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FDA ADVISORY COMMITTEES: CONFLICTS OF INTEREST AND VOTING RELATIVE TO BENCHMARKS

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January 2015

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EXECUTIVE SUMMARY

Background

The Food and Drug Administration (FDA) is charged with assuring that drugs, biologics, and medical devices are sufficiently safe and effective for consumer use. For about half of the drugs it reviews—typically those that are relatively specialized or require accelerated review—the FDA obtains the advice of outside experts.[1] These experts participate on advisory committees (ACs), which make recommendations to the FDA on the safety and effectiveness of drugs under review.

In recent years, some have expressed concerns that financial ties between AC experts and drug companies may bias their recommendations in favor of drug approval, ultimately harming the public through exposure to unsafe or ineffective drugs.[2] In response to such concerns, 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.[3] Further, beginning in 2009, the Obama administration began to take additional steps to limit the prevalence of conflicted members serving on ACs.

Limiting the number of conflicted experts who can serve on ACs, however, presents costs associated both with finding qualified, non-conflicted members and appointing less-qualified AC members. If financial ties between experts and drug companies lead to FDA approval of unsafe or ineffective drugs, these costs may be justified. If financial ties have no impact on drug approval decisions, however, such policies can impose net costs on society, especially if less expert committee members misinterpret the scientific data and recommend approval of unsafe or ineffective drugs.

Data and Methodology

In 2013, the Searle Civil Justice Institute (SCJI) released a report that found no statistically significant difference between conflicted and non-conflicted member voting, and no evidence that the presence of conflicted members impacted AC recommendations.[4] Utilizing the same sample of decisions as the 2013 Report, this Report examines the extent to which the presence of conflicts impacts voting and AC decisions relative to ultimate FDA decisions and to stock market predictions. These measures arguably serve as objective benchmarks of unbiased and informed voting. By measuring the difference in voting decisions between conflicted and non-conflicted members relative to these benchmarks, this Report attempts to control for potential systematic differences in the drugs that conflicted and non-conflicted members (and ACs) consider or in individual characteristics.

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[1] *See* Susan L. Moffitt, *The Policy Impact of Public Advice: The Effects of Advisory Committee Transparency on Regulatory Performance*, *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 FDA approved drugs.

[2] *See, e.g.,* 151 Cong. Rec. H4245 (daily ed. Jun. 8, 2005) (statement of Rep. Hinchey). *See also* 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); Peter Lurie, et al., *Financial Conflicts of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 JAMA 1921 (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 (last visited May 10, 2013); 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&.

[3] FDA Amendments Act of 2007, Pub. L. No. 110-85, § 701 (codified as amended in scattered sections of 21 U.S.C.).

[4] George Mason University School of Law, Law & Economics Center, Searle Civil Justice Institute, FDA Advisory Committees: An Empirical Examination of Conflicts of Interest (June 2013), *available at* http://masonlec.org/site/rte_uploads/files/FDA%20Report%20June%202013.pdf.

Key Findings

- **Consistent with the 2013 Report, this Report finds almost no evidence that conflicts impact AC voting decisions.**
- **Decisions by ACs with conflicted members – and votes by conflicted AC members – to recommend drugs are more likely to be consistent with the ultimate FDA decision and stock market predictions than non-conflicted ACs and non-conflicted AC members.**
- **To the extent that the FDA decisions and stock market predictions provide benchmarks of "correct" voting decisions, these results suggest that limiting the ability of conflicted members to serve on ACs may reduce the overall quality of ACs.**
- **If anything, the data suggest that conflicts are associated with a lower propensity to recommend drug approval, which is the opposite of the concern that has motivated recent reforms.**
- **There is no evidence that ACs with conflicts are less likely than non-conflicted ACs to vote in line with the FDA's ultimate decision.**
    - ACs recommended approval for 69.6 percent of the drugs in the sample.
    - The FDA approved 73.2 percent of the drugs in the sample.
    - Compared to the FDA benchmark, non-conflicted ACs and ACs with at least one conflicted member are equally likely to recommend drug approval.
    - In multivariate analysis, the proportion of AC members with conflicts has no impact on the probability that an AC decision is contrary to the FDA's ultimate decision regarding a drug.
- **Conflicted members' votes recommending drug approval are more consistent with the FDA's ultimate decision than non-conflicted members' votes.**
    - Relative to non-conflicted members, AC members with conflicts are around 40 percent less likely to disagree with the ultimate FDA decision to approve a drug.
- **The stock market is rarely surprised by AC recommendations, suggesting that investors are adept at predicting AC decisions based on publicly available information.**
    - Only 25 percent of measured cumulative abnormal returns (CARs) are statistically distinguishable from zero, and the average CAR for the full sample is statistically indistinguishable from zero.
- **Recommendations by conflicted ACs are less likely than those by non-conflicted ACs to surprise investors.**
    - The average CAR for all decisions by conflicted ACs is statistically indistinguishable from zero.
    - Only 42 percent of all approval decisions that surprised the market are from conflicted ACs, although they comprise 55 percent of the sample.
    - The average CAR for approval recommendations by conflicted ACs is statistically indistinguishable from that of non-conflicted ACs, and 25 percent lower than that of non-conflicted ACs for rejection recommendations.
- **Conflicted and non-conflicted members' votes are equally likely to disagree with stock market predictions.**

FDA ADVISORY COMMITTEES:
CONFLICTS OF INTEREST AND VOTING RELATIVE TO BENCHMARKS

1. Introduction

The Food and Drug Administration (FDA) is charged with assuring that drugs, biologics, and medical devices are sufficiently safe and effective for consumer use. For about half of the drugs it reviews—typically those that are relatively specialized or require accelerated review—the FDA obtains the advice of outside experts or special government employees (SGEs).[1] These experts participate on advisory committees (ACs), which make recommendations to the FDA on the safety and effectiveness of drugs under review.

In recent years, some have expressed concerns that financial ties between AC experts and drug companies may bias their recommendations in favor of drug approval, ultimately harming the public through exposure to unsafe or ineffective drugs.[2] 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. 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 briefs, or serve on review boards. Drug companies, moreover, fund research studies at universities and research institutes that employ these experts. In response to such concerns, 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.[3] Further, in 2009, the Obama administration began to take additional steps to limit the prevalence of conflicted members serving on ACs.

Limiting the number of conflicted experts who can serve on ACs, however, presents its own costs associated with finding qualified, non-conflicted members and appointing less-qualified AC members.[4] 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.[5] If financial ties between experts and drug companies

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[1] *See* Susan L. Moffitt, *The Policy Impact of Public Advice: The Effects of Advisory Committee Transparency on Regulatory Performance*, *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 there is generally little public information on the number of FDA drug rejections that did not involve an advisory committee.

[2] *See, e.g.,* 151 Cong. Rec. H4245 (daily ed. Jun. 8, 2005) (statement of Rep. Hinchey). *See also* Troyen A. Brennan, et al., *Health Industry Practices that Create Conflicts of Interest*, 295 JAMA 429 (Jan. 25, 2006), *available at* http://jama.jamanetwork.com/article.aspx?articleid=202261 (last visited May 10, 2013); Peter Lurie, et al., *Financial Conflicts of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 JAMA 1921 (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 (last visited May 10, 2013); 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&.

[3] FDA Amendments Act of 2007, Pub. L. No. 110-85, § 701 (codified as amended in scattered sections of 21 U.S.C.).

[4] Goldman Sachs Analyst Jami Rubin suggested that following the 2007 Act, some AC members were less qualified to judge the safety and efficacy of new drugs than in the past. Telephone Interview with Jami Rubin, Analyst, Goldman Sachs (May 14, 2014).

[5] Lisa Richwine, *FDA Official Sees Drug Approvals Rising*, Reuters (May 9, 2011), *available at* http://www.reuters.com/article/2011/05/09/us-summit-fda-approvals-idUSTRE7485B120110509.

lead 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. On the other hand, if financial ties have no impact on drug approval decisions, such policies can impose net costs on society – especially if less expert committee members misinterpret scientific data and recommend approval of unsafe or ineffective drugs.

In 2013, the Searle Civil Justice Institute (SCJI) released a report that examined this empirical question.[10] Using data from 316 AC meetings on 416 drug evaluations and over 5,700 individual votes, the 2013 Report found no statistically significant difference between conflicted and non-conflicted member voting. Further, the 2013 Report also found no evidence that the presence of conflicted members impacted AC recommendations.

Utilizing the same data set, this Report examines the extent to which the presence of conflicts impacts voting and AC decisions as compared to ultimate FDA decisions and stock market predictions. These measures arguably serve as objective benchmarks of unbiased and informed voting. The FDA's approval decisions come from its staff scientists who are experts in evaluating the safety and effectiveness of new drugs. Unlike AC members who may episodically evaluate a single drug, the FDA staff evaluates hundreds of drugs each year and never receives compensation from drug companies. Investor judgment about the safety and efficacy of a new drug is also likely to be accurate, and reflected in the share price of drug sponsor companies. Accordingly, an AC decision that surprises the market – as reflected in abnormal stock returns – can be classified as "incorrect," in the sense that it was contrary to what informed outside experts expected given the available evidence. By measuring the difference in voting decisions between conflicted and non-conflicted members relative to these benchmarks, this Report attempts to control for potential systematic differences in the drugs that conflicted and non-conflicted members (and ACs) consider, or in individual AC member characteristics.

Consistent with the 2013 Report, this Report finds little statistically significant evidence of a difference between conflicted and non-conflicted voting relative to these benchmarks. These results suggest that attempts to sharply limit the number of conflicted AC members are unlikely to provide any benefits in terms of curtailing biased voting. At the same time, limiting the pool of available expertise could lead to lower quality AC decisions, ultimately harming consumers.

This Report proceeds as follows. Section 2 provides a brief background on ACs and recent related literature. Section 3 discusses data sources and collection, and describes the sample. Section 4 presents the main empirical results grouped by the two benchmarks, and Section 5 concludes.

2. Background

2.1. FDA Advisory Committees

Advisory committees are panels of experts that assist the FDA in evaluating drugs. Outside experts primarily comprise ACs, although ACs also have permanent non-voting members from the FDA staff who administer the meetings. The ACs are categorized in line with the 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. The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) – the focus of this Report – have seventeen and six different advisory committees, respectively. 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

[10] George Mason University School of Law, Law & Economics Center, Searle Civil Justice Institute, FDA Advisory Committees: An Empirical Examination of Conflicts of Interest (June 2013), *available at* http://masonlec.org/site/rte_uploads/files/FDA%20Report%20June%202013.pdf.

drug-specific, matters. Each AC can be as small as nine or as large as twenty-six members, but most consist of eleven to thirteen members. The AC's recommendations are not binding on the FDA.

The staff screens AC members 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.[11] The 2013 Report provides a detailed description of AC member selection. 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 and predictable effect on the member's financial interests.[12] 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.

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 conflict waivers to allow them to participate in a meeting.[13] 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 of $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."[14]

2.2 Prior Literature on FDA Conflicts of Interest

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.[15] Most of this published work, however, is anecdotal, editorial, or based on survey data.[16]

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[11] Ethics in Government Act of 1978, Pub. L. No. 95-521, 92 Stat. 1824 (1978) (codified at 5 U.S.C. app. § 101(f)(3) (2012)) ("each officer or employee in the executive branch, including a special government employee . . .").

[12] 18 U.S.C. § 208 (2012); 21 U.S.C. § 379d-1 (2012) (amended by the FDA Amendments Act of 2007, Pub. L. No.110-85, §. 701).

[13] FDA Amendments Act of 2007, Pub. L. No. 110-85, §. 701 (codified as amended in scattered sections of 21 U.S.C.).

[14] 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.

[15] Editorial, *Experts and the Drug Industry*, N.Y. Times, Mar. 4, 2005, *available at* http://select.nytimes.com/gst/abstract.html?res=FB0F12F73B590C778CDDAA0894DD404482.

[16] 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 (2000); J.P. Kassirer, *A Piece of My Mind: Financial Indigestion*, 284 JAMA 2156 (2000); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just A Gift?*, 283 JAMA 373 (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 (2000); Hamilton Moses, et al., *Collaborating with Industry – Choices for the Academic Medical Center*, 347 N. Eng. J. Med.

Only a few studies bring substantial data to bear on these questions. Most find a weak association between AC member conflict of interest and drug approval decisions, and that exclusion of conflicted AC members would not have changed the ultimate AC 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.[17] Another study considered an even smaller sample of AC meetings from 1998 through 2005.[18] It constructed 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. A more recent study differs from these and ours in that it considers any vote, not just the vote to approve a new drug, as an opportunity to measure a bias in conflicted AC member voting. It finds that AC members with conflicts associated solely with the sponsor vote more favorably.[19]

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.[20] 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.

1371 (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 (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 (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 (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 (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 (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,(2005); Robert Steinbrook, *Financial Conflicts of Interest and the Food and Drug Administration's Advisory Committees*, 353 N. Eng. J. Med. 116 (2005); Lindsay Hampson, et al., *Patients' Views on Financial Conflicts of Interest in Cancer Research Trials*, 355 N. Eng. J. Med. 2330 (2006); Eric G. Campbell, et al., *Financial Relationships Between Institutional Review Board Members and Industry*, 355 N. Eng. J. Med. 2321 (2006); Troyen Brennan, et al., *Health industry practices that create conflicts of interest: a policy proposal for academic medical centers*, 295 JAMA 429,(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 (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.

[17] Peter Lurie, et al., *Financial Conflicts of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 JAMA 1921, (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 (last visited May 10, 2013).

[18] *See* Diana Zuckerman, National Research Center for Women and Families FDA Advisory Committees: Does Approval Mean Safe? (Aug. 28, 2006), *available at* http://center4research.org/newsite/wp-content/uploads/2006/09/FDA-Report-v7.pdf (last visited May 14, 2013).

[19] Genevieve Pham-Kanter, *Revisiting Financial Conflicts of Interest in FDA Advisory Committees*, 92 Milbank Quarterly. 446 (2014). The main result of this study could be driven by the few meetings that have large numbers of votes. For example, our study defines a vote as whether a member votes to recommend approval for a drug. Sometimes, members vote on the safety and efficacy of a drug separately, but a drug must be safe and effective to be approved, so approval requires a yes vote on both. Other votes may be taken, such as whether a particular surrogate endpoint used to support a drug's effectiveness should be used rather than a more traditional endpoint, such as mortality. The mean number of votes per meeting in the Pham-Kanter study is 5, with a maximum of 17. Hence, some meetings with 17 votes are weighted much more heavily than a meeting with only one vote.

[20] U.S. Gov. Accountability Office, GAO-08-640, FDA Advisory Committees: Process for Recruiting Members and Evaluating Potential Conflicts of Interest (2008).

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.[21] 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. The second study examined the relation between conflicts of interest and AC member voting using a larger sample covering January 2001 through March 2008.[22] 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.[23] 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.

3. Data

This Report focuses on the outcomes of advisory committee meetings for drugs between January 1997 and December 2012. We limit our analysis to party matters that involve a vote on whether (1) to approve a new drug or biologic; (2) to keep a drug on the market based on a risk assessment; or (3) 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).[24] Most of the votes in the sample involve new drug or biologic approvals.

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 votes on whether the drug's clinical evidence establishes the drug as safe enough for marketing, and then votes on 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.

3.1 Data Sources and Collection Method

The data from this Report were collected from the raw filings of the AC meetings (announcements, transcripts, committee rosters, minutes, and statements of conflicts of interest) from 1997-2012.[25] For each meeting of interest in the study, first- and second-year law 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[26] – and compiled the relevant meeting and member data. Following compilation, the data set was thoroughly

[21] 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).

[22] *Id*.

[23] Moffitt, *supra* note 1.

[24] 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.

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ere disclosed because they required conflict waivers.

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.

3.2 Overview of the Sample[27]

The dataset has information on 316 party matter meetings discussing a total of 416 new or previously approved drugs and biologics, and 5,719 votes placed by individual AC members.[28] 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. Until 2008, between 15 and 35 percent of voting members received conflict waivers, with an average of about 23 percent. 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.

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. About 89 percent of all committee members are experts, and they comprise about 94 percent of the conflicted members. 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 percent of conflicts are related to competitor firms and 25 percent are related to the drug sponsor. Overall, consulting represents the most common conflict (about 39%), followed by stockholding (28%), speaking fee (11%), and review board (11%).[29]

4. Empirical Results

If one wanted to examine the impact of conflicts on the propensity to vote "correctly" one would have to have an objective benchmark of the "correct" decision. In the context of the ACs under study, this would mean having an objective measure of whether a drug is truly safe and effective, and hence merited approval. The empirical analysis in the 2013 Report showed no statistically significant difference in voting patterns between conflicted and non-conflicted members, and found that the presence of conflicted members did not change AC outcomes. Although this analysis suggests that conflicts do not affect voting patterns, it does not necessarily provide information on whether conflicts impact the propensity for AC members to vote "correctly;" there is no reason to assume that non-conflicted AC members provide the ideal benchmark. For example, non-conflicted members may vote to approve drugs too frequently or too infrequently. Further, because conflicts are not assigned randomly, the mix of drugs that conflicted members consider may differ systematically from those considered by their non-conflicted counterparts. That is, merely finding equality in voting patterns between conflicted and non-conflicted AC members does not rule out the possibility that conflicted members vote "incorrectly" compared to an objective benchmark. In this section, we analyze AC decisions and individual votes relative to two plausible benchmarks.

The first benchmark is the FDA's ultimate decision. Many FDA staff members are hired specifically for their scientific backgrounds and expertise in evaluating the safety and effectiveness of new drugs and biologics. Further, unlike AC members who may episodically evaluate a single drug, the FDA staff evaluates hundreds of drugs each year. Finally, FDA staff are employed directly by the entity that is

[27] Readers are referred to the 2013 SCJI Report, *supra* note 6, for a more detailed discussion of the sample.

[28] 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.

[29] 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. 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.

politically accountable for poor decision-making, reducing principal-agent issues that arise for both conflicted and non-conflicted AC members.[30]

FDA managers can face pressure from Congress, consumer groups, industry groups, lobbies, firms, disease-specific organizations, and the popular press to overrule their staff member decisions. One study shows that these pressures can speed up the FDA process, posing the risk of hasty and improper decisions.[31] However, a more recent study shows that shorter FDA review times do not lead to the approval of more drugs with adverse side effects.[32] Although these pressures may impact FDA decisions, they are unlikely to systematically bias FDA decisions in one direction or another.[33] Additionally, some have argued that agencies such as the FDA can be "captured" by one of the interests groups, typically the regulated industry.[34] Thus, if the FDA is beholden to drug company interests, we should expect to see a convergence between FDA decisions and conflicted AC decisions. If this is the case, our test would be biased against finding conflicts of interest impact AC voting relative to the FDA decision, because both the AC vote and the FDA decision would be driven by the same financial or cultural considerations. Although the interests of the pharmaceutical industry in general would bias the FDA toward approval, for any specific drug approval decisions, there will be winners and losers within the pharmaceutical industry. Thus, a systematic bias towards the pharmaceutical industry in general is less likely. Further, there is a literature suggesting that risk aversion causes the FDA to be biased *against* drug approval. Drug approvals that subsequently prove harmful are much more likely to draw public attention and concomitant political costs than drug denials, even if denials are more harmful to society.[35] If this is the case, our tests will be biased in the opposite direction because FDA approval rates will be too low.

Investor judgment about the safety and effectiveness of a drug is the second benchmark. Investment companies hire scientific experts to evaluate the scientific information supporting potential new drugs, and advise their clients about the likelihood of AC and FDA approval.[36] Investor judgment about the safety

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[30] Some have argued that because the drug division of the FDA is partly funded with fees paid by companies sponsoring new drugs (e.g. through PDUFA), that the FDA is biased in favor of drug approval. Conversely, others argue that because approved drugs that eventually are withdrawn for safety reasons often lead to Congressional inquiries and sanctions, the FDA is biased against new drug approvals. Nevertheless, the scientific staff of the FDA is not directly subject to these forces, unlike an AC member who receives a consulting fee directly from a drug company. Therefore, we take their judgments to be plausibly unbiased. Likewise, we can say that an AC member's votes are unbiased if they do not tend to deviate in one direction or another from the FDA's ultimate decisions.

[31] Daniel P. Carpenter, *Groups, the Media, Agency Waiting Costs, and FDA Drug Approval*, 46 Am. J. Pol. Sci, 490 (2002).

[32] Henry Grabowski & Y. Richard Wang, *Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patient Safety? An Analysis of the 1992 Prescription Drug User Fee Act*, 51 J.L. & Econ. 377 (2008).

[33] The most recent example is Plan B contraception, but this involved the availability of the drug over-the- counter for younger women as opposed to an approval. *See* Meredith Wadman, *Drug Agency Accused of Political Bias,* NATURE, (2011), *available at* http://www.nature.com/drugdisc/news/articles/437179a.html (last visited October, 25, 2014). We are not aware of a case involving a new drug approval.

[34] *See* George Stigler, *The Theory of Economic Regulation*, 2 Bell J. Econ. & Mgmt. Sci., 3 (1971), and Daniel Carpenter & David A. Moss, Preventing Regulatory Capture: Special Interest Influence and How to Limit It, (Cambridge University Press 2014).

[35] *See*, *e.g.*, Ernst R. Berndt et al., *Assessing The Impacts Of The Prescription Drug User Fee Acts (PDUFA) On The FDA Approval Process*, 8 Forum for Health Economics & Policy (2005):

> Researchers such as Peltzman [1974], Olson [1997,1998,2004] and Carpenter [2002] have long argued that personnel at the FDA are considerably more worried about committing Type 1 errors (approving a drug that is unsafe and/or lacks efficacy) than Type 2 errors (not approving a safe and effective drug). Given the costs and punishments that can be meted out by Congress for Type 1 errors, it is not surprising that many observers believe that Type 1 errors have received disproportionate attention. While the costs of delaying life-saving and quality of life-improving medications are real and impose pain and suffering on patients seeking new medicines, these costs from Type 2 errors are not nearly as visible as the Type 1 errors.

[36] Goldman Sachs Analyst Jami Rubin suggested in an interview that Wall Street analysts like herself pay close attention to company information releases about new drugs leading up to an AC meeting and find that it is consistent with the information presented to the AC. Analysts make informed judgments about the merits of the new drug based on that

and efficacy of a new drug is also likely to be accurate, and reflected in the share price of drug sponsor companies. If the scientific information about safety and effectiveness of the new drug shows that it merits approval (rejection), but an AC votes to reject (approve) it, then the stock price will fall (rise) significantly. Accordingly, an AC decision that surprises the market – as reflected in abnormal returns measured through event studies – can be classified as "incorrect" in the sense that it is contrary to the best judgment of outside experts. For example, if an AC approval recommendation were to cause large positive returns, it would suggest that outside experts were expecting the AC to recommend rejection.

It is possible that some new information besides the voting is released in an AC meeting that can surprise investors. We do not expect this consideration to impact the results for several reasons. First is the long development process (averaging 15 years) during which firms report clinical progress to investors and the FDA. Second is the fact that the drug sponsor must publicly file the case that they will present to the AC several months ahead of the AC meeting to give AC members time to prepare. Likewise, the FDA's analysis of the case is publicly filed. Stock analysts typically follow a particular drug's development for many years and have met privately with firm managers, so that they and their investors likely have at least as much information about the drug as AC members. In any event, there is no reason to think that new information released would systematically impact stock prices in one direction.

Another possible issue that potentially could impact interpretation of the results is investor anticipation of biased voting. That is, if investors knew which committees had conflicted members, they might be able to anticipate biased decisions. In this case, we would expect no stock market reaction even if conflicts biased voting because the probability that the bias impacted drug approval had already been capitalized into the share price. We think this is unlikely to be the case for three reasons. First, information on about 80 percent of the member conflicts in our sample is not made public until it is read out at the start of the particular AC meeting.[37] Second, we select an event window that covers the meeting day and two days before and after so that any investor reaction to the conflicts read at the start of the meeting, or perhaps leaked just before, will be part of the CAR that we measure. Finally, our 2013 report showed that removing conflicted members' votes changed only five AC recommendations, and three of the five changes were more favorable, not less. If the presence of conflicts is unlikely to impact AC decisions, there is little reason to assume that the stock market would anticipate such an impact.

In what follows we examine the impact of conflicts generally, as well as the separate impacts of sponsor and competitor conflicts. In one sense, AC members with sponsor and competitor conflicts should have different incentives: sponsor-conflicted members should be biased in favor of approval and competitor-conflicted members should be biased toward rejection. However, conflicts – whether sponsor or competitor – could act as a proxy for alignment with the pharmaceutical industry in general. For example, even though an AC member may have a current conflict involving a competitor, she may have had past relationships with the sponsor drug company (that are beyond the temporal range of the conflicts check), may hope to receive grant or consulting money from the sponsor in the future, or may want to be seen as sympathetic toward sponsors generally to secure future consulting income from a variety of drug companies. Indeed, in our sample a significant proportion of conflicted members have both competitor and sponsor conflicts for the same meeting.[38]

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information. Nevertheless, they are occasionally surprised by an AC decision. Telephone Interview with Jami Rubin, Analyst, Goldman Sachs (May 14, 2014).

[37] Before November 2005, the FDA publicly disclosed conflicts of interest waivers at the start of an AC meeting. From November 2005 to October 2007, the FDA was required to disclose waivers on its website under the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act (Pub. L. No. 109-97, § 795, 119 Stat. 2120, 2164-65). After October 2007, the FDA has been required to disclose waivers under the FDA Amendments Act of 2007. As a robustness check, specifications of the regressions in section 4.1 were run confining the analysis to meetings before 2006, the year in which some information on conflicts began appearing on the FDA web site prior to the AC meeting. If investor anticipation of conflicted members voting in favor of their financial interests were biasing the tests against finding a relationship between conflicts and CARs, we should expect to find a significant relationship in the pre-2006 period. The results from these regressions (available upon request) are nearly identical to those of the full sample.

[38] 12.9 percent of conflicted members for which there is information about type of conflict had both competitor and sponsor conflicts.

4.1 Conflict Effects Benchmarked on the FDA

Each new drug sponsor in our study provides to an AC and the FDA scientific evidence supporting the safety and effectiveness of its drug. AC members and FDA staff could read the evidence differently on occasion. Indeed, the FDA often forms ACs to get different experts' opinions on the evidence to better inform its own decisions. Nevertheless, having read the AC's recommendation and associated explanation, along with the original information provided by the sponsor, we expect that the FDA commonly will agree with the AC recommendation.

For ease of exposition and comparison to ultimate FDA decisions, we will refer to AC recommendations in general as "decisions," or more specifically as approvals or rejections. Of course, they are only recommendations to the FDA. Our null hypothesis, therefore, is that AC decisions do not differ from FDA decisions in a statistically significant manner. The alternative hypothesis is that relative to non-conflicted ACs, ACs with conflicted members will vote more frequently than the FDA for drug approval.

For some context about AC and FDA decisions, consider Table 1, which presents the rates of approval for the ACs and the FDA during our full 1997 to 2012 sample period, as well as subsamples for ACs with and without conflicted members.

Table 1
FDA and AC Approval Rates by Presence of Conflict

	AC Approval	FDA Approval	Difference
Full Sample	69.6	73.2	-3.6
Conflicted AC	70.0	75.2	-5.2
Sponsor Only	80.0	90.0	-10.0
Competitor Only	67.7	73.6	-3.1
Non-Conflicted AC	69.1	71.1	-2.0

The first row in Table 1 presents the approval rates for the FDA and ACs. The FDA approval rate is 3.6 percentage points higher than ACs. The first column shows that conflicted ACs approve at a slightly higher rate than non-conflicted ACs. However, this may reflect a difference in the mix of drugs that necessitate ACs retaining conflicted experts. Examining approval rates relative to FDA approval rates can control for such potential confounding factors. If ACs tainted with conflicts were more likely than non-conflicted ACs to approve drugs, we would expect to see a smaller gap between FDA and AC voting for conflicted panels, but the opposite is true. The second and fifth rows in Table 1 show that conflicted ACs approve at a rate that is 5.2 percentage points *less* than the FDA approval rate, while non-conflicted ACs approve at a rate that is only 2 percentage points less than the FDA's rate, although this difference is not statistically significant. Examining ACs that are composed of only sponsor or competitor-conflicted members reveals the same pattern; approval rates are lower than FDA approval rates for both types of conflicts, and these differences are larger than those for non-conflicted ACs, although none of these differences are statistically significant. If the FDA decision represents an unbiased benchmark of “correct”

voting, these results may imply that ACs with conflicted members vote too infrequently to approve drugs, but it is contrary to a claim that ACs with conflicted members tend to be biased *toward* drug approval.[39]

Table 2 considers the subsample of 65 drugs for which the AC and the FDA decisions differ. If one assumes that disagreements between ACs and the FDA are purely random, and each case is equally likely to result in a disagreement, then disagreements should be distributed uniformly across approvals and rejections. Because ACs approve (reject) 69.6 percent (30.4%) of all cases, the proportions of AC-FDA disagreements involving approvals (rejections) should be approximately the same.

Table 2
Distribution of FDA/AD Disagreements by AC Decision

	All Disagreements	Non-Conflicted	Conflicted		
			Any	*Sponsor Only*	*Competitor Only*
Number of Drugs	65	28	37	4	12
AC Approves When FDA Rejects	38.5%	42.9%	35.1%	25%	41.7%
AC Rejects When FDA Approves	61.5%	57.1%	64.9%	75%	58.3%

Although the disagreement sample sizes are relatively small, all of the proportions in Table 2 differ significantly from the associated full sample proportions. For example, ACs approve 69.6 percent of the drugs that they consider, yet only 38.5 percent of the AC-FDA disagreements involve cases where the AC recommends approval. That is, when an AC recommends that a drug be approved, the FDA seldom rejects it. Similarly, ACs reject 30.4 percent of the drugs that they consider, yet rejections account for 61.5 percent of the cases in which ACs and the FDA disagree. This pattern is more pronounced for conflicted than non-conflicted ACs: only 35.1 percent of AC-FDA disagreements involve conflicted AC approvals, compared to 42.9 percent for non-conflicted ACs. When we examine ACs that have only sponsor or competitor conflicts, the pattern is the same: disagreements are less likely for AC approval decisions than for rejections, although the difference for competitor only conflicts is not statistically different from zero. These results are contrary to the bias hypothesis, which predicts that AC approvals would represent a higher proportion of AC-FDA disagreements for conflicted (or sponsor conflicted) ACs than non-conflicted ACs. Further, although the conflicted ACs are in agreement with the FDA more often than non-conflicted ACs, the rate of agreement is greater for rejections and even greater when sponsor conflicts are involved. That is, conflicted ACs are more likely than non-conflicted ACs to disagree with FDA approval decisions; greater disagreement on approvals is clearly not in the industry's favor and is not

[39] The result for sponsor-conflicted ACs does not support the results of one study that considered all types of votes, not just approve-reject votes, and found that sponsor-conflicted AC members voted in favor of the sponsor's position. *See* Genevieve Pham-Kanter, *Revisiting Financial Conflicts of Interest in FDA Advisory Committees*, 92 Milbank Quarterly. 446 (2014).

consistent with ACs and the FDA acting in concert because they are both captured by the pharmaceutical industry.

The univariate analysis provides little support for the bias hypothesis, so we next use multivariate logit analysis to control simultaneously for multiple possible determinants of AC-FDA disagreements. This multivariate analysis will provide a clearer answer to the question of the extent to which conflicts impact AC decisions relative to the FDA benchmark. More formally, we use logit regression to model the odds of a disagreement between the AC and the FDA on a specific drug matter as a function of the proportion of AC members who are conflicted and other exogenous variables designed to control for possible confounding factors. We estimate various specifications of the following general logit equation:

$$log\left(\frac{P_i}{1-P_i}\right) =$$

$$\alpha + B_1 \cdot \%CONFLICT_i + B_2 \cdot AC\_APPROVES_i + B_4 \cdot \%CONFLICT * AC\_APPROVES_i + B_3 \cdot MARGIN_i + B_4 \cdot AFTER2007, \quad (1)$$

where P_i is the probability that AC_i's decision differs from that of the FDA, ($1 - P_i$) is the probability that they agree, and $\left(\frac{P_i}{1-P_i}\right)$ is the "odds" that AC_i and the FDA disagree. The variable of primary interest, %*CONFLICT*$_i$, is the percentage of AC_i members with a conflict.[40] *AC_APPROVES* equals 1 when the AC approves, and 0 when it rejects, the drug in question. We also include an interaction between these variables to examine the extent to which conflicts impact the odds of FDA disagreements differently for AC approvals or rejections. In one regression, we break the %*CONFLICT*$_i$ variable into the conflicts associated with the sponsor (%SPON*CONFLICT*$_i$,) and the conflicts associated with the competitors (%COM*CONFLICT*$_i$,) to see if there is a different impact by conflict type.

MARGIN controls for the AC voting margin – the difference between the number of "yes" and "no" votes. The vote margin may be a proxy for the complexity of the decision, with small margins indicative of more potential for disagreement, but such complex cases could require relatively expert members who are also more often conflicted. *AFTER2007* equals 1 for meetings held in 2008 and after and 0 otherwise, and controls for the impact of the 2007 Act, which may have affected the composition of experts serving on ACs.[41] The parameter α is the regression constant representing the average odds for the comparison group of ACs (*i.e.,* those for whom all binary variables equal 0).

Results are reported in Table 3. The first specification suggests that the proportion of conflicted members serving on an AC has no significant impact on the odds of AC-FDA disagreement. When controls for whether the AC vote was to approve the drug, and an interaction between *%CONFLICT* and approval are added, there is still no statistically measurable impact of *%CONFLICT* on the odds of AC-FDA disagreement. Not surprisingly given the univariate results, the odds of disagreement fall dramatically when the AC votes to approve. The parameter estimate on *%CONFLICT*AC_APPROVES* suggests that

[40] Specifications were also run using the number of conflicted members serving on an AC and a dummy variable equal to one if any AC member is conflicted, and results were similar.

[41] Also starting after 2007, AC voting is done electronically instead of orally and sequentially. Some believed that the votes of the earlier voters could sway the votes of later voters toward the earlier voters. Urfalino (2013) finds some evidence of this in that there are fewer unanimous AC votes after 2007. This implies that the vote margins could be smaller following 2007 and perhaps have a different effect in our regressions. We tested for the effect of an interaction variable of MARGIN and AFTER2007 and found no statistically significant effect (results available on request). Philippe Urfalino, *Secret-Public Voting in FDA Advisory Committees*, *in* Private and Public Debate and Voting, editors Jon Elster and Arnaud Le Pillouer, Cambridge University Press, (2014).

these odds are even lower for ACs with a greater percentage of conflicted members, although it is statistically insignificant at standard levels.

Table 3
Meeting-Level Logit Analysis of AC-FDA Disagreement

	(1)	(2)	(3)	(4)	(5)	(6)
%CONFLICT	.91	2.37	1.25	2.32	1.86	
	(.90)	(.37)	(.84)	(.49)	(.64)	
%SPONCONFLICT						14.47
						(.59)
%COMCONFLICT						.275
						(.54)
AC_APPROVES		.29***	.34***	.29***	.28***	.452*
		(.001)	(.002)	(.002)	(.002)	(.07)
%CONFLICT*AC_APPROVES		.06	.05*	.03*	.04	
		(.11)	(.10)	(.08)	(.12)	
%SPONCONFLICT*AC_APPROVES						.0002
						(.23)
%COMCONFLICT*AC_APPROVES						.03
						(.36)
MARGIN			.88***	.90**	.88**	.84***
			(.01)	(.03)	(.02)	(.003)
AFTER2007			.72	.64	-	-
			(.36)	(.24)		
Committee Effects				Y	Y	Y
Year Effects				N	Y	Y
X^2	.01	35.24	44.65	43.48	31.65	36.64
P	.90	.001	.001	.001	.001	.002
N	414	414	414	363	363	246

Notes: Dependent variable is AC-FDA disagreement, which is equal to 1 when the FDA does not follow the AC recommendation for a specific drug, and 0 otherwise. Estimated odds ratios reported. N equals 414 because for two of drugs considered, the FDA decisions were not clear cut, but were conditional approvals. N also falls for fixed effects because there is no variation in outcome for some committees, which were dropped. P-values in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

Specification (3) adds additional controls that may be correlated with AC-FDA disagreement and the presence of conflicted members. The results support a negative and statistically significant relation between AC voting margin and the odds of AC-FDA disagreement, whereas the 2007 Act does not appear to have had any significant impact. The parameter estimate on *%CONFLICT*AC_APPROVES*, suggests a large negative relationship between AC-FDA disagreement on approval decisions and the proportion of conflicted members serving on an AC.

Specifications (4) and (5) add year and committee fixed effects to control for unobservable variables that are correlated with the proportion of conflicted members, but also impact the rate of AC-FDA disagreement. As with the other specifications, the estimated parameter on *%CONFLICT* is statistically insignificant. The estimate on *AC_APPROVES* still indicates that disagreement is less likely when an AC votes to approve a drug, and the estimate on the interaction term, *AC_APPROVES*CONFLICT*, suggests again that conflicted ACs are less likely to disagree with the FDA when the AC votes to approve than non-conflicted ACs, although it just escapes significance at standard levels when year effects are added. The estimate on *MARGIN* again implies a wider vote margin significantly reduces the odds of disagreement. Finally, the last specification breaks down the conflicts by sponsor or competitor. Both estimates are

insignificant, as are their interaction terms. Consistent with the other specifications, AC approval and the vote margin appear to be the only significant drivers of AC-FDA disagreement.

Next, we consider the impact of conflicts on individual voting relative to the FDA benchmark. The analysis better isolates the effect of conflict by associating it with particular AC members as opposed to particular committees. Further, the much larger sample size will provide the tests with more power to detect the impacts of conflicts.

Table 4 examines the relationship between AC member conflicts and the rate of member disagreement with FDA decisions. For all FDA decisions, or for approvals and rejections taken separately, conflicted members vote in line with the FDA more frequently than non-conflicted members. If conflicts significantly influence AC members to vote to approve too often, one would expect to find them disagreeing with the FDA's rejections more frequently than do non-conflicted members, but Table 4 shows the opposite, although none of the differences between conflicted and non-conflicted vote rates are statistically significant at conventional levels. When conflicts are broken down by type, both competitor and sponsor-conflicted AC members disagree with the FDA less frequently than their non-conflicted counterparts, but only one difference is statistically significant at standard levels.

Table 4
Conflicts and the Rate of AC Member-FDA Disagreement

	No Conflict	Conflict		
		Any	*Sponsor*	*Competitor*
Votes	5,045	650	87	312
All FDA Decisions	25.0%	23.7%	20.7%	20.8%**
FDA Approves	24.2%	23.4%	21.7%	20.5%
FDA Rejects	27.0%	24.7%	16.7%	21.8%

**Significantly different from No Conflict group at 5% level. “Any” conflict category greater than the sum of “Sponsor” and “Competitor” categories because 249 members have both competitor and sponsor conflicts and information on type of conflict is available only after 2001.

To examine the impact of multiple factors simultaneously, Table 5 reproduces the logit regressions in Table 3, but with the unit of observation as AC member *i*'s vote, rather than an AC decision. The dependent variable is the log odds that an AC member's vote differs from the FDA decision. *CONFLCIT* is a binary variable equal to 1 if the member has a conflict of interest. *APPROVE_VOTE* is equal to 1 if the member voted to approve the drug in question, and *CONFLICT*APPROVE_VOTE* is an interaction variable designed to measure the extent to which conflicted and non-conflicted members vote differently depending on the direction of their vote. The bias hypothesis predicts that the odds of a conflicted member disagreeing with the FDA would be larger (relative to a non-conflicted member) when the member votes to approve.

Table 5
Voting-Level Logit Analysis of AC-FDA Disagreement

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
CONFLICT	.93	1.51	1.09	1.11	1.10		
	(.30)	(.31)	(.62)	(.54)	(.61)		
SPONCONFLICT						1.19	1.01
						(.68)	(.99)
COMCONFLICT						1.35	1.65*
						(.22)	(.07)
APPROVE_VOTE		.16***	.17***	.17***	.15***	.22***	.19***
		(.001)	(.001)	(.001)	(.001)	(.001)	(.001)
CONFLICT*		.64**	.57**	.57**	.54**		
APPROVE_VOTE		(.05)	(.02)	(.02)	(.02)		
SPONCONFLICT						.27	. 27
*APPROVE_VOTE						(.12)	(.14)
COMCONFLICT						.48**	.34***
*APPROVE_VOTE						(.05)	(.01)
CREDENTIALS			.85*	.86	.96	.88	.99
			(.08)	(.12)	(.71)	(.22)	(.96)
EXPERT			1.01	.98	.90	.94	.85
			(.96)	(.93)	(.39)	(.64)	(.24)
TOTAL_CONFLICTS			1.04**	1.05**	1.17***	.98	1.11***
			(.03)	(.04)	(.001)	(.35)	(.01)
MARGIN			.93***	.92***	.94***	.89***	.89***
			(.001)	(.001)	(.001)	(.001)	(.001)
Committee Effects	N	N	N	N	Y	N	Y
Year Effects	N	N	N	Y	Y	N	Y
X^2	.53	876.3***	800.0***	867.0***	1,172.2***	568.7***	835.9***
P	.47	.001	.001	.001	.001	.001	.001
N	5,695	5,695	4,803	4,803	4,701	3,733	3,675

Notes: Dependent variable is AC-FDA disagreement, which is equal to 1 when the FDA and AC member votes are opposite and 0 otherwise. Estimated odds ratios reported. N falls for fixed effects models because there is no variation in outcome for some committees, which were dropped. P-values in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

Specification (1) is the simplest. The estimated odds ratio of *CONFLICT* is close to one and statistically insignificant, suggesting that the odds of voting contrary to the ultimate FDA decision are essentially the same for conflicted and non-conflicted members. Specifications (2) – (5) add additional controls, including year and committee fixed effects, and although the estimated odds ratio for *CONFLICT* is greater than one, it remains insignificant in each specification. As seen for estimations using meeting level data, whether or not the AC member votes to approve (*APPROVE_VOTE*) appears to be the strongest explanatory variable. Similarly, the odds of disagreement are 83-85 percent less likely when the member votes to approve compared to when they vote to reject. The significant estimates on *APPROVE_VOTE*CONFLICT* imply that the odds of disagreement are further reduced by between 37 and 43 percent for a conflicted member compared to a non-conflicted member. As with the meeting level analysis, most AC-FDA disagreements arise when the AC votes to reject a drug.

Specifications 3 through 5 include two variables to measure whether a member's professional credentials (*CREDENTIALS*) or their designation as an expert committee member (*EXPERT*) affects the odds of disagreement. *CREDENTIALS* is equal to 1 if the voter is affiliated with a top-ten medical institution in the relevant field (e.g., oncology, anesthesiology, etc.) as ranked by U.S. News and World Report at the time of the meeting, and *EXPERT* is equal to 1 if the voter is an expert member of the AC. Top experts could be more (or less) likely to vote consistently with the FDA, but may also be more likely to have conflicts. We find that only the estimate on *CREDENTIALS* in specification 3 weakly supports the notion that expertise reduces the odds of disagreement. The variable *TOTAL_CONFLICTS* is the number of conflicted members on the AC, and controls for the possible influence of multiple conflicted members. Having multiple conflicted members appears to have a slight positive impact on the odds of disagreement with the FDA. As we observed in the meeting-level regressions, larger voting margins are associated with a smaller likelihood of disagreement with the FDA, which is consistent with margin operating as a proxy for close calls.

Finally, specifications (6) and (7) examine competitor and sponsor conflicts separately, both with and without year and committee effects. Sponsor conflicts have no statistically measurable impact on voting, but in the fullest model, competitor conflicts appear to be associated with increased odds of disagreement. Further, the interaction between *COMCONFLICT* and *APPROVE_VOTE* suggests that members with competitor conflicts are more likely than non-conflicted members to vote against a drug that the FDA ultimately approves.

* * *

Taken together, the meeting and individual level analysis lends little support for the bias hypothesis. Conflicted ACs are less likely than non-conflicted ACs to approve drugs that the FDA believes do not merit approval, and conflicted members are less likely than their non-conflicted counterparts to cast approval votes that are inconsistent with the ultimate FDA decision. The only support for the bias hypothesis is that in one specification, members with competitor conflicts appear to disagree with the FDA more often than non-conflicted members (p-value = 0.07), and that these disagreements are more likely when the conflicted member votes against a drug that the FDA ultimately approves. This finding is consistent with the bias hypothesis if one takes the view that conflicted members' biases reflect only their current conflict. This finding, however, is contrary to the bias hypothesis under a broader view that as repeat players all conflicted members will tend to be biased in favor of sponsor interests (i.e., drug approval).

4.2 Conflict Effects Benchmarked on the Stock Market

The previous section finds almost no evidence that conflicts have an impact on whether AC members vote in a biased manner, where bias is measured relative to the FDA's decision. In this section, we examine how conflicts impact AC decision-making relative to stock market predictions, as identified through the event study method. [42]

The event study method relies on the assumption that stock prices are set efficiently; a widely held view in the finance literature. [43] The idea is that all publicly available information relevant to valuing a

[42] Stephen J. Brown & Jerold B. Warner, *Measuring Security Price Performance*, 8 J. Fin. Econ. 205, 205-258, (1980).
[43] The modern efficient markets hypothesis was established by Professor Eugene Fama, who won the 2013 Nobel Prize in Economics for this work. *See* Eugene Fama, *The Behavior of Stock Market Prices,* 38 J. Bus., 34 (1965); Eugene Fama, *Efficient Capital Markets: A Review of Theory and Empirical Work*, 25 J. Fin., 383 (1970).

company's stock is reflected in its price. This view is particularly appropriate here because information on potential new drugs attracts a great deal of attention from investors. Many Wall Street investment firms hire drug industry experts to assist them in valuing drug stocks. Indeed, there are many services that carefully track the progress and compile the clinical results of drugs under development.[44] Therefore, drug companies' stock prices should reflect all publicly available information about the likelihood that a new drug merits AC approval.

Besides finance journals, event studies of drug company events have on occasion appeared in medical journals.[45] Simply stated, the result of an event study is the portion of a stock's return caused by an information surprise. An example of a surprise is when investors expect an AC to recommend approval but instead they recommend rejection. The surprise or "abnormal" portion of the associated drug stock's return (called the cumulative abnormal return, or "CAR") is computed by subtracting the company's normal return from what the stock actually earned over the days surrounding the announcement of rejection. The Appendix provides the technical details of the event study empirical method.

We use event study results in two ways. First, at the meeting level, we test whether the proportion of conflicted members serving on an AC is related to the likelihood that the stock market is surprised. A direct relationship would suggest that conflicts tend to bias decisions relative to informed investors' expectations. Second, we investigate the extent to which conflicts affect the propensity for individual AC members to vote contrary to stock market predictions, which serve as proxies for unbiased voting.

4.2.1 Sample and Event Study Method

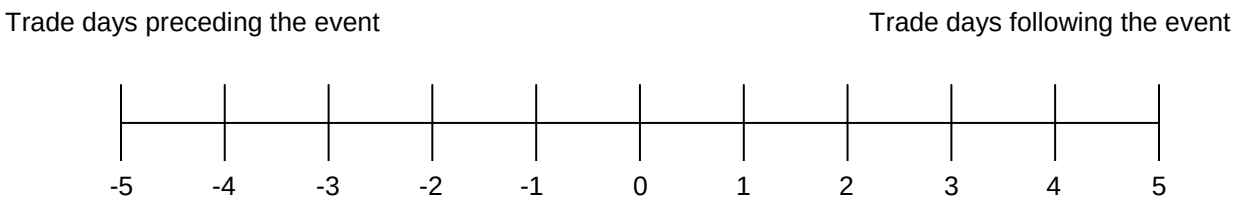
Each meeting provides a vote announcement, which we define as an event. Our sample of events includes all of the AC meetings during the 1997 to 2012 sample period. The stock return data for the companies involved in the events is obtained from the Center for Research in Security Prices (CRSP). Some meetings involved companies that are privately held or whose stocks are solely traded on foreign exchanges. The CRSP database does not contain stock returns for these firms, so they are not included in this analysis. Nevertheless, the sample is likely to represent the exploitable effects of the events reasonably well because CRSP covers the foreign pharmaceutical firms whose stocks are traded in the U.S., and because most of the excluded firms are privately held. Of the 414 potential events, we are able to obtain stock returns for 322 companies.

Figure 1 illustrates the basic structure of the data used to measure an abnormal return for each company's stock. The day that the results of the voting are announced is labeled day 0, that is, the event day. One could simply compute the abnormal stock return on that day to measure the effect of any surprise announcement on a particular company's stock, but the typical event study reports the cumulative abnormal stock returns (CARs) for the event day plus some trading days around the event. For example, the trade day that occurs 3 days before the event is labeled -3 in the figure.

[44] These include Thomson's Investigational Drug Database, Thomson-Derwent, PharmaProjects, What's in the Pipeline, and NDA Pipeline (now part of Inteleos). They sell the information to researchers, experts, consultants, and investment analysts. The upshot is that drug stock prices should reflect the detailed level of information available about the likelihood that a new drug merits approval (rejection) by an advisory committee. If a new drug merits approval, its company's stock price will be relatively high, but if the advisory committee recommends that the drug be rejected, the stock price will fall. Robert Steinbrook, *Wall Street and Clinical Trials*, 353 New Engl. J. Med 1091 (2005).

[45] Felix Oberholzer-Gee & S. Noorein Inamdar, "Merck's Recall of Rofecoxib – a Strategic Perspective," 351 New Engl. J. Med, 2147 (2004).

Figure 1
Time-Line of Return Data Used to Compute Cumulative Abnormal Returns



The reason most event studies include some adjacent days' abnormal returns is that some information leakage could occur just before the event, or it could take some time following the event for the information to be fully digested by investors. These surrounding days plus the event day are called the event "window." Using a window of days around the event is particularly appropriate for FDA meeting announcements. Some meetings take place over two days and information leaks on the progress of the voting could occur on the first day.

To account for potential information leaks or lags, we report CARs for two days before and two days after the meeting announcement day (a total of five trading days). Using a shorter window could miss some of the effects of the AC's decision. Using a longer window, say five days before and after the announcement, risks the chance that other significant company events occur in the window, and consequently, our CAR is contaminated and does not measure only the abnormal return associated with the AC's decision.[46]

4.2.2 Meeting Level Analysis

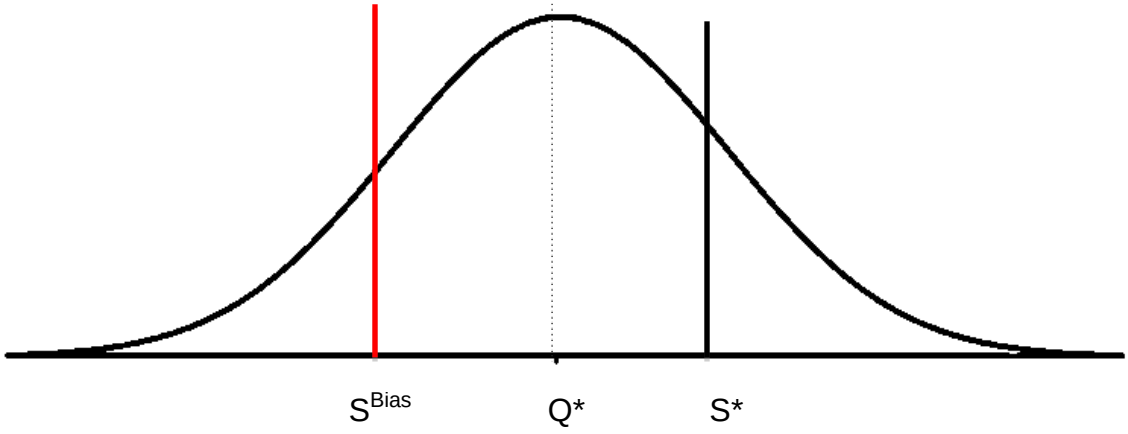
In this part, we examine whether stock market price reactions to AC decisions are consistent with the hypothesis that conflicted ACs will be more likely to approve drugs than their non-conflicted counterparts. To motivate our test, suppose that a drug company's stock price is V. If the AC recommends approval (rejection), the stock price will climb (fall) to V_H (V_L). Assume that unbiased observers view all the available information to estimate the *ex ante* probability, p, that the AC will recommend the drug. The current stock price should be:

$$V = p\,V_H + (1 - p)V_L\ . \qquad (2)$$

Figure 2 illustrates how p is formed. The horizontal axis depicts the range of drug "quality" – a composite of its safety and effectiveness. Suppose that Q* is the best estimate by outside observers of the quality of a drug under review, with the probability distribution surrounding Q* representing uncertainty associated with this estimate. If S* (assumed to be public knowledge) is the standard that a drug must meet for an unbiased AC to recommend approval, then p will be equal to the area of under the probability distribution to the right of S*, in this case less than 50 percent.

[46] The Factiva database was searched for potentially contaminating events during the five-day windows for our sample of 322 events. In 64 cases, we found announcements that could have impacted stock returns, for example, an earnings announcement. When we exclude these events, the results are little changed. For the regressions, we also tried keeping the events in the sample and adding a dummy variable that equaled one for a positive contaminating event (e.g., surprisingly good earnings), minus one for a negative contaminating event (e.g., surprisingly poor earnings), and zero otherwise. This variable was never significant in the regressions.

Figure 2
Effect of AC Bias on Stock Market Quality Estimation



Due to random differences in information or interpretation, ACs and investors will not always agree on quality, but as long as the differences in their quality assessments are not consistently in one direction, stock prices will not change much on average after AC decisions. Thus, if ACs make unbiased decisions, average CARs surrounding announcements should tend toward zero. Suppose, however, that unbeknownst to investors, conflicted ACs employ a lower standard for drug approval, S^{Bias}. In such cases, the true probability that the AC will approve the drug depicted in Figure 2 is p^{Bias}, which is equal to the area under the probability distribution to the right of S^{Bias} and is greater than p.[47] This implies that conflicted ACs will recommend approval more frequently than unbiased ACs considering the same set of drugs, including some drugs on which investors would place only a small *ex ante* chance of approval. In this manner, conflicted ACs will surprise the market with unexpected approvals more often than their non-conflicted counterparts. Accordingly, the bias hypothesis predicts that decisions by conflicted ACs should be associated with positive and significant CARs.

Table 6 groups CARs surrounding AC meetings by the presence of conflicted members on the AC making the decision.[48] For the full sample, the market appears to do a pretty good job anticipating AC decisions; only 25 percent of the measured CARs (81) are statistically significant. [49] For all 322 announcements in the sample, the range of abnormal returns is quite large (-92% to 216%), but the average CAR is a miniscule -0.97 percent and statistically indistinguishable from zero. [50]

[47] This scenario is equivalent to biased ACs systematically overestimating the quality of drugs (shifting the probability distribution associated with Q* to the right), but employing the unbiased standard.
[48] We set the CAR surrounding an event equal to zero unless it is statistically significant at $p > .10$ for a one-tailed test. Results for measured CARs regardless of statistical significance are nearly identical.
[49] Note that there are more AC announcements for meetings including a conflicted member than for meetings with no conflicted members (177 versus 145). In the full sample, the proportion is about 50% (210 conflict, 204 no conflict). The greater representation of conflicted AC meetings in the CAR sample is likely due to the fact that we do not have return data for private firms so they do not appear in this analysis. Because many conflicts involve AC members' stock ownership, and private firms have no publicly traded stock, it is less likely that AC members will have conflicts for meetings that involve private firms.
[50] Gelbach *et al*. point out that because CARs are often not normally distributed, using a parametric test to determine a CAR's significance can be too conservative. Indeed, we find that we can reject the hypothesis of normality for 194 CARs out of a total of 322 events. Therefore, we apply their sample quantile test (SQ) to determine the five percent significance for

Table 6
Cumulative Abnormal Returns
By Conflict Type

			Conflict		
		No Conflict	*Any*	*Sponsor Only*	*Competitor Only*
Total Announcements With CRSP Data	322	145	177	11	53
All AC Decisions	-0.97%	-2.05%	-0.08%	0%	6.23%**
AC Approves	4.40%	5.53%	3.50%	0%	11.32%
AC Rejects	-14.18%	-19.45%	-9.46%**	0%	-7.92%*

Notes: **Significantly different from No Conflict at 5% level, one-tailed test; * Significantly different from No Conflict at 10% level, one-tailed test.

Examining the differences in CARs associated with conflicted and non-conflicted ACs does not provide support for the bias hypothesis. First, the measured CARs for conflicted and non-conflicted ACs are small, negative, and statistically indistinguishable from zero (and from each other). As noted above, if conflicts lead to more cases of unwarranted approvals, we would expect to see positive CARs for conflicted ACs. Further, conflicted ACs are associated with 59 percent of events that do not surprise the market, a rate slightly above their 55 percent share of the sample.

Approval decisions are expected to be associated with positive CARs for both conflicted and non-conflicted ACs (because the market will not perfectly predict outcomes). If conflicts bias members toward approval, however, average approval CARs for conflicted ACs should be higher than for non-conflicted ACs because a larger proportion of the approval decisions for conflicted ACs would be unexpected.

The last two rows of Table 6 show approval and rejection announcements in isolation. Contrary to the bias hypothesis, only 42 percent (13) of the approval decisions that surprised the market come from conflicted ACs, despite conflicted ACs comprising the majority of the sample. Even if the absolute number of market surprises is smaller, average CARs for conflicted ACs could still be larger if they were associated with approvals that would be quite unexpected from an unbiased AC. The data do not support this test either. The average measured CARs associated with approval decisions by conflicted ACs are statistically indistinguishable from zero and from CARs associated with non-conflicted AC decisions (3.5% versus 5.53%).

Conflicted ACs are also associated with a minority of market surprises involving rejections (43%), and the measured CAR for rejection events involving conflicted ACs is significantly smaller (in absolute value)

each CAR. There are seven events that are not statistically significant at the five percent level using a normal distribution, but are significant using the SQ test. *See* Jonah Gelbach *et al*., *Valid Inference in Single Firm, Single Event Studies*, 15 Am. L. & Econ. Rev. 495 (2013).

than those for non-conflicted ACs (-9.46% versus -19.45%). Together, these results suggest that conflicted ACs arrive at decisions that are more in line with investor predictions than non-conflicted ACs.

The last two columns of Table 6 further separate ACs into those with only sponsor or only competitor conflicts. None of the 11 ACs that contain only sponsor-conflicted members are associated with statistically significant CARs. The difference between competitor-conflicted and non-conflicted ACs are mostly insignificant, and are in a direction inconsistent with the bias hypothesis. If AC members with competitor conflicts were biased, they should reject more drugs than non-conflicted members, leading to larger (in absolute value) negative CARs associated with rejection events and negative average CARs. However, average CARs are positive and CARs surrounding rejections are less than half (in absolute value) of non-conflicted ACs. Both of these differences are statistically significant. Also inconsistent with the bias hypothesis, which would predict fewer surprise approvals from ACs tainted with competitor conflicts, measured competitor-conflicted CARs are larger than (but statistically equivalent to) those associated with non-conflicted ACs for approval decisions.

Table 7 reports the results of ordinary least squares regression to study the impact of conflicts on the extent to which AC decisions are consonant with stock market predictions as measured by CARs. The dependent variable is the estimated CAR.[51] We use the same set of independent variables from the AC-FDA regressions, and as in that analysis, %CONFLICT is the variable of primary interest, measuring the percent of the conflicted AC members.[52] The simplest specification (1) shows that, with no control variables, there is no statistically significant relationship between CARs and the proportion of AC members who have conflicts. This is consistent with Table 6 where the average CARs for announcements by ACs with conflicted members is small and nearly identical to average CARs for announcements by ACs with no conflicted members.

[51] We set the CAR surrounding an event equal to zero unless it is statistically significant at $p > .10$ for a one-tailed test. Results for measured CARs regardless of statistical significance are nearly identical.

[52] As with the FDA benchmark regression in the previous section, we also ran specifications (not reported) using number of conflicts and a dummy equal to one if there is any conflicted member. Results were nearly identical.

Table 7
Conflicts and Cumulative Abnormal Returns Around AC Announcement Events

	(1)	(2)	(3)	(4)	(5)
%CONFLICT	-.028	.145*	.198***	.249***	
	(.50)	(.07)	(.01)	(.001)	
%SPONCONFLICT					.493
					(.25)
%COMCONFLICT					.12
					(.42)
AC_APPROVES		.222***	.212***	.240***	.221***
		(.00)	(.00)	(.00)	(.00)
%CONFLICT*AC_APPROVES		-.255***	-.234***	-.266***	
		(.002)	(.01)	(.01)	
%SPONCONFLICT*AC_APPROVES					-.582
					(.19)
%COMCONFLICT*AC_APPROVES					-.156
					(.38)
MARGIN			.003	.003	.005
			(.46)	(.28)	(.20)
AFTER_2007			.04	-	-
			(.32)		
Year Effects	N	N	N	Y	Y
Committee Effects	N	N	N	Y	Y
R^2	.0004	.12	.13	.15	.11
N	322	322	322	322	231

Notes: Dependent variable is measured cumulative abnormal return associated with announcement event; *p*-values from robust standard errors clustered at the committee level in parentheses; ***Significant at 1% level; **Significant at 5% level; *Significant at 10% level.

As we add additional control variables (including year and committee fixed effects) in specifications (2) through (4), the effect of *%CONFLICT* becomes positive and statistically significant. However, although the average difference in measured CARs appears to grow with the percentage of conflicted members serving on an AC, the interaction between AC approval and %*CONFLICT* suggests – again consistent with the univariate results in Table 6 – that these measured differences come predominantly from rejection events. Specifically, the point estimates suggest that the presence of conflicted members is associated with smaller CARs (in absolute value) for both approval and rejection decisions. For example, in specification (4), a one percent increase in the percentage of conflicted AC members is associated with a 24 percent increase in CARs for rejection events and a 1.7 percent reduction (.249 - .266) in CARs for approval events. That is, in general, conflicted ACs' decisions are more likely to be in line with stock market predictions. The final specification controls separately for the percentage of sponsor and competitor conflicted members. Although none of the parameter estimates are significantly different from zero, their signs and magnitudes suggest that the type of conflict has little impact on voting, as both %*SPONCONFLICT* and %*COMCONFLICT* are associated with smaller (in absolute value) CARs for both approval and rejection decisions.

4.2.3 Voting Level Analysis

Having examined the relation between the stock market reaction and conflicts measured at the committee level, we next examine the relation at the AC member voting level. If the stock market prediction represents an unbiased benchmark for expected drug approval, the bias hypothesis predicts that conflicted AC members should vote more frequently for approval than the stock market deems warranted.

Using CAR data, we construct a variable that describes when one can be confident that the stock market is surprised by an AC decision. We assume that if the CAR fails a 10 percent (1-tailed) significance test, the stock market was not surprised by the AC's decision, and therefore, had predicted the AC decision. If the CAR is positive (negative) and statistically significant at a 10 percent level (one-tailed test), and the AC voted to approve (reject), then the stock market had instead predicted rejection (approval).

Table 8 presents the results from a logit regression in which the dependent variable is the log odds that an AC member's vote differs from the stock market prediction. CONFLICT, the variable of primary interest, is a dummy variable equal to one if member *i* is conflicted, and zero otherwise. The remaining control variables are the same as those presented in the vote-level logit regressions in Table 5, which examined AC member disagreements with FDA decisions.

Table 8
Logit Analysis of Stock Market-AC Member Voting Disagreement

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
CONFLICT	.80**	1.21	1.07	1.07	1.04		
	(.03)	(.25)	(.73)	(.73)	(.84)		
SPONCONFLICT						1.26	1.62
						(.61)	(.33)
COMCONFLICT						1.55*	1.44
						(.10)	(.22)
APPROVE_VOTE		.25***	.24***	.24***	.23***	.33***	.32***
		(.001)	(.001)	(.001)	(.001)	(.001)	(.001)
CONFLICT*APPROVE		.49***	.68	.66*	.69		
_VOTE		(.001)	(.11)	(.09)	(.15)		
SPONCONFLICT						.34	.34
*APPROVE_VOTE						(.13)	(.15)
COMCONFLICT						.53*	.53*
*APPOVE_VOTE						(.06)	(.09)
CREDENTIALS			.88	.90	.98	.88	1.02
			(.18)	(.27)	(.81)	(.24)	(.90)
EXPERT			1.19	1.17	1.07	1.14	1.04
			(.16)	(.20)	(.56)	(.32)	(.81)
TOTAL_CONFLICT			.96**	.93***	.98	.89***	.82***
			(.02)	(.001)	(.31)	(.001)	(.01)
MARGIN			.96***	.97***	1.01	.93***	.98
			(.001)	(.001)	(.32)	(.001)	(.29)
Year Effects				Y	Y	N	Y
Committee Effects				N	Y	N	Y
X^2	5.1**	476.6***	456.2***	886.4***	850.4***	567.7***	709.2***
P	.02	.001	.001	.001	.001	.001	.001
N	4,279	4,279	3,618	3,614	3,556	2,790	2,749

Notes: Dependent variable is Member-Stock market disagreement, which is equal to 1 when a member votes contrary to what the stock market predicted based on event study results. Estimated odds ratios reported. N falls for fixed effects models because there is no variation in outcome for some committees, which were dropped. P-values in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

Specification (1) shows that the odds of a conflicted AC member disagreeing with the stock market prediction are 20 percent less than for a non-conflicted member. This effect disappears, however, as more control variables are added. As with the FDA benchmark regressions, specification (2) suggests that most votes that are inconsistent with stock market predictions are votes against drug approval, and that this pattern is even more pronounced for conflicted members. As member-specific (*EXPERT* and *CREDENTIALS*) and AC-specific (*MARGIN* and *TOTAL_CONFLICT*) controls, as well as year and committee fixed effects, are added in specifications (3)-(5), *CONFLICT*APPROVE_VOTE* becomes insignificant, suggesting no difference between conflicted and non-conflicted member voting relative to stock market predictions.

Consistent with the notion that large vote margins are a proxy for "easy" decisions, and hence more easily predicted by the market, *MARGIN* appears to have small negative effects on the probability that a member's vote will disagree with stock market predictions. That the number of conflicted members also is associated with slightly lower odds of voting contrary to stock market expectations is consistent with the observation that most AC decisions are to approve, and that the presence of conflicts is associated with lower CARs for approval decisions.

Finally, columns (6) and (7) report estimates that control for whether the member had a sponsor or competitor conflict. There is no statistically measureable relationship between the presence of a sponsor conflict and voting relative to stock market predictions. There is, however, some evidence that competitor-conflicted members' rejection votes are about 50 percent more likely to disagree with stock market predictions than non-conflicted members. There is also weak evidence that competitor-conflicted members' approval votes are less likely to disagree with the stock market predictions than their non-conflicted counterparts.

* * *

Together, the stock market benchmark results provide little evidence for the bias hypothesis. The meeting level analysis shows that ACs with a larger proportion of conflicted members are less likely to make decisions contrary to investor expectations. To the extent that investor expectations are a proxy for "correct" decisions, these results suggest that conflicts improve the accuracy of decision making. Although there is some statistically weak evidence that members with competitor conflicts are more likely than non-conflicted members to differ with stock market predictions for rejection votes, the vote level analysis finds no significant relationship between conflicts overall, or sponsor conflicts specifically, and votes contrary to stock market expectations.

5. Conclusion

The FDA often forms committees of external experts to make recommendations on new drugs before it makes its final decision. These experts typically have highly specialized knowledge about a particular class of drugs. The same qualifications that make them experts in the FDA's eyes make them attractive consultants and clinical advisors for drug companies. Some have expressed concern that their financial ties to drug companies compromises their votes, leading to recommendations biased in favor of drug approvals, and as a consequence, lead to unsafe and ineffective drugs on the market. Furthermore, some prior academic work has provided a modicum of empirical support for this worry. At the same time, observers both inside and outside the FDA have argued that stringent rules limiting conflicted members from serving on ACs will reduce the competence of FDA decision-making.

Consistent with the 2013 Report, we find little evidence that conflicts lead to biases in favor of drug company interests. The proportion of conflicted members serving on an AC has no statistically measurable impact on the probability that an AC decision is contrary to that of the FDA. The presence of conflicted members, moreover, reduces the probability of disagreement with the FDA for approval decisions. The empirical results thus suggest that if anything, conflicted ACs are more likely than their non-conflicted counterparts to disagree with the FDA's decision to approve a drug. Results using the stock market as a benchmark are similar: conflicted ACs' decisions surprise the stock market less frequently and are associated with smaller average abnormal returns than those made by their non-conflicted counterparts. These results suggest that conflicted ACs tend to arrive at decisions that are more consistent with predictions by outside experts than non-conflicted ACs, perhaps reflecting their greater expertise. Analysis of individual AC member voting also suggests little relationship between the presence of a conflict and voting decisions relative to either benchmark, although there is some evidence that competitor-conflicted members may vote to reject drugs more frequently than non-conflicted members relative to both the FDA and stock market benchmarks. These findings are consistent with the bias hypothesis if one takes the view that conflicted members' biases reflect only their current conflict. However, it is contrary to the bias hypothesis under a broader view that as repeat players all conflicted members will tend to be biased in favor of sponsor interests (i.e., drug approval).

In line with the 2013 results, this Report suggests that recent policies to limit the ability of well-qualified experts to serve on ACs could impose net costs on society. The presence of conflicts appears to have no statistically measurable impact on the accuracy of AC decision-making, measured as either consistency with the FDA or stock market predictions. If anything, conflicts lead to too few approval recommendations, which is the opposite of the concern that has motivated recent AC reforms. The results here suggest that preventing conflicted experts from serving on ACs could reduce the quality of FDA decision-making, which ultimately could harm consumers.

Appendix A: Event Study Details

We computed all event-study results using Eventus software, stock returns from the Center for Research in Security Prices (CRSP) database, and the market model. The market model is used as part of a common method to compute an abnormal return. The model defines the return one can expect from a stock on a particular trading day, given the stock's risk (beta) and the market return for the day. A stock's beta is a measure of its risk relative to the stock market as a whole. By definition, the market beta has a value of 1. A stock that is twice (half) as risky as the stock market has a beta of 2 (0.5). On days when the stock market increases (decreases) by, say, 2%, a stock with a beta of 2 should increase (decrease) by 4%.

The market model parameters (beta and alpha) for each firm are estimated with daily returns from a period preceding the event, in this case, starting 46 trading days before the event and going backward in time at least 63 trading days (three months) and up to 255 trading days (one year) if a company has 255 days available in the CRSP data set. The market model is

$$R_{it} = \alpha_i + \beta_i R_{mt} + \varepsilon_{it} \quad (1B)$$

where R_{it} is firm i's daily stock return on day t, R_{mt} is the market return on day t represented by the CRSP equal-weighted index return, α_i and β_i are the market model parameters measured by ordinary least squares coefficients for firm i, and ε_{it} in the error term for firm i at time t. Here we use up to one year of a firm's daily stock returns to gauge its risk. The returns come from a time period before the event windows so that the event itself does not influence the risk measure.

The normal or expected return on a particular day t, for stock i, is measured as:

$$E[R_{it}] = \hat{\alpha}_i + \hat{\beta}_i R_{mt} \ . \quad (2B)$$

The coefficients in (1B) are estimated over the 255 trading days before the event window. They are used to calculate, A_{it}, the risk-adjusted (abnormal) return on a particular day t for firm i as,

$$A_{it} = R_{it} - E[R_{it}] = R_{it} - \hat{\alpha}_i - \hat{\beta}_i R_{mt} \ . \quad (3B)$$

We compound these abnormal returns over the days of the event window to find the cumulative abnormal return (CAR) for a single firm.

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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.

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