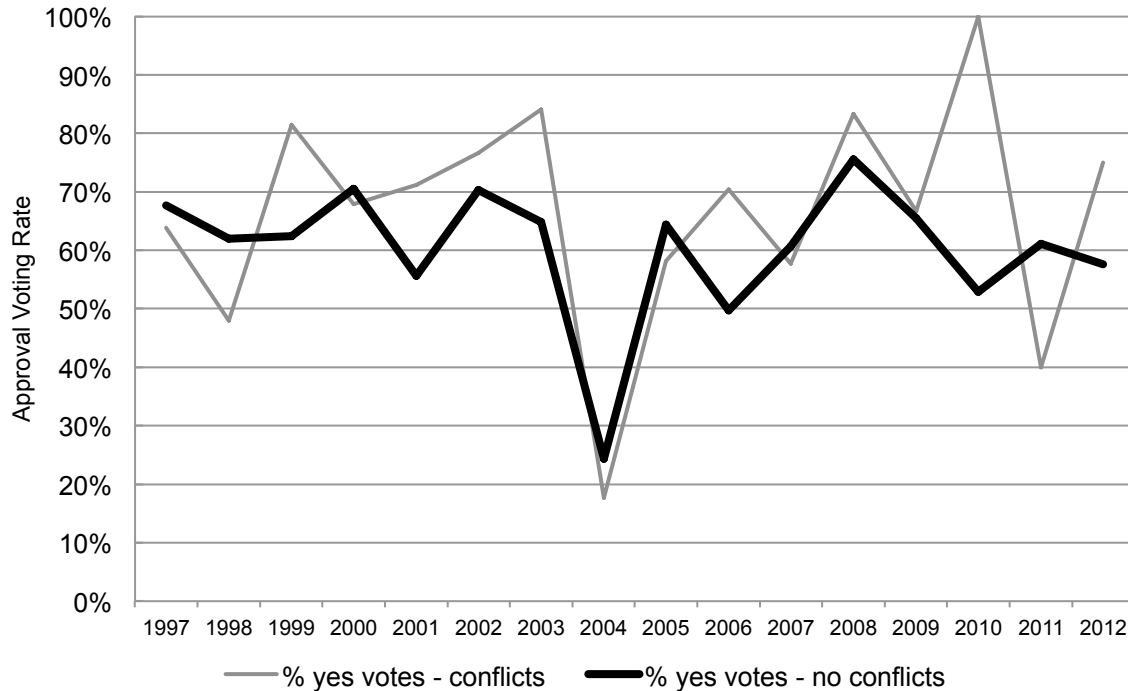
Figure 8 plots the rate of approval votes placed by both conflicted and non-conflicted members. The graph shows a slightly larger rate for conflicted members in favor of recommending drug approval.

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<sup>43</sup> Although in related contexts, some believe that even small rewards bias physicians' decisions. See Brennan, *supra* note 5.

<sup>44</sup> Moffitt, *supra* note 2.

FIGURE 8  
APPROVAL VOTING RATE BY PRESENCE OF A CONFLICT:  
1997–2012



Conflicted members cast 663 votes of the total 5,719 votes recorded for our full sample period, or an average of about 11.6 percent of the votes. With the exception of three years (1997, 1998, 2005), the average rate of approval voting for conflicted members exceeds that for non-conflicted members. Over the entire sample, the average rate of approval voting by conflicted members (64.9%) exceeds the average rate of approval voting by non-conflicted members (62.3%). Based on a simple difference in proportions test, this 2.6 percentage point difference is weakly statistically significant ( $p$ -value = .10).<sup>45</sup>

Table 4 below shows that the rate of conflicted and non-conflicted members voting for approval varies substantially across members grouped by expertise and by committee standing. Among experts, who make up the bulk of our sample, conflicted members vote for approval at a 64.2 percent rate, while non-conflicted experts vote for approval at a 62.6 percent rate. This 1.6 percentage point difference is not statistically significant at conventional levels, which we take to be  $p$ -values less than or equal to

<sup>45</sup> This evidence is in line with the JAMA study covering a shorter sample period of 2001 to 2004 in that it shows that conflicted AC members' voting in favor of drug approval more frequently than non-conflicted members.

0.10.<sup>46</sup> It is also worth noting that conflicted experts vote for approval at lower rates than both conflicted patient and consumer representatives, although only the latter difference is statistically significant.<sup>47</sup>

TABLE 4  
APPROVAL VOTING RATES BY MEMBER CHARACTERISTICS

Member Groups	Grouped by Expertise			Grouped by Committee Standing		
	Expert	Consumer Rep	Patient Rep	Permanent Member	Temporary Member	Chairman
Conflict	64.2%	69.0%	85.7%	63.3%	67.4%	67.1%
No conflict	62.6%	55.9%	68.2%	62.7%	61.7%	64.7%
Difference (p-value)	1.6% (0.22)	13.1% (0.08)	17.5% (0.08)	0.6% (0.42)	5.7% (0.06)	2.4% (0.35)

Conflicted consumer representatives vote in favor of drug approval quite frequently (69.0%). This is somewhat surprising because consumer organizations often criticize the FDA's practice of waiving some conflicts of interest. Non-conflicted consumer representatives are least likely to vote for approval (55.9%). The large 13.1 percentage point difference in approval voting rates is statistically significant at the 8 percent level, but consumer reps represent a relatively small part of the sample.

Conflicted patient reps vote for approval at the highest rate; 85.7 percent of the time. When they have no financial conflicts, they still vote for approval 68.2 percent of the time. Patient reps comprise an even smaller part of the sample than consumer reps, but the 17.5 percentage point difference is large enough to be statistically significant at the 8 percent level.

Conflicted permanent committee members vote for approval about as frequently as non-conflicted permanent members (63.3% vs. 62.7%). Conversely, conflicted temporary members vote for approval at a 67.4 percent rate compared to a 61.7 percent rate for non-conflicted temporary members. The 5.7 percentage point difference is statistically significant at the 6 percent level. This shows that conflicts appear to have little effect on experts' rate of approval voting, but that is not the case for temporary members.

<sup>46</sup> We consider a p-value between 0.05 and 0.10 to indicate weak significance, and a value less than or equal to 0.05 to indicate strong significance.

<sup>47</sup> 69% (consumer) vs. 64.2% (expert), *p-value* = .30; 85.7% (patient) vs. 64.2% (expert), *p-value* .05.

One possible explanation for why permanent members are little affected by conflicts is that they could worry about their voting reputations developed over their four-year terms. Recall that all conflicts are read aloud at the start of the AC meeting, so members know who has conflicts. This could cause them to suppress the effects of their financial conflicts, or it could cause them to overcompensate for the appearance of bias by voting "no" more frequently than they otherwise would. Temporary members may be less concerned about appearances because they typically serve for only one committee meeting.

The committee chairmen are permanent members, but when conflicted, they vote for approval at a 67.1 percent rate compared to a 64.7 percent rate when they have no conflicts of interest. This 2.4 percentage point difference, however, is not statistically significant, partly because of the small sample size of chairmen.

Recall that Figure 6 shows that the majority of conflicts are associated with competitor drug firms as opposed to the firms sponsoring new drugs. The FDA could be less likely to waive a conflict with respect to the drug sponsor because that type of conflict could be a more potent motivator to sway voting in favor of the sponsor's drug. Conversely, one could expect that if conflicted members vote their financial interests, then members with conflicts associated with competitor firms would vote against the new drug more frequently.

TABLE 5  
APPROVAL VOTING RATES BY CONFLICT TYPE

	Conflict Type	
	Sponsor	Competitor
Conflict	65.1%	65.1%
No Conflict	62.3%	62.3%
Difference	2.8%	2.8%
( <i>p</i> -value)	(0.27)	(0.14)

Table 5 reports approval voting rates broken down by sponsor and competitor conflicts. AC members with sponsor conflicts vote for approval at the same rate as those with competitor conflicts (65.1%).<sup>48</sup> Further, the data show that members with competitor conflicts are more likely to vote for approval than those without conflicts. This finding is in contrast with the JAMA study, which found a stronger relation between conflicts and approval voting for competitor-conflicted members than for sponsor-conflicted members. Part of the reason for their results could be that they have a much smaller number of observations on which to base their tests. Evidence that competitor-conflicted members vote for approval at statistically equivalent rates to sponsor-

<sup>48</sup> Note that only 60 percent of the conflicted sample observations had details about whether the conflict was with respect to the sponsor or the competitor.

conflicted members and non-conflicted members, suggests that factors other than financial self-interest are driving conflicted members' voting decisions.

## 5.2 Logit Analysis

This section employs logit regression analysis to examine the relationship between the presence of conflicts and member voting. This approach allows for simultaneous control of multiple factors that are likely to affect AC member voting. In the logit model, the log of the odds that an AC member votes for approval is estimated as a function of member characteristics, such as the presence of a conflict or whether the member is an expert or a consumer representative, and meeting characteristics, such as the drug under consideration. The estimated parameters in the model indicate the direction and magnitude of the effect that an independent variable has on the odds that an AC member votes for approval.

More technically, the logit model for AC member voting can be written as follows:

$$\log\left(\frac{P_i}{1-P_i}\right) = \alpha + B_1 \cdot CONFLICT_i + B_2 \cdot TYPE_i + B_3 \cdot STANDING_i + \delta_j + e_i,$$

where  $P_i$  is the probability that AC member  $i$  votes for approval, which implies that  $(1 - P_i)$  is the probability that the member votes against approval, and the term  $\left(\frac{P_i}{1-P_i}\right)$  is the "odds" that member  $i$  votes for approval. *CONFLICT* is a binary variable equal to 1 if the member has a conflict, and 0 otherwise.<sup>49</sup> *TYPE* controls for whether the member is an expert, consumer representative, or patient representative, and *STANDING* controls for whether member  $i$  is a permanent or temporary member, or the chair. The term  $\delta_j$  is a control for the drug type under consideration for a given AC vote, the parameter  $\alpha$  is the regression constant representing the average voting odds for the comparison group of AC members (*i.e.*, those for whom all binary variables equal 0), and  $e_i$  is an error term. Estimates of various specifications of this logit equation are reported in Table 6.

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<sup>49</sup> Specifications were also run with the average and median dollar amounts of conflicts with nearly identical results to those reported which use the binary *CONFLICT* indicator.

TABLE 6  
LOGIT REGRESSION RESULTS

	Specification									
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
<i>CONFLICT</i>	1.12 (.21)	1.12 (.21)	1.10 (.27)	1.08 (.40)			1.14 (.39)	1.14 (.39)		
<i>SPONSOR</i>					1.23 (.36)	1.21 (.41)			.91 (.80)	1.02 (.95)
<i>COMPETITOR</i>					1.09 (.47)	1.06 (.67)			1.29 (.23)	1.26 (.33)
<i>CONSUMER</i>		.78** (.02)	.78** (.02)	.78** (.02)	.75*** (.01)	.75*** (.01)	.57*** (.00)	.57*** (.00)	.54*** (.00)	.54*** (.00)
<i>PATIENT</i>		1.34** (.04)	1.38** (.02)	1.39** (.02)	1.39** (.02)	1.39** (.02)	2.24*** (.00)	2.24*** (.00)	2.35*** (.00)	2.35*** (.00)
<i>TEMP</i>			.95 (.35)	.94 (.31)	.94 (.29)	.94 (.26)	1.07 (.45)	1.07 (.45)	1.06 (.51)	1.06 (.51)
<i>CHAIR</i>			1.09 (.46)	1.08 (.47)	1.08 (.52)	1.08 (.53)	1.23 (.18)	1.23 (.18)	1.26 (.16)	1.26 (.16)
<i>2007* CONFLICT</i>				1.57 (.26)				1.18 (.75)		
<i>2007* SPONSOR</i>						1.70 (.65)				.16 (.18)
<i>2007* COMPETITOR</i>						1.45 (.64)				1.17 (.80)
DRUG EFFECTS	N	N	N	N	N	N	Y	Y	Y	Y
$X^2$	1.62	12.16***	14.04**	15.41**	16.35***	17.49**	37.84***	37.94***	41.98***	43.51***
<i>N</i>	5,719	5,719	5,719	5,719	5,406	5,406	4,124	4,124	3,910	3,910

Notes: Dependent variable log odds of "yes" vote for AC member; odds ratios reported; *p*-values in parentheses; unanimous votes excluded from regressions with drug-effects;  
\*\*\*Significant at 1% level; \*\*Significant at 5% level.

Column (1) reports the estimate of the simplest specification, which controls only for the presence of a conflict. The parameter estimate of 1.12 indicates that, on average, the odds of a conflicted AC member voting for approval are about 12 percent higher than for a non-conflicted member. However, because only  $p$ -values of .10 or less are considered statistically significant, with a  $p$ -value of .21, the hypothesis that there is no effect of a conflict on the odds of voting for approval cannot be rejected. Thus, conflicts appear to have no statistically significant effect on voting.

Column (2) reports a specification that adds controls for whether the member is a consumer representative or patient representative. Because the “expert” type is the omitted category, the estimate on *CONSUMER* of .78 indicates that, on average, the odds of a consumer representative voting for approval are about 22 percent less than an expert. Similarly, the results suggest that the odds of a patient representative voting for approval are about 34 percent higher than an expert. Both estimates are statistically significant at standard levels, and again the estimated effect for *CONFLICT* is statistically insignificant. Column (3) reports the results from a specification that adds controls for standing. The parameter estimates on *TEMP* and *CHAIR* suggest that controlling for the presence of a conflict and member type, there is no difference in voting patterns across AC member standing. The estimates on *CONFLICT*, *CONSUMER*, and *PATIENT* remain nearly identical in terms of magnitude and statistical significance.

Column (4) introduces an additional control for conflicts that occurred after 2007 to account for the possibility that the screening mechanism in place after the 2007 Act was better at screening out conflicts that may lead to biased voting. The estimated parameter on *2007\*CONFLICT* indicates that conflicted members after 2007 were actually *more* likely to vote for approval than those before the legislation went into effect. However, this estimate is statistically insignificant, so the hypothesis of no effect cannot be rejected. The estimates of the other controls remains nearly identical in terms of magnitude and statistical significance, again indicating that the presence of a conflict and member standing have no effect on the odds of voting for approval.

Column (5) controls for whether the conflict was with respect to the drug sponsor or a competitor.<sup>50</sup> The estimated parameters on both *SPONSOR* and *COMPETITOR* are greater than one, suggesting the presence of either type of conflict increases the odds of voting for approval. Like the effect of *CONFLICT* in previous specifications, however, the estimated effects of *SPONSOR* and *COMPETITOR* are not statistically significant.

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<sup>50</sup> The number of observations falls from 5,719 to 5,406 because information for type of conflict is available only after 2001.

Column (6) replicates the specification reported in Column(4) for these more precise conflict controls to see if the post 2007 FDA policies had any effect on the selection of conflicted members. The estimated parameters on both *2007\*SPONSOR* and *2007\*COMPETITOR* are greater than one (suggesting that conflicted members were *more* likely to vote for approval after 2007), but again both are highly statistically insignificant, as are the estimates on *SPONSOR* and *COMPETITOR*.<sup>51</sup>

The final specifications reported in columns (7)–(10) replicate the analysis reported in columns (3)–(6), but include controls for each specific drug under consideration, which is likely to impact voting by all members.<sup>52</sup> Even with the inclusion of these controls, the magnitudes and significance of the controls remain similar.<sup>53</sup> The estimated effect of a conflict continues to be zero as the estimated parameters on *CONFLICT*, *SPONSOR*, and *COMPETITOR* are all statistically insignificant, as are the interactions with the post-2007 policy change.

Consistent with the univariate analysis, the presence of a conflict appears to have no statistically significant effect on AC member voting even when controlling for member type and standing, and for the drug under consideration. Finally, although the 2007 policy change clearly reduced the number of conflicted members serving on an AC, it does not appear to have had any impact on how those conflicted members vote relative to those chosen under the previous regime.

### 5.3 Meeting Level Analysis

This part duplicates analyses found in previous studies on FDA voting by examining the extent to which the presence of conflicts affects AC meeting outcomes. The meeting-level outcome is the number of "yes" votes and "no" votes for a particular new drug or biologic.

For these analyses, we characterize a conflicted member's conflict in three ways: (1) any type of conflict, (2) a conflict with respect to a competitor company, and (3) a conflict with respect to the company sponsoring the new drug. Because for some conflicted members the conflict type (competitor or sponsor) is not reported, the sum of the competitor and sponsor conflicts is less than the total number of conflicted members. In addition, we limit the sample period for the analyses to 1997 to 2007, because (as illustrated in Figure 6) there are very few conflicted members after 2008.

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<sup>51</sup> Specifications were run using 2009 as the break point, to account for changes that occurred when the Obama administration took office, and all conflict and conflict interaction variables remain insignificant. The inability to detect any post-2007 effect may be due to the very low number of conflicted members in from 2008-2012.

<sup>52</sup> Further, specific drugs may be correlated both with voting and the presence of a conflict, if, for example, they involve highly specialized knowledge that increases the difficulty of finding non-conflicted members. In this scenario, failure to include drug-specific effects could bias the estimate on *CONFLICT*. Specifications run with group effects rather than drug effects produced nearly identical results.

<sup>53</sup> The number of observations falls for these specifications because unanimous decisions are excluded.

Accordingly, there is little variation in the level of conflicts across meetings after 2008. This adjustment reduces our sample from 416 drugs or biologics to 236.

The first meeting-level test reported in Table 7 measures the correlation between the percentage of members who are conflicted for a given AC and the percent of approval votes across all meetings. For all three conflict measures, the correlation is positive, and the point estimate of the correlation is largest for the sponsor-type conflicts. These estimated correlations, however, are indistinguishable from zero at a conventional level of statistical significance. Therefore, although meetings with higher proportions of conflicted members also have higher rates of approval voting on average, there is low statistical confidence in the positive relation.

TABLE 7  
IMPACT OF CONFLICTS ON MEETING-LEVEL VOTING OUTCOMES:  
1997–2007

Meeting-Level Tests	Any Conflict Type	Competitor Type	Sponsor Type
Correlation between percent of members conflicted and percent of approval votes ( <i>p</i> -value)	0.076 (0.244)	0.036 (0.586)	0.098 (0.133)
<i>P</i> -value for rank-sum test ( $H_0$ : distribution of conflicted members is the same for ACs that approve and reject drugs under consideration)	(0.121)	(0.622)	(0.118)
If conflicted members excluded from voting, how many approval decisions would have changed?	5	1	0
If conflicted members excluded from voting, would voting totals become:			
Less favorable	128	61	41
More favorable	41	20	15
No change	67	155	180

In the second meeting-level test, we measure the voting result of each meeting as a dichotomous outcome of either drug approval (“yes” votes > “no” votes) or drug rejection, as opposed to the percent of “yes” votes. Meetings with tie votes (“yes” votes = “no” votes) are excluded here. We rank the meetings by the percent of conflicted members at each meeting, and then split the sample into a subsample of meetings where the AC votes in favor of the drug, and another where they vote to reject the drug. This “rank-sum” method provides a statistical test for the hypothesis that the distributions of conflicts are the same for ACs that approve and reject drugs. We find that for all three conflict measures, we cannot reject the hypothesis that the distribution of conflicts is the same whether the AC votes for approval or for rejection.

The third meeting-level test considers whether any of the 236 meeting outcomes would have changed if the votes of conflicted members were excluded. The meeting outcomes here are approval, rejection, or tie. We find very little effect of excluding conflicted members from the meetings. Excluding only sponsor-related conflicted members has no effect, and excluding only competitor-related conflicted members changes only one meeting outcome (from rejection to approval). For any conflict type, there are five changes.<sup>54</sup> Two are changes from a tie to reject, one from a tie to approve, one from reject to tie, and one from reject to approve. Even for this small sample of changes, removing conflicted members who supposedly vote too often for approval does not consistently lead to more rejections.<sup>55</sup>

The fourth meeting-level test measures the vote outcome as the difference between the number of “yes” and “no” votes. For the competitor and sponsor conflicts separately, the net effect of excluding conflicted members is most commonly no change. But when there is a change, it is much more common for the vote to become less favorable than it is for it to become more favorable. And when any type of conflict is considered, excluding conflicted members usually leads to less favorable outcomes.

These results are consistent with the notion that conflicts lead to more votes for approval, but we know from the previous meeting-level tests that it seldom affects the net result of whether the AC recommends approval or rejection. Furthermore, excluding members with competitor conflicts has a larger net effect than excluding those with sponsor conflicts. One might have expected conflicts associated with the sponsor's drug to induce more “yes” voting than conflicts associated with a competitor's drug. Finally, because even non-conflicted members vote “yes” more frequently than they vote “no,” randomly selecting a member to exclude should make the vote less favorable on average. Overall, the analyses at the meeting level show very little evidence that AC member's conflicts lead to changes in approval decisions.

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<sup>54</sup> The total number of “conflict” changes is greater than the sum of “sponsor” and “competitor” conflicts because conflicts were broken down by subset only after 2002.

<sup>55</sup> It is possible that conflicted members could have swayed non-conflicted member to vote with them, hence, the influence of the conflicts could still be present in the vote outcome after conflicted members are excluded. This is one reason why it is important to compare the vote outcome to an unbiased assessment of the merits of the drug being considered by the AC. This is the subject of future work.

## 6. CONCLUSION

The FDA uses external experts before making approval decisions with respect to drugs that may require highly specialized knowledge. The same qualifications that make these experts attractive candidates to sit on ACs, however, often create financial ties between experts and drug companies. Some have expressed concern that these financial ties will cause experts to be biased in favor of drug approvals, leading to unsafe and ineffective drugs on the market. Further, some prior academic work has provided a modicum of empirical support for this worry. At the same time, observers both within and outside the FDA have pointed out that stringent rules limiting conflicted members from serving on ACs will reduce the competence of FDA decision-making.

This Report employs an augmented data set on AC member voting from 1997–2012 to examine this empirical question. Overall, there is no statistically significant relationship between the presence of a financial conflict and votes in favor of drug approval. Univariate analysis finds a small (2.6 percentage points) and weakly significant ( $p$ -value = .10) positive difference in approval voting rates between conflicted and non-conflicted AC members. This difference, however, appears to be driven largely by significant positive difference in approval voting rates between conflicted and non-conflicted consumer and patient representatives, which make up a relatively small portion of all AC members. There is no statistically significant difference in voting rates between conflicted and non-conflicted experts. This conclusion is bolstered in multivariate logit analysis, which controls for presence of a conflict, as well as AC member type and standing, and drug-effects. Examination of the effect of conflicts on meeting outcomes suggests that the presence of conflicts has almost no effect on drug approval decisions. Prohibiting all AC members who had a sponsor-related conflict from voting would not have changed any voting outcomes, and removing competitor-related conflicts would have resulted in one additional approval.

The results in this Report suggest that policies limiting the ability of well-qualified experts to serve on ACs likely impose net costs on society. The presence of conflicts does not appear to have a statistically measurable effect on expert voting. Preventing conflicted experts from serving on ACs, however, is likely to reduce the quality of FDA decision-making. If policy makers are concerned about conflicts affecting approval voting rates, perhaps the focus should be on consumer and patient representatives as these groups exhibit large and statistically significant differences in approval voting between conflicted and non-conflicted members. Exclusion of conflicted consumers and patient representatives, moreover, would not reduce the expertise available to the FDA.

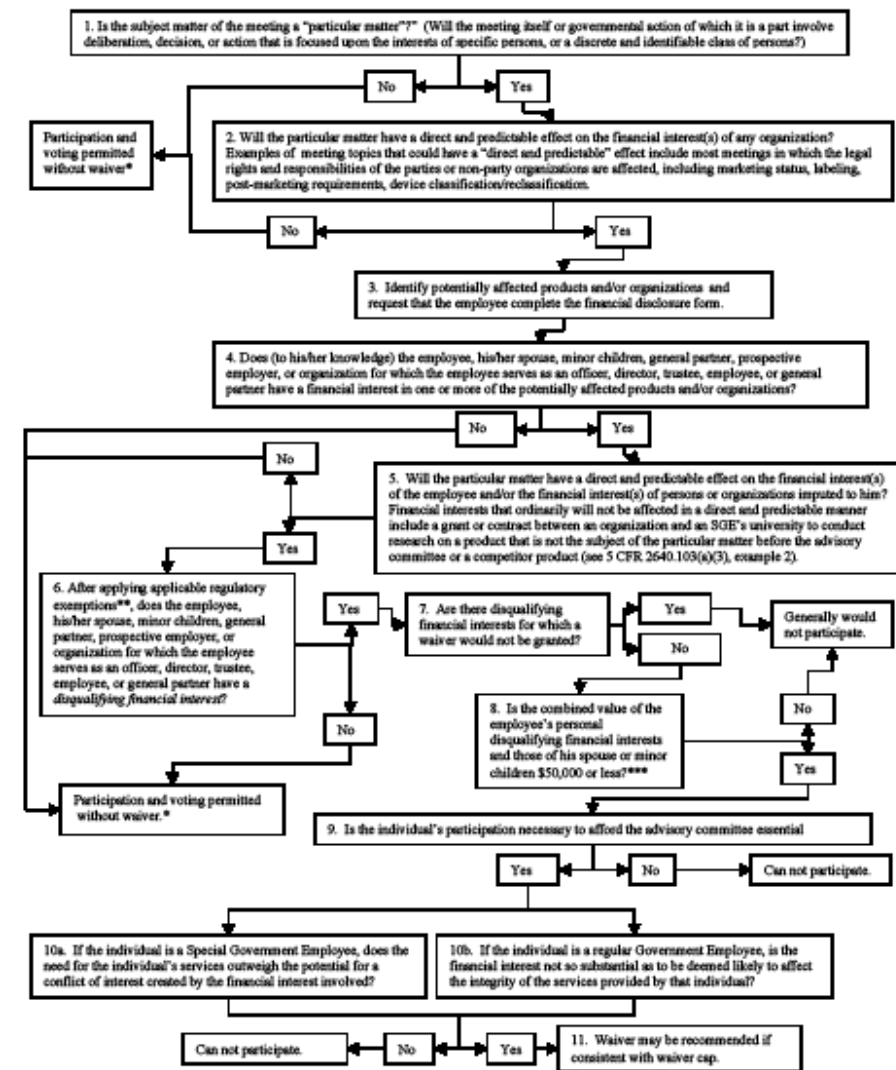
Whether ACs serve merely as a way for Congress to provide political cover or as an efficient means of producing the best standard of care in the face of ever increasing technical complexity, expert committees could become the norm in healthcare as political and budget pressures build to change the way healthcare treatment decisions are made. The merits of using expert committees instead of market forces for these decisions are beyond the scope of our work. If these committees become widespread,

however, this Report can provide guidance for forming not only the FDA's rules for constructing ACs, but also the types of expert committees envisioned by the Obama administration's new healthcare law (Patient Protection and Affordable Care Act).

Of course, it is important to emphasize that one cannot draw firm conclusions about the direction of voting biases solely based on the rate of approval voting by particular groups of members. If conflicted members vote for approval more often than non-conflicted members, one needs an unbiased benchmark of “correct” voting against which to measure the member voting. The next phase of the FDA project studies this issue by comparing AC member voting to the ultimate FDA decision and by using stock price reactions to AC decisions.

## Appendix A

### Flow Chart of the Advisory Committee Member Selection Process for Specific Meetings



\*In some cases, an employee will have a financial interest or relationship that, while not a disqualifying financial interest, may cause a reasonable person with knowledge of the relevant facts to question his impartiality in the matter. See 5 CFR 2635.502. Such matters should be evaluated under that regulatory standard and, if appropriate, an impartiality determination should be requested.

\*\*The applicable regulatory exemptions are found in 5 CFR 2640.301-306.

\*\*\*In rare cases, staff may pursue whether a conflict of interest waiver is appropriate where the combined value of the employee's personal disqualifying financial interests and those of his

