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March 9, 2006

Honorable Andrew C. von Eschenbach, M.D.
Acting Commissioner
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Dear Dr. von Eschenbach:

The Food and Drug Administration appears to be seriously mischaracterizing its analysis of the regulatory issues surrounding Plan B, the emergency contraception pill.

We already know that FDA created a regulatory "Catch 22" to justify the predetermined political decision to block over-the-counter sales of Plan B. It was only after repeated urging from the FDA itself — despite a lack of scientific justification — that the manufacturer proposed over-the-counter access to women sixteen and over and prescription access for those younger. Yet the agency then used these age restrictions to justify an indefinite delay, claiming that it needs more time to assess whether an over-the-counter switch can be restricted based on age; how such a restriction could be enforced; and whether a product with a single package can legally be marketed differently to different populations.

Previously undisclosed documents reveal that in addition to having created the situation it now protests as too complex to solve, FDA has seriously mischaracterized its consideration of the regulatory questions at stake. Despite FDA's claims that it needs time to analyze the "novel" issues, the agency had apparently been considering them for at least a year before its August 2005 decision to delay action. The documents also show that during this period, FDA's Office of Chief Counsel repeatedly brushed aside the requests of agency officials for a dispositive legal analysis. In essence, the agency was well aware of the regulatory questions that would arise when it suggested age restrictions, but simply did not resolve them in a timely manner.

The documents I have obtained, along with continuing questions about FDA's document retention policies, do not reflect well on FDA. They further undermine the agency's contention that the Plan B decision was based on legitimate science-based factors. I am writing to ask for an explanation of the new documents and FDA's actions.

Background

Over the last several years, FDA repeatedly urged Plan B's sponsor, Barr Laboratories, to consider and propose age restrictions on over-the-counter access. Yet once Barr proposed such a plan, the agency claimed that the questions it raised were too difficult to solve.

Barr submitted an application to sell Plan B over the counter, without restrictions, in April 2003. A GAO investigation found that FDA suggested age restrictions in discussions with the sponsor as early as September 2002 and again in October 2003.[1] According to minutes of a February 2004 meeting, FDA Commissioner Mark McClellan "directed" FDA staff to "continue to work with the sponsor on a marketing plan to limit availability of the product over the counter and to consider the most appropriate age groups to be restricted from access to the product."[2]

In March 2004, Barr submitted an amendment to its application, proposing a dual-marketing plan with over-the-counter access for women sixteen and above, and prescription access for those younger.[3]

In May 2004, FDA issued a not-approvable letter to Barr Laboratories.[4] FDA wrote that the March 2004 amendment proposing a dual-marketing plan was preliminary and incomplete, and that therefore the agency had only reviewed the proposal to offer unrestricted over-the-counter access. FDA then denied the application on the grounds that there was insufficient data on use among women under sixteen, despite consensus among agency advisors and staff on the public health benefit and safety of making Plan B more accessible.[5]

In the May 2004 letter, FDA told Barr that it could either submit more data on adolescent safety or provide more information on the dual-marketing approach:

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[1] Government Accountability Office, *Food and Drug Administration: Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual* (GAO-06-109) (Nov. 14, 2005).

[2] *Id.* at 18.

[3] Letter from Steven Galson, Acting Director, Center for Drug Evaluation and Research, FDA, to Joseph A. Carrado, Senior Director, Regulatory Affairs, Barr Laboratories (May 7, 2004) (online at http://www.fda.gov/cder/drug/infopage/planB/planB_NALetter.pdf).

[4] *Id.*

[5] FDA, Center for Drug Evaluation and Research, Nonprescription Drugs Advisory Committee (NDAC) in Joint Session with the Advisory Committee for Reproductive Health Drugs (ACRHD) Meeting (Dec.16, 2003) (online at http://www.fda.gov/ohrms/dockets /ac/03/transcripts/4015T1.DOC); *FDA: Plan B Sales Rejected Against Advice; Official Denies That Politics Blocked Contraceptive's Over-the-Counter Status*, Washington Post (May 7, 2004).

> [Y]ou could supply additional information in support of the revised indication to allow for marketing of Plan B as a prescription-only product for women under the age of 16 years and a nonprescription product for women 16 years and older, including draft product labeling. If you take the latter approach, your response to this letter would have to include details of how you propose to implement simultaneous prescription and nonprescription marketing of Plan B for women of different ages in a single packaging configuration while complying with all relevant statutory and regulatory requirements for labeling and marketing of this product.[6]

In July 2004, Barr submitted an amended application with age restrictions. FDA determined that the amended application constituted a complete response to the not approvable letter.[7]

In August 2005, FDA announced an indefinite delay of action on the amended Plan B application. According to FDA, the amended application raised "difficult and novel" regulatory questions, and the agency therefore initiated a public comment period on whether FDA should initiate a rulemaking.[8] The agency told Barr Laboratories:

> Your application has presented us with three difficult and novel issues. Specifically, you have proposed that Plan B be marketed in a single package, and sold either as Rx or OTC, depending on the age of the patient. While the Agency has allowed the same active ingredient to be marketed both Rx and OTC based on indication, strength, dosage form and route of administration, the Agency has never determined whether a drug may be both Rx and OTC based on the age of the individual using the drug. A related concern is how, as a practical matter, an age-based distinction could be enforced. In addition, we have never been confronted with whether the Rx and OTC versions of the same active ingredient may be marketed in a single package.[9]

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[6] Letter from Steven Galson, *supra* note 3.

[7] Letter from FDA Commissioner Lester M. Crawford to Joseph A. Carrado, Senior Director, Regulatory Affairs, Barr Laboratories (Aug. 26, 2005) (online at http://www.fda.gov/cder/drug/infopage/planB/Plan_B_letter20050826.pdf). The letter acknowledges that the submission on July 21, 2004 "constituted a complete response to our May 6, 2004 Not Approvable action letter."

[8] Food and Drug Administration, *Advance Notice of Proposed Rulemaking, 21 CFR Part 310 [Docket No. 2005N–0345] Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-The-Counter Drug Product* (Aug. 26, 2005) (online at http://www.fda.gov/bbs/topics/NEWS/2005/cd0584.pdf).

[9] Letter from FDA Commissioner Lester M. Crawford, *supra* note 7.

A statement by then-FDA Commissioner Lester Crawford expressed similar views:

> The issues that we were asked to resolve, and the proposal that was put forward by Barr Labs, presented us with many difficult and novel policy and regulatory issues. In some cases, the questions we were asked to answer were unprecedented for this agency. ... What we are saying today is that the Agency is unable at this time to reach a decision on the approvability of the application because of these unresolved regulatory and policy issues that relate to the application we were asked to evaluate. ... These rules have lots of implications that aren't always easy to anticipate at first blush.[10]

The questions that Dr. Crawford says the agency was "asked to answer" were purely a result of the agency's actions. The very age restrictions that FDA had suggested for years had become the agency's justification for indefinite delay on the Plan B application.

The New Documents

Documents that I have received call into question FDA's assertions about the "novelty" of the regulatory questions raised by the dual-marketing plan. These documents show that policy staff both analyzed and outlined potential solutions for the regulatory questions at least 15 months before FDA publicly claimed that the questions were so "novel" that they required an indefinite delay. Furthermore, the documents indicate that FDA's Office of Chief Counsel was aware of the relevant regulatory questions for at least as long, yet apparently failed to complete a dispositive legal analysis. In effect, it appears that FDA was not surprised by the regulatory questions; instead, it simply failed to complete an analysis that could have paved the way for approval.

In April 2004, Jane Axelrad, Associate Director for Policy at FDA's Center for Drug Evaluation and Research (CDER), wrote to several colleagues, including then-Acting Director of CDER Dr. Steven Galson (who signed the May 2004 not approvable letter) and Acting Deputy Commissioner of Operations Dr. Janet Woodcock. The email stated, "Attached is a brief summary of the results of our analysis of the issues associated with the Barr proposal on Plan B. As it has not been shared outside the Center, I would appreciate if you could keep it close hold."[11] The memo attached to the email poses the question: "If FDA finds that Plan B's directions for use are adequate for safe and effective self-medication by women 16 and older, but cannot similarly find the directions adequate for women under age 16, can FDA approve Barr's proposal?"[12]

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[10] FDA, *FDA Takes Action on Plan B; Statement by FDA Commissioner Lester M. Crawford* (Aug. 26, 2005) (online at http://www.fda.gov/bbs/topics/NEWS/2005/NEW01223.html).

[11] Email from Jane Axelrad to FDA staff (Apr. 13, 2004).

[12] CDER, *Plan B Proposal to Market Plan B as Joint OTC/RX* (Draft).

The memo reviews statutory and regulatory requirements and concludes that "approval would be consistent with precedent" and that "Rx and OTC Plan B could be marketed in the same package and comply with applicable statutory and regulatory provisions."[13] It then describes how Barr could comply with provisions related to package labeling, directions for use, and advertising.[14] Based on Ms. Axelrad's email, this memo apparently represents only a summary of a more detailed analysis conducted by CDER.

Other documents reveal that well before the August 2005 decision, agency officials were asking the Office of Chief Counsel (OCC), which is the part of FDA that ultimately determines if a particular course of action is legally sustainable, to assess the regulatory questions that a dual-marketing plan would raise. In one of these documents, an April 1, 2004, review, a Deputy Division Director noted that Commissioner McClellan and senior management had asked OCC to assess a restricted distribution plan that would exclude adolescents:

> FDA legal counsel was asked to assess whether the restrictions outlined are feasible within the current regulatory framework prior to taking the not-approvable action on this [application] so that this distribution plan can be requested by the FDA within the non-approval letter for future consideration in a re-submission.[15]

This review was apparently not completed by OCC. Minutes from a teleconference held just prior to the May 2004 not approvable letter indicate:

> Barr's March 11, 2004 submission of a marketing plan for OTC availability for older women and prescription for adolescents under 16 years was forwarded to the Office of the Chief Counsel (OCC) but no final review was done.[16]

In a May 14, 2004, email, Dr. John Jenkins, Director of the Office of New Drugs, wrote to Dr. Galson, Dr. Woodcock, and other colleagues to set out a schedule for expeditious consideration of the questions that would be raised by limiting over-the-counter-access to women 16 and over. According to this email, the amended application would be subject to the Prescription Drug User Fee Act (PDUFA), which sets performance goals for FDA consideration of drug applications. Dr. Jenkins wrote:

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[13] *Id.*

[14] *Id.*

[15] *Deputy Division Director Summary Review of New Drug Application* (NDA 21-045) 49 (Apr. 1, 2004).

[16] CDER, *Meeting Notes of Internal Meeting on Not-Approvable Decision ("Teleconference Minutes")* (May 5, 2004).

> We will have a 6-month PDUFA clock for this Class 2 resubmission. I would propose that we will need to get OCC to agree to complete their review by the end of month 3, or month 4 at the latest, so that there will be time in the review cycle to complete any negotiations about any changes needed to the labeling (assuming they find the proposal legal). ... I would hope that you and Janet [Woodcock] would coordinate with [Chief Counsel] Dan Troy to have OCC continue to review the draft proposal that was submitted on the last round so that they will be able to meet the timelines we will need on the next round to make a definitive decision within the PDUFA goal date.[17]

Since Barr submitted its full dual-marketing proposal in July 2004, this timeframe would have required OCC to complete its review three to four months later, by October or November 2004.[18] However, a conclusive review apparently did not occur. Despite receiving the dual-marketing proposal in March 2004, despite the analysis performed by CDER's policy office, and despite the expiration of the PDUFA deadlines, FDA states that it has still not resolved the relevant regulatory questions.

The Federal Records Act

When GAO's report was released in November of 2005, I wrote to Secretary Leavitt along with a number of my colleagues.[19] In addition to requesting more information about the Plan B decision, we asked why FDA staff had told GAO that, in apparent violation of the Federal Records Act, emails from the Office of the Commissioner were deleted daily and backup files were only retained for 16 days.

In your response of January 27, 2006, you wrote, "In this case there is no evidence that there was any deviation from both customary practice and compliance with the law. Any speculation to the contrary has no basis in fact."[20] Respectfully, our concern was not speculative. A July 2005 email from the Office of the Commissioner to GAO states explicitly that "[Commissioner and Deputy Commissioner for Operations] Drs. Crawford and Woodcock delete their emails on a daily basis and the emails are held in backup for 16 days."[21] Even if, as the

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[17] Email from John K. Jenkins, Director, Office of New Drugs, to Steven Galson et al. (May 14, 2004). The Prescription Drug User Fee Act sets performance goals for the completion of FDA reviews of various types of applications.

[18] Barr Laboratories, *Barr Submits Response to FDA in Support of Over-the-Counter Status for Plan B(R) Emergency Contraceptive* (Jul. 22, 2004) (online at http://www.barrlabs.com).

[19] Letter from Rep. Henry Waxman *et al.* to Secretary Michael Leavitt (Nov. 14, 2005) (online at http://www.democrats.reform.house.gov/Documents/20051117133505-58156.pdf).

[20] Letter from Dr. Andrew C. von Eschenbach to Rep. Henry A. Waxman (Jan. 27, 2006).

[21] Email from Office of the Commissioner, FDA, to GAO (Jul. 7, 2005).

agency later claimed, backup files were retained for 16 weeks, the practice would not approach the standards required by the Federal Records Act nor FDA's document retention policy.[22]

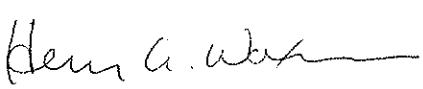
Conclusion

FDA has justified its indefinite delay of the Plan B decision by citing the "difficult and novel" issues raised by the scientifically unsupported age restrictions that it urged be added to the amended application. But the internal agency documents I have obtained reveal that the supposedly "novel" regulatory questions raised by the application had been under consideration by the agency for over a year. It appears that the Office of Chief Counsel simply failed, despite repeated requests, to produce a dispositive analysis.

I request an explanation of the agency's actions in the case of Plan B, including all documents from CDER's regulatory analysis and an account of why the Office of Chief Counsel apparently failed to respond to repeated requests for a timely legal analysis of Barr's amended application. If the lawyers did in fact prepare an analysis, please explain why FDA announced in August 2005 that it was unable to resolve the key regulatory questions by that time. In addition, please address the apparent violation of the Federal Records Act.

I ask that you respond to this letter by March 27, 2006.

Sincerely,



Henry A. Waxman
Ranking Minority Member

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[22] Under the Federal Records Act, no records of the federal government may be "alienated or destroyed" except under the regulations promulgated by the Archivist and the schedules submitted by the agencies. 44 USC 3314; 36 C.F.R. 1228.100. Electronic messages such as emails have been held to be "records" under the Federal Records Act and must be retained even if printed copies exist. Armstrong v Executive Office of the President, Office of Admin. (1993, App DC) 303 US App DC 107, 1 F3d 1274. FDA's policy statement on email information notes that emails that qualify as records "must be retained" and that "[b]ackups of e-mail files ... are not to serve any archival purpose and should not be used as a records management tool." The FDA statement also notes that even "routine administrative correspondence" must be retained for two years. Food and Drug Administration, *Policy Statement for Management of Email Information*, from *FDA Automated Information Systems Security Policies and Procedures Manual.*