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RED TAPE TIGHTROPE: REGULATING FINANCIAL CONFLICTS OF INTEREST IN FDA ADVISORY COMMITTEES

I. INTRODUCTION

In 2001, the Food and Drug Administration (FDA) approved the oral contraceptive Yasmin for use.¹ A similar contraceptive, Yaz, was approved in 2006.² Both drugs are manufactured by Bayer, a pharmaceutical company. As early as 2004, Bayer scientists reported that Yasmin carries a “‘several-fold increase’ in reporting rates for blood clots compared to three other oral contraceptives, and that Yasmin’s rate of all serious adverse events was ‘10 fold higher’ than that of other products.”³ Despite this, the FDA approved Yaz two years later, though it contained the same hormone that caused the blood clots in Yasmin.⁴ A 2009 study found that this hormone, drospirenone, increased a user’s risk of venous thromboembolism by a factor of 6.3.⁵

Yaz and Yasmin have been linked to 100 deaths, and over 10,000 lawsuits have been filed against Bayer claiming that consumers have been harmed by taking the contraceptives.⁶ In December 2011, the FDA reexamined Yaz and Yasmin.⁷ A panel voted to include the risk of blood clots on labels, though it declined to require Bayer to indicate that the risk was any greater than that for other contraceptives, despite a study published in the *British Medical Journal* that indicated that the risk of

1. *Yasmin Prescription Drug Pharmaceutical Information*, THE DRUG LIBRARY, <http://www.the.druglibrary.com/drug-0127.html> (last visited Sept. 1, 2014).

2. *FDA Approves YAZ(R), The First Oral Contraceptive to Offer Drospirenone in a 24-Day, Active-Pill Regimen*, MED. NEWS TODAY (Mar. 21, 2006, 12:00 AM), <http://www.medicalnewstoday.com/releases/39844.php>.

3. Jeanne Lenzer & Keith Epstein, *The Yaz Men: Members of FDA Panel Reviewing the Risks of Popular Bayer Contraceptive Had Industry Ties*, WASH. MONTHLY (Jan. 9, 2012, 9:24 AM), http://www.washingtonmonthly.com/ten-miles-square/2012/01/the_yaz_men_members_of_fda_pan034651.php.

4. *Id.*

5. A. van Hylckama Vlieg et al., *The Venous Thrombotic Risk of Oral Contraceptives, Effects of Oestrogen Dose and Progestogen Type: Results of the MEGA Case-Control Study*, 339 BRIT. MED. J. 561, 561 (2009). Venous thromboembolism “is the development of a blood clot (thrombus) in a vein due to reduced blood flow and abnormal coagulation.” *Venous Thrombosis and Embolism*, MDGUIDELINES, <https://www.mdguidelines.com/venous-embolism-and-thrombosis/definition> (last visited Sept. 1, 2014) (website log-in required).

6. Pam Belluck, *More Detail on Risk Urged for a Contraceptive Label*, N.Y. TIMES, Dec. 9, 2011, at A1, available at http://www.nytimes.com/2011/12/09/health/policy/stronger-label-urged-for-yaz-and-yasmin-contraceptives.html?_r=0.

7. *Id.*

blood clots were twice as high for users of Yaz and Yasmin than for other contraceptives.⁸ The FDA panel voted 15-11 to allow the contraceptives to remain on the market, finding that their benefits to consumers outweighed their risks.⁹ Scientists and consumer advocates soon observed, however, that four (possibly five) members of the FDA panel had financial ties to Bayer, and all four voted to keep the drugs on the market.¹⁰ They each had disclosed these conflicts of interest to the FDA, and the FDA allowed them to vote on the panel anyway.¹¹ In February 2013, Bayer faced roughly 13,600 lawsuits in the United States regarding the contraceptives, excluding claims already settled.¹² Further, as of February 2013, Bayer had also “reached agreements, without admission of liability, to settle the claims of approximately 4,800 claimants in the U.S. for [about \$1 billion.]”¹³ Yaz and Yasmin are still on the market, and Bayer profited \$1.42 billion from them in 2012.¹⁴

This incident is only the latest of several in recent years that have caused many to question the FDA’s transparency and bias in its review and approval processes. Conflict of interest within FDA advisory committees has been discussed before,¹⁵ but several new regulations have loosened FDA conflict of interest requirements, and recent events such as the Bayer incident raise questions as to whether the current regulations are effective. Further examination of these issues is in order. This Note explores the depths of financial conflicts of interest in these processes, how they are regulated, and how they *should* be regulated. Part II

8. *Id.*; see also Øyvind Lidegaard et al., *Risk of Venous Thromboembolism From Use of Oral Contraceptives Containing Different Progestogens and Oestrogen Doses: Danish Cohort Study, 2001-9*, 343 BRIT. MED. J. d6423 (2011), available at <http://www.bmj.com/content/343/bmj.d6423>.

9. Merrill Goozner, *Conflict of Interest Scandal Rocks FDA*, THE FISCAL TIMES (Jan. 12, 2012, 6:26 PM), <http://www.thefiscaltimes.com/Blogs/Gooz-News/2012/01/12/Conflict-of-Interest-Scandal-Rocks-FDA.aspx#page1>.

10. Lenzer & Epstein, *supra* note 3.

11. *Id.*

12. *Annual Report 2012: 32. Legal Risks*, BAYER GRP., http://www.annualreport2012.bayer.com/en/legal-risks.aspx#32_1 (last updated Feb. 28, 2013). Bayer had settled all but 5,000 claims in the United States by October 18, 2013. BAYER GRP., STOCKHOLDERS’ NEWSLETTER, FINANCIAL REPORT AS OF SEPTEMBER 30, 2013: THIRD QUARTER OF 2013: BAYER CONTINUES POSITIVE BUSINESS MOMENTUM 65, available at <http://www.stockholders-newsletter-q3-2013.bayer.com/en/bayer-stockholders-newsletter-3q-2013.pdf>.

13. BAYER GRP., BAYER ANNUAL REPORT 2012, at 273 (2013), available at <http://www.annualreport2012.bayer.com/en/bayer-annual-report-2012.pdf>.

14. *Id.* at 70 (figure in report was converted from euros to dollars to reach \$1.2 billion).

15. See Merrill Goozner, *Conflicts of Interest in the Drug Industry’s Relationship with the Government*, 35 HOFSTRA L. REV. 737 (2006); Saurabh Anand, Note, *Using Numerical Statutory Interpretation to Improve Conflict of Interest Waiver Procedures at the FDA*, 83 S. CAL. L. REV. 649 (2010).

discusses current conflict of interest regulations imposed upon the FDA. Part III examines the arguments for loosening regulations. Part IV addresses the argument for tightening regulations, including a more in-depth discussion of the Yaz/Yasmin incident as well as other drug scandals that implicate the integrity of the FDA. Part V assesses the legitimacy of these arguments and makes a recommendation for avoiding conflicts of interest on advisory committees that jeopardize public safety.

II. BACKGROUND AND CURRENT FINANCIAL CONFLICT OF INTEREST LAW IMPOSED UPON THE FDA

The FDA regulates approximately twenty-five cents per dollar spent in the United States.¹⁶ In 2008, this figure included \$466 billion in food sales, \$60 billion in cosmetics, \$18 billion in vitamin supplements, and \$275 billion in drugs.¹⁷ Drug expenditures alone reached \$329 billion in 2011 and nearly \$326 billion in 2012.¹⁸

Given these figures, the ubiquity of drugs in America should come as no surprise. The Mayo Clinic estimates that 70% of Americans take at least one prescription drug, and that over half take at least two.¹⁹ Between 11% and 20% of Americans take five or more prescription drugs in a given month.²⁰ The very wealthy and the very poor tend to take more prescription drugs and more frequently than the middle class.²¹ The very

16. Gardiner Harris, *The Safety Gap*, N.Y. TIMES MAG. (Oct. 31, 2008), <http://www.nytimes.com/2008/11/02/magazine/02fda-t.html>; *Executive Summary: Strategic Plan for Regulatory Science*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm> (last updated Jan. 16, 2013).

17. Harris, *supra* note 16.

18. *U.S. Prescription Drug Spending Drops For First Time In 58 Years*, CBS NEWS (May 9, 2013, 2:25 PM), <http://www.cbsnews.com/news/us-prescription-drug-spending-drops-for-first-time-in-58-years/>. This article attributes the 1% spending decrease from 2011 to 2012 to both remaining effects of the Great Recession and to increased availability of generic drugs. IMS Health predicts that drug sales will rise again in 2014 by more than 4% because of “fewer brand-name drugs losing patent protection and also an influx of newly insured patients” as the Affordable Care Act goes into effect. Katie Thomas, *U.S. Drug Costs Dropped in 2012, But Rises Loom*, N.Y. TIMES, Mar. 19, 2013, at A1, available at <http://www.nytimes.com/2013/03/19/business/use-of-generics-produces-an-unusual-drop-in-drug-spending.html>.

19. Press Release, Mayo Clinic News Network, Nearly 7 in 10 Americans Take Prescription Drugs, Mayo Clinic, Olmsted Medical Center Find (June 19, 2013), <http://newsnetwork.mayoclinic.org/discussion/nearly-7-in-10-americans-take-prescription-drugs-mayo-clinic-olmsted-medical-center-find>.

20. *Id.*; QIUPING GU, CHARLES F. DILLON, & VICKI L. BURT, NAT’L CTR. FOR HEALTH STATISTICS, PRESCRIPTION DRUG USE CONTINUES TO INCREASE: U.S. PRESCRIPTION DRUG DATA FOR 2007–2008 (2010), available at <http://www.cdc.gov/nchs/data/databriefs/db42.pdf>. The Mayo Clinic study estimates 20%, while Gu et al.’s study estimates 11%.

21. David Maris, *Who is Popping All Those Pills?*, FORBES MAG. (July 24, 2012, 9:24 AM), <http://www.forbes.com/sites/davidmaris/2012/07/24/1-in-3-american-adults-take-prescription-drugs/>.

poor, often the least educated, are the most likely to be taking four or more prescription drugs at a time.²² Americans consume 80% of the world's pain medication.²³ Setting aside growing criticism that American healthcare professionals overmedicate their patients and focus on treatment-based care rather than prevention,²⁴ the FDA has a direct impact on drug safety. Its failures, whether through negligence, ignorance, or corruption, pose an immediate danger to the nearly three quarters of American citizens who use prescription drugs.

A. The "Shared Pool" Dilemma

The FDA approves drugs and devices through advisory committees of experts and representatives. The FDA uses fifty-one committees "to obtain independent expert advice on scientific, technical, and policy matters."²⁵ The experts include academicians and practitioners in all healthcare fields.²⁶ Committees also include industry representatives "[a]lmost without exception,"²⁷ a consumer advocate, and sometimes a patient representative.²⁸ (Industry representatives are non-voting members and are

One could argue that the middle class is mentally and/or physically healthier than the poor or the wealthy; a less controversial explanation, and the one that Maris takes, is that the wealthy have the most comprehensive insurance policies, the poor often have Medicaid benefits, and thus the middle class is subjected to the most out-of-pocket expenses. *Id.*

22. *Id.* For an explanation of the widening educational gap associated with income, see Sabrina Tavernise, *Poor Dropping Further Behind Rich in School*, N.Y. TIMES, Feb. 10, 2012, at A1, available at <http://www.nytimes.com/2012/02/10/education/education-gap-grows-between-rich-and-poor-studies-show.html>.

23. Michael Zennie, *Americans Consume Eighty Percent of the World's Pain Pills as Prescription Drug Abuse Epidemic Explodes*, DAILY MAIL (May 10, 2012, 11:45 AM), <http://www.dailymail.co.uk/news/article-2142481/Americans-consume-80-percent-worlds-pain-pills-prescription-drug-abuse-epidemic-explodes.html#ixzz2A41u3Aps>.

24. See, e.g., RAY MOYNIHAN & ALAN CASSELS, *SELLING SICKNESS: HOW THE WORLD'S BIGGEST PHARMACEUTICAL COMPANIES ARE TURNING US ALL INTO PATIENTS* (2005); Dominick L. Frosch et al., *Creating Demand for Prescription Drugs: A Content Analysis of Television Direct-to-Consumer Advertising*, 5 ANN. FAM. MED., January/February 2007, at 1, available at <http://www.annfammed.org/content/5/1/6.full.pdf>.

25. *Advisory Committees*, FDA.GOV, <http://www.fda.gov/AdvisoryCommittees/default.htm> (last updated Sept. 22, 2014). This page states that it has fifty committees and panels, but a different FDA page explains that there are now fifty-one. *July 17, 2012: FDA-TRACK Advisory Committees Quarterly Briefing Summary*, FDA.GOV, <http://www.fda.gov/AboutFDA/Transparency/track/ucm314987.htm> (last updated Apr. 15, 2013).

26. *Advisory Committees: Membership Types*, FDA.GOV, <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/MembershipTypes/default.htm> (last updated Jan. 22, 2014).

27. *Advisory Committee Industry Representatives*, FDA.GOV, <http://www.fda.gov/oc/advisory/industry.html> (last visited Sept. 1, 2014).

28. *Advisory Committees: Membership Types*, *supra* note 26.

not subject to conflict of interest regulations.²⁹) The scientific experts on these committees are also in high demand, precisely for their expertise, as consultants or clinicians for regulated industry.³⁰ Nyssa Ackerley explains, “[a]cademic and institutional research also increasingly relies on industry sources for funding. This situation, whereby the same experts are in demand by both the federal government and regulated industry, has been described . . . as the ‘shared pool dilemma.’”³¹ Excluding these experts from decision-making on FDA advisory committees leaves only a “pool of ‘experts’ less qualified than those disqualified, by virtue of the simple fact that [the more qualified experts] are so pre-eminent in their fields that industry seeks out their advice and services.”³²

Katherine McComas states that this shared pool dilemma rests upon two assumptions: first, “that a finite number of qualified experts exists for any given topic,” and second, “that the mere presence of a real or potential conflict of interest may result in a member acting in a biased manner.”³³ The assertion that too few non-conflicted experts exist to fill panels may be somewhat supported by the fact that roughly 23% of the FDA’s committee positions remain vacant.³⁴ The FDA also sometimes has trouble convening a non-conflicted panel, which is arguably as detrimental to patients as eradicating conflicts from the panels.³⁵

29. See, e.g., NYSSA ACKERLEY ET AL., MEASURING CONFLICT OF INTEREST AND EXPERTISE ON FDA ADVISORY COMMITTEES, EASTERN RESEARCH GROUP, INC. (2007), available at <http://www.fda.gov/oc/advisory/ergcoireport.pdf>.

30. *Id.* (citing Elizabeth R. Glodé, *Advising Under The Influence?: Conflicts Of Interest Among FDA Advisory Committee Members*, 57 FOOD & DRUG L.J. 293 (2002)).

31. *Id.* at 1–3 (citing Katherine A. McComas et al., *Conflicted Scientists: The “Shared Pool” Dilemma of Scientific Advisory Committees*, 14 PUB. UNDERSTANDING SCI., no. 3, at 285, 287 (2005), available at http://www.ssoar.info/ssoar/bitstream/handle/document/22384/ssoar-2005-3-mccomas_et_al-conflicted_scientists_the_shared_pool.pdf?sequence=1).

32. Richard Epstein, *Unshackle the FDA From Rules That Kill Innovation*, FORBES (Mar. 15, 2012, 6:11 PM), <http://www.forbes.com/sites/richardepstein/2012/03/15/unshackle-the-fda-from-rules-that-kill-innovation/>. Epstein, a law professor at New York University, describes himself as “a law professor with eclectic interests and three homes.” He teaches many subjects, “strongly resisting all forms of specialization.” *Richard Epstein, Contributor*, FORBES, <http://www.forbes.com/sites/richardepstein/> (last visited Sept. 22, 2014).

33. McComas et al., *supra* note 31, at 287.

34. The percent of vacant committee positions reached 33% in 2010. The FDA’s efforts to reduce these vacancies were successful, with a 20% vacancy rate by the end of 2012. Perhaps due to the federal budget sequestration, the rate slowly started to rise, reaching 23% in June 2013, but had subsided to 17% by March 2014. *Percent of FDA Advisory Committee Member Positions Vacant at the End of the Month*, FDA.GOV, <http://www.accessdata.fda.gov/FDA/Track/track?program=advisory-committees&id=AdvComm-FDA-PercentVacant> (last updated Mar. 31, 2014).

35. See, e.g., Thomas Sullivan, *U.S. House Energy and Commerce PDUFA Hearing: Transformation of the FDA*, POL’Y & MED. (July 21, 2011, 5:06 AM), <http://www.policymed.com/2011/07/us-house-energy-and-commerce-pdufa-hearing-transformation-of-the-fda.html> [hereinafter PDUFA Hearing]; see also Matthew Herper, *A Health Care Reform Law for the FDA*, FORBES (June

The shared pool dilemma, if it exists, leads to two possible outcomes, both of which carry frightening risks. First, the most qualified experts will sit on advisory committees, though some of them will necessarily have financial conflicts. On the other hand, if conflicted experts are excluded, the experts deciding the fate of a drug will be less qualified to make such an impactful decision than their conflicted counterparts. That is, those committee members with comparatively less expertise will be deciding the profits of an industry and the health of the patients potentially affected by the drug's approval or rejection. The merits of the shared pool dilemma, and therefore the necessity that the FDA choose between these two uncomfortable outcomes, is discussed in Part III.

McComas examines the difficulty of finding both qualified and disinterested experts.³⁶ Though there may never be a way to prove a causal relationship between a committee member's conflict of interest and a biased vote, this should not relieve the FDA of its duty to minimize that possibility. This apparent difficulty has caused a multitude of conflict of interest regulation to clarify precisely who is eligible to sit on an advisory committee,³⁷ which conflicts can be disregarded, and which cannot. Yet, despite this, the conflict-related scandals persist, drugs get recalled, and people die.³⁸ The next Section discusses these laws and their success at filtering advisors with financial conflicts.

27, 2012, 11:31 AM), available at <http://www.forbes.com/sites/matthewherper/2012/06/27/a-health-care-reform-law-for-the-fda/>. Herper cites Eli Lilly's blood thinner Effient as an example of a drug for which the FDA had difficulty convening a panel. However, he neglects to mention the details of the difficulty. In fact, Eli Lilly persuaded the FDA to remove from the panel a cardiologist who had openly questioned both the drug's effectiveness and its risks. Effient was approved unanimously, despite a letter to the FDA from one of the drug's inventors urging the committee not to approve the drug until it had gone through more rigorous clinical trials. The FDA later formally admitted it was wrong to have dismissed the cardiologist from the panel. Jim Edwards, *FDA Admits It Was Wrong to Ax Critic of Lilly's Effient*, CBS NEWS (July 16, 2009, 3:28 PM), http://www.cbsnews.com/8301-505123_162-42842161/fda-admits-it-was-wrong-to-ax-critic-of-lillys-effient/.

36. McComas et al., *supra* note 31, at 291–92.

37. See, e.g., Federal Advisory Committee Act, Pub. L. No. 92-463 (codified at 5 U.S.C. App. 2 (2012)); 18 U.S.C. § 208 (2012) (basic criminal conflict of interest statute); FDA, GUIDANCE FOR THE PUBLIC, FDA ADVISORY COMMITTEE MEMBERS, AND FDA STAFF ON PROCEDURES FOR DETERMINING CONFLICT OF INTEREST AND ELIGIBILITY FOR PARTICIPATION IN FDA ADVISORY COMMITTEES (2008), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf> [hereinafter GUIDANCE FOR THE PUBLIC].

38. See, e.g., Belluck, *supra* note 6.

B. Current Conflict of Interest Regulations Imposed Upon the FDA

Financial conflicts of interest impact FDA review and approval processes in two major ways. First, investigators compensated by study sponsors may feel pressure to produce results satisfactory to the sponsor, which are often and increasingly pharmaceutical companies.³⁹ Thus, the studies presented to FDA advisory committees are often not objective, either because of investigators' selective inattention to certain outcomes, deliberate manipulation of data, or somewhere in between on the spectrum.⁴⁰ The second way conflicts of interest may affect the approval process occurs when investigators compensated by the study's sponsors are the same individuals sitting on an FDA panel that votes to allow a product to reach the market.⁴¹ Though of course the same individuals may be implicated in either type of conflict, this Note focuses primarily on the second. The first implicates the integrity of individuals and drug companies; the second implicates the integrity of the FDA. The approval process is the final step before a potentially deadly (or life-saving, or completely inefficacious) drug reaches the market. This phase, more than any other phase in a drug's life cycle from its inception to public consumption, must be free of personal financial conflicts.⁴²

39. See, e.g., Thomas Bodenheimer, *Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1539–44 (2000); Jeff Herman, *Saving U.S. Dietary Advice from Conflicts of Interest*, 65 FOOD & DRUG L.J. 285, 297 (2010) (citing Eric G. Campbell et al., *Looking a Gift Horse in the Mouth: Corporate Gifts Supporting Life Sciences Research*, 279 J. AM. MED. ASS'N 995, 997 (1998)); Paul A. Rochon, *A Study of Manufacturer-Supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Arthritis*, 154 ARCH. INTERN. MED. 157 (1994) (investigators who received money from industry often reported that the donor's drug was safer than alternatives, despite the fact that the data supported such a conclusion less than half the time); Andreas Lundh et al., *Industry Sponsorship and Research Outcome*, COCHRANE DATABASE OF SYSTEMATIC REVIEWS no. 12, at 1–2 (2012), <http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000033.pub2/pdf> (subscription required) (concluding, among other things, that industry-sponsored studies tended to have “less agreement between the results and the conclusions than . . . non-industry sponsored studies”).

40. For a discussion on the many types of funding bias, see David Michaels, *It's Not the Answers That Are Biased, It's the Questions*, WASH. POST (July 15, 2008), available at <http://www.washingtonpost.com/wp-dyn/content/article/2008/07/14/AR2008071402145.html>; see generally HARRY STACK SULLIVAN, FORTUNATE AND UNFORTUNATE USES OF SELECTIVE INATTENTION, IN CLINICAL STUDIES IN PSYCHIATRY 42 (1956) (discussing how selective inattention can be beneficial by helping one focus on the significant by ignoring the irrelevant, and can also yield harmful results when significant details are ignored).

41. See, e.g., Lenzer & Epstein, *supra* note 3.

42. That research companies manipulate trial data is unfortunate, but not surprising. See, e.g., David B. Resnik, *Financial Interests and Research Bias*, 8 PERSP. ON SCI., no. 3, at 255 (2000). This is why the FDA must be all the more scrupulous in the approval process; the FDA should be able to assure the public that there was one stage in the drug's development where the decision to market it was determined by unconflicted participants.

Applicants for FDA approval of a product relying on clinical studies must disclose financial arrangements between the sponsor and the investigator.⁴³ Members of an advisory committee must also disclose to the FDA financial ties to the applicant,⁴⁴ so ignorance of such a conflict is typically not at issue. Rather, the conflicts are disclosed, usually from both ends; what to do with the knowledge of these conflicts (or not to do, as is often the case), is left to the FDA. The FDA does not include in its mission statement an attempt to eradicate conflict of interest from advisory committees; its mission with respect to drugs, as it should be, is simply to ensure their safety and effectiveness.⁴⁵ Whether this goal can be achieved without eradicating conflict of interest, however, is another question. The amount of conflict of interest laws and regulations suggests an acknowledgment of the disastrous potential the “shared pool dilemma” carries with it. These laws are discussed below.

1. Federal Advisory Committee Act

Advisory committees are not unique to the FDA; approximately 1,000 advisory committees exist at any given time, serving hundreds of federal agencies.⁴⁶ Any advisory committee established by a federal agency must comply with the Federal Advisory Committee Act of 1972 (FACA).⁴⁷ FACA serves as a congressional recognition of “the merits of seeking the advice and assistance of [United States] citizens.”⁴⁸ It also regulates the committees to ensure that committee advice is “relevant, objective, and

43. Disclosure requirements are codified at 21 C.F.R. § 54 (2000). Applicants are required to disclose: (1) financial arrangements between the study’s sponsor and its investigator when the study’s outcome “could increase the monetary value of the clinical investigator’s financial interest;” (2) “payments over \$25,000 made by the sponsor to the investigator or institution during a clinical trial or within one year” of its completion; (3) proprietary interests in the tested product, including patent, trademark, or copyright interests;” and (4) equity interests in the sponsor over \$50,000 in a publicly held sponsoring company during the trial or within one year of its completion. Jennifer A. Henderson & John J. Smith, *Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls*, 57 FOOD & DRUG L.J. 445, 450–51 (2002).

44. Ethics in Government Act of 1978, 5 U.S.C. App. 4 (2012). The financial disclosure form potential committee members must submit to the FDA is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048297.pdf>.

45. 21 U.S.C. § 393(b)(2)(B) (2012).

46. *Federal Advisory Committee Act (FACA) Brochure*, U.S. GEN. SERVS. ADMIN., <http://www.gsa.gov/portal/content/101010> (last updated May 19, 2014).

47. Pub. L. No. 92-463 (codified at 5 U.S.C. App. 2 (2012)). The committees are overseen by the U.S. General Services Administration pursuant to the law. *Id.*

48. *FACA Brochure*, *supra* note 46.

open to the public,” and that committees act efficiently and “[c]omply with reasonable cost controls and record keeping requirements.”⁴⁹

FACA is primarily geared toward efficiency, record keeping, and public disclosure.⁵⁰ It requires disclosure of the identities of advisory committee members, existence of committees themselves, and funds at a committee’s disposal.⁵¹ Despite the inclusion of “objectivity” in its purpose, the law contains no limit upon who can sit on a committee, save for the ambiguous requirement that committees be “fairly balanced in terms of the points of view represented and the functions to be performed.”⁵² This balance inquiry is a case-by-case determination and depends on the authority of the agency.⁵³ All views need not be represented to meet this balance requirement.⁵⁴

Indeed, the FDA has deliberately removed certain viewpoints from advisory committees. While waivers are granted for financial conflicts of interest, “intellectual conflicts of interest” are apparently taken much more seriously.⁵⁵ Dr. Sidney Wolfe, the committee’s consumer advocate and the director of Public Citizen’s health research group,⁵⁶ was removed from the advisory committee that approved Yaz and Yasmin because his widely-read newsletter, “Worst Pills, Best Pills,” had already called for banning the drug because of its safety risks.⁵⁷ An exasperated Dr. Wolfe stated that if being informed and subsequently forming an opinion based on that information constituted an intellectual conflict of interest, “many more

49. *Id.*

50. *FACA 101*, U.S. GEN. SERVS. ADMIN., <http://www.gsa.gov/portal/content/244333> (last updated June 11, 2014).

51. *FACA*, Pub. L. No. 92-463. It places advisory committees under congressional jurisdiction and requires House and Senate committees to conduct continuing reviews of advisory committees under their jurisdiction, determining their necessity, the appropriateness of their functions, and compliance with the law. *Id.*

52. 5 U.S.C. App. 2 § 5(b)(2) (2012).

53. *See, e.g.*, 60 Comp. Gen. 386 (1981).

54. *Id.* Though all views need not be represented on an advisory committee, the issue of whether a committee is sufficiently balanced is justiciable. *See, e.g.*, *Cargill, Inc. v. United States*, 173 F.3d 323 (5th Cir. 1999).

55. Susan Todd, *FDA Disqualifies Public Citizen’s Chief Advocate From Meeting On Risky Birth Control*, NJ.COM (Dec. 6, 2011, 10:41 PM), http://www.nj.com/business/index.ssf/2011/12/fda_disqualifies_public_citize.html.

56. Public Citizen is a national non-profit consumer advocacy group founded in 1971. *About Us*, PUBLIC CITIZEN, <http://www.citizen.org/Page.aspx?pid=2306> (last visited Sept. 1, 2014).

57. Goozner, *supra* note 9. Goozner incorrectly refers to the newsletter as “Best Pills, Worst Pills.” Wolfe also co-authored a 960-page book titled *Worst Pills, Best Pills: A Consumer’s Guide to Avoiding Drug-Induced Death or Illness*, along with Larry Sasich and Peter Lurie. Peter Lurie, M.D., M.P.H., to be discussed *infra*, is extensively well-versed on conflicts of interest in FDA advisory committees.

members of advisory committees would have to be excluded.”⁵⁸ A spokesperson for the FDA simply stated, “We do value Dr. Wolfe’s contributions . . . but we are committed to preserving the integrity of the committee process.”⁵⁹

FACA also requires that any new legislation regarding advisory committees contain “appropriate provisions to assure that the advice and recommendations of the advisory committee will not be inappropriately influenced by the appointing authority or by any special interest, but will instead be the result of the advisory committee’s independent judgment.”⁶⁰ By itself, this “independent judgment” requirement is unhelpful as it does not provide guidance on how to balance these interests. However, it provides some groundwork for later legislation affecting disclosure requirements, conflict waivers, and other regulations for FDA advisory committees.

2. *Government in the Sunshine Act (Freedom of Information Act)*

The Government in the Sunshine Act of 1976 (the “Act”) amended the Freedom of Information Act.⁶¹ It provides that, with ten exemptions, “every portion of every meeting of an agency shall be open to public observation” and requires advance notice of such meetings.⁶² The Act also imposes procedural requirements an agency must take before determining that an exemption applies.⁶³

The relevant exemptions include release of information likely to “disclose matters specifically exempted from disclosure by [another] statute,” “disclose trade secrets and [privileged or confidential] commercial or financial information,” or “concern the agency’s issuance of a subpoena [or] the agency’s participation in a civil action or proceeding.”⁶⁴

Federal courts, not the agencies, are responsible for interpreting the statute.⁶⁵ But inasmuch as the FDA is involved in determining propriety of information, it usually errs on the side of confidentiality.⁶⁶ Courts have

58. Todd, *supra* note 55.

59. *Id.*

60. 5 U.S.C. App. 2, § 5(b)(3) (2012).

61. 5 U.S.C. § 552 (2012).

62. 5 U.S.C. § 552b(b) (2012).

63. *Id.*

64. *Id.* § 552b(c)(3), (4), (10).

65. Pub. Citizen Health Research Grp. v. Food & Drug Admin., 704 F.2d 1280 (D.C. Cir. 1983).

66. See, e.g., Aaron S. Kesselheim & Michelle M. Mello, *Confidentiality Laws and Secrecy in Medical Research: Improving Public Access to Data on Drug Safety*, 26 HEALTH AFF’S, no. 2, at 486

fallen on either side of the balancing test weighing the proprietary nature of information against the public interest in disclosure.⁶⁷ Regardless of the reasons for withholding such information, nondisclosure necessarily limits the public's access to the information upon which FDA advisory committee members base their decisions. The FDA has explained, "[i]nformation that will be considered by the advisory committee (i.e., the briefing package) is posted online prior to the meeting, with appropriate redaction of non-public information."⁶⁸

Mark Goldberger, a former director of a Center for Drug Evaluation and Research ("CDER") office, stated that "[g]enerally, FDA takes the advice of advisory committees."⁶⁹ Although the FDA is not required to explain the reasons for accepting or rejecting the vote of the advisory committee, it imposes upon itself the obligation to publicize the basis for any decision not to heed the advisory committee's recommendation.⁷⁰

The Act does shed light on the nature of advisory meetings, and perhaps most importantly, allows access to these meetings.⁷¹ However, its

(2007), available at <http://content.healthaffairs.org/content/26/2/483.full.pdf> ("[T]he FDA continued to limit release of submitted data, invoking the commercial-and-confidential-information provision in FOIA to oppose requests for unreleased information based on the prospect of substantial competitive harm.").

67. *Id.* See also *Teich v. Food & Drug Admin.*, 751 F. Supp. 243 (D.D.C. 1990) (holding that clinical mechanisms and data are not trade secrets and that release of information is in the public interest); *Pub. Citizen Health Research Grp. v. Food & Drug Admin.*, 185 F.3d 898 (D.C. Cir. 1999) (holding that data are not trade secrets, but may nonetheless be confidential); *Citizens Comm'n on Human Rights v. Food & Drug Admin.*, 1993 WL 1610471 (C.D. Cal. May 10, 1993), *aff'd in pertinent part*, 45 F.2d 1325 (9th Cir. 1995) (holding that data was a protected trade secret).

68. TRANSPARENCY TASK FORCE FDA, FDA TRANSPARENCY INITIATIVE: DRAFT PROPOSALS FOR PUBLIC COMMENT REGARDING DISCLOSURE POLICIES OF THE U.S. FOOD AND DRUG ADMINISTRATION 57 (2010) [hereinafter TRANSPARENCY TASK FORCE], available at <http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf>.

69. *FDA's Drug Review Process: Continued*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm> (last updated Apr. 25, 2014); see also Andrew Pollack, *Diet Drug Wins Panel's Approval*, N.Y. TIMES, May 11, 2012, at B1, available at <http://www.nytimes.com/2012/05/11/health/diet-drug-wins-approval-of-fda-advisers.html>; Lenzer & Epstein, *supra* note 3.

70. TRANSPARENCY TASK FORCE, *supra* note 68, at 57.

71. The Administrative Conference of the United States notes that despite the statute's commendable objectives,

its actual effect is to discourage collaborative deliberations at multi-member agencies, because agency members are reluctant to discuss tentative views in public . . . [A]gencies resort to escape devices, such as holding discussions among groups of fewer than a quorum of the agency's membership (which are not covered by the Act), communicating through staff, exchanging written messages, or deciding matters by 'notation voting' (i.e., circulating a proposal and having members vote in writing).

Government in the Sunshine Act, ADMIN. CONF. OF THE U.S. (ACUS.GOV), <http://www.acus.gov/research/the-conference-current-projects/government-in-the-sunshine-act/> (last visited Sept. 1, 2014).

exemptions, particularly the exemption allowing for other statutory exemptions, may undermine its effectiveness.⁷²

3. 18 U.S.C. § 208 (*Basic Criminal Conflict of Interest Statute*)

The Ethics Reform Act of 1989 amended 18 U.S.C. § 208, the basic criminal conflict of interest statute.⁷³ The statute, titled *Acts Affecting A Personal Financial Interest*, prohibits an employee of the executive branch (including special government employees, which encompasses advisory committee members) from participating in a government matter in which the member or anyone in the member's immediate family has a financial interest.⁷⁴

Section 208(b) allows for several exceptions. Thus, disclosure of a financial relationship with the very industry that has developed the product to be approved does not preclude an advisory committee member from sitting on the committee or even from voting; members may be granted waivers for participation in meetings pursuant to these exceptions.⁷⁵

Waivers are often granted because the need for the member's apparent expertise outweighs the potential damage his or her conflict of interest may cause. Waivers can be granted if the value of the financial interest is fully disclosed and the agency determines that "the interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such officer or employee."⁷⁶ A waiver need not be granted to allow participation if the financial interest is "too remote or too inconsequential to affect the integrity of the services of the Government officer."⁷⁷ Finally, specifically regarding advisory committee members, a waiver may be granted if the official responsible for appointing the advisor certifies in writing that "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved."⁷⁸ Finally, denial of a waiver under any provision in sub-section (b) does not preclude the granting of a waiver under another subsection.⁷⁹

72. In the Yaz/Yasmin incident, for example, the FDA and one of the implicated advisory committee members cited the confidentiality provisions of the Ethics in Government Act (5 U.S.C. Appx. 4 §§ 101-505) as a basis for withholding financial information. Lenzer & Epstein, *supra* note 3.

73. Pub. L. No. 101-194, 103 Stat. 1716 (1989).

74. 18 U.S.C. § 208(a) (2012).

75. *Id.* § 208(b).

76. *Id.* § 208(b)(1).

77. *Id.* § 208(b)(2).

78. *Id.* § 208(b)(3).

79. *Id.* § 208 (c)(2).

4. *Food and Drug Administration Amendments Act of 2007(FDAAA)*

The Food and Drug Administration Amendments Act of 2007 (“FDAAA”) amended the Food, Drug, and Cosmetic Act.⁸⁰ Title VII of the FDAAA controls conflicts of interest.⁸¹

Section (b) of the statute deals with recruitment. It states that the FDA Secretary shall

develop and implement strategies on effective outreach to potential members of advisory committees at . . . academic research centers, professional and medical societies, and patient and consumer groups; seek input from professional medical and scientific societies; [and] at least every 180 days, request referrals for potential members of advisory committees from a variety of stakeholders.⁸²

These “stakeholders” include product developers and patient groups, but not patient safety or consumer advocates. Perhaps surprisingly, recruitment activities may include advertising at medical and scientific conferences.⁸³ The Secretary is also obliged to ensure that he or she has “access to the most current expert advice.”⁸⁴

If a committee member is granted a waiver pursuant to 18 U.S.C. § 208(b)(1) or (b)(3), the Secretary shall disclose on the FDA website, no later than fifteen days prior to an advisory committee meeting:

the type, nature, and magnitude of the financial interests of the advisory committee member to which such determination or certification applies and . . . the reasons . . . for such determination or certification, including, as appropriate, the public health interest in having the expertise of the member with respect to the particular matter before the advisory committee.⁸⁵

The Secretary must also submit an annual report including the number of those disqualified from participation pursuant to 18 U.S.C. § 208.⁸⁶

At least once every five years, the Secretary must review FDA guidance with respect to the application of § 208 and update such

80. 21 U.S.C. § 301-399f (2012).

81. 21 U.S.C. § 379d-1 (2012).

82. *Id.* § 379d-1(b)(1).

83. *Id.* § 379d-1(b)(2).

84. *Id.* § 379d-1(b)(3).

85. *Id.* § 379d-1(c)(1).

86. *Id.* § 379d-1(e)(1)(a).

guidance “as necessary to ensure that [FDA] receives appropriate access to needed scientific expertise, with due consideration of the requirements of such section 208.”⁸⁷

Until July 9, 2012, in granting a waiver, the Secretary of the Department of Health and Human Services could allow the member to vote on the committee or sit on the committee as a non-voting member.⁸⁸ The Food and Drug Safety and Innovation Act (FDSIA), among other things, loosened these conflict of interest provisions.⁸⁹ The participation without voting option is completely dissolved. The current statute allows for waivers, but, perhaps sensibly, does not allow for the conclusion that a committee member’s conflict is too minor to preclude his presence and contribution to the meeting, but too significant to allow him to vote. Such an arrangement may suggest to other members, “this person is an expert, but her judgment may be clouded.” On the other hand, the deletion of the directive that “a member of an advisory committee may not participate . . . in an advisory committee meeting if such member . . . has a financial interest that could be affected by the advice given to the Secretary with respect to such matter”⁹⁰ suggests that the real intention of the deletion was to loosen the conflict of interest requirements. Indeed, the Union of Concerned Scientists has decried the FDSIA’s relaxing of conflict of interest requirements, arguing that with the \$700 million it spent on lobbying between 2009 and 2011, the drug industry had purchased undue influence on FDA advisory meetings.⁹¹ At the same time, the group expressed appreciation that the bill retained the disclosure requirement for advisors with conflicts.⁹²

The new statute also deleted a portion of the law requiring the percentage of committee members with waivers be reduced each year from 2008 to 2012.⁹³ The law used 2007 waivers as a base number, and allowed for 95% of this number to be granted in 2008, down to 75% of the 2007 base number in 2012.⁹⁴ This provision has since been struck (meaning that the FDA may grant as many waivers as it deems necessary), but the FDA

87. *Id.* § 379d-1(f)(1–2).

88. Pub. L. No. 110-85, Title VII, § 701(a), 121 Stat. 900 (repealed July 9, 2012).

89. Food and Drug Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012).

90. Pub. L. No. 110-85, Title VII, § 701(a), 121 Stat. 900 (repealed July 9, 2012).

91. Press Release, Union of Concerned Scientists, Industry-Driven FDA Bill a Missed Opportunity for Patients: While Some Provisions are Positive, Congress Emphasized Speed Over Safety in New Law (June 26, 2012), *archived at* https://web.archive.org/web/20120710111758/http://www.ucsusa.org/news/press_release/fda-bill-1370.html.

92. *Id.*

93. Pub. L. No. 110-85, Title VII § 701(c)(2)(c).

94. *Id.*

never came close to reaching the cap between 2010 and the cap's elimination in 2012.⁹⁵ In the first six months of 2013, the percentage of participating committee members granted waivers was zero for all but two months, and peaked in March at 2.8%.⁹⁶ This is fairly representative of the pattern since the FDA started publishing these data in 2010.⁹⁷ If this self-reporting is accurate, it appears that the FDA may subject itself to stricter rules than those Congress loosened for it in 2012.

5. *FDA Guidelines*

The language of the waiver statutes is ambiguous, and no statute specifies criteria that the Secretary should use in deciding whether to allow a committee member to vote. As a result, the FDA issued guidelines in 2008.⁹⁸ The document states: "This unified, simpler approach will improve consistency within the agency in considering advisory committee participation and will provide greater clarity to the public regarding how FDA selects members."⁹⁹ Notably, nowhere does the document suggest that allowing committee members with financial interests to make committee decisions compromises the integrity of the FDA's advisory committees. The focus of the guidelines appears more on appeasing the public with transparency regarding conflicts of interest than attempting to eliminate them.¹⁰⁰

95. *Percent of Advisory Committee Members Participating in Meetings in the Month Who Were Granted Waivers*, FDA.GOV, <http://www.accessdata.fda.gov/FDA/track/track?program=advisory-committees&id=AdvComm-waivers> (last updated Mar. 31, 2014) [hereinafter *Percent Granted Waivers*].

96. *Id.*

97. *Id.*

98. See GUIDANCE FOR THE PUBLIC, *supra* note 37.

99. *Id.* at 6–7.

100. However, the FDA has traditionally protected the privacy interests of industry and has stated that only "rarely" would the public interest require disclosure of financial information. See FDA, GUIDANCE FOR CLINICAL INVESTIGATORS, INDUSTRY, AND FDA STAFF: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS 23 (2011), archived at <https://web.archive.org/web/20121126053826/http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM256525.pdf>.

In the 2011 guidelines for investigators and industry, the FDA appeared to change its stance somewhat, possibly in the wake of public criticism. The guidelines stated that the FDA

is striving to achieve a proper balance between transparency and the right to privacy of clinical investigators with respect to their financial arrangements as expressed in the agency's protection of privacy regulation (21 C.F.R. pt. 21). The agency is considering various options for disclosure, such as [disclosing financial information] upon product approval for marketing.

Id. at 24. For whatever reason, this language and any notion of the need to balance consumers' interest in financial transparency with industry's interest in privacy was omitted from the 2013 guidelines. See FDA, GUIDANCE FOR CLINICAL INVESTIGATORS, INDUSTRY, AND FDA STAFF: FINANCIAL

The waiver guidelines profess to be stricter than the previous guidelines released in 2000.¹⁰¹ For example, the guidelines state:

Although 18 U.S.C. 208(b)(3) authorizes the agency to grant a waiver to [a special government employee (“SGE”)] where a balancing test is met—“the need for the individual’s services outweighs the potential for a conflict of interest created by the financial interest involved”—FDA will also apply to all waivers for SGEs the generally stricter standard established by section 712 (c)(2)(B) of the Act, requiring a showing that the waiver “is necessary to afford the committee essential expertise.”¹⁰²

The new guidelines consist of ten steps to follow when determining whether to grant a waiver. The first five steps are mostly formalities, and the last five delve into the significance of the conflict and whether the conflict is “likely to affect the integrity of the services provided by that individual.”¹⁰³ These guidelines appear to solidify the waiver rules

DISCLOSURE BY CLINICAL INVESTIGATORS (2013), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>. Perhaps the FDA believes it has successfully struck the correct balance, or perhaps the FDA feels it need not re-fuel a dying fire with any discussion of “balancing” interests as long as the public is not complaining about the status quo.

101. GUIDANCE FOR THE PUBLIC, *supra* note 37, at 7.

102. *Id.*

103. *Id.* The steps are:

Step 1—Is the Subject Matter of the Meeting a “Particular Matter?” . . .

Step 2—Will the particular matter have a direct and predictable effect on the financial interest(s) of any organization? . . .

Step 3—Identify Potentially Affected Products/Organizations and Request that the Employee Complete the Financial Disclosure Form. . . .

Step 4—Does the employee, or [those] whose interests are imputed to him, have a financial interest in [the] potentially affected products and/or organizations? . . .

Step 5—Will the Particular Matter Have a Direct and Predictable Effect on the Financial Interest of the Employee and/or [those] Whose Interests are Imputed to Him? . . .

Step 6—After Applying Applicable Regulatory Exemptions, Does the Employee or Persons/Organizations Whose Interests are Imputed to Him Have a Disqualifying Financial Interest? . . .

Step 7—Are There Disqualifying Financial Interests For Which a Waiver Would Not Be Considered? . . .

Step 8—Is the Combined Value of the Employee’s Personal Disqualifying Financial Interests and Those of His Spouse and Minor Children \$50,000 or Less? . . .

Step 9—Is the Individual’s Participation Necessary to Afford the Advisory Committee Essential Expertise? . . .

Step 10(a)—If the Individual is a Special Government Employee, Does the Need for the Individual’s Services Outweigh the Potential for a Conflict of Interest Created by the Financial Interest Involved? . . .

codified in 18 U.S.C. § 208. They create a single linear path by which waivers may be granted, and would seem to preclude many conflicted committee members from participating on advisory boards.¹⁰⁴

In sum, those with financial ties to the applicant for approval of a new drug or device must disclose this fact, and the FDA has significant discretion in choosing whether to waive the prohibition from the individual participating in the advisory committee meetings reviewing the product. The vast majority of its limitations are self-imposed. The next Section will address how the guidelines are actually implemented, the prevalence of conflicts and waivers, and how financial relationships affect market approval for drugs and devices.

Step 10(b)—If the Individual is a Regular Government Employee, Is the Financial Interest Not So Substantial as to be Deemed Likely to Affect the Integrity of the Services Provided by that Individual? . . .

Step 11—Waiver May Be Recommended If Consistent With Waiver Cap.

Id. at 8–23. In 2012, the waiver cap was eliminated. An example of an issue that is not “a particular matter” may be a committee member training session on practices and procedures. If the issue is not a particular matter, all members may participate. If it is, the analysis proceeds to Step 2.

Step 6 is really where the waivers in 18 U.S.C. § 208 are implicated. The waiver guidelines up to this point are not more stringent; they are more linear (if more tedious). They have not weeded out any committee members through Step 5. At Step 6, staff members are instructed to consider exemptions listed in 5 C.F.R. 2640.202, such as relevant mutual funds, employee benefit plans, investment trusts, etcetera. Regarding Step 7, a waiver would not be granted to a special government employee who is the principal investigator of the particular matter to be discussed and is receiving or will receive compensation from its sponsor. *Id.* at 16.

Finally, Congress has eliminated the waiver cap since the issuance of these guidelines.

104. The Code of Federal Regulations also provides guidelines for granting waivers pursuant to section 208. 5 C.F.R. § 2635.401 states in part:

Notwithstanding that his acquisition or holding of a particular interest is proper, an employee is prohibited in accordance with § 2635.402 of this subpart from participating in an official capacity in any particular matter in which, to his knowledge, he or any person whose interests are imputed to him has a financial interest, *if the particular matter will have a direct and predictable effect on that interest.*

5 C.F.R. § 2635.401 (1997) (emphasis added). The final qualifier weakens the strength of the guidance, and opens the door to overlooking financial conflict justified by the fact that the particular matter may not have a “direct and predictable effect” on the committee member’s “interest.”

The statute provides a relevant example of a direct and predictable affect: A special government employee (“SGE”) whose principal employment is as a researcher at a university is appointed to serve on an advisory committee that has been convened to conduct a preliminary evaluation of the new kidney dialysis device developed by Alpha Medical under contract with the employee’s university. Alpha’s contract with the university requires the university to undertake additional testing of the device to address issues raised by the committee during its review. The committee’s actions will have a direct and predictable effect on the university’s financial interest.

Id.

6. *Practical Effect of the Rules: Pervasiveness of Committee Members with Waivers and Outcome-Determinative Votes by Waiver Grantees*

The financial disclosure requirements may appear sufficient to safeguard against advisory committee members voting with their own financial self-interest—rather than the public interest—in mind, and the FDA repeatedly and fervently argues that they do.¹⁰⁵ For example, in 1991, the Inspector General of the Department of Health and Human Services submitted a management advisory report to the FDA discussing its failures regarding financial conflict of interest.¹⁰⁶ The absence of a mechanism for collecting data on these conflicts among clinical investigators studying products undergoing FDA review, he argued, could constitute a “material weakness” under the Federal Managers’ Financial Integrity Act.¹⁰⁷ The FDA ultimately created financial disclosure rules but denied any “material weakness.”¹⁰⁸

FDA spokesperson Morgan Liscinsky stated that the waiver rate has stayed below 5% in recent years.¹⁰⁹ 85% of waivers received were granted under 18 U.S.C. § 208(b)(3) (allowing a waiver when the potential for conflict of interest is outweighed by the need for the individual’s services).¹¹⁰

A study by Dr. Peter Lurie found that of 221 meetings held by sixteen advisory committees, 73% contained at least one financial conflict of interest, and only 1% of advisory committee members were recused.¹¹¹ For

105. See, e.g., FDA, FINANCIAL DISCLOSURES BY CLINICAL INVESTIGATORS (1998) (codified at 21 C.F.R. § 54), available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119145.htm>; FDA, Comment on “Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings,” FDA.GOV (July 24, 2006), <http://www.fda.gov/oc/advisory/analysis.html> (attempting to discredit the conclusions of Peter Lurie et al., *Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 J. AM. MED. ASS’N 16 (2006), available at <http://jama.jamanetwork.com/article.aspx?articleid=202754#qundefined>). Dr. Lurie’s study is a statistical analysis of the voting patterns of FDA committee members based on their financial ties to the products they voted to approve.

106. FINANCIAL DISCLOSURES BY CLINICAL INVESTIGATORS, *supra* note 105.

107. *Id.* The Federal Managers’ Financial Integrity Act (“FMFIA”) requires federal agencies to submit an annual report on their internal control systems to protect against waste, abuse, and mismanagement, including any “material weakness.” Pub. L. No. 97-255, 96 Stat. 814 (1982) (codified at 31 U.S.C. § 3512 (2012)).

108. FINANCIAL DISCLOSURES BY CLINICAL INVESTIGATORS, *supra* note 105.

109. Alex Philippidis, *FDA Backtracks on Conflict-of-Interest Rule Changes for Advisory Panel Members*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Mar. 5, 2012), <http://www.genengnews.com/keywordsandtools/print/3/26290/>.

110. ACKERLEY ET AL., *supra* note 29.

111. See Lurie et al., *supra* note 105. See also ACKERLEY ET AL., *supra* note 29 (measuring

advisory committee members and voting consultants combined, 38% had a financial conflict of interest.¹¹² Another independent study found that the median total dollar value of financial interest for members with waivers was \$14,500.¹¹³ The study found no relationship between measures of expertise and the total dollar value of the financial conflict; those with waivers tend to have higher levels of expertise than those who do not.¹¹⁴ Importantly, Lurie et al. also found that, despite these prevalent conflicts, “excluding advisory committee members and voting consultants with conflicts would not have altered the overall vote outcome at any meeting studied.”¹¹⁵

However, even a waiver-free committee does not necessarily mean it is conflict-free. The FDA subjects disclosures to fairly rigorous scrutiny, but it considers a member conflicted, and therefore subject to scrutiny, only if the member’s conflict of interest occurred within the preceding twelve months.¹¹⁶ This is significantly lower than the conventional requirement for disclosure for scientific institutions and journals.¹¹⁷ This is what happened in the Bayer scandal; the members with financial ties to Bayer were deemed not to be conflicted because the transactions in question had occurred over a year prior to the committee meetings. Furthermore, conflicts are self-reported through disclosures; though the penalties for failing to disclose required information is fairly steep,¹¹⁸ such failures have occurred without penalty¹¹⁹ and it is not implausible that they still do.

conflict of interest on FDA advisory committees, expertise, and whether expertise can be maintained without members with conflicts of interest).

112. Lurie et al., *supra* note 105.

113. See ACKERLEY ET AL., *supra* note 29, at 4–1.

114. Lurie et al., *supra* note 105.

115. *Id.*

116. Susan F. Wood & Jillian K. Mador, *Uncapping Conflict of Interest?*, 340 SCIENCE, no. 6137, at 1172 (2013); see also GoozNews (Merrill Goozner), Response Comment to *A Theory on Why The FDA Hid Conflicts of Interest*, GOOZNEWS (Jan. 16, 2012, 8:48 PM), <http://gooznews.com/?p=3521> (“I read [Ackerley et al.’s 2007] study closely. It found, based on published articles in the medical literature, that there were sufficient non-conflicted expertise available to staff FDA advisory committees, but that it would take extra work by the agency to identify and recruit them. In the last few years, the FDA has appointed far fewer conflicted scientists to its ACs than it did a decade ago. Why wasn’t that extra work put in [in the Yaz/Yasmin] case? [The] agency concluded that the conflicts were more than a year old and therefore did not requiring “waiving” or disclosing. However, when I specifically asked the agency about that, its p.r. spokeswoman dodged the question.”).

117. Wood & Mador, *supra* note 116, at 1172.

118. 18 U.S.C. § 216 (2012). See Janice Hopkins Tanne, *Former FDA Head Is Fined \$90 000 for Failing to Disclose Conflicts of Interest*, 334 BRIT. MED. J., no. 7592, at 492 (2007).

119. See Letter from Anne Milgram, Attorney Gen. for the State of N.J., to Joshua M. Sharfstein, M.D., Acting Comm’r of the FDA (May 5, 2009), available at <http://www.nj.gov/oag/news/releases09/050509-FDA-letter.pdf> (“[D]espite the fact that Synthes’ failure to adequately disclose these interests should have been obvious from even a cursory review of its FDA submissions, the FDA

Finally, the FDA is free to waive conflicts it considers de minimis and thus not likely to affect a committee member's vote. Unfortunately, as intricate as FDA guidelines are, there is no set standard for what amount or percentage of net worth constitutes more than de minimis.¹²⁰

This Note does not suggest that conflicts of interest are frequently outcome determinative.¹²¹ It acknowledges to a small degree the legitimacy of the shared pool dilemma, and the tension between the public interest in approving a drug for the market in a timely manner and in meticulously scanning every committee member's finances for evidence of bias. Rather, this Note suggests that the consequences of the few instances when the public has been harmed by a drug approved by a committee with one or more members with conflicts of interest are significant enough to warrant a more thorough examination of the factors weighed when determining the necessity that a person with financial interests in the drug to be reviewed contribute to the decision to approve it.

This opinion is far from unanimous, and the next Part examines and critiques the arguments that the public is better served not by tightening FDA conflict of interest laws, but by loosening them.

III. CONFLICT OF INTEREST LAWS HARM PATIENTS, INDUSTRY, AND THE APPROVAL PROCESS

Three main arguments have been set forth for loosening FDA conflict of interest laws. First, some feel that the restrictions of current laws do not serve the public because they delay patients' access to treatment, particularly when patients have no viable alternative.¹²² Second, the burdens the current restrictions impose on the medical and pharmaceutical industries may hinder these industries' competitiveness in a global market,

did nothing to regulate these conflicts. A number of the disclosure forms were signed and dated, but were otherwise left blank. Others indicated that the clinical investigator had a significant equity interest in the product, but did not attach the requisite details. But the FDA approved Synthes' applications for premarket approval without any delay or further inquiry into this issue.”)

120. 18 U.S.C. § 208(b)(2) (2012); Goozner, *supra* note 116.

121. The evidence suggests that such financial conflicts have no statistically measurable effect on the outcome. Goozner, *supra* note 116. However, this does not mean conflicts are not playing a role in some decision-making, and when drugs are approved and ultimately end up harming the public, a conflicted panel was often behind the decision to approve the product. *See, e.g., 10 On FDA Vioxx Panel Had Ties To Companies*, MSNBC.COM (Feb. 25, 2005, 6:14 PM), <http://www.msnbc.msn.com/id/7031927/ns/health-arthritis/t/fda-vioxx-panel-had-ties-companies/#.UPslzyer-So>.

122. Epstein, *supra* note 32.

where competitors do not face similar restrictions.¹²³ Finally, Sharon Jacobs argues practically that the FDAAA, including its conflict of interest provisions, was reactionary legislation in response to the Vioxx scandal¹²⁴ and that its primary effect is little more than unnecessary red tape overburdening an already resource-strained agency.¹²⁵ I will discuss each of these arguments in turn.

A. *Delaying Access to Treatment is Harmful to Patients*

In January 2013, an online petition circulated on Change.org urging the FDA to approve a drug for Duchenne Muscular Dystrophy.¹²⁶ The author is Jenn McNary, the mother of two sons, both of whom have the disease, but only one son was enrolled in a clinical trial of the drug treatment.¹²⁷ McNary wrote that her son being treated has improved to the point that he no longer needs a wheelchair, but her other son is steadily worsening, and will need a tracheotomy and a feeding tube if he does not receive the drug treatment soon.¹²⁸ Every day, she watches the life-saving potential of earlier access to treatment and the devastating consequences of delay.

McNary is not alone in her position. Though she does not address the reasons for a slow approval process, other patient groups point specifically at conflict of interest regulations as an unnecessary and harmful component of the approval process. On October 26, 2011, dozens of patient groups submitted a letter to Senators Tom Harkin and Michael

123. Matthew Herper, *The Truly Staggering Cost Of Inventing New Drugs*, FORBES (Feb. 10, 2012, 7:41 AM), <http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/>.

124. Discussed *infra* Part III.

125. This much, at least, is true. Senator Ted Kennedy claimed that “the FDA gold standard” had been tarnished by the scandal. David Graham, Associate Director for Science and Medicine in the FDA’s Office of Drug Safety, stated that “today in 2004, we’re faced with what may be the single greatest drug safety catastrophe in the history of this country.” Sharon B. Jacobs, *Crises, Congress, and Cognitive Biases: A Critical Examination of Food and Drug Legislation in the United States*, 64 FOOD & DRUG L.J. 599, 615 (2009) (citing *The FDA, Merck and Vioxx: Putting Patient Safety First: Hearing Before the S. Fin. Comm.*, 108th Cong. 14 (2004) (testimony of David Graham)).

126. Jenn McNary, *FDA: Please, Approve The Medicine My Boys Need To Survive—Both Of My Sons Deserve To Live*, CHANGE.ORG, <http://www.change.org/petitions/fda-please-approve-the-medicine-my-boys-need-to-survive-both-of-my-sons-deserve-to-live> (last visited Sept. 1, 2014). Change.org is an online petition platform that boasts of over twenty million users in 196 countries. <http://www.change.org/about> (last visited Sept. 1, 2014).

Duchenne Muscular Dystrophy is a type of muscular dystrophy that expresses itself only in males and progresses much more rapidly than most other types of muscular dystrophy. *Duchenne Muscular Dystrophy*, PUBMED HEALTH, <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001724/> (last updated Feb. 3, 2014).

127. McNary, *supra* note 126.

128. *Id.*

Enzi, Chairman and Ranking Member of the Senate Committee on Health, Education, Labor and Pensions, pleading with them to loosen the conflict of interest laws to which advisory committee members are subject.¹²⁹ The letter explains, “our organizations promote efforts to bring better treatments and cures to those struggling with diseases. Many of these conditions have no adequate treatments and, therefore, it is imperative that we challenge hurdles that impede the quality and efficiency of the treatment development process.”¹³⁰ 18 U.S.C. § 208(b)(3), again, provides a waiver for when the need for an individual’s services outweighs the potential for a conflict of interest. The letter explains that this exception is reasonable, balanced, and “recognizes that some potential SGE’s may come to the FDA with ties . . . that may pose some conflict of interest, but that the primary issue must be the government’s need for their services.”¹³¹ Law professor Richard Epstein states that complaints like these “have come primarily from patients groups representing the users and consumers of pharmaceutical products, for whom new drugs and devices often spell the difference between life and death,” not from industry.¹³²

Janet Woodcock, the director of the FDA’s drug center, also expresses concern about the procedural burdens of conflict of interest laws. She testified that the restrictions have slowed the advisory committee process, and that sometimes the FDA will discover a tie to a pharmaceutical company only at the end of a long process of searching for experts,¹³³ and then the agency is forced to start anew.¹³⁴ Marc Boutin, executive vice

129. Letter to Senators Tom Harkin and Michael Enzi, Members of the Cong. Comm. on Health, Educ., Labor, & Pensions (Oct. 26, 2011), *available at* http://www.rarediseases.org/docs/policy/HELPLetter_102011Senate.pdf.

130. *Id.*

131. *Id.*

132. Epstein, *supra* note 32.

133. This is curious given that potential committee members are legally required to disclose these ties themselves.

134. PDUFA Hearing, *supra* note 35. Janet Woodcock, one should note, is not free from accusations of conflict influencing her decisions. In 2009, Amphastar Pharmaceuticals Inc., complained that it had been delayed in a “six-year effort to win approval for a generic version of Lovenox, a multi-billion-dollar blood thinner.” Alicia Mundy, *Drug Chief at the FDA Is Accused Of Conflict*, WALL ST. J. (Aug. 12, 2009, 11:59 PM), <http://online.wsj.com/article/SB125003545637224263.html>. “Dr. Woodcock co-authored a scientific paper with scientists at Momenta Pharmaceuticals Inc.,” a competitor pharmaceutical company, “while both companies were battling to win FDA approval of their generic blood thinners.” *Id.* The article identified the cause of over 100 deaths due to a Chinese-imported heparin; Momenta’s stock jumped 17% in a single day. Amphastar pointed to emails between Woodcock and one of Momenta’s founders and a medical conference the two attended together in Thailand in 2007. *Id.* Dr. Woodcock at first refused to recuse herself from the approval decisions of both companies’ drugs, but later did, after which the FDA determined that no conflict of interest existed. Ed Silverman, *No Conflict of Interest For FDA’s Woodcock*, PHARMALOT (Feb. 5, 2010, 8:00 AM), *archived at* <https://web.archive.org/web/20110724045252/http://www>.

president of the National Health Council, testified that the organization is “deeply concerned that the challenges in identifying experts for advisory committees are leading to delays in patient access to new treatments.”¹³⁵ He notes that the FDA itself wrote that “optimal representation is often difficult to achieve given the strict conflict-of-interest regulations that apply”¹³⁶ Boutin and other advocates for less burdensome regulations argue that many patients’ needs for currently unavailable treatments outweighs the need for an advisory committee to be absolutely dissociated from the product it evaluates.¹³⁷

The harm to patients caused by the delay in market approval is obvious with respect to access to treatment, but Thomas Philipson and Eric Sun argue that such delays have economic costs to patients as well.¹³⁸ These costs reach the patients in two major ways. First, lack of access to the most effective treatment may result in lost wages due to absenteeism (or sometimes, death).¹³⁹ The second way is more indirect; Philipson and Sun contend that shorter trial phases and speedier reviews will save trial sponsors money, which will help underwrite the costs of producing and marketing the next generation’s drugs.¹⁴⁰ They estimated the effects of

pharmalot.com/2010/02/no-conflict-of-interest-for-fdas-woodcock/ (blog no longer active, original text on file with author).

135. Testimony of Marc Boutin, Exec. Vice President & Chief Operating Officer, Nat’l Health Council Before the House Energy and Commerce Subcomm. on Health: PDUFA V: Medical Innovations, Jobs, and Patients, at 8 (July 7, 2011), *available at* http://democrats.energycommerce.house.gov/sites/default/files/image_uploads/Testimony_HE_07.07.11_Boutin.pdf.

136. *Id.* at 9.

137. *Id.* Boutin in his testimony advocated for the fifth reauthorization of the Prescription Drug Fee User Act (“PDUFA”), which allows drug manufacturers to pay the FDA a fee in exchange for an expedited approval process. The President signed this Act into law on July 9, 2012 as part of the Food and Drug Safety and Innovation Act. *PDUFA V: Fiscal Years 2013–2017*, FDA.Gov <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> (last updated Dec. 26, 2013).

138. THOMAS J. PHILIPSON & ERIC SUN, COST OF CAUTION: THE IMPACT ON PATIENTS OF DELAYED DRUG APPROVALS, MANHATTAN INST. FOR POL’Y RES. (2010), *available at* http://www.manhattan-institute.org/pdf/fda_02.pdf.

139. *Id.* at 4–5.

140. *Id.* at 2. In general, a drug must be tried in three “phases” before the FDA will approve it for market use and one postmarket phase. Phase I is the first time a drug is administered to a human being. Phase I studies are meant to determine the safety of a drug, how it is metabolized and excreted, and safe dosage. They do not measure effectiveness. They generally consist of twenty to eighty subjects, usually healthy volunteers, and drugs are administered at sub-therapeutic levels. A drug will proceed beyond Phase I only if Phase I studies do not reveal “unacceptable toxicity.” Phase II studies measure effectiveness and continue to identify safety issues. Drugs are administered at therapeutic levels against a control group; the number of subjects usually ranges from a few dozen to 300. In Phase III, treatment is given to more subjects (1000–3000) to confirm the drug’s effectiveness, monitor side effects, and compare it to currently available treatments. At this point the FDA may approve the drug, require more testing, or reject it. Phase IV, the final phase, is primarily a polishing phase; postmarketing studies obtain additional information, such as the treatment’s risks, benefits, and

releasing three drugs to patients one and three years earlier. For example, a year's earlier access to a certain antiretroviral treatment for patients with AIDS would be worth \$16,000.¹⁴¹ The value of three years' earlier access would be \$46,000. For the entire cohort of patients with AIDS that would seek such treatment, "the value of one year's earlier access would be \$19 billion. The value of three years' earlier access would be \$53 billion."¹⁴² Philipson and Sun note that while certainly drug companies also benefit from speedier market approval, the benefit is not as great as that which patients would receive, either proportionally or in absolute terms.¹⁴³ They quantify the arguments of other proponents of a more streamlined review process, and affirm the idea that patients' interests, in terms of quality and quantity of life as well as economics, lie in faster market approval.¹⁴⁴

B. Delaying Market Approval Hinders Economic Competitiveness

While the FDA's mission statement with respect to drugs is simply to ensure their safety and effectiveness,¹⁴⁵ others, including many in Congress, consider the FDA's mission much more sweeping. These

optimal use. *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA.GOV, <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last updated May 28, 2014). Phase 0 trials now exist as well, created in response to the FDA's Investigational New Drug ("IND") guidance. Phase 0 Trials are non-therapeutic and are meant as a weed-out process of unsafe or clearly ineffective drugs, administered for brief durations and at sub-therapeutic levels. They are not widely utilized at this point. Shivaani Kummur et al., *Phase 0 Clinical Trials: Conceptions and Misconceptions*, 14 *CANCER J.*, no. 3, at 133–37 (2008).

141. PHILIPSON & SUN, *supra* note 138, at 5.

142. *Id.*

143. They also thoroughly stress the study's limitations. They focused on three drugs widely known to be safe and highly effective, while of course drugs being tested for market approval may still be marked by precarious unknowns. In other words, the risk-benefit analysis yields favorable results when the risks are low and the benefits are high. These variables are far less certain for drugs still being tested in clinical trials, and that is precisely the point of clinical trials followed by a thorough review process.

144. Concededly, Philipson and Sun do not discuss conflicts of interest in the approval process as a cause for delay in approval. Clinical trials, which can last up to twelve years, and the scarcity of trial subjects certainly hinder access to treatment more than the delay caused by determining an acceptable panel of experts. That said, the authors' ultimate point—that delays in the approval process hinders patients' much-needed access to treatment—is perfectly consistent with and supports the argument for loosening conflict-of-interest regulation on the same justification. Moreover, Philipson and Sun's study was part of the Manhattan Institute's *Project FDA*, and the program's mission statement specifically mentions conflict rules as one of the burdens of FDA effectiveness. PHILIPSON & SUN, *supra* note 138, at 18 ("Unfortunately, in our zeal to reduce risks, regulate potential conflicts, and mandate transparency, we may reduce incentives for companies to develop and market improved products . . . ; inhibit doctors from collaborating with companies in designing safer and more effective products; and slow the FDA's efforts to bring its oversight activities into conformity with the latest scientific and technical advances.").

145. 21 U.S.C. § 393(b)(2)(B) (2012).

advocates for less stringent regulation also argue that FDA conflict of interest laws render the United States less competitive in medical and pharmaceutical industries.¹⁴⁶

Colorado U.S. Senator Michael Bennet wrote to FDA commissioner Margaret Hamburg expressing a desire to reform FDA regulations to put the FDA in a position to foster innovation and “serve as a driver of the global economy.”¹⁴⁷ “I believe we have an opportunity to do good things for patients and a critical sector of the U.S. economy,” Bennet wrote.¹⁴⁸ In 2011, Bennet, along with Amy Klobuchar (D-MN) and Richard Burr (R-NC), cosponsored the Medical Device Regulatory Improvement Act in 2011, which would “restore the appropriate balance to conflicts of interest requirements by requiring the FDA [medical device committees] to be subject to the same conflicts of interest requirements as the rest of the federal government.”¹⁴⁹ This sentiment suggests a much bolder purpose for the FDA, specifically that it should actively facilitate growth of the U.S. and global economy, rather than merely ensure that food and drugs are safe and effective. In other words, the FDA should be concerned for the economic interests of drug and device manufacturers.

The cost of inventing a drug and getting it approved for market use is disputed, but advocates for a faster approval time estimate that it is extremely and unnecessarily costly.¹⁵⁰ Matthew Herper asserts that the average cost of developing a drug is \$4 billion and can reach up to \$11 billion.¹⁵¹ He clarifies that the more commonly used figure, \$1 billion to

146. See, e.g., Thomas Sullivan, *Medical Device Regulatory Improvement Act Introduced: Senators Call for Reducing Arbitrary Conflict of Interest Quotas on FDA Panels*, POL’Y & MED. (Oct. 14, 2011, 12:12 PM), <http://www.policymed.com/2011/10/medical-device-regulatory-improvement-act-introduced-senators-call-for-reducing-arbitrary-conflict-o.html>.

147. Press Release, Michael F. Bennet, Bennet Urges FDA to Work to Foster Innovation, Drive Global Economy (Aug. 18, 2011), <http://www.bennet.senate.gov/newsroom/press/release/?id=388b128b-7cab-40d6-8124-c527dca0d055> (full text of letter within Press Release).

148. *Id.*

149. Sullivan, *supra* note 146; S. 1700, 112th Cong. § 3 (2011), available at <http://www.gpo.gov/fdsys/pkg/BILLS-112s1700is/pdf/BILLS-112s1700is.pdf>. The bill has been referred to the Committee on Health, Education, Labor, and Pensions. *S.1700—Medical Device Regulatory Improvement Act*, CONGRESS.GOV, <http://beta.congress.gov/bill/112th-congress/senate-bill/1700/actions> (last visited Sept. 25, 2014).

Ed Silverman, reporting on the bill for Pharamlot (a healthcare regulation blog that has since been deleted), points out that Senator Klobuchar received campaign donations from Medtronic, and Senator Burr received contributions from multiple drug and device manufacturers, including Pfizer, Merck, GlaxoSmithKline and Medtronic. Ed Silverman, *What Vacancies? FDA Conflict Rules & Advisory Panels*, PHARMALOT (Nov. 30, 2011, 8:23 AM), archived at <https://web.archive.org/web/2011103191406/http://www.pharmalot.com/2011/11/what-vacancies-fda-conflict-rules-advisory-panels/> (blog no longer active, original text on file with author).

150. Herper, *supra* note 123.

151. *Id.*

\$1.3 billion, is the cost of bringing the particular drug to market, but his figure is a more accurate representation of pharmaceutical companies' costs because it accounts for the fact that most drugs developed are not approved, and that "\$4 billion in research dollars spent for every drug that is approved."¹⁵² For those who feel that the FDA should consider the interests of the industry and the U.S. economy, relaxing conflict of interest rules—assuming, as these individuals like Mr. Epstein do, that such relaxation would not result in a detriment to patient safety—only makes sense.

C. Conflict Regulation Unnecessarily Burdens the FDA, Which Harms Industry and Patients

Diane Dorman, the Vice President for Public Policy of the National Organization for Rare Disorders, explained that current FDA conflict of interest laws "have resulted in a system that is out of balance to the point that conflict avoidance is the primary driver of who serves on Advisory Committees, regardless of the extent of the conflict, the uniqueness of their expertise, or the government's need for their services."¹⁵³ Michael Boutin has stated that "efforts to maintain the public's trust may now be superseding the need to secure necessary expertise to the detriment of the advisory committee process as a whole."¹⁵⁴ He also contends that "late recusals from an advisory committee due to a conflict of interest have led to a meeting cancellation and a delay in the FDA's approval of the application."¹⁵⁵

The more resources the FDA expends on a single drug or approval process, the less it has to spend on other tasks. In 2011, Congress increased FDA funding by nearly 3% to a mere \$3.8 billion per year.¹⁵⁶ Many argue the FDA could carry out its mission more effectively with less unnecessary red tape.¹⁵⁷ When the FDA's already limited resources are

152. *Id.*

153. Testimony of Diane Edquist Dorman, Vice President, Public Policy, National Organization for Rare Disorders ("NORD") Before the U.S. House of Representatives Comm. on Energy & Commerce Subcomm. on Health (Feb. 1, 2012), *available at* http://democrats.energycommerce.house.gov/sites/default/files/image_uploads/Testimony_HE_02.01.12_Dorman.pdf.

154. Boutin, *supra* note 135, at 7.

155. *Id.* at 8.

156. Dina ElBoghdady, *FDA Funding Boosted Through Lobbying Effort*, WASH. POST (Nov. 30, 2011), http://www.washingtonpost.com/business/economy/fda-funding-boosted-through-lobbying-effort/2011/11/23/gIQAXHQ6CO_story.html. In light of the fact that the FDA regulates 25% of every dollar spent in the United States, \$3.8 billion seems unreasonably small. Harris, *supra* note 16.

157. *See, e.g., Barton Urges FDA To Cut Red Tape That Hurts Health Care And Stifles Innovation*, PHARMACY CHOICE (July 20, 2011), <http://www.pharmacychoice.com/news/article>.

strained, delays in the approval process “at times creates acrimonious litigation between the FDA and innovators, not to mention disillusionment among desperate patients.”¹⁵⁸

Epstein echoes these sentiments in more colorful, even accusatory language: “current FDA conflict of interest rules regard doctors and scientists with any financial connections with drug and device manufacturers as corrupt skills, who should be banished from its sacred precincts.”¹⁵⁹ He implies that the current regulations are insulting to healthcare professionals and states that “[a]ny conflict of interest rule must . . . preserve the FDA’s broad access to a large pool of the most qualified scientists. Disqualification should be done on a case by case basis, upon proof of specific concerns, not by broad decrees.”¹⁶⁰

Former FDA commissioner Andrew von Eschenbach and law professor Ralph Hall also blame FDA inefficiencies on “a decades-old regulatory process that is outmoded and needlessly long.”¹⁶¹ They detail three areas

cfm?Article_ID=754627. Representative Joe Barton (R-Ennis/Arlington), Chairman Emeritus and senior Republican on the Energy and Commerce Committee, stated that “[r]egulations have consequences and the benefits should outweigh the costs. This hearing exposes the problems associated with unnecessary red-tape and it is time the leadership at the FDA did something to fix it. If they are unwilling to do so, they should be replaced.” *Id.*

Representative Barton’s comments are curious given that Congress has at least as much power to correct over-regulation as the agency. Moreover, many feel that the FDA is critically underfunded. A former commissioner of the FDA explains, “Congress has starved the agency of critical funding, limiting its scientists’ ability to keep up with peers in private industry and academia.” Andrew von Eschenbach, *Toward a 21st-Century FDA*, WALL ST. J. (Apr. 15, 2012, 6:15 PM), <http://online.wsj.com/article/SB10001424052702303815404577331673917964962.html> (subscription required). One of the results, von Eschenbach explains, is a slower drug and device approval process. *Id.* Notably, Representative Barton voted against increasing funding to the FDA. *HR 2112—Appropriations for Agriculture, Rural Development, and the Food and Drug Administration—Key Vote*, PROJECT VOTE SMART, http://votesmart.org/bill/13994/37381/27082/appropriations-for-agriculture-rural-development-and-the-food-and-drug-administration#.UPHHXG_NaSp (last visited Sept. 25, 2014).

158. Von Eschenbach, *supra* note 157.

159. Epstein, *supra* note 32.

160. *Id.* A strong argument could be made that a bright-line rule lends itself to abuse less than granting waivers at the discretion of a committee or administrator, but Epstein’s point is that committee members do not abuse their positions.

161. Andrew von Eschenbach & Ralph Hall, *FDA Approvals Are a Matter of Life and Death*, WALL ST. J. (June 17, 2012, 7:13 PM), <http://online.wsj.com/article/SB10001424052702303753904577454163076760768.html> (subscription required). The authors also suggest that the FDA’s approval process is tedious and lags behind federal drug agencies in Europe and Canada. This once widely-held belief has been heavily contested and arguably debunked. *See, e.g.*, Karen N. Peart, *In Drug-Approval Race, U.S. FDA Ahead of Canada, Europe*, YALE NEWS (May 16, 2012), <http://news.yale.edu/2012/05/16/drug-approval-race-us-fda-ahead-canada-europe>. The median time between submission and approval was 322 days at the FDA, 366 days at the European Medicines Agency, and 409 days at Health Canada. Joseph Ross, an author of the study, discusses the study and its implications in *More Proof FDA is Faster than Other Drug Regulators*, FORBES (June 19, 2012,

for improvement in the regulatory scheme for the premarket approval process that would serve patients, industry, and the FDA itself. First, they advise creation of alternatives to clinical trials; second, increased and better quality postmarket surveillance, which would remove some of the imperative that the FDA be positive of the correct decision upon approval; and third, collaboration with stakeholders.¹⁶² They believe that collaboration, not severing contact, with experts simply because they have financial stakes in a product's approval, will lead to better patient care and better economic outcomes.

None of these advocates for loosening conflict of interest regulations propose to do so at the expense of patient safety; rather, they believe the regulations are overly burdensome to both industry and to the FDA, and harm patients more than help them.

IV. CONFLICT OF INTEREST LAWS ARE NECESSARY TO PROTECT THE PUBLIC, AND THIS INTEREST OUTWEIGHS THE BURDENS CONFLICT REGULATION IMPOSES ON INDUSTRY AND THE FDA

Advocates for strengthening conflict of interest laws come out swinging just as hard as their opposition, and their arguments are at least as cogent. First, they point to incidents of products being approved by a conflicted committee that ultimately harms the public as evidence of ineffectively screening members that affect the integrity of the approval process. A second argument is one to which industry might be receptive; conflict waivers can work against industry's interests, such as when committee members' conflicts stem from associations to competitor companies. Third, advocates for maintaining conflict regulations say that industry's estimated costs of developing a drug are greatly overstated (and even if they are not, their profits dwarf these costs). Fourth, they argue that the "shared pool dilemma" does not actually exist, but that experts exist in sufficient numbers to satisfy the vacancies on FDA committees. I will discuss each of these arguments in turn. Finally, I suggest that patient groups' "last hope" argument to make drugs meant to treat life-threatening conditions more readily available is a grave risk, because it opens doors for pharmaceutical companies to take advantage of patients with these conditions and their families.

10:15 AM), <http://www.forbes.com/sites/matthewherper/2012/06/19/more-proof-fda-is-faster-than-other-regulators/> (guest post by Joseph Ross).

162. Von Eschenbach & Hall, *supra* note 161.

A. *Committees with Conflicts Have Approved Drugs That Have or Could Have Harmed the Public*

This Section describes past committee meetings with conflicted members that approved drugs that may have harmed the public. While the following cases of dangerous drugs being approved and re-approved by committees with conflicts of interest is not direct evidence that the conflicts were outcome-determinative, it is important to consider that the presence of conflicted members can influence other members' votes. Diana Zuckerman, president of the National Research Center for Women & Families, argues both from personal experience and from a study she conducted, that a strong sway toward committee approval occurs when conflicted members are present. "Our study indicates that even one committee member with a financial conflict of interest could easily influence the votes of the entire committee," she said.¹⁶³ She stated:

I've seen how members with financial ties to the company or product often talk more at the meetings. They may talk more because they know more[, or] because they want to show the company how smart or helpful they are. Whatever the reason, their greater participation can be influential. Many advisory committee members ask no questions and make no comments at these meetings, until required to explain their votes. The advisory committee members with more direct knowledge of the products, including those with financial ties to the company or the product can greatly influence the vote when they talk more, ask softball questions or steer the conversation toward topics of benefit to the company.¹⁶⁴

It is with this understanding the following cases should be considered.

163. Peter Mansell, *Are US Advisory Committees a Pushover?* PHARMATIMES (Sept. 1, 2006), http://www.pharmatimes.com/Article/06-09-01/Are_US_advisory_committees_a_pushover.aspx?rl=1&rlurl=/06-11-15/Debate_on_industry_influence_rumbles_on.aspx.

164. Diana Zuckerman, *FDA Panels: Too Many Conflicts Or Too Little Expertise?*, CANCER PREVENTION & TREATMENT FUND (June 12, 2013), <http://www.stopcancerfund.org/in-the-news/press-releases/fdapanel-too-many-conflicts-or-too-little-expertise/>.

1. *The Rezulin Scandal*

The FDA's approval and subsequent withdrawal of Rezulin was one of the first major public relations crises for the agency.¹⁶⁵ "Rezulin was the first of a new class of drugs designed to treat Type II . . . diabetes," and its manufacturer, Warner-Lambert, highly marketed the drug to physicians and the public even before its trial data were submitted to the FDA for the approval process, paying over 300 doctors to spread the word about the new treatment.¹⁶⁶ "The Endocrinologic and Metabolic Drugs advisory committee unanimously recommended that the drug be approved."¹⁶⁷ The FDA granted "fast-track" approval in January 1997¹⁶⁸ despite explicit warnings of the danger of liver toxicity.¹⁶⁹

By the fall of 1997, however, the agency had received numerous reports that the drug was causing liver failure among patients, with four confirmed deaths. Working with Warner-Lambert, FDA issued new labels recommending that patients taking Rezulin have their liver functions monitored every two to three months. In December 1997, British authorities withdrew the drug from the U.K. market following six deaths linked to Rezulin. FDA again modified its labeling to require monthly monitoring of liver function. After reports of at least thirty-one fatalities attributable to Rezulin usage, [FDA] Commissioner Jane Henney [reconvened] the advisory committee to again evaluate the drug's safety.¹⁷⁰

Four of twelve of the committee members were granted waivers, including two members newly appointed to the committee on the eve of the meeting: Dr. Mayer B. Davidson and Dr. Saul M. Genuth.¹⁷¹ Both of these men had received income in the preceding two years "as leaders of a private diabetes education group funded exclusively by the makers of Rezulin."¹⁷² The grounds for the waivers were not made public.¹⁷³ After The Los

165. Glodé, *supra* note 30, at 308.

166. *Id.*

167. *Id.*

168. David Willman, *FDA's Approval and Delay in Withdrawing Rezulin Probed*, L.A. TIMES (Aug. 16, 2000), <http://articles.latimes.com/2000/aug/16/news/mn-5139>.

169. David Willman, *2 New FDA Panelists Have Ties to Rezulin Maker*, L.A. TIMES (Mar. 25, 1999), <http://articles.latimes.com/1999/mar/25/news/mn-20841> [hereinafter *Ties to Rezulin*].

170. Glodé, *supra* note 30, at 308-09.

171. David Willman, *FDA Advised to Restrict Rezulin Use for Diabetes*, L.A. TIMES (Mar. 27, 1999), <http://articles.latimes.com/1999/mar/27/news/mn-21447/2> [hereinafter *FDA Advised*].

172. Willman, *Ties to Rezulin*, *supra* note 169.

173. Willman, *FDA Advised*, *supra* note 171.

Angeles Times revealed these financial ties, Davidson recused himself from participating, but the other three members with conflicts did not.¹⁷⁴ The committee recommended by a vote of 8-4 that Rezulin remain on the market.¹⁷⁵ By March of 2000, “FDA had ninety reports of patient liver failure among patients taking Rezulin; in sixty-three of these cases, the patients died.”¹⁷⁶ The agency finally asked Warner-Lambert to withdraw the drug from the market, and the company agreed.¹⁷⁷

2. *The Vioxx Scandal*

FDA safety researcher David Graham estimates that the anti-inflammatory drug Vioxx caused 140,000 cases of serious heart disease¹⁷⁸ and up to 60,000 deaths between 1999 and 2004, when Merck, its manufacturer, voluntarily pulled it from the market.¹⁷⁹ In February 2005, an FDA advisory committee voted 17–15 to allow the drug to return to the market.¹⁸⁰ Ten of the thirty-two committee members had financial ties to either Pfizer or Merck (the committee also voted on Pfizer’s drug Celebrex, similar to Vioxx).¹⁸¹ Nine of the ten voted for re-introduction of the drugs.¹⁸²

While the FDA was apparently unaware of Vioxx’s risks in its original approval¹⁸³ (because Merck submitted to the FDA fabricated data

174. Glodé, *supra* note 30, at 309.

175. Willman, *FDA Advised*, *supra* note 171. It is also worth noting that nine of the ten physicians who presented on the effectiveness and safety of the drug were paid Warner-Lambert consultants. See JEROME P. KASSIRER, M.D., ON THE TAKE: HOW MEDICINE’S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH 48 (2005). Further, the top diabetes researcher at the National Institutes of Health (which oversees the FDA) was paid \$78,455 by Warner-Lambert between 1995 and 1997. Willman, *Ties to Rezulin*, *supra* note 169. The FDA has been strengthening its conflict of interest regulation for researchers and trials in parallel with its regulation for advisory committee members. See, e.g., GUIDANCE FOR CLINICAL INVESTIGATORS (2013), *supra* note 100.

176. Glodé, *supra* note 30, at 309.

177. Press Release, U.S. Dep’t of Health & Human Servs., Rezeulin to be Withdrawn from the Market (Mar. 21, 2000), available at http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab6c.htm.

178. Daniel Carlat, *Diagnosis: Conflict of Interest*, N.Y. TIMES (June 13, 2007), available at http://www.nytimes.com/2007/06/13/opinion/13carlat.html?_r=0.

179. Matthew Herper, *David Graham on the Vioxx Verdict*, FORBES (Aug. 19, 2005, 6:31 PM), http://www.forbes.com/2005/08/19/merck-vioxx-graham_cx_mh_0819graham.html.

180. *10 On FDA Vioxx Panel Had Ties To Companies*, *supra* note 121.

181. *Id.*; *Conflicts of Interest on COX-2 Panel*, CTR. FOR SCI. IN THE PUB. INTEREST (Feb. 25, 2005), <http://www.cspinet.org/new/200502251.html>.

182. *10 On FDA Vioxx Panel Had Ties To Companies*, *supra* note 121.

183. Rita Rubin, *How Did Vioxx Debacle Happen?*, USA TODAY (Oct. 12, 2004), http://usatoday30.usatoday.com/news/health/2004-10-12-vioxx-cover_x.htm.

appearing to augment the drug's analgesic effects¹⁸⁴ and attempted to obfuscate serious adverse events¹⁸⁵), the FDA knew Vioxx's risks as early as 2000.¹⁸⁶ In September 2001, the FDA wrote Merck's CEO, stating: "Your promotional campaign discounts the fact that in [your own] study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug"¹⁸⁷ And yet, ten committee members voted to reintroduce Vioxx on the market. Given that Vioxx generated \$2.5 billion in the year preceding its pull from the market,¹⁸⁸ some believe that this vote demonstrated that when given the chance, conflicted experts will consciously or otherwise risk lives for their own financial interest.¹⁸⁹

3. *The Yaz/Yasmin Scandal*

Though Vioxx has certainly caused more harm to the public, the Yaz/Yasmin scandal perhaps better demonstrates the depths of what consumer advocates see as rife corruption within the FDA because of the many ways conflicts impacted the approval process. Not only did five participating committee members have financial interests in the decision,¹⁹⁰ but Dr. Wolfe was precluded from participating because of an "intellectual conflict of interest,"¹⁹¹ and an expert report warning of the drugs' serious safety risks was excluded from consideration because "the date to submit documents had passed."¹⁹² Finally, as stated earlier, the FDA did not issue any waivers to committee members because their conflicts arose over a year earlier. This interpretation of financial conflict of interest is dubious.

184. Keith J. Winstein & David Armstrong, *Top Pain Scientist Fabricated Data in Studies, Hospital Says*, WALL ST. J. (Mar. 11, 2009, 12:01 AM), <http://online.wsj.com/article/SB123672510903888207.html>.

185. SHARI L. TARGUM, REVIEW OF CARDIOVASCULAR SAFETY DATABASE 34 (2001), available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf.

186. Rubin, *supra* note 183.

187. Letter from the FDA to Raymond V. Gilmartin, Merck CEO (Sept. 17, 2001), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166383.pdf>.

188. *Merck to Begin Paying \$4.85B in Vioxx Settlements*, NJ.COM (July 17, 2008, 3:04 PM), http://www.nj.com/news/index.ssf/2008/07/merck_to_begin_paying_485b_in.html.

189. See generally Justin Biddle, *Lessons from the Vioxx Debacle: What the Privatization of Science Can Teach Us About Social Epistemology*, 21 SOC. EPISTEMOLOGY 1, Jan.–Mar. 2007, at 31.

190. Lenzer & Epstein, *supra* note 3.

191. *Id.*

192. *Id.*

In this incident, the depths of conflict reached the chair of the committee, Julia Johnson. Johnson had conducted clinical trials on behalf of Bayer. Another committee member, Paula Hillard, was a paid consultant to Bayer.¹⁹³ Elizabeth Raymond, another committee member, conducted clinical trials sponsored by Barr, which has a licensing agreement with Bayer. Committee member Anne Burke received research funding from Bayer. A fifth advisor received consulting fees from a law firm representing Bayer.¹⁹⁴ FDA spokeswoman Morgan Liscinsky confirmed that no waivers were issued to committee members.¹⁹⁵ This fact raises the issue of waivers. As explained above, the FDA has issued progressively fewer waivers in recent years,¹⁹⁶ which it touts as a minimization of conflicted committee members. This incident suggests, quite the contrary, that participation of conflicted members may be as high as ever, but that the FDA either deliberately or negligently fails to formally recognize this by issuing a waiver.

In addition, the advisory committee decided not to consider a 196-page report by former FDA Commissioner David Kessler “prepared for attorneys suing Bayer on behalf of the more than 10,000 women who claim to have been harmed by the drug” because the report was submitted too late.¹⁹⁷ This may suggest that the advisory committee was deliberately

193. The voting members are required to state for the record why they voted as they did. Interestingly, Dr. Hillard voted “yes” because the risk of blood clots associated with taking the drug were less than the risk of blood clots for pregnant persons. In fact, the committee member who spoke before Dr. Hillard explained this rationale, and Dr. Hillard said “Ditto.” They apparently would not consider the risk of blood clots compared to the risk for non-pregnant persons and persons taking other forms of oral contraceptives. FDA CTR. FOR DRUG EVALUATION & RESEARCH, JOINT MEETING OF THE ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE 403 (2011), *available at* <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM288721.pdf>.

The risk of blood clots with Yaz and Yasmin, as stated earlier, is approximately tenfold that associated with other forms of oral contraceptives. Lenzer & Epstein, *supra* note 3. Dr. Johnson voted “yes” because she did not “think the data is sufficient, with the current studies, to be able to say that there is a risk.” *Id.* at 406. Dr. Burke voted “yes,” stating “while I acknowledge that there does seem to be a moderate increased risk, it’s still lower than the risks of pregnancy.” *Id.* at 413. Dr. Raymond voted “yes” because “[o]ral contraceptives prevent pregnancy and many other serious health conditions, and these effects clearly outweigh the relatively low risk of venous thromboembolism.” *Id.* (Bayer was at this time under investigation for illegally promoting off-label uses for Yaz and Yasmin. Jef Feeley & Margaret Cronin Fisk, *Bayer May Have Pitched Birth-Control Pill for Unapproved Use*, BLOOMBERG NEWS (Nov. 21, 2011, 7:19 PM), <http://www.bloomberg.com/news/2011-11-21/bayer-may-have-touted-birth-control-pills-for-unapproved-use-e-mails-show.html>.)

194. Lenzer & Epstein, *supra* note 3.

195. *Id.*

196. *Percent Granted Waivers*, *supra* note 95.

197. *The Latest Advisory Committee Stumbles at FDA*, GOOZNEWS (Dec. 7, 2011), <http://gooznews.com/?p=3421>.

resisting voices that opposed the drug's approval and the information that supported them.¹⁹⁸ Dr. Kessler's report detailed the dangers of drospirenone, the synthetic hormone in Yaz and Yasmin, and accused Bayer of deliberately withholding from the FDA data demonstrating the dangers of the hormone.¹⁹⁹ Though of course Kessler's report could be considered not objective because it was prepared for plaintiff's attorneys, certainly the perspectives of pharmaceutical companies are equally biased.

The FDA explained its exclusion of Dr. Kessler's report on the dangers of drospirenone as a procedural bar. This may well be true, but this committee systematically eliminated the opinions of two experts²⁰⁰ that both warned of the serious safety risks associated with the hormone in Yaz and Yasmin. Dr. Kessler's report was previously under seal and released to the FDA for consideration upon its unsealing. If the committee's only purpose was to determine the safety of the drug, some wonder, why not consider all the available evidence, especially evidence suggesting the drug poses a life-threatening danger?²⁰¹ These factors suggest to advocates for greater oversight that the FDA's lax approach to conflicts of interest is harming the public.

B. Conflict Waivers Can Work Against Industry and the Approval Process

The drug industry often assumes that conflict of interest regulation in the approval process is necessarily harmful to the industry.²⁰² However, the inverse of this assertion, that less regulation is beneficial to the industry, is not always true. It depends on the players in the industry being

198. Dr. Kessler's report is available at <http://gooznews.com/wp-content/uploads/2011/12/20111207-DavidKessler-court-brief-on-safety-of-Yasmin-from-Bayer.pdf>.

199. *Former FDA Commish: Bayer Hid Yasmin Data*, EXPERT BRIEFINGS (Dec. 6, 2011, 2:13 PM), <http://www.expertbriefings.com/news/former-fda-commish-bayer-hid-yasmin-data/>.

200. Dr. Kessler was a former FDA commissioner, and in 2009 Dr. Wolfe was appointed to a four-year term on the FDA's Drug Safety and Risk Management Committee. Philip J. Hilts, *Clinton Retains Bush Appointee as F.D.A. Chief*, N.Y. TIMES (Feb. 27, 1993), available at <http://www.nytimes.com/1993/02/27/us/clinton-retains-bush-appointee-as-fda-chief.html>. Alicia Mundy, *A Wolfe in Regulator's Clothing: Drug Industry Critic Joins the FDA*, WALL ST. J. (Jan. 9, 2009, 12:01 AM), <http://online.wsj.com/article/SB123145489435265929.html>.

201. See, e.g., Margaret Cronin Fisk & Jef Feeley, *Bayer Withheld Yasmin Data From U.S., Former Agency Chief Tells Court*, BLOOMBERG NEWS (Dec. 5, 2011, 11:01 PM), <http://www.bloomberg.com/news/2011-12-05/bayer-withheld-yasmin-clot-risk-data-from-u-s-ex-agency-head-tells-court.html>.

202. See, e.g., Andrew Entzminger, *Medical Panel Rules Called Too Restrictive*, WASHINGTON TIMES (Nov. 3, 2010), available at <http://www.washingtontimes.com/news/2010/nov/3/report-fdas-conflict-interest-rules-too-restrictiv/>; RICHARD A. EPSTEIN, MANHATTAN INST., *HOW CONFLICT-OF-INTEREST RULES ENDANGER MEDICAL PROGRESS AND CURES* (2010), available at http://www.manhattan-institute.org/pdf/fda_03.pdf.

implicated. In the spring of 2007, an FDA advisory committee approved the prostate cancer treatment drug Provenge (manufactured by Dendreon) by a vote of 13–4.²⁰³ Two of the panelists who voted against the drug, Howard Scher and Maha Hussain, “quietly wrote FDA officials to veto [the] panel recommendation”²⁰⁴ because there was no solid evidence that Provenge slowed the progression of the disease, extending a patient’s life by four months.²⁰⁵ Both panelists who wrote had ties to other drug manufacturers making competitor prostate cancer drugs, Dr. Scher being the lead investigator for another manufacturer’s prostate cancer drug.²⁰⁶ The FDA declined to approve the drug, and Dendreon’s stock plummeted over 60% within a day.²⁰⁷ Provenge was not approved until April of 2010,²⁰⁸ and its stock, after an initial boom upon approval, has stagnated due to the fact that competing treatments were available by the time it was approved.²⁰⁹ Additionally, a patient group filed suit against the FDA and some of its officials for the delay, most of which was summarily dismissed on grounds of ripeness, finality, and sovereign immunity.²¹⁰ Patients and their advocates threatened Scher and Hussain to the extent that they required bodyguards, and Dr. Scher stated concern that this behavior could

203. Ed Silverman, *Provenge, FDA Panels and Conflicts of Interest*, PHARMALOT (July 6, 2007, 6:01 PM), archived at <https://web.archive.org/web/20080907225921/http://www.pharmalot.com/2007/07/provenge-fda-panels-and-conflicts/> (blog no longer active, original text on file with author); Sharon Begley, *Insight: New Doubts About Prostate-Cancer Vaccine Provenge*, REUTERS (Mar. 30, 2012, 9:29 AM), <http://www.reuters.com/article/2012/03/30/us-provenge-idUSBRE82T07420120330>.

204. Ed Silverman, *The FDA, Conflicts of Interest & Provenge E-mails*, PHARMALOT (Apr. 26, 2011, 9:06 AM), archived at <https://web.archive.org/web/20120719035414/http://www.pharmalot.com/2011/04/the-fda-conflicts-of-interest-provenge-e-mails/> (blog no longer active, original text on file with author).

205. Maggie Mahar, *Medicare Will Pay \$93,000 for Provenge: A Big Win for Wall Street*, HEALTHBEAT (Apr. 4, 2011), <http://www.healthbeatblog.com/2011/04/medicare-will-pay-93000-for-provenge-a-big-win-for-wall-street/>.

206. Silverman, *supra* note 204.

207. Catherine Arnst, *Pressure for Provenge Approval*, BLOOMBERG NEWS (July 30, 2007), <http://www.businessweek.com/stories/2007-07-30/pressure-for-provenge-approvalbusinessweek-business-news-stock-market-and-financial-advice>.

208. Begley, *supra* note 203. Scher points to the fact that the clinical studies did not meet their primary endpoints, “which renders the significance of the results from any subsequent analyses as ‘exploratory’ and ‘hypothesis generating.’” He also points to methodological flaws, including the fact that the placebo administered may actually have had harmful effects, thus creating the appearance that Provenge was slowing the progression of the disease in the test subjects. Perhaps most importantly, the study’s authors in their analysis conceded that the effects of Provenge were not statistically significant. Both letters written to the FDA urging it not to approve Provenge are available at <http://deepcapture.com/wp-content/uploads/2009/07/leakedletters.pdf>.

209. William Meyers, *Dendreon’s Provenge Revenue Trends*, SEEKING ALPHA (Jan. 9, 2013, 12:02 PM), <http://seekingalpha.com/article/1102781-dendreon-s-provenge-revenue-trends>.

210. *CareToLive v. von Eschenbach*, 525 F. Supp. 2d 938 (S.D. Ohio 2007), *aff’d sub nom* *CareToLive v. Eschenbach*, 290 F. App’x 887 (6th Cir. 2008).

dissuade doctors from voicing concerns about the drugs being evaluated in the approval process.²¹¹

Hussain and Scher may or may not have been justified in their concerns for the drug's efficacy; while some consumer advocates decry the delay as proof that conflicts of interest guided FDA actions that resulted in earlier deaths for thousands of men,²¹² others have challenged the efficacy of the drug and the credibility of the studies, just as Scher and Husaain did.²¹³ But their conflicts raise serious questions. Was their opinion objective? Would they have gone so far as to write the FDA commissioner personally were it not for their conflicts? Would patient advocates have reacted so violently if the committee were free of conflict? To be sure, individuals and groups without conflicts question the vaccine's effectiveness²¹⁴—perhaps if these people were the ones to voice their concerns on the advisory committee, their opinions would not have been questioned so fiercely. This episode demonstrates the dangers of conflicts playing a role in the approval process for industry and for the integrity of and public trust in the approval process itself.

C. *The “Shared Pool Dilemma” Does Not Exist*

The “shared pool dilemma” is the idea that the most qualified experts on any given drug or device will usually have financial conflicts of interest because drug and device companies will have sought out their expertise.²¹⁵ Acceptance that this dilemma exists necessitates the conclusion that conflicts of interest on advisory committees are unavoidable, perhaps even preferable.

On August 3, 2011, the non-profit Project On Government Oversight (“POGO”) sent a letter to FDA commissioner Margaret Hamburg urging

211. Andrew Pollack, *Doctors Threatened for Opposing Drug*, N.Y. TIMES (June 4, 2007), http://www.nytimes.com/2007/06/04/world/americas/04iht-docs.4.5991628.html?_r=0.

212. William Faloon, *FDA Delay of One Drug Causes 82,000 Lost Life-Years*, LIFE EXTENSION MAG., Nov. 2010, available at http://www.lef.org/magazine/mag2010/nov2010_FDA-Delay-of-One-Drug-Causes-Lost-Life-Years_01.htm.

213. See Begley, *supra* note 203; *Understanding Prostate Cancer: Diagnosis & Treatment*, WEBMD, <http://www.webmd.com/prostate-cancer/guide/understanding-prostate-cancer-treatment?> (last visited Sept. 25, 2014).

214. See, e.g., Joel T. Nowak, *A New Controversy Surrounding Provenge Continues to Complicate the Decision to Use It*, ADVANCEDPROSTATECANCER.NET (Mar. 31, 2012), <http://advancedprostatecancer.net/?p=3140>.

215. McComas et al., *supra* note 31.

her not to weaken conflict of interest standards.²¹⁶ POGO points to several reports suggesting that the shared pool dilemma need not exist. They cite a federally funded research report by Harvard University's Dr. Eric Campbell, which concluded that nearly 50% of research academics have no ties to industry and that approximately one-third of these researchers are full professors.²¹⁷ They also pointed to a survey of participants who created clinical care guidelines for cardiology on behalf of the American College of Cardiology and the American Heart Association. Of the participants, 44% had no financial conflicts of interest.²¹⁸ They further note that two journalists for the British Medical Journal ("BMJ") cited nearly 100 medical experts without corporate ties in 2008.²¹⁹ Notably, the BMJ authors write:

Beyond the list's usefulness to journalists, we hope that it will also be used by government agencies, medical journal editors, and professional societies as they seek out experts to serve as editorialists and members of clinical guideline and advisory panels. The FDA, for example, has a copy of the list.²²⁰

All these findings suggest that the shared pool dilemma may not actually exist. As Lenzer and Brownlee maintain, conflicted scientists may be easier to find due to their names being on industry-sponsored publications,²²¹ but in most cases they are not the exclusive experts in their field. The POGO letter concedes that convening a conflict-free panel is "an additional hurdle," but, as they say, "that is exactly the point: we want expert advice that is as free as possible from the influence of industry."²²² The fact that conflicted scientists may be easier to find than non-conflicted

216. Letter from Project On Gov't Oversight to Margaret Hamburg, FDA Comm'r (Aug. 3, 2011), available at <http://pogoarchives.org/m/ph/fda/fda-advisory-panels-letter-20110803.pdf> [hereinafter Letter to Margaret Hamburg].

217. *Id.* (citing Darren E. Zinner et al., *Participation of Academic Scientists in Relationships With Industry*, 28 HEALTH AFF., no. 6, at 181,425 (2009), available at <http://content.healthaffairs.org/content/28/6/1814.full.pdf>).

218. *Id.* (citing Todd B. Mendelson et al., *Conflicts of Interest in Cardiovascular Clinical Practice Guidelines*, 171 ARCHIVES OF INTERNAL MED., no. 6, at 577–85 (2011), available at <http://archinte.jamanetwork.com/article.aspx?articleid=226953#qundefined>).

219. *Id.* (citing Jeanne Lenzer & Shannon Brownlee, *Medicine and the Media: Is There an (Unbiased) Doctor in the House?*, 337 BRIT. MED. J. 206 (2008)). The POGO letter also discusses the fact that conflict of interest waivers are granted at a rate of less than 5%. However, as I discuss above, the percentage of committee members granted waivers may not be an accurate reflection of which members are conflicted.

220. Lenzer & Brownlee, *supra* note 219.

221. *Id.*

222. Letter to Margaret Hamburg, *supra* note 216.

scientists may be the basis for the insistence that the shared pool dilemma is real, but no statistical analyses exist to contradict Lenzer and Brownlee's findings. Ed Silverman points out that committee position vacancies have been steadily declining in recent years, suggesting that, "despite the protestations from the pols who want the [regulations] loosened," finding members without conflicts of interest is not as difficult as some would have the public believe.²²³

D. The Economic Costs of Developing a Drug are Overstated

A perhaps less important argument in favor of thorough conflict of interest regulations is that the cost of developing a drug is not the staggering figure pharmaceutical companies claim it to be, and thus the burden imposed on industry by the time required to convene a conflict-free panel is less significant. Though Matthew Herper and others estimate the cost of developing a drug to be in the billions,²²⁴ a 2011 study published in the journal *BioSocieties* disputes that estimate.²²⁵ The most commonly used figure, \$1 billion, is based on a 2003 study conducted by the Tufts Center for the Study of Drug Development.²²⁶ PhRMA, a trade group representing pharmaceutical companies, estimated that inflation would make that figure approximately \$1.3 billion in 2011 dollars.²²⁷ Comparative healthcare professor Donald Light and economics professor Rebecca Warburton co-authored the *BioSocieties* article.²²⁸ They explain that the Tufts study was critically flawed due to sampling error, overestimates of inflation, and a failure to account for the fact that a significant percentage of development costs are federally funded.²²⁹ Most importantly, the Tufts study invited only twenty-four drug companies to participate in a survey, ten of which responded, and "if the Tufts Center group made any effort of its own to verify the information it received from the drug companies, the group makes no mention of it in the study."²³⁰

223. Silverman, *supra* note 149.

224. Herper, *supra* note 123.

225. Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 *BIOsocieties* 34 (2011), available at http://www.pharmamyths.net/files/Biosocieties_2011_Myths_of_High_Drug_Research_Costs.pdf (weblink to article with original pagination).

226. *Id.*

227. Timothy Noah, *The Make-Believe Billion: How Drug Companies Exaggerate Research Costs to Justify Absurd Profits*, SLATE (Mar. 3, 2011, 9:19 PM), http://www.slate.com/articles/business/the_customer/2011/03/the_makebelieve_billion.single.html.

228. Light & Warburton, *supra* note 225.

229. *Id.* at 37–42; Noah, *supra* note 227.

230. Noah, *supra* note 227.

Light and Warburton argue that when the data is corrected for the quantifiable methodological flaws, the more accurate figure in 2011 dollars is \$55 million.²³¹ They further state that the \$55 million figure may be high because it is based on self-reports from drug companies themselves; “the audited costs of all clinical trials submitted by pharmaceutical companies in the late 1990s to the Internal Revenue Service averaged only \$22.5 million.”²³²

In 2009, the approval process took approximately thirteen months for standard drugs and nine months for priority applications.²³³ Given that the pharmaceutical company spends nineteen times more on advertising than it does on basic research,²³⁴ it does not seem unreasonable to ask these multi-billion dollar companies to wait the thirteen months—or however long it takes—to ensure that experts without conflicts of interest have deemed their product safe and effective.²³⁵

E. Approving Drugs Faster for Patients in Need May Lead to a Slippery Slope of Capitalizing on their Desperation

This final argument has not been stated clearly by the FDA, but is implicit in its reluctance to kowtow to the demands of patients’ groups. In November 2013, the FDA announced that it would not expedite the drug eteplirsen for approval for treatment of Duchenne Muscular Dystrophy while its safety and effectiveness is vetted through more sufficient trial data.²³⁶ It will not be eligible for approval for about two more years. The

231. *Id.*

232. Light & Warburton, *supra* note 225, at 47.

233. FDA, FY2010: PERFORMANCE REPORT TO THE PRESIDENT AND CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT 4 (2010), available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf>.

234. Donald W. Light & Joel R. Lexchin, *Pharmaceutical Research and Development: What Do We Get For All That Money?*, 345 BRIT. MED. J. e4348 (Aug. 7, 2012), available at http://www.pharmamyths.net/files/BMJ-Innova_ARTICLE_8-11-12.pdf.

235. For a breakdown of Fortune 500 pharmaceutical company profits in 2012, see *Fortune 500: Industries*, CNN.COM, <http://money.cnn.com/magazines/fortune/fortune500/2012/industries/21/> (last visited Sept. 1, 2014). Pharmaceutical companies may also argue that the time a drug spends in the approval process is time lost on its patent. See, e.g., Charles L. Hooper, *Pharmaceuticals: Economics and Regulation*, CONCISE ENCYCLOPEDIA OF ECON. (2d ed. 2008), available at <http://www.econlib.org/library/Enc/PharmaceuticalsEconomicsandRegulation.html>. However, both Congress and the FDA have the power to extend exclusivity rights to drug companies for the duration the drug spent in the approval process, and frequently acts on this power. WENDY H. SCHACHT & JOHN R. THOMAS, CRS REPORT FOR CONGRESS, PHARMACEUTICAL PATENT TERM EXTENSIONS: A BRIEF EXPLANATION (2002), available at <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RS21129.pdf>.

236. Joseph Walker, *FDA Wants More Testing of Muscular-Dystrophy Drug*, WALL ST. J. (Nov. 12, 2013, 4:23 PM), <http://online.wsj.com/news/articles/SB10001424052702304644104579193581328336774> (subscription required).

Duchenne Muscular Dystrophy community, including Jenn McNary, was “outraged,” but a regulatory affairs executive at a drug firm stated, “If we’re going to charge someone for a drug, we have to think there’s going to be a clinical benefit; otherwise it’s just hope.”²³⁷ Notably, the study only involves twelve boys and all evidence of improvement is indirect.

Conflicts of interest are not the reason the FDA has yet to approve the drug, and McNary does not care what the reasons are; she just wants her son’s devastating condition to improve. This is what makes her particularly sympathetic and equally vulnerable, and this vulnerability is precisely the reason the FDA attempts to remain impervious to the desires of patient groups. If it did otherwise, it would open the door to the possibility that the desperation of patients and their families could be used against them.

The FDA declined to expedite approval because a similar drug created by another company failed, and because “[r]egulators . . . questioned the validity of data showing an increased walking ability for patients taking eteplirsen because some boys couldn’t take the test.”²³⁸ Again, only twelve boys are participating in the study, and apparently some of them weren’t available to be tested for improvement. In both drugs’ tests, the levels of dystrophin—the muscle-protecting protein that Duchenne blocks—increased in the subjects, which is supposedly an indicator of their improvement. However, their overall condition still deteriorated at a later stage in the rival drug company’s study. The FDA stated that negative results from the longer study “raises considerable doubt about the biomarker, and consequentially, its ability to reasonably likely predict clinical benefit.”²³⁹

The patient community may be “outraged,” but what is the alternative? In many cases, it will be false hope and real money spent on a drug or device that will ultimately fail. If the FDA bows to the will of these groups and pharmaceutical companies and takes shortcuts in approval and review processes for products meant to treat life-threatening conditions, be they in the conflict of interest vetting process or review of trial data, it ultimately may fail its duty of ensuring that the products it approves for market are safe and effective.

237. *Id.*

238. *Id.*

239. *Id.*

V. RECOMMENDATIONS AND CONCLUSION

Advocates for both easing and tightening conflict have legitimate arguments; both point to examples of conflict regulations preventing a desired outcome or causing a disastrous outcome. Patients have been harmed both by receiving unsafe but FDA-approved products and by not having access to a much-needed, but not yet approved, product. Quantitative studies have been conducted to determine the prevalence of conflict and whether conflicts lead to inappropriate approval or rejection of a product (although these studies are usually limited to conflicts that are reported). Von Eschenbach and Hall write: “There is a compelling argument for letting patients and their doctors decide what risks to take.”²⁴⁰ This may be true, but it assumes that patients and doctors are thoroughly aware of the risks. The FDA’s task is to assess that risk and decide which products’ benefits outweigh their harms and which do not. The FDA is supposed to be an *independent* body that assures us that the products we use are more likely to help us than to harm us. Knowing that the committee on the FDA that made such a determination is free from financial interests that might cloud one’s judgment should help patients and doctors better assess the risks of using any given drug or device.

Those on both sides of the debate appear not to appreciate just how much the risk-benefit analysis depends on the condition being treated. For example, applying the appropriate risk-benefit analysis, Ms. McNary’s son with Duchenne Muscular Dystrophy should have access to the drug that is apparently helping her other son walk again, as long as she is made fully aware that improvement is unlikely based on the longer study of the competitor drug. Drugs for diabetes or high cholesterol, on the other hand, should not be as quickly available to patients; other treatments already exist, and the conditions are not as acutely serious.

I suggest a balanced, sliding-scale approach based on the severity of the condition and the need for treatment. In June of 2012, Theresa Mullin, from the FDA’s Center for Drug Evaluation and Research, gave a presentation on the risk-benefit analysis applied in the approval process.²⁴¹ Its five key considerations are (1) severity of the condition to be treated,

240. Von Eschenbach & Hall, *supra* note 161.

241. Theresa Mullin, *Patient-Focused Drug Development*, FDA.GOV (June 20, 2012), <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM310754.pdf?source=govdelivery>.

(2) unmet medical need, (3) benefit, (4) risk, and (5) risk management.²⁴² Such a framework should be used not only in considering whether to approve a drug or device, but also in considering whom to allow to sit on advisory committees. If the condition is very severe *and* there is an unmet need for the treatment, waivers should be granted *if* doing so is necessary to expedite approval. If one of these three conditions is not met, no waivers should be granted under any circumstances.

Furthermore, the FDA must not rely exclusively on self-reporting to determine a committee member's conflicts of interest. If the FDA lacks the resources to check committee members' financial interests thoroughly, Congress should grant it the power to raise user fees. Drug companies currently pay fees for expedited review; we should ensure that the review is objective. Finally, waivers must be granted to each participating member with a conflict of interest; the process should not allow for waiving the waiver process for conflicts deemed too small or too long ago. The waiver, the person granted it, and the type of conflict must be part of the public record (but not the magnitude of the conflict). This way, the public will have access to the existence of all conflicts on committees. Not only will patients and their physicians then have more information when making treatment decisions, but a committee member will also have to vote knowing that his or her conflict is public knowledge.

These modest steps strike an appropriate balance between the need for beneficial drugs and the need to protect patients from harmful ones. They would lead to greater transparency and accountability in the FDA approval process, and could potentially save lives.

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242. *Id.*; see also Thomas Sullivan, *FDA: Food and Drug Administration Safety and Innovation Act (FDASIA) and Patient Focused Drug Development*, POL'Y & MED. (July 17, 2012, 5:26 AM), <http://www.policymed.com/pdafa/>.

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