



January 11, 2012

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via email: Margaret.Hamburg@fda.hhs.gov

Subject: Joint advisory committee meeting on Yaz and Yasmin: Industry Ties

Dear Dr. Hamburg:

Since its creation thirty years ago, the Project On Government Oversight (POGO), a nonprofit, nonpartisan organization, has identified instances of financial conflicts of interest in the federal government and successfully pressed to correct them. We recently learned of industry ties among four members, including the acting chair, of a joint meeting last month of two FDA advisory committees—ties that were not disclosed to the public at the committee meeting.

We are writing to ask that you examine several problems related to this episode. We also ask that you inform us of the FDA's plans to take corrective action.

Joint meeting of advisory committees

On December 8, 2011, two FDA advisory committees, the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (referred to as the “joint committee” or “joint meeting”), met to consider the benefits and risks of the oral contraceptives Yaz and Yasmin and related contraceptives containing the drug drospirenone.¹ Yaz and Yasmin, manufactured by Bayer HealthCare Pharmaceuticals, Inc. (hereafter “Bayer”), are among the most popular and profitable oral contraceptives in the U.S. An Associated Press article recently stated that “Yaz, Yasmin and related drospirenone-containing pills were Bayer’s second-best-selling franchise last year at \$1.6 billion in global sales.”²

¹ Department of Health and Human Services, Food and Drug Administration, “Advisory Committees: December 8, 2011: Joint Meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting Announcement,” December 8, 2011.

<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm273236.htm> (Downloaded January 10, 2012) (hereinafter Joint Meeting)

² Matthew Perrone, “FDA ties newer birth control drugs to blood clots,” Associated Press, October 27, 2011. http://www.mercurynews.com/health/ci_19209887 (Downloaded January 10, 2012)

The FDA scheduled this joint meeting because of growing concerns, reported in the medical and lay press,³ about the risks of Yaz and Yasmin to the health of the women who take them. According to some medical experts,⁴ these women—who received “roughly 13 million prescriptions for Yaz and two generic versions of the drug” in 2010⁵—are at significantly higher risk of venous thromboembolism than women taking contraceptives not containing drospirenone. Venous thromboembolism is a potentially lethal disorder that begins with deep venous thrombosis (clots forming abnormally within veins).⁶ The clots may dislodge suddenly (thromboembolism) and travel to the lungs, where they can cause serious injury or sudden death.

The FDA asked the members of the joint committee to vote on whether the benefits of the drospirenone-containing oral contraceptives outweighed the risks.⁷ A majority of the joint committee (15 of the 26 voting members⁸) voted that the benefits of Yaz, Yasmin, and other drospirenone-containing oral contraceptives outweigh the risks.⁹ This conclusion, if accepted by the FDA, could allow the sale of Yaz and Yasmin to continue unhindered.

Safety studies

Before they voted, the joint committee members discussed and compared the results of ten epidemiologic studies of women taking oral contraceptives.¹⁰ Each study examined the risk of venous thromboembolism among women taking Yaz, Yasmin, or other drospirenone-containing contraceptives and compared this risk with the risk of thromboembolism among women taking oral contraceptives not containing drospirenone. These were large studies; some of them included hundreds of thousands of women.

³ Duff Wilson, “Study: Yaz Has Higher Risks of Blood Clots,” *The New York Times*, October 26, 2011. <http://prescriptions.blogs.nytimes.com/2011/10/26/study-yaz-has-higher-risks-of-blood-clots/> (Downloaded January 10, 2012); Mathew Perrone, “FDA revisits safety of newer birth control drugs,” Associated Press, December 5, 2011. <http://news.yahoo.com/fda-revisits-safety-newer-birth-control-drugs-173653387.html> (Downloaded January 10, 2012) (hereinafter “FDA revisits safety of newer birth control drugs”)

⁴ Susan S. Jick and Rohini K. Hernandez, “Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data,” *British Medical Journal*, 342: d2151, April 21, 2011. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3081040/?tool=pubmed> (Downloaded January 10, 2012) (hereinafter *British Medical Journal* study); Department of Health and Human Services, Food and Drug Administration, *Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints* (CHC-CVD final report 111022v2). <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf> (Downloaded January 10, 2012) (hereinafter *Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints* (CHC-CVD final report 111022v2))

⁵ “FDA revisits safety of newer birth control drugs”

⁶ Department of Health and Human Services, National Institutes of Health, National Heart Lung and Blood Institute, “What Is Deep Vein Thrombosis?” October 28, 2011. <http://www.nhlbi.nih.gov/health/health-topics/topics/dvt/> (Downloaded January 10, 2012)

⁷ Transcript of the December 8, 2011, joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, prepared by Tscribe, a private third-party contractor, p. 108. <http://www.pogo.org/resources/public-health/minutes-fda-advisory-committee-meeting-december-8.html> (hereinafter Joint Meeting Transcript)

⁸ Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, “Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee: Meeting Roster,” December 8, 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM284777.pdf> (Downloaded January 11, 2012)

⁹ Email from Morgan Liscinsky, FDA Spokeswoman, to Nick Schwellenbach, Project On Government Oversight, January 10, 2012. (hereinafter Morgan Liscinsky Email)

¹⁰ Joint Meeting Transcript

- Three of the published studies were funded by Bayer. These studies supported the conclusion that the risks were comparable—that women taking Yaz or Yasmin were not at higher risk of venous thromboembolism than women taking other oral contraceptives.¹¹
- In aggregate, seven other studies, not funded by Bayer, supported the opposite conclusion, namely, that the risk of thromboembolism with Yaz or Yasmin was higher than the risk with oral contraceptives not containing drospirenone.¹² In particular, this was the conclusion of a large epidemiologic study funded by the FDA and reported online on November 27, 2011.¹³ The authors of this report indicated that their study added another positive finding to the increasing body of evidence linking drospirenone-containing oral contraceptives, such as Yaz and Yasmin, to increased risk of venous thromboembolism relative to standard oral contraceptives.¹⁴

For those impacted by drospirenone-containing oral contraceptives, this was far more than a scientific debate. Among the possible victims and family members of victims was a woman named Cindy Rippe,¹⁵ who told the joint committee that on one Christmas Eve she had to give CPR to her daughter Elizabeth, who had switched to Yasmin two months earlier, when Elizabeth was struck by pulmonary emboli in both of her lungs. Elizabeth died in an emergency room, Rippe told the joint committee. “She had taken generic Ortho Tri-Cyclen for over one year without any problems,” Rippe said, “If Elizabeth had been clearly warned that Yasmin had more risk, maybe twice as much risk than other pills, she never would have switched to Yasmin, never, and she would be alive today.”¹⁶

In Europe, the public is warned of the higher risks with drospirenone-containing oral contraceptives, Rippe told the joint committee.¹⁷ Rippe went on: “Australia warns, Canada warns, England warns. England tells their daughters that the totality of available evidence now

¹¹ Project On Government Oversight, “The Ten Studies: A List,” January 10, 2012. <https://www.documentcloud.org/documents/282765-ten-epidemiologic-studies-jan-10-2012.html> (hereinafter “List of Ten Studies”)

¹² “List of Ten Studies”

¹³ *Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints (CHC-CVD final report 111022v2)*

¹⁴ The actual statement in the November 27, 2011, report was as follows: “In conclusion, the study results . . . provides another positive finding to the increasing body of evidence linking DRSP to increased risk of VTE relative to standard CHC pills,” where DRSP is drospirenone/ethinyl estradiol tablets, VTE is venous thromboembolism, and CHC is combined hormonal contraceptives: *Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints (CHC-CVD final report 111022v2)*, p. 31. The conclusion of another study published in 2011 in the *British Medical Journal* is as follows: “The risk of non-fatal venous thromboembolism among users of oral contraceptives containing drospirenone seems to be around twice that of users of oral contraceptives containing levonorgestrel, after the effects of potential confounders and prescribing biases have been taken into account.” *British Medical Journal* study, p. 1.

¹⁵ The transcript of the joint meeting only provides a phonetic spelling of her name. According to the transcript, her last name is “Rippy.” Joint Meeting Transcript, p. 61. However, her last name is spelled “Rippe” in an NPR story about the meeting: Richard Knox, “With Doubts, FDA Panel Votes For Yaz And Related Contraceptives,” *NPR*, December 9, 2011. <http://www.npr.org/blogs/health/2011/12/09/143434891/with-doubts-fda-panel-votes-for-yaz-and-related-contraceptives> (Downloaded January 10, 2012)

¹⁶ Joint Meeting Transcript, p. 62.

¹⁷ Joint Meeting Transcript, p. 62.

clearly shows that the risk of venous thromboembolism for Yasmin is higher. Higher. Not the same, not questionable, not unclear—higher.”¹⁸

Certain highly relevant information was not examined at the December 8 joint meeting.¹⁹ In particular, former FDA Commissioner David M. Kessler, M.D., introduced an expert report in an ongoing lawsuit against Bayer.²⁰ In it, he cites internal Bayer documents. According to Dr. Kessler, in June 2004, Bayer employees wrote in a draft paper that

Compared to the three other OCs [oral contraceptives], Yasmin has a several fold increase in the reporting rates for DVT [deep vein thrombosis], PE [pulmonary embolism] and confirmed VTEs [venous thromboembolism]... When considering only serious AEs [adverse events], the reporting rate for Yasmin was 10 fold higher than that with the other products which were very similar in magnitude.²¹

Dr. Kessler’s report was filed by Bayer in federal court as a sealed exhibit to a motion to exclude expert testimony from trials in Yaz litigation. The federal judge ultimately decided to unseal Dr. Kessler’s report, which allowed it to be released to the public. However, according a lawyer for the plaintiffs, FDA decided not to provide the report to the joint committee meeting because it was not unsealed or available to the public until after the previously published deadline of November 23, 2011, for submissions of materials for the Committee’s review.²²

Industry ties

Were the individual members of the joint committee voting strictly on the basis of their expert professional judgment, as the public has a right to expect? Or might the votes of some of the joint committee members have been influenced by past, present, or potential future monetary payments or other benefits?

One advisory committee member, Paula Hillard, M.D., professor of obstetrics and gynecology at Stanford University School of Medicine, had financial arrangements with Bayer that appeared to have created a financial conflict of interest.²³ Publicly available documents indicate that this conflict was in existence as recently as 2010. Dr. Hillard was and still is listed on the medical school’s website as a paid consultant receiving \$5,000 or more per year from a division of Bayer.²⁴ In response to a query from POGO, a Stanford spokeswoman emailed that “In 2010, Dr.

¹⁸ Joint Meeting Transcript, p. 62.

¹⁹ Joint Meeting Transcript

²⁰ *In Re: Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Products Liability Litigation, Case 3:09-md-02100-DRH-PMF, Document 2223-1, Filed December 30, 2011, Second Supplemental Expert Report, David A. Kessler, MD.* <http://www.pogo.org/resources/public-health/kessler-report-yasmin.html> (hereinafter *Kessler Report*)

²¹ *Kessler Report*

²² Email from Donald C. Arbilit, attorney for the plaintiffs *In Re: Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Products Liability Litigation, Case 3:09-md-02100-DRH-PMF, Document 2223-1*, and Nick Schwellenbach, Project On Government Oversight, January 11, 2012.

²³ Email from Margarita J. Gallardo, Stanford University, to Nick Schwellenbach, Project On Government Oversight, January 9, 2012. (hereinafter *Gallardo Email*); Stanford School of Medicine, “Paula Hillard: Industry Relationships,” 2012. <http://med.stanford.edu/profiles/obgyn/frdActionServlet?choiceId=showCOIs&&fid=8093> (Downloaded January 10, 2012) (hereinafter “*Paula Hillard: Industry Relationships*”)

²⁴ “*Paula Hillard: Industry Relationships*”

Hillard's reimbursements from Bayer for consulting were less than \$10,000."²⁵ Furthermore, according to the Stanford spokeswoman, in Dr. Hillard's disclosure to the FDA, "she informed the FDA that she attended two Bayer meetings in 2010. The first, in October, discussed a range of oral contraceptives which contain drospirenone. A second meeting in November was related to the use of the levonorgestrel intrauterine system, a device not under consideration by the panel."²⁶ Her spokeswoman also stated that "Dr. Hillard did no work for Bayer in 2011."

"Dr. Hillard has fully disclosed to the best of her recollection all required information regarding potential conflicts of interest to the FDA," the spokeswoman emailed.²⁷ Through the spokeswoman, Dr. Hillard issued a "no comment" when asked if her ties to Bayer in any way affected her judgment on the vote.²⁸

Dr. Hillard has a long relationship with Bayer and was seen by the company as a "Yasmin advocate," according to internal Bayer documents described by former FDA Commissioner Dr. Kessler in a December 26, 2011, report he prepared as an expert witness for plaintiffs.²⁹ Several thousand women are suing Bayer for injuries they say are caused by Yaz and Yasmin, and for Bayer's allegedly deceptive marketing practices.³⁰ Bayer filed a motion under seal to exclude the opinions stated in Dr. Kessler's report,³¹ which attached his report as a sealed exhibit. However, the federal judge issued an order unsealing the motion and the exhibits,³² which made Dr. Kessler's report publicly available on January 3, 2012.

As early as March 2003, Bayer intended to implement a plan "to educate this Key Opinion Leader," a reference to Dr. Hillard, according to Dr. Kessler's report which quoted a Bayer employee. The plan to engage Dr. Hillard, according to Dr. Kessler, involved discussing the risk of venous thromboembolism.³³ As mentioned above, a key issue at the December 8 joint meeting was whether the risks of venous thromboembolism with Yaz and Yasmin outweighed the benefits.

²⁵ Gallardo Email

²⁶ Gallardo Email

²⁷ Gallardo Email

²⁸ Gallardo Email

²⁹ Kessler Report, p. 4.

³⁰ *Kerry Sims v. Bayer Corporation, et al.*, Case 3:09-cv-100012-DRH-PMF, Document 46-1, Filed December 31, 2009. <https://www.documentcloud.org/documents/282745-kerry-sims-v-bayer-et-al-complaint.html>; According to a news report, there are over "10,000 suits over injuries allegedly caused by the drugs." Jef Feeley and Naomi Kresge, "Bayer Judge Postpones First Yaz Trial, Orders Birth-Control Cases Mediated," *Bloomberg*. January 5, 2012. <http://www.bloomberg.com/news/2012-01-05/bayer-judge-postpones-first-yaz-trial-orders-birth-control-cases-mediated.html> (Downloaded January 10, 2012)

³¹ *In Re: Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Products Liability Litigation*, Case 3:09-md-02100-DRH-PMF, Document 2223-2, Filed December 30, 2011. <https://www.documentcloud.org/documents/282744-bayer-complaint-letter.html> (Downloaded January 10, 2012)

³² On the court docket, the judge issued an order on January 3, 2012, that directed the clerk of the court to unseal the exhibits. *In Re: Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Products Liability Litigation*, Case 3:09-md-02100-DRH-PMF, Signed by Chief Judge David R. Herndon on January 3, 2011.

³³ Kessler Report, p. 3; Email from Barry Lee to Beth Bell regarding "Medical Center of Delaware Education meeting," March 14, 2003. <https://www.documentcloud.org/documents/283011-email-regarding-hillard-march-2003.html>

From 2008 through the end of 2010, Dr. Kessler recounts numerous Bayer documents that describe Dr. Hillard's involvement as a "Bayer trained speaker" and her involvement in "promotional" programs.³⁴ For instance, a "Bayer Tactical Brief" dated January 2010 describes a "video shoot with Dr. Paula Hillard to illustrate patient counseling techniques on the safety of YAZ."³⁵

Also, according to Dr. Kessler, Dr. Hillard was paid \$6,200 for one and half days of service in October 2010. Dr. Kessler pointed to documents list as Dr. Hillard as advising Bayer on October 16-17, 2010, concerning Yaz. Dr. Kessler said she advised Bayer on the benefits and limitations of a study of Yaz's safety.³⁶

Earlier, in 2008, a "Bayer Corporate Account Update" stated:

New west coast speaker...Paula Hillard, MD recently relocated from Cincinnati, OH to Stanford—this enables us to now have another huge Mirena and Yasmin advocate here in Nor Cal—she will be well utilized!³⁷

In addition, three additional joint committee members had past financial arrangements with companies with a stake in the December 8 meeting's outcome. One of these three was the acting chair of the December 8 joint meeting on Yaz and Yasmin.

At no point during the meeting was there a disclosure of Dr. Hillard's or the following three joint committee members' past ties to Bayer, which were as follows:

- Julia V. Johnson, M.D., chaired the meeting of the FDA advisory committee. She is professor and chair of the department of obstetrics and gynecology at University of Massachusetts Medical School. On a university web page, Dr. Johnson acknowledged doing work involving Bayer products that preceded 2009. Dr. Johnson conducted four clinical trials, including work on hormonal products containing drospirenone, for Bayer (or Berlex, which was acquired by Bayer³⁸) from 2005 through 2008.³⁹ In response to an inquiry from POGO, Dr. Johnson emailed POGO that "Research was done at my former institution testing products from Bayer and Berlex, but there were no grants" and there

³⁴ *Kessler Report*, pp. 4-6.

³⁵ *Kessler Report*, p. 5; Bayer HealthCare Pharmaceutical, "Tactical Brief."

<https://www.documentcloud.org/documents/282488-tactical-brief-on-video-shoot-with-paula-hillard.html>

³⁶ *Kessler Report*, pp. 5-6. Bayer HealthCare, "Women's HealthCare Scientific Advisory Board: Safety Studies & Pharmacovigilance," October 16-17, 2010. <https://www.documentcloud.org/documents/282489-bayer-scientific-advisory-board-lists-paula.html> (Downloaded January 10, 2012); Bayer HealthCare, "Women's Healthcare Scientific and Health Economics & Outcomes Research Advisory Boards: YAZ Flex & CADDY," October 16-17, 2010. <https://www.documentcloud.org/documents/282490-bayer-scientific-advisory-board-on-yaz-lists.html> (Downloaded January 10, 2012)

³⁷ *Kessler Report*, p. 4; Bayer HealthCare Pharmaceuticals, "Quarter 3, 2008 Report."

<http://www.pogo.org/resources/public-health/bayer-corporate-account-update-yasmin-quarter-3-2008.html>

³⁸ Bayer HealthCare Pharmaceuticals, "About Our New Company." <http://www.berlex.com/html/aboutbhc.htm> (Downloaded January 10, 2012)

³⁹ University of Massachusetts Medical School, "UMass Profiles: Julia V Johnson MD."

<http://profiles.umassmed.edu/profiles/ProfileDetails.aspx?From=Pinfo&Person=1258> (Downloaded January 10, 2012)

was no “personal funding... The hormonal product was menopausal hormone therapy and not oral contraceptives as reviewed on 12/8.” She added that the “FDA is aware of my research.”⁴⁰ When asked whether her ties to Bayer biased her judgment on her December 8 vote, she emailed to POGO that “I have no bias for Bayer or Berlex products. When there are studies that contradict, further research must be done to determine patient risk.”⁴¹

- Anne E. Burke, M.D., is an assistant professor of obstetrics and gynecology at The Johns Hopkins Bayview Medical Center. In the financial disclosure section of a 2008 article in the journal *Obstetrics & Gynecology*, this joint committee member acknowledged receiving research funding from Bayer.⁴² In another 2008 article in the journal *Contraception*, Dr. Burke disclosed a “Conflict of Interest” based upon receipt of research funding from Bayer.⁴³ Dr. Kessler cites a Bayer document listing Dr. Burke as a “Bayer Contraception Expert.”⁴⁴ Dr. Burke told POGO that she does not get currently—and has not in the last several years—received funding from Bayer or Berlex to be a “Contraception Expert” for them. She added that she disclosed to the best of her knowledge all her relevant activities to the FDA. And “in no way, did any of the imputed conflicts past and present affect my analysis of the information presented at the [December 8] meeting, nor my decision on the issue,” said Dr. Burke.⁴⁵
- Elizabeth G. Raymond, M.D., is a senior medical associate at Gynuity Health Projects in New York. According to *The Washington Monthly*, which first reported on these members’ ties to industry, Dr. Raymond “conducted studies funded by Barr, which has a licensing agreement with Bayer for generic versions of Yaz.”⁴⁶ Dr. Raymond told POGO via email that “I disclosed all of my potentially relevant activities to FDA. FDA

⁴⁰ Email from Dr. Johnson to Nick Schwellenbach, Project On Government Oversight, January 9, 2012. (hereinafter Dr. Johnson Email)

⁴¹ Dr. Johnson Email

⁴² Mitchell D. Creinin, MD, et al., “Multicenter Comparison of the Contraceptive Ring and Patch: A Randomized Controlled Trial,” *Obstetrics & Gynecology*, February 2008, Vol. 111, Issue 2, Part 1, pp. 267-277. http://journals.lww.com/greenjournal/Fulltext/2008/02000/C_Reactive_Protein_Concentrations_and_Subsequent.4.aspx (Downloaded January 10, 2012)

⁴³ Jeffrey T. Jensen, et al., “Effects of switching from oral to transdermal or transvaginal contraception on markers of thrombosis,” *Contraception*, September 1, 2008, Vol. 78, Issue 6, pp. 451-458. [http://www.contraceptionjournal.org/article/S0010-7824\(08\)00368-5/fulltext](http://www.contraceptionjournal.org/article/S0010-7824(08)00368-5/fulltext) (Downloaded January 10, 2012)

⁴⁴ Kessler Report, p. 7; “Bayer Document.” <https://www.documentcloud.org/documents/282491-anne-burke-listed-as-bayer-contraception-expert.html> (Downloaded January 10, 2012)

⁴⁵ Phone conversation between Dr. Anne Burke and Nick Schwellenbach, Project On Government Oversight, January 11, 2012.

⁴⁶ Jeanne Lenzer and Keith Epstein, “The Yaz Men: Members of FDA panel reviewing the risks of popular Bayer contraceptive had industry ties,” *The Washington Monthly*, January 9, 2012.

http://www.washingtonmonthly.com/ten-miles-square/2012/01/the_yaz_men_members_of_fda_pan034651.php# (Downloaded January 10, 2012); Bayer HealthCare Pharmaceuticals, “Bayer concludes supply and licensing agreements for Yasmin® and YAZ® with Barr for the United States,” June 24, 2008.

http://pharma.bayer.com/scripts/pages/en/news_room/news_room/news_room60.php (Downloaded January 11, 2012) (hereinafter “Bayer concludes supply and licensing agreements for Yasmin® and YAZ® with Barr for the United States”)

determined that I had no conflict of interest, which was appropriate since I do not.”⁴⁷ She said her study funded by Barr was over and submitted as a paper in May 2008, which was a month before Barr signed its agreement with Bayer in June 2008.⁴⁸ Furthermore, Dr. Raymond told POGO “my work funded by Barr (which did not involve drospirenone) did not in any way affect my judgment regarding my vote.”⁴⁹

In response to a query from POGO, the FDA reiterated what was said at the joint meeting.⁵⁰ During the meeting, the designated federal officer stated there were no members of the joint committee with conflicts of interest, according to the transcript. The FDA officer stated that the “FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws.” The officer added that committee members and temporary voting members had “been screened for potential conflicts of interest of their own, as well as those imputed to them....Based on the agenda for today’s meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting,” the designated federal officer concluded.⁵¹

The vote⁵²

All four joint committee members with past or current financial ties to companies with a stake in the decision voted “yes” on whether the benefits of the drospirenone-containing oral contraceptives outweighed the risks.⁵³ The vote of the whole joint committee was 15 “yes” and 11 “no.”⁵⁴

Dr. Burke said she voted yes because:

I don’t think I was expecting it to be more effective than other pills on the market, and while I acknowledge that there does seem to be a moderate increased risk, it’s still lower than the risks of pregnancy. And like some other folks who have spoken, a no vote

⁴⁷ Email from Elizabeth G. Raymond, M.D., Gynuity Health Projects, to Nick Schwellenbach, Project On Government Oversight, January 9, 2012. (hereinafter Elizabeth G. Raymond Email)

⁴⁸ Elizabeth G. Raymond Email; “Bayer concludes supply and licensing agreements for Yasmin® and YAZ® with Barr for the United States”

⁴⁹ Elizabeth G. Raymond Email

⁵⁰ Morgan Liscinsky Email

⁵¹ Joint Meeting Transcript, pp. 3-4.

⁵² Above, in the text of this letter, we describe the first vote, which the FDA posed to the joint committee members as follows: “VOTE: Do you believe that, in the general population of women who desire contraception, the benefits of the (DRSP)-containing oral contraceptives for prevention of pregnancy outweigh their risks?” (DRSP is drospirenone.) As noted in the text, there were 15 yes votes and 11 no votes. The second and final vote was posed to joint committee members as follows: “VOTE: Do you believe the current (DRSP) labels adequately reflect the risk/benefit profile for these products?” There were 5 yes votes and 21 no votes: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, “Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee: Questions to the Committee,” December 8, 2011.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugAdvisoryCommittee/UCM284776.pdf> (Downloaded January 11, 2012)

⁵³ Morgan Liscinsky Email

⁵⁴ Morgan Liscinsky Email

sounded like it would be—to take the product off the market. I’m not quite sure that’s necessary at this point.⁵⁵

Advisory committee member Enrique Schisterman, Ph.D., explained that he “voted no because there are plenty of other alternatives that do not show any increased risk. One of the main things is do not harm. And even a small excess of risk is no—we shouldn’t take that lightly.”⁵⁶ Dr. Schisterman is senior investigator and chief of the epidemiology branch of the National Institute of Child Health and Human Development.⁵⁷

Industry ties on other FDA advisory committees

In 2005, *The New York Times* revealed that 10 out of 32 members of an FDA advisory committee that reviewed the pain medicines Celebrex, Bextra, and Vioxx had consulted for the manufacturers of those drugs. An FDA employee stated, according to the *Times*, before meetings of the committee that “The Food and Drug Administration acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.”⁵⁸

The *Wall Street Journal*, in two articles in 2010, reported that two members of another FDA advisory committee examining the diabetes drug Avandia received payments from drug makers. One had been a paid speaker for the maker of Avandia,⁵⁹ the other a paid speaker for one of Avandia’s rivals.⁶⁰ Both said they had told the FDA about these financial arrangements, but another advisory committee member told the *Journal* he wishes the committee had known about their fellow members’ ties.⁶¹

Questionable impartiality and conflicts of interest

These cases may demonstrate the failure of the FDA to adequately determine potential conflicts of interest and questionable impartiality. Most members of FDA advisory committees are Special

⁵⁵ Joint Meeting Transcript, p. 112.

⁵⁶ Joint Meeting Transcript, p. 112.

⁵⁷ Department of Health and Human Services, National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Division of Epidemiology Statistics and Prevention Research, “Enrique F. Schisterman, Ph.D.”

<https://science.nichd.nih.gov/confluence/display/despr/Enrique+F.+Schisterman,+Ph.D.> (Downloaded January 10, 2012)

⁵⁸ Gardner Harris and Alex Berenson, “10 Voters on Panel Backing Pain Pills Had Industry Ties,” *The New York Times*, February 25, 2005. <http://www.nytimes.com/2005/02/25/politics/25fda.html> (Downloaded January 10, 2012) To learn this, the *Times* had asked the Center for Science in the Public Interest to examine disclosures by the members in medical journal articles.

⁵⁹ Alicia Mundy, “Panelist Who Backed Avandia Gets Fees From Glaxo,” *The Wall Street Journal*, July 20, 2010. http://online.wsj.com/article/NA_WSJ_PUB:SB10001424052748704720004575377552600421936.html (Downloaded January 10, 2012) (hereinafter “Panelist Who Backed Avandia Gets Fees From Glaxo”)

⁶⁰ Alicia Mundy, “Glaxo Rival Paid Fees to Doctor Who Voted Against Avandia,” *The Wall Street Journal*, July 20, 2010. http://online.wsj.com/article/NA_WSJ_PUB:SB10001424052748704723604575379292803755042.html (Downloaded January 10, 2012)

⁶¹ “Panelist Who Backed Avandia Gets Fees From Glaxo”

Government Employees (SGEs).⁶² FDA appears not to be following the federal regulation (5 C.F.R. 2635.502) regarding personal and business relationships with respect to the SGEs who serve on FDA advisory committees, though FDA guidance on determining conflict of interest of committee members specifically refers to this regulation.⁶³ The regulation stipulates that the agency should review and authorize the SGE's participation whenever "circumstances would cause a reasonable person with knowledge of the relevant facts to question [the employee or SGE's] impartiality in the matter."⁶⁴

At a minimum, the financial disclosure forms of all members should be thoroughly reviewed by the FDA before each meeting to determine whether questions might arise about an advisory committee member's impartiality with regard to the subject(s) of the meeting. If such questions arise, the FDA must clearly document why that member is authorized or not to participate in the meeting, and the documentation should be made publicly available online before the meeting occurs.

The FDA's current guidelines on public disclosure of conflicts of interest

We recognize your efforts to improve and clarify the guidelines for disclosure of financial conflicts among members of advisory committees. In your April 21, 2010, letter to FDA staff⁶⁵ you noted that the draft guidance document of March 2010 would expand the public disclosure of a committee member's financial arrangements whenever a waiver is issued.⁶⁶

Nonetheless, the FDA's review of the joint committee's industry ties proves once again, if further proof were needed, that the draft guidelines of March 2010 are inadequate. When the final guidelines are released, they will presumably be very similar to the draft guidelines. If we are right about this, the requirements for public disclosure under the new guidelines will continue to be too weak and thus will enable experts to serve on advisory committees despite conflicts that are not disclosed to the public, as occurred during the review of Yaz and Yasmin.

⁶² Department of Health and Human Services, Food and Drug Administration, "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers: Draft Guidance," March 2010, p. 3.

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM209201.pdf> (Downloaded January 10, 2012) (hereinafter "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers: Draft Guidance")

⁶³ Department of Health and Human Services, Food and Drug Administration, "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," August 2008, p. 12.

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf> (Downloaded January 11, 2012) (hereinafter "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")

⁶⁴ 5 C.F.R. 2635.502, <http://www.gpo.gov/fdsys/pkg/CFR-2011-title5-vol3/pdf/CFR-2011-title5-vol3-sec2635-502.pdf> (Downloaded January 10, 2012)

⁶⁵ Department of Health and Human Services, Food and Drug Administration, "Advisory Committees: Commissioner's letter to FDA staff on disclosure of financial conflicts of interest," April 21, 2010.

<http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm209001.htm> (Downloaded January 10, 2012) (hereinafter "Advisory Committees: Commissioner's letter to FDA staff on disclosure of financial conflicts of interest")

⁶⁶ "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers: Draft Guidance"

We ask that you ensure that the FDA's new guidelines include stronger requirements for public disclosure, particularly of advisory committee members' financial arrangements.

Fuller public disclosure

On August 16, 2010, we wrote you and others at FDA about public disclosure of each advisory committee member's financial arrangements. In that document we argued for public disclosure through a simple mechanism: online posting of Form FDA 3410 for every SGE serving on an advisory committee.⁶⁷

Every SGE serving as a member of an FDA advisory committee must file a FDA 3410 form with the FDA. The form requests information about "Current Financial Interests" and "Past Financial Interests."⁶⁸ For the great majority of advisory committee members, all the information in the form remains known only to officials in the FDA.

Occasionally, advisory committee members are granted waivers that allow them to serve on the committee despite their real or apparent conflicts of interest. For these members, the FDA chooses certain information on the FDA 3410 form and makes this information public as a part of the waiver process.

Thus, of the total financial information in the FDA 3410 forms for an advisory committee meeting, only a very small fraction is made public.⁶⁹ There have been other cases of FDA advisory committees with members who have industry ties that could be construed as conflicts of interest, but who have not received a waiver and have not had to publicly disclose their ties. These ties are then unknown to the other committee members and the public. One obvious way to mitigate this problem is to post all completed FDA 3410 forms.

Controversy over past versus current financial interests

There is a lack of agreement inside and outside the FDA on the requirements for disqualifying an expert from service on an advisory committee based on the expert's *past* financial interests. In a May 2007 letter to FDA, a general counsel for PhRMA argued that divested or past financial interests should not disqualify or limit participation in FDA advisory committees.⁷⁰ In contrast, a

⁶⁷ Public Comment submitted by Ned Feder, M.D., Staff Scientist, Project On Government Oversight, regarding "The Finances of FDA Advisory Committee Members: If Information Must be Withheld, Let it be Done Openly: The review of Avandia: Present disclosure policies are not strong enough," August 16, 2010. <http://pogoarchives.org/m/ph/public-comment-nf-20100810.pdf>

⁶⁸ Department of Health and Human Services, Food and Drug Administration, "Confidential Financial Disclosure Report for Special Government Employees." <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048297.pdf> (Downloaded January 10, 2012) (hereinafter "Confidential Financial Disclosure Report for Special Government Employees")

⁶⁹ "The law permits FDA to grant waivers for experts on its advisory committees. FDA may not exceed a cap set in the law on the number of waivers to be granted. For fiscal year 2010, this cap is set at about 13% of all advisory committee members participating in advisory committee meetings; we currently are granting waivers for less than 5%." "Advisory Committees: Commissioner's letter to FDA staff on disclosure of financial conflicts of interest"

⁷⁰ Public Comment submitted by Scott M. Lassman, General Counsel, PhRMA, regarding "Docket Number 2007D0101; Draft 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; 72 Fed.

March 2007 FDA draft guidance document suggests that whenever a particular financial interest would be disqualifying if currently held, then that same interest could be regarded as disqualifying if held within the preceding 12 months.⁷¹

This March 2007 FDA draft guidance document notes the importance of public perception:

Although financial interests that are not currently held do not constitute a conflict of interest under 18 U.S.C. 208, we believe that the public may perceive some previously held financial interests in organizations potentially affected by advisory committee recommendations as problematic.⁷²

Moreover, March 2010 draft guidelines state:

FDA screens advisory committee members broadly for covered relationships that could present even the appearance that they have conflicts of interest that could affect their impartiality.⁷³

There's a particularly important reason for the FDA to deal more aggressively with past financial interests. A federal regulation (5 C.F.R. 2635.502) indicates that the existence of a conflict of interest does not depend exclusively on current financial ties between a federal employee and an interested party. Instead, a conflict of interest may exist for a particular matter whenever "circumstances would cause a reasonable person with knowledge of the relevant facts to question his impartiality in the matter."⁷⁴

In your April 21, 2010, letter to FDA staff, you wrote that dealing with an advisory committee member with a conflict of interest is "a difficult judgment call best made by senior career agency officials."⁷⁵ We agree, but we also believe that this judgment call should not be made by FDA officials behind permanently closed doors. If an advisory committee member has past financial interests that a reasonable person might regard as creating a conflict of interest, those past interests should be disclosed to the other committee members and the public—regardless of the decision by FDA officials that the past interests either do or do not create a conflict of interest.

Reg. 13805," May 21, 2007, p. 4. <http://www.fda.gov/ohrms/dockets/DOCKETS/07d0101/07D-0101-EC42-Attach-1.pdf> (Downloaded January 10, 2012)

⁷¹ Department of Health and Human Services, Food and Drug Administration, "Draft 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," March 2007. <http://www.fda.gov/oc/advisory/waiver/coiguidedft.html> (Downloaded January 11, 2012) (hereinafter "Draft 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")

⁷² "Draft 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"; This language was removed from subsequent guidance issued in August 2008. "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"

⁷³ "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers: Draft Guidance," p. 3.

⁷⁴ 5 C.F.R. 2635.502

⁷⁵ "Commissioner's letter to FDA staff on disclosure of financial conflicts of interest"

Need for meaningful enforcement of disclosure

Form FDA 3410 states:

Falsification of information or failure to file or report information required to be reported may subject you to disciplinary action by your employing agency or other appropriate authority. Knowing and willful falsification of information required to be reported may also subject you to criminal prosecution.⁷⁶

The FDA should have other means of discipline for failure to fully and accurately disclose relevant ties in their Form FDA 3410 other than criminal prosecution, which requires difficult-to-acquire proof of intent to deceive, or an SGE's employer to discipline the SGE. An administrative penalty, such as being barred from participation on an advisory committee or financial penalty, should be considered.

Conclusion

We are troubled by the industry ties of some of the FDA joint committee members who reviewed the safety of Yaz and Yasmin on December 8, 2011. Because of the industry ties of these members, the joint committee's conclusion—which amounted to an endorsement of the safety of these oral contraceptives—should be disregarded. A new advisory committee—without questionable impartiality or any conflicts of interest—should re-evaluate the safety of Yaz and Yasmin.

In the future, if a reasonable person would have questions about the impartiality of any member of an advisory committee regarding a matter before the committee, the FDA should not allow that member to participate in the matter and should make public the relevant information about that committee member.

Finally, the FDA's forthcoming guidelines on public disclosure are meant to deter conflicts of interest. However, as this episode shows, the draft guidelines are too weak. The FDA should draft new guidelines requiring fuller public disclosure of possible financial conflicts of interest. Such disclosure could be accomplished by online posting of each member's FDA 3410 form with redactions as allowed under the law. In addition, the guidelines should address the matter of impartiality beyond a direct conflict of interest. If the FDA issued language to rely on 5 C.F.R. 2635.502 in the upcoming guidance, FDA reviewers would integrate the question of impartiality into their reviews of possible conflicts of interest.

Please inform us how the FDA plans to deal with these problems.

Sincerely,



Danielle Brian
Executive Director



Ned Feder, M.D.
Staff Scientist

⁷⁶ "Confidential Financial Disclosure Report for Special Government Employees"