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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

GAO Highlights

Highlights of GAO-06-109, a report to congressional requesters

Why GAO Did This Study

In April 2003, Women's Capital Corporation submitted an application to the Food and Drug Administration (FDA) requesting the marketing status of its emergency contraceptive pill (ECP), Plan B, be switched from prescription to over-the-counter (OTC). ECPs can be used to prevent an unintended pregnancy when contraception fails or after unprotected intercourse, including cases of sexual assault. In May 2004, the Acting Director for the Center for Drug Evaluation and Research (CDER) issued a "not-approvable" letter for the switch application, citing safety concerns about the use of Plan B in women under 16 years of age without the supervision of a health care practitioner. Because the not-approvable decision for the Plan B OTC switch application was contrary to the recommendations of FDA's joint advisory committee and FDA review staff, questions were raised about FDA's process for arriving at this decision. GAO was asked to examine (1) how the decision was made to not approve the switch of Plan B from prescription to OTC, (2) how the Plan B decision compares to the decisions for other proposed prescription-to-OTC switches from 1994 through 2004, and (3) whether there are age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives. To conduct this review, GAO examined FDA's actions prior to the May 6, 2004, not-approvable letter for the initial application.

www.gao.gov/cgi-bin/getrpt?GAO-06-109

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crossen at (202) 512-7115 or crossen@gao.gov.

FOOD AND DRUG ADMINISTRATION

Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual

What GAO Found

On May 6, 2004, the Acting Director of CDER rejected the recommendations of FDA's joint advisory committee and FDA review officials by signing the not-approvable letter for the Plan B switch application. While FDA followed its general procedures for considering the application, four aspects of FDA's review process were unusual. First, the directors of the offices that reviewed the application, who would normally have been responsible for signing the Plan B action letter, disagreed with the decision and did not sign the not-approvable letter for Plan B. The Director of the Office of New Drugs also disagreed and did not sign the letter. Second, FDA's high-level management was more involved in the review of Plan B than in those of other OTC switch applications. Third, there are conflicting accounts of whether the decision to not approve the application was made before the reviews were completed. Fourth, the rationale for the Acting Director's decision was novel and did not follow FDA's traditional practices. The Acting Director stated that he was concerned about the potential behavioral implications for younger adolescents of marketing Plan B OTC because of their level of cognitive development and that it was invalid to extrapolate data from older to younger adolescents. FDA review officials noted that the agency has not considered behavioral implications due to differences in cognitive development in prior OTC switch decisions and that the agency previously has considered it scientifically appropriate to extrapolate data from older to younger adolescents.

The Plan B decision was not typical of the other 67 proposed prescription-to-OTC switch decisions made by FDA from 1994 through 2004. The Plan B OTC switch application was the only one during this period that was not approved after the advisory committees recommended approval. The Plan B action letter was the only one signed by someone other than the officials who would normally sign the letter. Further, there are no age-related marketing restrictions for any prescription or OTC contraceptives that FDA has approved, and FDA has not required pediatric studies for them. FDA identified no issues that would require age-related restrictions in the review of the original prescription Plan B new drug application.

In its comments on a draft of this report, FDA disagreed with GAO's finding that high-level management was more involved with the Plan B OTC switch application than usual, with GAO's discussion about when the not-approvable decision was made, and with GAO's finding that the Acting Director of CDER's rationale for denying the application was novel. However, GAO found that high-level management's involvement for the Plan B decision was unusual for an OTC switch application and FDA officials gave GAO conflicting accounts about when they believed the decision was made. The Acting Director acknowledged to GAO that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented for an OTC application, and other FDA officials told GAO that the rationale differed from FDA's traditional practices.

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Abbreviations

ACRHD	Advisory Committee for Reproductive Health Drugs
CDER	Center for Drug Evaluation and Research
ECP	emergency contraceptive pill
FDA	Food and Drug Administration
NDA	new drug application
NDAC	Nonprescription Drugs Advisory Committee
OTC	over-the-counter
PDUFA	Prescription Drug User Fee Act
PREA	Pediatric Research Equity Act
sNDA	supplemental new drug application
STD	sexually transmitted disease
WCC	Women's Capital Corporation

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November 14, 2006

Congressional Requesters

In April 2003, Women's Capital Corporation (WCC) submitted an application to the Food and Drug Administration (FDA) requesting that the marketing status of its emergency contraceptive pill (ECP), Plan B, be switched from prescription to over-the-counter (OTC).¹ ECPs can be used to prevent unintended pregnancy when contraception fails or after unprotected intercourse, including cases of sexual assault. Plan B had been approved for use as a prescription drug by FDA in 1999 and is most effective when taken as soon as possible, but no later than 72 hours, after intercourse. By law, FDA may approve the switch of a prescription drug to OTC status if use of the drug is safe and effective for self-medication in accordance with proposed labeling.² Since 1975, when FDA formalized the current process for approving prescription-to-OTC switches, FDA has approved approximately 90 applications to change the marketing status of a prescription drug to OTC.

According to FDA's operational policies, reviews of OTC switch applications occur in its Center for Drug Evaluation and Research (CDER).³ OTC switch applications for drugs that are "first-in-a-class,"⁴ such as Plan B, are reviewed by two of the six offices of drug evaluation within CDER—including the Office of Drug Evaluation V, which reviews all OTC switch applications, and the office of drug evaluation that has the relevant expertise for the proposed switch drug.⁵ In addition, CDER can request a joint meeting of advisory committees that it has established to

¹FDA defines prescription-to-OTC switch as the OTC marketing of a product that was once a prescription drug product for the same indication, strength, dose, duration of use, dosage form, population, and route of administration. In this report, the phrase "OTC switch" refers to a prescription-to-OTC switch.

²See 21 U.S.C. § 353(b)(1); 21 C.F.R. § 310.200(b) (2005).

³FDA's operational policies are in its manuals of policies and procedures.

⁴A class of drugs refers to a category based on the chemical ingredients of the drugs. "First-in-a-class" refers to the first drug to be reviewed for an OTC switch within a class of drugs.

⁵In this report, FDA review staff refers to the staff in the Offices of Drug Evaluation III and V who reviewed the Plan B OTC switch application. The CDER structure described in this report is the one that existed at that time.

seek scientific advice about its decisions from outside experts. The joint advisory committee meeting is conducted by the advisory committee that has expertise in OTC drugs and the advisory committee that has relevant expertise for the proposed OTC switch drug. After review of the OTC switch application and advice of the joint advisory committee, the directors of both offices of drug evaluation make a decision. If the directors of the offices concur on the decision for the application, they generally will both sign and issue an action letter.⁶ If the directors do not concur with one another, the application is sent to the next level of review—the Director of the Office of New Drugs within CDER, who then makes the decision and signs and issues the action letter. However, the Director of CDER can also decide on an application and sign and issue the action letter.

The Plan B application went to the Office of Drug Evaluation V, which includes the Division of Over-the-Counter Drug Products, and the Office of Drug Evaluation III, which includes the Division of Reproductive and Urologic Drug Products, where it was reviewed. In December 2003, a joint meeting of two FDA advisory committees, the Nonprescription Drugs Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD), recommended in a vote of 23 to 4 that the proposed OTC switch for Plan B be approved. FDA review staff also agreed that Plan B should be granted OTC status. On May 6, 2004, the Acting Director of CDER⁷ signed a "not-approvable" letter for the switch to

⁶An action letter is a written communication to the sponsor from FDA stating the outcome of the review of an application. The sponsor or applicant is the person or entity that assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations.

⁷The current Director of CDER was appointed to this position on July 29, 2005. However, he held the title of Acting Director from fall 2003 until his appointment. Prior to his appointment to Acting Director, he was Deputy Director of CDER. Because he was Acting Director during most of the time covered by this report—for those events associated with the initial Plan B OTC switch application through the May 6, 2004, decision—we use the title of Acting Director for him in this report.

OTC,⁸ citing safety concerns about the use of Plan B in women under 16 years of age without the supervision of a practitioner licensed by law to administer the drug.⁹ On July 22, 2004, Barr Pharmaceuticals, Inc.,¹⁰ submitted an amended application for the proposed Plan B switch to market Plan B OTC for women 16 years of age and older and as a prescription drug for those under 16 years of age.¹¹

Because the not-approvable decision for the initial Plan B OTC switch application was contrary to the recommendations of the joint advisory committee and the FDA review staff, you raised questions about FDA's process for arriving at its decision on the initial application. In this report, for the initial Plan B OTC switch application, we examined (1) how the decision was made to not approve the switch of Plan B from prescription to OTC, (2) how the Plan B decision compares to the decisions for other proposed prescription-to-OTC switches from 1994 through 2004, and (3)

⁸A not-approvable letter is a letter to the sponsor from FDA stating that the agency does not consider the application approvable because of one or more deficiencies in the application. See 21 C.F.R. § 314.120. There are two other types of action letters: the approval letter and the approvable letter. The approval letter indicates that the application is approved and the drug may go OTC. An approvable letter is similar to the not-approvable letter in that there are one or more deficiencies in the application precluding its approval. See 21 C.F.R. § 314.110. FDA officials stated that the difference between a not-approvable letter and an approvable letter is that a not-approvable letter is generally issued when more studies are required and an approvable letter is generally issued if there are sufficient data, but some outstanding concerns still exist.

⁹Besides physicians, other health care providers, such as nurse practitioners and physicians' assistants, may be licensed by law to administer drugs. While only FDA may change a drug's status from prescription to OTC, the practice of pharmacy is state controlled, allowing each state to decide who may prescribe a drug. While most states do not allow pharmacists to prescribe drugs, eight states (Alaska, California, Hawaii, Maine, Massachusetts, New Hampshire, New Mexico, and Washington) allow pharmacists to prescribe ECPs or provide them in accordance with approved physician protocols.

¹⁰In February 2004, WCC sold the rights to market Plan B to Barr Pharmaceuticals, Inc. In October 2003, as the purchase of Plan B by Barr Pharmaceuticals, Inc., was being finalized, Barr began acting as the agent for WCC regarding Plan B.

¹¹On August 26, 2005, FDA announced it had completed its review of the amended application and concluded that the scientific data were sufficient to support the safe use of Plan B in an OTC setting for women 17 years of age and older. However, FDA delayed taking action on the amended application to seek public comment on marketing issues related to this decision. See also 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, 70 Fed. Reg. 52050 (2005). Accordingly, as of November 4, 2005, Plan B may not be legally marketed OTC.

whether there are age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives.

To address our objectives, we examined documents, including the official minutes from meetings of FDA staff and the written reviews of the adequacy of the Plan B OTC switch application prepared by FDA staff in the Offices of Drug Evaluation III and V and the Office of New Drugs, related to the review of, and decision on, the Plan B OTC switch application, and we interviewed FDA staff and officials who conducted the reviews and were involved in the decision. We also reviewed FDA's manuals of policies and procedures and *The CDER Handbook* to determine how FDA considers an application to switch a drug from prescription to OTC.¹² We interviewed members of FDA's two advisory committees that met jointly to discuss the Plan B OTC switch application, and we reviewed the transcript of its meeting. We compared the FDA decision for Plan B to FDA's decisions for other proposed prescription-to-OTC switch applications from 1994 through 2004. We interviewed officials from Barr Pharmaceuticals, Inc., the company currently sponsoring the Plan B application for the prescription-to-OTC switch, and WCC, the original sponsor of the Plan B switch application. In addition, we reviewed documents and interviewed FDA officials regarding age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives. We also interviewed representatives from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, Concerned Women for America, and the Planned Parenthood Federation of America, Inc., regarding FDA's safety concerns for Plan B and other contraceptives. Our work examined only events and communications within FDA and between FDA and the Plan B sponsor; we did not consider any communications that may have occurred between FDA officials and other executive agencies. Our work examined only FDA's actions prior to the May 6, 2004, not-approvable letter for the initial application, and we did not examine aspects of FDA's subsequent deliberations about Plan B. (See app. I for details regarding our scope and methodology and app. II for a copy of the May 6, 2004, not-approvable letter for the initial application.) We conducted our work from September 2004 through November 2005 in accordance with generally accepted government auditing standards.

¹²The *CDER Handbook* contains information on the center's processes and activities. It was created for industry officials, health professionals, academics, and the general public, and it is available at www.fda.gov/cder/handbook/startpag.htm (downloaded Dec. 8, 2004).

Results in Brief

On May 6, 2004, the Acting Director of CDER rejected the recommendations of the joint advisory committee and FDA review officials by signing the not-approvable letter for the Plan B switch application, concluding a review process that began on April 16, 2003, when WCC submitted a standard supplemental new drug application (sNDA) requesting that Plan B be made available without a prescription. While FDA followed its general procedures for considering the application, four aspects of FDA's review process were unusual. First, the Directors of the Offices of Drug Evaluation III and V, who would normally have been responsible for signing the Plan B action letter, disagreed with the decision and did not sign the not-approvable letter for Plan B. The Director of the Office of New Drugs also disagreed and did not sign the letter. Second, FDA's high-level management was more involved in the review of Plan B than in those of other OTC switch applications. For example, FDA review staff told us that they were told early in the review process that the decision would be made by high-level management. Third, as documented in the reviews of FDA staff and in our interviews with FDA officials, there are conflicting accounts of whether the decision to not approve the application was made before the reviews were completed. Fourth, the rationale for the Acting Director of CDER's decision was novel and did not follow FDA's traditional practices. Specifically, the Acting Director was concerned about the potential impact that the OTC marketing of Plan B would have on the propensity for younger adolescents to engage in unsafe sexual behaviors because of their lack of cognitive maturity compared to older adolescents. He also stated that it was invalid to extrapolate data from older to younger adolescents in this case. FDA review officials noted that the agency has not considered behavioral implications due to differences in cognitive development in prior OTC switch decisions and that the agency has considered it scientifically appropriate to extrapolate data from older to younger adolescents.

The decision to not approve the Plan B OTC switch application was not typical of the other 67 prescription-to-OTC switch decisions made from 1994 through 2004. FDA's joint advisory committee considered 23 OTC switch applications during this period; the Plan B OTC switch application was the only 1 of those 23 that was not approved after the joint committee voted to recommend approval of the application. Also, the Plan B action letter was the only one signed by the Director of CDER, in this case the Acting Director of CDER, instead of the directors of the offices or divisions that reviewed the application, who would normally sign an action letter.

There are no age-related marketing restrictions for safety reasons for any of the prescription or OTC contraceptives that FDA has approved, and FDA has not required pediatric studies for them. All FDA-approved OTC contraceptives are available to anyone, and all FDA-approved prescription contraceptives are available to anyone with a prescription. For hormonal contraceptives, FDA assumes that suppression of ovulation would be the same for any female after menarche,¹⁹ regardless of age. FDA did not identify any issues that would require age-related restrictions in its review of the original application for prescription Plan B, and prescription Plan B is available to women of any age.

In its comments on a draft of this report, FDA disagreed with three of our findings. First, FDA disagreed with our finding that the involvement of high-level management in the Plan B decision was unusual because their involvement is likely in high-profile and controversial regulatory decisions. Although we agree that high-level management involvement is more likely to occur with high-profile regulatory decisions, we found that the level of high-level management involvement for the Plan B decision was unusual for OTC switch applications. The other examples of high-level management involvement given to us by FDA officials during the course of our work involved decisions about the marketing of prescription drugs. Second, FDA disagreed with our discussion about when the decision to deny the switch application was made. We maintain that the draft report accurately noted that FDA officials gave us conflicting accounts about when they believed the not-approvable decision was made. Third, FDA disagreed with our finding that the Acting Director of CDER's rationale for denying the application was novel and did not follow FDA's traditional practices. We found that the Acting Director's rationale was novel because it explicitly considered the differing levels of cognitive maturity of adolescents of different ages, and that, because of the Acting Director's views about these differences in cognitive maturity, he concluded that it was inappropriate to extrapolate data related to risky sexual behavior from older to younger adolescents. The Acting Director acknowledged to us that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented for an OTC application. In addition, other FDA officials told us that the agency had not previously considered whether younger adolescents would use a product differently than older adolescents. Therefore, we believe that our finding is correct.

¹⁹Menarche is the initial menstrual period, normally occurring between a female's 9th and 17th year.

and we have revised the report to more clearly describe the reasons for our finding.

Background

Within FDA, CDER oversees the switch of drugs from prescription to OTC. Generally, prescription drugs are drugs that are safe for use only under the supervision of a health care practitioner. Approved prescription drugs that no longer require such supervision may be marketed OTC.¹⁴ In applying this standard, FDA will authorize a prescription-to-OTC switch only after it is determined that the drug in question has met the following FDA criteria: (1) it has an acceptable safety profile based on prescription use and experience;¹⁵ (2) it has a low potential to be abused; (3) it has an appropriate safety and therapeutic index;¹⁶ (4) it has a positive benefit-risk assessment; and (5) it is needed for a condition or illness that is self-recognizable, self-limiting,¹⁷ and requires minimal intervention by a health care practitioner for treatment.¹⁸ FDA tries to determine if the OTC availability of a prescription drug will prevent or delay someone from seeking needed medical attention.

One class of OTC drugs switched from prescription status, the nicotine products (such as Nicorette gum), has restricted access based on age—they are available OTC only to persons 18 years of age or older.

Studies for Prescription-to-OTC Switches

Generally, drugs considered for a prescription-to-OTC switch involving the same indication, strength, dose, duration of use, dosage form, patient population, and route of administration as the prescription drug require fewer new studies regarding safety and efficacy because such studies have already been submitted as part of the original new drug application

¹⁴See 21 U.S.C. § 353(b)(1), 21 C.F.R. § 310.200(b).

¹⁵An appropriate safety profile means that a drug that has been on the market has proven that it continues to be safe.

¹⁶The safety and therapeutic index is the ratio between the toxic dose and the therapeutic dose of a drug and is used as a measure of the relative safety of the drug for a particular treatment.

¹⁷A self-limiting condition or illness is one that without treatment runs a definite course within a limited period.

¹⁸These criteria are from the transcript of the joint advisory committee meeting held on December 16, 2003, to discuss the Plan B OTC switch application. They were presented by an FDA official at the meeting.

(NDA).¹⁹ FDA also requires sponsors to address concerns related to consumers' ability to self-diagnose and self-treat the condition. Thus, sponsors generally submit additional studies, such as an actual use study, which examines consumers' ability to self-diagnose, and a label comprehension study, which examines how consumers interpret the drug's proposed label. In addition to these actual use and label comprehension studies, FDA requires sponsors to submit updated safety information on adverse events reported for the prescription form of the drug.

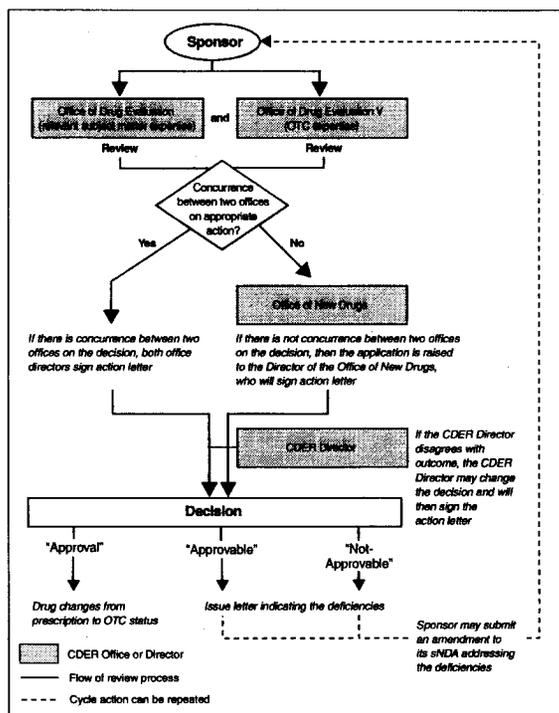
FDA Process for Switching First-in-a-Class Prescription Drug to OTC

Figure 1 shows the flow of an OTC switch application of a first-in-a-class drug through the decision process within CDER. To begin the process for a prescription-to-OTC switch, the sponsor submits an efficacy supplement to an approved NDA.²⁰ This sNDA is sent to the FDA Office of Drug Evaluation that oversaw the original NDA and usually is the office with relevant expertise. This Office of Drug Evaluation is generally responsible for reviews of the primary effectiveness data and safety results. After an application has been determined to be complete, a reviewer from this office assesses the design, general effectiveness, and safety of the product. If the application is determined to be incomplete, this office will issue a "refusal to file" letter to the sponsor, detailing the omissions or inadequacies that led to this decision.

¹⁹Drugs that involve a different indication, strength, dose, duration of use, dosage form, patient population, or route of administration may require additional efficacy and safety studies. For example, the OTC switch of ibuprofen in 1984 was for a lower dose than prescription ibuprofen and, therefore, required new studies showing the efficacy of the lower dose.

²⁰An efficacy supplement may include a submission for proposed changes in the labeling of an approved product for a new indication, new dosage regimen, or significant alteration in the patient population.

Figure 1: Flow of an OTC Switch Application through the Decision Process within CDER for First-In-a-Class Drug



Source: FDA.

Note: As part of their decision process, the Offices of Drug Evaluation also get input from CDER's Office of Drug Safety. They also may convene a meeting of advisory committees.

When an Office of Drug Evaluation with relevant expertise receives a fileable sNDA for an OTC drug switch, it notifies the Office of Drug Evaluation V and its Division of Over-the-Counter Drug Products, which has relevant expertise in OTC drug products. Generally, the Office of Drug Evaluation V oversees the review of (1) the suitability of the product for OTC use and (2) safety experiences during the marketing of the prescription product. A reviewer from this office assesses studies related to OTC marketing, including the actual use and label comprehension studies. CDER's Office of Drug Safety conducts additional reviews of the label comprehension studies, reviews postmarketing safety data of the prescription drug, and provides reports to reviewing staff in other offices upon request.

FDA can convene advisory committee meetings for prescription-to-OTC switch applications. Advisory committees include outside experts, such as medical professionals and researchers, who provide FDA with independent advice and recommendations. Members review data submitted by the sponsor or presented by FDA review staff, address questions, and vote, either supporting or opposing a switch from prescription-to-OTC status. Advisory committees conduct open meetings and offer members of the public the opportunity to express their views. FDA considers the advisory committees' recommendations in its deliberations. However, the agency decides whether to adopt these recommendations on a case-by-case basis and is not required to follow the committees' recommendations.

FDA review staff from the appropriate offices of drug evaluation review the data presented, interpret the findings, and make recommendations to the respective office directors on whether the proposed OTC switch should be approved. Once these reviews are completed, they are sent to the directors of both the office of drug evaluation with relevant expertise and the Office of Drug Evaluation V. If both directors agree with each others' review recommendation, the directors of the relevant offices of drug evaluation prepare an action package²¹ and an appropriate action letter for review, concurrence, and their final signatures. If the office directors do not concur on the decision, the application is reviewed by the Office of New Drugs. The Director of CDER is not directly involved in the

²¹An action package is a compilation of (1) FDA-generated documents related to the review from submission to final action of an NDA or efficacy supplement from the sponsor; (2) documents, such as meeting minutes and pharmacology reviews, pertaining to the format and content of the application; and (3) labeling submitted by the sponsor.

approval of all drugs, but may overrule the decisions of subordinate officials.

The authority to approve an OTC switch application ultimately rests with the Secretary of Health and Human Services. This approval authority is delegated to the Commissioner of FDA, then to other high-level management officials, and eventually to other FDA officials within lower levels of the agency. This delegated authority allows decisions to be made at lower levels within the agency but assumes that management agrees with these decisions. The FDA Commissioner and other officials within the Office of the Commissioner usually do not have a role in OTC switch decisions, but have the authority to overrule the decisions of other FDA officials.

Contraceptives

There are several types of contraceptive drugs and devices, including barrier methods, intrauterine devices, spermicides, and hormonal methods. Several types of hormonal methods of contraception are available, including birth control pills, injectable hormones, hormonal implants, and ECPs. FDA has approved two ECPs, Preven and Plan B, for use by prescription, and Plan B is the first drug in its class to go through the review process by FDA to determine whether it should be allowed to be sold OTC.²² ECPs are high dose birth control pills and have been available by prescription since 1998, when FDA approved Preven, a dedicated²³ combined ECP containing the hormones estrogen and progestin.²⁴ Prior to 1998, many physicians instructed patients to take

²²In 1997, a notice in the *Federal Register* stated that the Commissioner of FDA had concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as emergency contraception, and requested submission of NDAs for this use. See Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception, 62 Fed. Reg. 9610 (1997). In 2004, the manufacturer stopped production of Preven.

²³A dedicated ECP is a drug expressly meant for use as an ECP; levonorgestrel is a synthetic progestin commonly used in birth control pills.

²⁴Estrogen is a hormone that is responsible for cyclic changes in the vagina and uterus. Progestin is a hormone that prepares the endometrium for implantation of the fertilized egg. These hormones in oral birth control pills suppress ovulation.

higher doses of oral contraceptive pills for emergency contraception, an "off-label" use.²⁵

Emergency Contraceptive Plan B

Plan B is a dedicated ECP containing only levonorgestrel, a type of progestin. The Plan B regimen is a two-pill dose of levonorgestrel (0.75 mg each) that is most effective when the first pill is taken as soon as possible, but no later than 72 hours, after contraceptive failure or unprotected intercourse. The second pill is taken 12 hours after the first pill. Research suggests that a levonorgestrel-only hormone regimen, such as Plan B, can reduce the risk of pregnancy by 89 percent if taken within the 72-hour window.²⁶ The time constraint for maximum effectiveness associated with Plan B has led many in the medical community and some reproductive health advocates to support switching Plan B to OTC, making it more readily available when needed. In addition, levonorgestrel-only regimens, such as Plan B, have fewer side effects than the combined ECP, reducing the incidence of two common side effects, nausea and vomiting, by 50 percent and 70 percent, respectively.

Research has shown that levonorgestrel-only hormonal emergency contraception, such as Plan B,²⁷ interferes with prefertilization events. It reduces the number of sperm cells in the uterine cavity, immobilizes sperm, and impedes further passage of sperm cells into the uterine cavity. In addition, levonorgestrel has the capacity to delay or prevent ovulation from occurring.²⁸

²⁵Off-label drug use occurs when physicians prescribe a drug for clinical indications other than those listed on the label.

²⁶World Health Organization, "Randomized Controlled Trial of Levonorgestrel Versus the Yuzpe Regimen of Combined Oral Contraceptives for Emergency Contraception," *The Lancet*, vol. 352 (1998): 428-433.

²⁷Horacio B. Croxatto and others, "Mechanism of Action of Hormonal Preparations Used for Emergency Contraception: A Review of the Literature," *Contraception*, vol. 63 (2001): 111-121; and H.B. Croxatto and others, "Pituitary-Ovarian Function Following the Standard Levonorgestrel Emergency Contraceptive Dose or a Single 0.75-mg Dose Given on the Days Preceding Ovulation," *Contraception*, vol. 70 (2004): 442-450.

²⁸Ovulation occurs when a mature egg is released from the ovary, is pushed down the fallopian tube, and is available to be fertilized.

ECPs have not been shown to cause a postfertilization event—a change in the uterus that could interfere with implantation of a fertilized egg.²⁹ Some researchers argue that an interference with the implantation of a fertilized egg is unlikely to happen because progestins, whether natural or synthetic, help to sustain pregnancy.³⁰ In addition, there is no evidence that one burst of levonorgestrel without estrogen can prevent implantation. However, researchers have concluded that the possibility of a postfertilization event cannot be ruled out, noting that it would be unethical and logistically difficult to conduct the necessary research.³¹ ECPs, including Plan B, do not interfere with an established pregnancy.

Aspects of FDA's Review of the Plan B Switch Application Were Unusual

On May 6, 2004, the Acting Director of CDER rejected the recommendations of a joint advisory committee and FDA review officials and signed the not-approvable letter for the Plan B OTC switch application. Four aspects of FDA's review process were unusual: officials who would normally have been responsible for signing an action letter disagreed with the decision and did not sign the not-approvable letter for Plan B; high-level management was more involved than for other OTC switch applications; conflicting accounts exist of whether the decision to not approve the application was made before the reviews were completed; and the rationale for the not-approvable decision was novel and did not follow FDA's traditional practices.

The Acting Director of CDER Rejected the Recommendations of a Joint Advisory Committee and FDA's Review Officials

On May 6, 2004, the Acting Director of CDER rejected the recommendations of a joint advisory committee and FDA review officials by signing the not-approvable letter for the Plan B OTC switch application. This action concluded a review process that began on April 16, 2003, when WCC submitted a standard sNDA requesting that Plan B be made available without a prescription. In the OTC switch application, the proposed OTC

²⁹Implantation is the embedding of the fertilized egg in the uterus six or seven days after fertilization. See A.L. Muller and others, "Postcoital Treatment with Levonorgestrel Does Not Disrupt Postfertilization Events in the Rat," *Contraception*, vol. 67 (2003): 415-419.

³⁰Horacio B. Croxatto, María E. Ortiz, and Andres L. Muller, "Mechanisms of Action of Emergency Contraception," *Steroids*, vol. 68 (2003): 1096-1098.

³¹It has not been possible to identify groups of women who had taken ECPs after fertilization so as to assess their effect on the establishment of a pregnancy. Therefore, there is no direct evidence, either for or against, the hypothesis that ECPs prevent pregnancy by affecting postfertilization events. See Croxatto, Ortiz, and Muller, "Mechanisms of Action of Emergency Contraception," 1096.

dose and administration schedule were identical to that for Plan B's prescription use. The application also included an actual use study and a label comprehension study to assess potential users' understanding of how to administer the product.

Following FDA's procedures for a review of an OTC switch application, the sNDA was submitted to the Office of Drug Evaluation III—which includes the Division of Reproductive and Urologic Drug Products, whose staff also reviewed the prescription Plan B application. Table 1 includes a brief timeline of events involving Plan B and the initial OTC switch application. (See app. III for a more detailed timeline.) On June 9, 2003, review staff within the Office of Drug Evaluation III determined the Plan B sNDA to be fileable and accepted it for review. The sNDA was then submitted to the Office of Drug Evaluation V—which includes the Division of Over-the-Counter Drug Products, whose staff have expertise with OTC drugs—for concurrent review, also in accordance with FDA's review procedures. FDA also convened a joint public meeting of two of its advisory committees—the NDAC and the ACRHD—during which the committees' members reviewed documentation and voted on answers to specific questions asked by FDA review staff from both offices, including whether Plan B should be granted OTC marketing status. On December 16, 2003, the members of the joint advisory committee voted 23 to 4 to recommend approving a switch in Plan B's marketing status from prescription to OTC.³² Members of the joint advisory committee also voted on other aspects of the Plan B application. For example, members voted 27 to 1 that Plan B could be appropriately used as recommended by the label and that the actual use data were generalizable to the overall population, including adolescents.

³²For this particular vote, 12 out of 13 members on the NDAC voted in favor of the proposed OTC switch for Plan B and 11 out of 15 members on the ACRHD also supported the switch (the final vote was 23 to 4 because 1 of the committee members of the ACRHD left before the vote). In addition, 1 advisory committee member submitted a letter to FDA, outlining why Plan B should not be approved for OTC use. Media reports have suggested that this letter was requested by someone within FDA. In its technical comments on a draft of this report, FDA stated that this letter was not solicited by the agency and noted that the letter itself does not represent that the agency requested the letter. We found that all of the points raised in the letter were already part of the public record because they had been discussed at the advisory committee meeting.

Table 1: Brief Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
July 28, 1999	FDA approved Plan B as a prescription form of emergency contraception.
April 18, 2002	Review staff within the Office of Drug Evaluation III denied WCC's proposal that FDA request that it conduct two pediatric studies—a pharmacokinetic study and a safety study—on the use of prescription Plan B in subjects as young as 12 years of age in exchange for extending the drug's market exclusivity for 6 months, as permitted under the Federal Food, Drug, and Cosmetic Act. ⁴
June 5, 2002	A briefing for the Office of the Commissioner was held to discuss the expected application to switch Plan B to OTC. Meeting attendees included the Deputy Commissioner, ⁵ the agency's Chief Counsel, the then-Director of CDER, the Director of the Office of New Drugs, and review staff within the Offices of Drug Evaluation III and V.
September 23, 2002	FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and the sponsor held a meeting during which FDA officials provided guidance on the OTC switch application, which was to be submitted. According to meeting minutes, FDA officials and the sponsor discussed behavioral issues in adolescents and the possibility of a behind-the-counter option or a possible age restriction. ⁶
April 16, 2003	WCC submitted an sNDA to FDA to allow Plan B to be sold OTC.
June 9, 2003	FDA set a Prescription Drug User Fee Act (PDUFA) goal date of February 22, 2004, to reach a decision on the application. ⁷
December 16, 2003	At a joint meeting of the NDAC and the ACRHD, members voted 23 to 4 to recommend approving the switch of Plan B from prescription to OTC.
January 15, 2004	A meeting was held during which the Acting Director of CDER informed review staff within the Offices of Drug Evaluation III and V that a not-approvable decision was "recommended" by the Office of the Commissioner. Minutes from this meeting also noted that attendees agreed that review staff would complete their reviews and collect additional data to be presented to the Commissioner and the Acting Director of CDER some time in February. Review staff within the Offices of Drug Evaluation III and V later noted in their completed reviews of the Plan B application that they were told at this meeting that the decision on the Plan B application would be made at a level higher than the Offices of Drug Evaluation.
January 21, 2004	A memorandum from the Director of the Office of Drug Evaluation V concluded that adequate data had been submitted to approve Plan B for OTC marketing.
January 23, 2004	A meeting was held between FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and Barr Pharmaceuticals, Inc./WCC. According to meeting minutes, FDA officials told the sponsor that the decision on the application would be made at a level higher than the Offices of Drug Evaluation. The Director of the Office of New Drugs told the sponsor that such a high-level decision was not typical.
February 2, 2004	Review staff within the Office of Drug Evaluation III requested that the sponsor reanalyze the adolescent data of the Plan B actual use study for those under 18 years of age.
February 13, 2004	FDA confirmed that it had extended the PDUFA goal date for a decision on the Plan B switch application for 90 days due to the submission of the requested reanalysis of adolescent data from the actual use study by the sponsor. The extended PDUFA goal date was May 21, 2004.
February 18, 2004	A briefing was held during which review staff within the Offices of Drug Evaluation III and V presented their analysis of additional summary data to the Commissioner on the use and behavior of adolescents in association with increased access to ECPs. According to meeting minutes, review staff recommended that Plan B have an OTC marketing status without restriction. The meeting minutes also noted that the Commissioner directed CDER to work with the sponsor on a marketing plan to limit the availability of Plan B in an OTC setting and to consider the most appropriate ages that should be restricted from OTC access.
February 26, 2004	Barr Pharmaceuticals, Inc., completed acquisition of the marketing rights of Plan B from WCC.

Date	Event
April 2, 2004	The Deputy Director of the Office of Drug Evaluation III completed the office's review of the Plan B application in which she recommended that the product be approved for use as an emergency contraceptive in the OTC setting without age restriction.
April 22, 2004	The Director of the Office of New Drugs issued his review, in which he concurred with the recommendations of both Offices of Drug Evaluation III and V. In his review, he recommended that the application be approved to permit OTC availability of Plan B without age restriction.
May 2, 2004	According to an internal FDA e-mail, the Acting Director of CDER contacted the Director of the Office of Pediatric Therapeutics, requesting assistance on language regarding cognitive development in adolescents.
May 5, 2004	A teleconference was held during which the Acting Director of CDER informed Barr Pharmaceuticals, Inc., officials of the not-approvable action and asked permission to release the not-approvable letter. According to FDA regulations, without consent of the sponsor, the agency cannot publicly release data or information contained in an application before an approval letter is issued. ⁸
May 6, 2004	FDA issued a not-approvable letter, denying Plan B OTC marketing status, citing a lack of adequate data regarding safe use among younger adolescents.

Source: GAO analysis of FDA data.

⁴See 21 U.S.C. § 355a(b), (c). FDA may request that manufacturers of new or already-marketed drugs conduct studies of their drugs in pediatric populations where it believes that such studies will lead to additional health benefits. Studies completed in accordance with FDA requirements entitle the manufacturer to an additional 6 months of marketing exclusivity. In its technical comments on the draft of this report, FDA stated that it did not ask for pediatric data for the prescription version of Plan B because the product's physiological effects are the same in younger and older women and because a health care practitioner is involved in dispensing prescription drugs.

⁵On September 23, 2005, the Commissioner of FDA, who was appointed on July 18, 2005, resigned from his position. He held the title of Deputy Commissioner from February 24, 2002, until March 28, 2004, when he was named Acting Commissioner. Because he was Deputy Commissioner during most of the time covered by this report—for those events associated with the initial Plan B switch application through the May 6, 2004, decision—we use the title of Deputy Commissioner for him in this report.

⁶Behind-the-counter is defined as a classification of drug products that do not require a prescription but are also unlike OTC products in that there is a measure of clinical oversight in their use. For behind-the-counter products, pharmacists are able to intervene by advising patients on the product's proper use and associated risks and by referring them to their physicians when appropriate. See Robert I. Field, "Support Grows for a Third Class of 'Behind-the-Counter' Drugs," *Pharmacy and Therapeutics*, vol. 30, no.5 (2005): 260-261.

⁷FDA, in collaboration with various stakeholders, including representatives from consumer, patient, and health care provider groups and the pharmaceutical and biotechnology industries, has developed performance goals for the time to complete the review of an application submitted to the agency. These goals have been incorporated by reference into PDUFA.

⁸See 21 C.F.R. § 314.430(d)(1).

A meeting was held on January 15, 2004, between officials within the office of the CDER Director and review staff within the Offices of Drug Evaluation III and V about the Office of the Commissioner's position on the acceptability of the Plan B OTC switch application. FDA's minutes from this meeting stated that the Acting Director of CDER informed review staff that a not-approvable letter was "recommended" based on the need for more data to clearly establish appropriate use in younger

adolescents.³⁰ Meeting minutes also stated that the Acting Director of CDER raised multiple issues, including the "very limited data" on younger adolescents in the actual use and label comprehension studies and concerns about younger adolescents' ability to appropriately use Plan B without a learned intermediary, such as a physician.³¹ The minutes also noted that the Acting Director of CDER raised possible options to address these concerns, including asking the sponsor to collect more data to show appropriate use by those 18 years of age and under or by limiting the availability of the product by, for example, restricting distribution to minors or restricting pharmacy access to a behind-the-counter option.³² According to review staff within the Offices of Drug Evaluation III and V who we spoke with and as documented in their respective reviews, at this January 2004 meeting the Acting Director of CDER also told them that the decision on the Plan B OTC switch application would be made at a "level higher than them [the Offices of Drug Evaluation]."³³

At this January 2004 meeting, review staff said they also told the Acting Director of CDER that they had not yet completed their reviews and that additional data existed on the use of ECPs in younger adolescents of which high-level management might not be aware. According to meeting minutes, it was agreed that review staff would complete their reviews as

³⁰Minutes of internal FDA meetings discussed in this report were written either by a staff member within the Office of Drug Evaluation III or by the Executive Secretariat within the Office of the Commissioner. For meeting minutes written by the staff member within the Office of Drug Evaluation III, attendees either reviewed or concurred with the minutes and documented this by including their names at the end of the minutes. For summaries written by the Executive Secretariat, there was no documentation of a review or of concurrence by attendees. FDA officials told us that summaries from meetings within the Office of the Commissioner are not reviewed or concurred with by attendees. The minutes for the January 15, 2004, meeting were written by a staff member within the Office of Drug Evaluation III.

³¹For this report, "younger adolescents" refers to postmenarcheal women 16 years of age and under.

³²Behind-the-counter is defined as a classification of drug products that do not require a prescription but are also unlike OTC products in that there is a measure of clinical oversight in their use. For behind-the-counter products, pharmacists are able to intervene by advising patients on the product's proper use and associated risks and by referring them to their physicians when appropriate. See Field, "Support Grows for a Third Class of 'Behind-the-Counter' Drugs," 260.

³³According to FDA officials we spoke with and FDA's manuals of policies and procedures we reviewed, because Plan B is a first-in-the-class drug, authority for deciding the action on the application would normally be delegated to the directors of the reviewing offices of drug evaluation.

well as obtain these data and present them to the Commissioner, who had expressed a willingness to meet with review staff to further discuss the data and these concerns. Review staff told us they then requested additional data from the sponsor and contacted academic researchers in the United States as well as international researchers about ongoing studies examining younger adolescents and behavioral changes associated with increased access to ECPs.³⁷ Review staff identified five additional studies in which ECPs were provided in advance to study participants. Review staff also reevaluated data previously submitted with the Plan B OTC switch application.

On February 18, 2004, review staff within the Offices of Drug Evaluation III and V presented their findings to high-level management, including the Commissioner and the Acting Director of CDER. According to interviews with officials from the Office of New Drugs and review staff within the Offices of Drug Evaluation III and V, and as documented in their respective reviews of the Plan B application, they said these data provided sufficient evidence that there was neither an increase in risky behaviors nor any difference in appropriate use between younger adolescents and older populations. According to FDA's minutes of this meeting, the Commissioner expressed multiple points, including the potential for changes in future contraceptive behaviors after adolescents took Plan B and that counseling by a learned intermediary might be beneficial, particularly for adolescents.³⁸ He also noted that he was not convinced that the additional studies used as evidence had "enough power" to determine if behavioral differences existed between adults and adolescents.³⁹ According to the minutes, the meeting ended with the conclusion that CDER staff would continue working 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

³⁷When FDA requested additional adolescent-use data from the sponsor, review staff determined that the data submitted were sufficient to warrant a major amendment to the sNDA. Thus, on February 13, 2004, FDA confirmed that it had extended the PDUFA goal date for the decision on the Plan B OTC switch application by 90 days from its original PDUFA goal date of February 22, 2004. The extended PDUFA goal date was May 21, 2004.

³⁸These meeting minutes were written by a staff member within the Office of Drug Evaluation III.

³⁹Having enough power means having a sample size large enough to statistically detect actual differences between two groups.

product." In addition, according to meeting minutes, the Commissioner requested a "rapid action" on the Plan B OTC switch application.⁴⁹

Four Aspects of FDA's Review of the Plan B OTC Switch Application Were Unusual

Aspects of FDA's review of the Plan B OTC switch application were unusual compared to the agency's regular review process. First, the FDA officials who would normally sign an action letter for an OTC switch application disagreed with the decision and did not sign the Plan B not-approvable letter, as a result, the Acting Director of CDER did so. Second, the review process for the Plan B OTC switch application was marked by a level of involvement by FDA high-level management that has not been typical for OTC switch applications. Third, conflicting accounts exist regarding when the decision to deny the application was made. Finally, the Acting Director of CDER's rationale for denying the application was novel for an OTC switch decision.

FDA Officials Normally Responsible for Signing the Action Letter Did Not Do So

By early April 2004, the reviews from the Offices of Drug Evaluation III and V were completed. The directors of these offices agreed with the recommendations of the joint advisory committee and review staff that Plan B should be made available without a prescription. Nonetheless, the office directors told us that they were asked by high-level management to draft a not-approvable letter. Both office directors also told us they did not agree with a not-approvable action and did not sign the not-approvable letter.

The issue was then raised to the Office of New Drugs. The Director of the Office of New Drugs reviewed the staff's analysis of the application and

⁴⁹We attempted to interview the individual who had been the Commissioner of FDA until March 2004. We were unable to arrange an interview, and he did not respond to written questions we submitted. However, he did provide a written comment to us. The former Commissioner noted that the initial Plan B decision was made after he left FDA and that his interactions with the Acting Director of CDER and other FDA staff in this case were consistent with his usual practices. We also attempted to interview the individual who had been the Deputy Commissioner until March 2004, when he became the Acting Commissioner (we refer to him as Deputy Commissioner in this report). We were unable to arrange an interview with him or obtain a response to our written questions prior to his departure from FDA in September 2006. His attorney subsequently provided a written statement on his behalf. According to the statement: (1) the Deputy Commissioner did not have a role in the review of the Plan B switch application; (2) the Acting Director of CDER briefed him after he became Acting Commissioner on the Acting Director's conclusions regarding Plan B, and he concurred with the Acting Director's decision; and (3) the Deputy Commissioner did not read the reviews of the application by the staff from the Offices of Drug Evaluation III and V and by the Director of the Office of New Drugs, and therefore, could not have any comments or concerns.

concurred with the recommendations of both office directors. He also did not sign the not-approvable letter. The Director of the Office of New Drugs told us that it was "very, very rare" that his office would become involved in the signing of an action letter. According to FDA manuals of policies and procedures and *The CDER Handbook*, the Office of New Drugs would review decisions from the offices of drug evaluation only if there was disagreement between these two reviewing offices. In the case of Plan B, there was no disagreement between the two reviewing offices of drug evaluation on the approvability of the application.

The Acting Director of CDER signed the not-approvable letter, which was issued on May 6, 2004. According to FDA, the Acting Director of CDER did not ask the Directors of the Offices of Drug Evaluation III and V or the Director of the Office of New Drugs to sign the not-approvable letter, nor was the letter presented to them for their signature, because it was known that they did not agree with the not-approvable action.

High-Level FDA Management Was More Involved Than Usual in the Review Process for the Plan B Prescription-to-OTC Switch Application

High-level FDA management became more involved than usual in the review process for the Plan B OTC switch application. According to review staff within the Offices of Drug Evaluation III and V that we spoke with and as documented in their respective reviews, at a meeting held on January 15, 2004, the Acting Director of CDER informed them that the decision for the Plan B OTC switch application would be made by high-level management. This action removed decision-making authority from the directors of the reviewing offices who would normally make the decision. According to minutes from a subsequent meeting between review officials and the sponsor on January 23, 2004, the Director of the Office of New Drugs informed the sponsor that such a high-level decision was not typical of CDER's procedures for drug approvals.

The Acting Director of CDER told us that management needed to be comfortable with review staff's final decision because of the high visibility and sensitivity of the Plan B OTC switch application. He and other senior FDA officials told us that involvement by high-level management stemmed from the agency's practice of delegated authority. In addition to highly visible and sensitive cases, they said that the Commissioner and the Director of CDER would also generally become involved in cases that would potentially have a far-reaching impact or in cases in which management had a different view or disagreed with review staff. Although such cases are rare, FDA officials cited other examples when high-level

FDA Officials Gave Conflicting Accounts of When the Decision to Not Approve Plan B Was Made

management was more involved in the review process for a drug application than normal—the approval of thalidomide for the treatment of leprosy in 1998⁴¹ and the approval of mifepristone for the termination of early pregnancy in 2000.⁴² Unlike Plan B, the examples FDA officials provided us did not involve OTC switch applications.

FDA officials gave conflicting accounts of when the not-approvable decision for the Plan B OTC switch application was made. FDA officials, including the Director and Deputy Director of the Office of New Drugs and the Directors of the Offices of Drug Evaluation III and V, told us that they were told by high-level management that the Plan B OTC switch application would be denied months before staff had completed their reviews of the application. The Director and Deputy Director of the Office of New Drugs told us that they were told by the Acting Deputy Commissioner for Operations⁴³ and the Acting Director of CDER, after the Plan B public meeting in December 2003, that the decision on the Plan B application would be not-approvable. They informed us that they were also told that the direction for this decision came from the Office of the Commissioner. The Acting Deputy Commissioner for Operations and the Acting Director of CDER denied that they had said that the application would not be approved. In addition, although minutes of the January 15, 2004, meeting stated that the Acting Director told review staff that a not-approvable decision was “recommended,” review staff documented that they were told at this meeting that the decision would be not-approvable. Both office reviews were not completed until April 2004.

⁴¹Leprosy is a chronic bacterial infection that primarily affects the skin, nerves, and mucus membranes and causes deformities of the face and extremities. For the thalidomide NDA, the Director of CDER at that time disagreed with review staff on whether the NDA should be approved. Review staff were concerned about the potential off-label use of the drug. However, the Director disagreed and overruled review staff and approved the thalidomide NDA.

⁴²For mifepristone, there was no disagreement between high-level management and the review staff on whether the NDA should be approved. Rather, the Commissioner at that time signed the approval letter out of concern regarding the protection of the identities of staff that had reviewed the application.

⁴³The Acting Deputy Commissioner for Operations was the Director of CDER when the initial Plan B OTC switch application was submitted in April 2003. She told us that she became the Acting Deputy Commissioner for Operations in March 2004, and that her role in the review of the initial Plan B OTC switch application was as a consultant to the Acting Director of CDER.

However, the Acting Director of CDER told us that he made the decision to not approve the Plan B OTC switch application shortly before signing the action letter. He also informed us that his decision was made in consultation with other high-level management officials, including the Commissioner and the Acting Deputy Commissioner for Operations, but that he was not directed to reach a particular decision. The Acting Director also told us that these high-level management officials agreed with his decision. When we asked the Acting Director about his meeting with officials from the Office of New Drugs in December 2003, he told us that he might have indicated to the Director and Deputy Director that the agency was “tending” or “thinking of going” in the direction of a not-approvable decision, but that this was not the final decision. Furthermore, although he told us that he was “90 percent sure” as early as January 2004, that the decision would be not-approvable, the Acting Director told us he made his final decision only in the last few weeks prior to issuing the action letter, after he had reviewed all of the documentation associated with the application.

The Acting Director of CDER told us that the rationale for his decision was not fully developed until a few days before the action letter was issued on May 6, 2004. According to internal FDA e-mails we reviewed, the Acting Director of CDER contacted the Director of the Office of Pediatric Therapeutics on May 2, 2004, requesting assistance on language regarding cognitive development during early adolescence to support his decision. According to these e-mails, the Director of the Office of Pediatric Therapeutics responded that she would consult with another official with a background in developmental pediatrics and would follow up with “behavioral science information as to why one cannot extrapolate decision making on safety issues” from older to younger adolescents.

The Acting Director's Rationale for the Not-Approvable Decision Was Novel and Varied from FDA's Traditional Practices

The rationale for the Acting Director of CDER's decision was novel and did not follow FDA's traditional practices. The Acting Director was concerned about the potential impact that the OTC marketing of Plan B would have on the propensity for younger adolescents to engage in unsafe sexual behaviors because of their lack of cognitive maturity. The Acting Director further concluded that because these differences in cognitive development made it inappropriate to extrapolate data from older to younger adolescents in this case, there was insufficient data on the use of Plan B among younger adolescents. FDA review officials disagreed with the Acting Director's rationale and noted that the agency had not considered behavioral implications resulting from differences in cognitive development in prior OTC switch decisions.

The Acting Director's Rationale Was Based on His Concerns about Risk-Taking in Younger Adolescents

The Acting Director of CDER told us he signed the not-approvable letter because of his concerns about the lack of cognitive development and the potential for risky behaviors among younger adolescents resulting from increased access to Plan B. For example, he noted increased access to Plan B could potentially result in an increase in unsafe sexual activity, particularly among younger adolescents—an age group, he noted, that has a tendency to engage in risky behaviors because of their level of cognitive development. This change in behavior could be represented by changes in measurable indicators, such as a decrease in condom use or an increase in the transmission of sexually transmitted diseases (STD).⁴⁴

In his memorandum on his review of the Plan B OTC switch application, the Acting Director of CDER also stated that because younger adolescents' cognitive maturity related to controlling impulsive behavior is less developed than older adolescents', he did not consider it appropriate to extrapolate data from older to younger adolescents in this case. (See app. IV for a copy of the Acting Director of CDER's memorandum.) He specifically noted the following:

"In making decisions about pediatric use, it is often possible to extrapolate data from one age group to another, based on knowledge of the similarity of the condition. However, in this case, adolescence is known to be a time of rapid and profound physical and emotional change. . . . Because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older ages to younger ages. I am uncomfortable with our current level of knowledge about the potential differential impact of OTC availability of Plan B on these age subsets."

Some other officials we spoke with supported the Acting Director's concerns about extrapolating data from older to younger adolescents. For example, the Director of the Office of Pediatric Therapeutics told us and

⁴⁴For the actual use study for the Plan B OTC switch application, an additional observation was included along with the two study objectives. This observation involved collecting and comparing data from study participants on the use of emergency and regular contraception, such as a change in condom use. These data were collected at the time participants enrolled in the study and compared to data collected during a follow-up, 4 weeks later. However, although these data were considered relevant to the application by the sponsor and FDA officials, the sponsor noted that the actual use study was not primarily designed for assessing the potential risk behaviors of potential users of Plan B in an OTC setting.

noted in e-mails to the Acting Director of CDER, which we reviewed, that the difference in cognitive development and maturity between older and younger adolescents and the potential impact this would have on behaviors warranted a separate analysis of this latter age group. In addition, one of the members of the joint advisory committee we spoke with said he was also concerned about extrapolating data from older to younger age groups because he perceived weaknesses in the actual use and label comprehension studies submitted by the sponsor.⁴⁵

Because of these concerns, the Acting Director concluded that the Plan B OTC switch application needed more data specific to younger adolescents. In the not-approvable letter, the Acting Director stated there were too few younger adolescents in the sponsor's actual use study to support the Plan B OTC switch application. Specifically, he highlighted that only 29 of 585 participants in the study were 14 years to 16 years of age and none were under 14 years of age. Although he acknowledged concerns about the difficulty of including younger adolescents in actual use studies, he told us that it was not impossible to enroll younger adolescents in studies, noting that studies for other products have been conducted involving younger participants, including those as young as infants. Some of the Acting Director's concerns regarding the low number of younger adolescents were also raised by other review staff and members of the joint advisory committee. For example, one FDA reviewer who recommended an approvable action on the Plan B OTC switch application noted that despite a reanalysis of the actual use study data of subjects aged 14 years to 17 years, the sample size was too small and "significantly limit[ed] assessment of potential risky/unsafe sexual behavior associated with OTC accessibility of Plan B."

Although review staff within the Offices of Drug Evaluation III and V presented him with additional data on sexual behaviors of younger adolescents in association with increased access to ECPs, the Acting Director of CDER determined that these data were not adequate to support the approval of Plan B for OTC use. He provided his reasoning in

⁴⁵This committee member told us he was specifically concerned that the actual use study was largely conducted in family planning clinics, saying this could bias the results of the study by potentially introducing study participants to health care professionals who could educate them on the use of ECPs. For the label comprehension study, he was concerned about the poor results among lower-educated participants. This committee member told us that literacy and age were a concern because younger age groups are by definition considered among the lower educated.

his memorandum, stating that these studies were either "not conducted in the general population or they provide[d] product education assistance beyond what adolescents would receive in an OTC situation, where no contact with a health care professional is expected."

The Acting Director of CDER's rationale varied from FDA's traditional practices by considering the potential implications OTC access of Plan B would have on the sexual behavior of younger adolescents based on their lack of cognitive maturity and by not accepting the validity of extrapolating data from older to younger adolescents. Although he acknowledged to us that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented, the Acting Director also told us that FDA had recently increased its focus on pediatric issues. He noted that pediatric issues were currently being raised in prescription drug reviews and believed the same should occur in OTC drug reviews.

FDA Review Officials Disagreed with the Acting Director's Rationale for the Not-Approvable Decision

FDA review staff, the Directors of the Offices of Drug Evaluation III and V, and the Director of the Office of New Drugs disagreed with the Acting Director of CDER's rationale for not approving the Plan B OTC switch application. FDA review officials, including those from the Office of New Drugs, noted that traditionally FDA has not considered whether younger adolescents would use an OTC product differently than older adolescents, and the Director of the Office of New Drugs told us that it was "atypical" to raise the question of maturity during a drug review. These officials also noted that FDA does not attempt to determine how a patient arrived at the need for a drug. Rather, drug evaluations usually begin with the need for a potential treatment already existing.

Review staff we spoke with acknowledged that certain behavioral concerns and unintended consequences are examined for an OTC switch application, such as whether making a drug OTC would delay a person from seeking medical treatment or if the drug would potentially be abused if it were more readily available. They told us that these issues are usually examined during a benefit-risk review, which is an analysis of potential medical outcomes. Review staff told us they examined benefit-risk issues for Plan B, and they concluded that concerns regarding the potential for

unsafe sexual behaviors among adolescents could not be supported.⁴⁶ In addition, the review of the label comprehension study from the Office of Drug Safety noted that potential users of the product would be able to appropriately use it if the sponsor made its suggested changes to the proposed labeling.⁴⁷ Also, at the public meeting, members of the joint advisory committee voted 27 to 1 that the actual use study demonstrated that consumers could properly use Plan B as recommended by the label. The members of the joint advisory committee also voted 28 to 0 that the literature review of Plan B included in the actual use study did not show that Plan B would be used as a regular form of contraception.

Furthermore, the review of the application from the Office of Drug Evaluation III, which included the benefit-risk assessment for Plan B, noted that having Plan B in an OTC setting would "pose little risk" to the potential user and that the risk of an adverse pregnancy outcome, such as lower birth weight babies and premature delivery, is much higher among younger adolescents. The review concluded that OTC access to Plan B in helping younger adolescents avoid unintended pregnancies would be "of particular value given the greater risk of an adverse pregnancy outcome in this high risk group." This review also noted that even for a large dose of the hormone used in Plan B, the "margin of safety appear[ed] to be high."

In an attempt to further address the Commissioner's and Acting Director's concerns about the potential for increased risky behavior by younger adolescents resulting from increased access to Plan B, review staff requested additional data from the sponsor and reviewed ongoing studies examining these concerns. FDA's reviewers concluded that increased access to ECPs did not result in (1) inappropriate use by adolescents as a substitute form of contraception, (2) an increase in the number of sexual partners or the frequency of unprotected intercourse, or (3) an increase in the frequency of STDs.

⁴⁶Only one of the review staff for the Plan B OTC switch application raised concerns regarding behaviors of younger adolescents. Recommending an approvable decision, he concluded in his written review of the application that (1) the actual use study had insufficient data on whether OTC accessibility of Plan B might be associated with risky (or unsafe) sexual behaviors over the long term, particularly among adolescents; (2) the behavioral literature did not provide strong evidence to address the inadequacies in the actual use study in assessing risky sexual behaviors in the target OTC populations; and (3) some behavioral studies in the literature suggested that providing ECPs in advance could encourage unsafe sexual behaviors in the study populations.

⁴⁷The changes proposed by the Office of Drug Safety were included as attachments to the office's review of the label comprehension study.

To reach these conclusions, review staff examined the five studies that provided supplies of ECPs in advance to study participants to assess the behavioral impact of OTC access. In one study, which included 2,090 women aged 15 years to 24 years, there was a decrease in unprotected sex among all age groups and no increase in the incidence of STDs compared to the baseline. Another study of 160 adolescent mothers included participants aged 14 years to 20 years. Although there were limited data available, this study concluded that there was no increase in unprotected intercourse and no decrease in condom use among participants. A third study of 301 adolescent women, aged 15 years to 20 years, showed similar results, with no increase in unprotected intercourse or STDs and no decrease in condom use.

FDA officials, including those from the Office of New Drugs, also disagreed with the Acting Director's determination that extrapolating data from older populations to younger adolescents was inappropriate. In their reviews, officials noted that data they reviewed showed that younger adolescents had outcomes similar to those of older populations. For example, the actual use study found that 82 percent of participants 16 years of age or under correctly took the second dose 12 hours later, compared to 78 percent of those 17 years and older.⁴⁸ Also, review staff said that overall the number of participants who were younger adolescents was adequate to draw conclusions about potential use among the adolescent population. Review staff told us they encouraged the sponsor to not limit enrollment or exclude adolescents from the actual use study and felt the study included a representative population of women that would potentially use Plan B. Some of the members of the joint advisory committee we spoke with also said they considered the number of younger adolescents in the actual use study as adequate.

In addition, the Director of the Office of New Drugs told us that the agency has not requested age-specific data often and that FDA often extrapolates findings, including findings on behaviors, from adults to adolescents. He added that given the agency's traditional processes and the data provided

⁴⁸Although there were 29 younger adolescents aged 16 years or under enrolled in the actual use study, only 22 used the product and provided follow-up data for this specific question. Of the 22 study participants who used the product and provided follow-up data, 18 reported that they correctly took the second dose 12 hours after the first. The total number of study participants aged 17 years or older who also used the product and provided follow-up data was 46. Of these 46 study participants, 36 reported that they correctly took the second dose 12 hours after the first.

in the Plan B OTC switch application, there was no reason to consider the extrapolations done in the staff's reviews as inappropriate.

Based on the reviews conducted by review staff and on the recommendations of the joint advisory committee, the Director of the Office of New Drugs concluded the following in his memorandum of his review of the Plan B OTC switch application, issued April 22, 2004 (a copy of this memorandum can be found in app. V):

"In my opinion, these studies provide adequate evidence that women of childbearing potential can use Plan B safely, effectively, and appropriately for emergency contraception in the non-prescription setting. The data submitted by the sponsor in support of non-prescription use of Plan B are fully consistent with the Agency's usual standards for meeting the criteria for determining that a product is appropriate for such use. . . . Such a conclusion is consistent with how the Agency has made determinations for other OTC products, including other forms of contraception available without a prescription. Further, I believe that greater access to this drug will have a significant positive impact on the public health by reducing the number of unplanned pregnancies and the number of abortions."

In his memorandum, the Director of the Office of New Drugs also noted that FDA has a "long history" of extrapolating findings from older populations to younger adolescents. He wrote that this type of extrapolation from older populations to younger adolescents had been done in clinical trials for both prescription and OTC drug approvals and that this practice was incorporated into the Pediatric Research Equity Act (PREA)—the law authorizing FDA to require pediatric studies in certain defined circumstances.⁴⁹ According to PREA, if the disease and the effects of the drug are "sufficiently similar" between adult and pediatric populations, it can be concluded that the effectiveness can be extrapolated from "adequate and well-controlled studies in adults" usually in conjunction with supplemental studies in pediatric populations. In addition, PREA provides that studies may not be necessary for all pediatric age groups, if data from one age group can be extrapolated to another.

Members of the joint advisory committee expressed similar conclusions to those of FDA review officials earlier at the public meeting in December 2003. During the public meeting, committee members voted 27 to 1 that

⁴⁹See 21 U.S.C. § 355c(a)(2)(B).

the actual use study data were generalizable to the overall population of OTC users, including adolescents.

Plan B Decision Was Not Typical of Other Proposed Prescription-to-OTC Switch Decisions

The decision to not approve the Plan B OTC switch application was not typical of the other 67 proposed prescription-to-OTC switch decisions made from 1994 through 2004. The decision of the Plan B application stands out from these other OTC switch applications for two reasons: it was the only decision that was not approved after the members of the joint advisory committee voted to recommend approval of the application, and the action letter was signed by the Acting Director of CDER instead of the directors of the offices where the application was reviewed.

Plan B Was the Only Prescription-to-OTC Switch Decision from 1994 through 2004 That Was Not Approved after the Joint Advisory Committee Voted to Recommend Approval of the Application

From 1994 through 2004, Plan B was the only prescription-to-OTC switch decision that was not approved after the joint advisory committee voted to recommend approval of the application. FDA advisory committees considered 23 OTC switch applications during this period; the Plan B OTC switch application was the only 1 of those 23 that was not approved after the joint advisory committee voted to recommend approval of the application. In addition, there has been only 1 other decision for an OTC switch application that did not follow the recommendations of the joint advisory committee. This other OTC switch application, for the drug Aleve, was approved for OTC status by FDA in 1994, although the joint advisory committee opposed the switch. The NDAC met jointly with the Arthritis Drugs Advisory Committee to discuss the OTC switch application for Aleve in June 1993 and recommended that the application not be approved. Following this meeting, the sponsor made changes to address the joint advisory committee's concerns, and as a result of these changes, FDA decided to approve the application.⁵⁰

⁵⁰Reasons that the joint advisory committee gave for the recommendation against the OTC switch included that the dose was too high, the labeling for people over 65 years of age was incorrect, and no additional labeling was included for children regarding the side effect of photosensitivity.

Plan B Was the Only Prescription-to-OTC Switch Decision from 1994 through 2004 in Which the Action Letter Was Signed by the Director of CDER

From 1994 through 2004, 94 action letters were issued during the review processes for the 68 prescription-to-OTC switch applications, and only 1 action letter—the not-approvable letter for Plan B—was signed by the Director, in this case the Acting Director, of CDER. Given that Plan B was a first-in-a-class drug, the Directors of the Offices of Drug Evaluation III and V would normally jointly sign the action letter. The Plan B application was 1 of 68 proposed OTC switch applications decided by FDA from 1994 through 2004, and 14 of those 68 applications, including the Plan B application, were issued not-approvable letters. Eight of those 14 applications were eventually approved. Plan B was the only contraceptive or emergency contraceptive proposed for an OTC switch during this period. Thirty-eight OTC switch applications, including Plan B, were for the same dose, population, and indication, and all but 3 applications were eventually approved.

There Are No Age-Related Restrictions for Safety Reasons for Any FDA-Approved Contraceptives

According to the Deputy Director of the Office of New Drugs, there are no age-related marketing restrictions for any FDA-approved contraceptives, and FDA has not required any pediatric studies. Condoms and spermicides are available to anyone OTC, while intrauterine devices, diaphragms, cervical caps, and hormonal methods of contraception, including ECPs, are available to anyone with a prescription. For hormonal contraceptives, FDA has assumed that suppression of ovulation is the same in all postmenarcheal females, regardless of age. The Deputy Director of the Office of New Drugs told us that all birth control pills, including ECPs, contain the following class labeling: "Safety and effectiveness of [trade name] have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated."

FDA officials from the Office of New Drugs explained that for an OTC switch, the safety and effectiveness issues have already been addressed during the initial approval process for the drug to become a prescription drug. For an OTC switch application, the review process is primarily focused on whether the drug meets the OTC switch criteria, specifically whether it is safe and effective for use in self-medicating.⁵¹

⁵¹In its technical comments on the draft of this report, FDA said that it also considers age in the labeling of OTC drug products. For example, FDA stated that there are many OTC drugs that have labels with dosing instructions based on age.

There were no safety issues that would require age-related restrictions that were identified with the original NDA for prescription Plan B. FDA approved this application upon determining that Plan B met the statutory standards of safety and effectiveness, manufacturing and controls, and labeling. The original NDA for Plan B for use as an emergency contraceptive contained an extensive safety database that included controlled trials and literature on over 15,000 women.²² The label for prescription Plan B makes no age distinctions about the pharmacological processes of the drug, and prescription Plan B is available to anyone with a prescription.

Agency Comments and Our Evaluation

FDA reviewed a *draft of this report* and provided comments, which are reprinted in appendix VI. FDA also provided technical comments, which we incorporated as appropriate.

In its comments, FDA disagreed with our finding that three aspects of its decision process for the May 2004, Plan B OTC switch application were unusual. First, FDA said that the involvement of high-level management in the Plan B decision was not as unusual as the draft report found. FDA commented that the Director of CDER is ultimately responsible for all decisions made within CDER, and that the Director of CDER is regularly involved in regulatory decisions that are not routine, including those that involve controversial issues. FDA also commented that the Director of CDER typically discusses high-profile and controversial regulatory decisions with officials within the Office of the Commissioner.

While we agree with FDA that the Director of CDER and other high-level officials generally are more likely to become directly involved in high-profile regulatory decisions and noted that in the draft of the report, we found that this level of involvement is unusual for OTC switch applications. The other examples of high-level management involvement given to us by FDA officials during the course of our work involved decisions about the marketing of prescription drugs. Also, it was unusual for the Acting Director of CDER to inform FDA's review staff that it had been determined that the Plan B decision would be made by high-level management. The Acting Director did so on January 15, 2004, before the review staff had completed their reviews of the application.

²²The database included trials conducted in the United States and other countries. Women in the study were above the age of consent for their own countries.

Second, FDA took issue with what it characterized as the tone of our discussion about when the decision was made to deny the Plan B OTC switch application. FDA commented that discussions about alternative regulatory actions ordinarily occur in the course of decision making within CDER and that it is inaccurate to conclude that a decision to deny the application was made several months before the not-approvable letter was issued. However, the draft report did not assert that a decision was actually made several months before the letter was issued. Rather, it accurately noted that FDA officials gave us conflicting accounts of when the not-approvable decision was made. The Director and Deputy Director of the Office of New Drugs and other officials told us that they were informed during December 2003 and January 2004 that the application would not be approved. The Acting Director of CDER denied this, and we reported that his rationale for the not-approvable decision was not fully developed until early May 2004.

Third, FDA disagreed with our finding that the Acting Director's rationale for denying the application was novel and did not follow FDA's traditional practices. FDA commented that the Acting Director's focus on the potential implications to the sexual behavior of adolescent women of approving the Plan B OTC switch application was appropriate and consistent with FDA's treatment of other OTC switch applications.

In response to this comment, we have revised the report to more clearly describe the reasons for our finding. We found that the Acting Director's rationale was novel because it explicitly considered the differing levels of cognitive maturity of adolescents of different ages, and that because of the Acting Director's views about these cognitive maturity differences, he concluded that it was inappropriate to extrapolate data related to risky sexual behavior from older to younger adolescents. In his May 6, 2004, memorandum, the Acting Director stated that "Because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older to younger ages." The Acting Director acknowledged that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented for an OTC switch application. In addition, other FDA officials told us that the agency had not previously considered whether younger adolescents would use a product differently than older adolescents. For example, the Director of the Office of New Drugs told us that it was "atypical" to raise the question of maturity during a drug review and that FDA has traditionally extrapolated findings from older to younger adolescents. Furthermore, in his April 22, 2004, memorandum, the Director of the Office of New Drugs said that "the Agency has a long history of extrapolating findings from

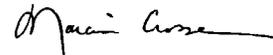
clinical trials in older patients to adolescents in both prescription and non-prescription approvals."

In addition, FDA disagreed with our statement in the draft report that the Directors of the Offices of Drug Evaluation III and V and the Director of the Office of New Drugs refused to sign the not-approvable letter. We used the term "refused" in the draft report because, in our interviews with them, all three of the directors told us that they did not agree with the not-approvable decision and did not sign the action letter, and one of the directors told us that she had been given an opportunity to sign the letter and refused to do so. However, in its comments, FDA said that the directors were not asked to sign the action letter because it was known that they disagreed with the Acting Director's decision. We have revised the report to reflect this.

In its technical comments, FDA asked us to emphasize that safety concerns regarding OTC use of drug would not be raised for prescription products because of the involvement of health practitioners. The draft report noted that prescription drugs are drugs that are safe for use only under supervision of a health care practitioner and that approved prescription drugs that no longer require such supervision may be marketed OTC.

We are sending copies of this report to the Acting Commissioner of the Food and Drug Administration and other interested parties. We will also provide copies to others upon request. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please contact me at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix VII.



Marcia Crosse
Director, Health Care

List of Requesters

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor,
and Pensions
United States Senate

The Honorable Carl Levin
Ranking Minority Member
Permanent Subcommittee on
Investigations
Committee on Governmental Affairs
United States Senate

The Honorable John D. Dingell
Ranking Minority Member
Committee on Energy and Commerce
House of Representatives

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives

The Honorable Jeff Bingaman
The Honorable Barbara Boxer
The Honorable Maria Cantwell
The Honorable Hillary Rodham Clinton
The Honorable Jon Corzine
The Honorable Mark Dayton
The Honorable Christopher J. Dodd
The Honorable Richard J. Durbin
The Honorable Tom Harkin
The Honorable Daniel K. Inouye
The Honorable James M. Jeffords
The Honorable Frank R. Lautenberg
The Honorable Barbara A. Mikulski
The Honorable Patty Murray
The Honorable Charles E. Schumer
The Honorable Debbie Stabenow
The Honorable Ron Wyden
United States Senate

Appendix I: Scope and Methodology

The Honorable Tammy Baldwin
The Honorable Sherrod Brown
The Honorable Lois Capps
The Honorable Benjamin L. Cardin
The Honorable Joseph Crowley
The Honorable Susan A. Davis
The Honorable Lloyd Doggett
The Honorable Sam Farr
The Honorable Bob Filner
The Honorable Maurice D. Hinchey
The Honorable Rush D. Holt
The Honorable Michael M. Honda
The Honorable Barbara Lee
The Honorable Nita M. Lowey
The Honorable Carolyn B. Maloney
The Honorable Edward J. Markey
The Honorable James P. Moran, Jr.
The Honorable Jerrold Nadler
The Honorable Eleanor Holmes Norton
The Honorable Janice D. Schakowsky
The Honorable Louise M. Slaughter
The Honorable Hilda L. Solis
The Honorable Edolphus Towns
The Honorable Mark Udall
The Honorable Chris Van Hollen
The Honorable Diane E. Watson
The Honorable Lynn C. Woolsey
House of Representatives

To examine how the decision was made to not approve the switch of Plan B from prescription to over-the-counter (OTC), we reviewed documents, such as the Plan B OTC switch action package related to the May 6, 2004, decision from the Food and Drug Administration (FDA). We examined documents produced by FDA, including official meeting minutes and the reviews of the Plan B OTC switch application from the Offices of Drug Evaluation III and V and the Office of New Drugs, related to the review of the Plan B OTC switch application. FDA officials told us that documentation was not available concerning some communications within FDA. It was not possible to determine whether such communications may have concerned the Plan B OTC switch application. However, we acquired sufficient information from other FDA documents and our interviews with FDA officials to fully address our objectives.

We interviewed FDA officials involved in the Plan B OTC switch application review, including officials from the Office of Drug Evaluation III, Office of Drug Evaluation V, Office of New Drugs, and Office of Drug Safety. We also interviewed the Acting Director of the Center for Drug Evaluation and Research (CDER), the Acting Deputy Commissioner for Operations, and the Director of the Office of Women's Health. We interviewed members of FDA's advisory committees that met jointly to discuss the Plan B OTC switch application—the Nonprescription Drugs Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD)—and reviewed the transcripts of the meeting. In addition, we interviewed officials from Barr Pharmaceuticals, Inc., the company currently sponsoring the Plan B application for the prescription-to-OTC switch, and Women's Capital Corporation (WCC), the original sponsor of the Plan B OTC switch application.

To examine how the Plan B decision compares to the decisions for other proposed prescription-to-OTC switches made from 1994 through 2004, we examined the recommendations of the joint advisory committee and if they were followed for Plan B and the proposed OTC switch drugs that were decided from 1994 through 2004. We reviewed action letters and interviewed FDA officials and review staff as well as other outside experts involved with the Plan B OTC switch application. We also interviewed officials from the Consumer Healthcare Products Association (the association representing OTC drug manufacturers) about the prescription-to-OTC switch process.

To determine if there were age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives, we reviewed FDA documents and interviewed FDA officials and review staff

regarding safety concerns for prescription Plan B and the safety concerns for other prescription and OTC contraceptives. We also interviewed representatives from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, Concerned Women for America, and the Planned Parenthood Federation of America, Inc., regarding safety concerns for Plan B and other contraceptives.

When the source of evidence we cited is from an interview, we identified the respondent's title and FDA office. Whenever possible, we reviewed documents to verify testimonial evidence from FDA officials. When this was not possible, we attempted to corroborate testimonial evidence by interviewing multiple people about the information we obtained. In situations where there was no concurrence among the interviewees, we presented all the information provided.

Minutes of the internal FDA meetings discussed in this report were written either by a staff member within the Office of Drug Evaluation III or by the Executive Secretariat within the Office of the Commissioner. For meeting minutes written by the office staff member, attendees either reviewed or concurred with the minutes and documented this by including their names at the end of the minutes. For summaries written by the Executive Secretariat, there was no documentation of a review or of concurrence by attendees included with these summaries. FDA officials told us that summaries from meetings within the Office of the Commissioner were not reviewed or concurred with by attendees.

To verify data we received from FDA regarding proposed prescription-to-OTC switch decisions made from 1994 through 2004 and the outcomes of advisory committee meetings for these drugs, we compared FDA's data with prescription-to-OTC switch data obtained from the Consumer Healthcare Products Association on OTC drug switches.

Our work examined only events and communications within FDA and between FDA and the Plan B sponsors; we did not consider any communications that may have occurred between FDA officials and other executive agencies. Our work examined only FDA's actions prior to the May 6, 2004, not-approvable letter, and we did not examine any aspects of FDA's subsequent deliberations about Plan B. We conducted our work from September 2004 through November 2005 in accordance with generally accepted government auditing standards.

Appendix II: Not-Approvable Letter for the Prescription-to-OTC Switch Application of Plan B, May 6, 2004



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

Barr Research, Inc.
Attention: Joseph A. Carrado, M.Sc., Ph.D.
Senior Director, Regulatory Affairs
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004-1401

Dear Dr. Carrado:

Please refer to your supplemental new drug application dated April 16, 2003, received April 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B® (0.75mg levonorgestrel) tablets.

We acknowledge receipt of your submissions dated July 25 (3) and 31, August 8 (2), September 4, 8, 9, and 15, October 6, 10, 15 (2), 17, 21, 24, 29, 30 and 31, December 3 and 9, 2003; and January 9 and 30, February 6, 10, 13, 20 and 24, and March 11 and 26, 2004.

This supplemental new drug application proposes nonprescription (over-the-counter (OTC)) availability of Plan B (0.75mg levonorgestrel) tablets for emergency contraception to reduce the chance of pregnancy after unprotected sex (if a contraceptive failed or if birth control was not used).

We have completed our review of this supplement and, for the reasons described below, find that the supplemental application is not approvable at this time under section 505(d) of the Act and 21 CFR 314.125(b).

You propose OTC status for Plan B for both adults and children based primarily on an actual use study in 585 subjects. Only 29 of the 585 subjects enrolled in the study were 14-16 years of age, and none was under 14 years of age.

In a December 16, 2003 joint meeting, the Nonprescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee considered your proposal to switch Plan B to nonprescription status. Although the Joint Committee recommended that your proposal to switch Plan B be approved, some members of the Joint Committee, including the Chair, raised questions concerning whether the actual use data were generalizable to the overall population of nonprescription users, chiefly because of inadequate sampling of younger age groups.

Based on a review of the data, we have concluded that you have not provided adequate data to support a conclusion that Plan B can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug. In your March 11, 2004, amendment, you proposed to change the indication to allow for marketing of Plan B as a prescription-only product for women

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Page 2

under 16 years of age and a nonprescription product for women 16 years and older. This preliminary proposal did not include draft product labeling to demonstrate how you propose to comply with both the prescription and nonprescription labeling requirements in a single packaging configuration. Because of the preliminary and incomplete nature of the proposal, we did not conduct a complete review of this amendment during this review cycle.

Before this application can be approved, you would have to provide data demonstrating that Plan B can be used safely by women under 16 years of age without the professional supervision of a practitioner licensed by law to administer the drug. Alternatively, you 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. We will have to assure ourselves that your proposed approach is consistent with our statutory authority. If you pursue the alternative approach, we also would request details of your proposed program to educate consumers, pharmacists, and physicians about the dual marketing of Plan B as both a prescription and nonprescription product, as well as your proposed program to monitor implementation of this novel approach.

Wide availability of safe and effective contraceptives is important to public health. We look forward to continuing to work with you if you decide to pursue either of these options.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(v)(8). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

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Page 3

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Divisions of Over-the-Counter Drugs and Reproductive and Urologic Drug Products to discuss what steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call the Regulatory Project Manager at (301) 827-4260.

Sincerely,

(See appended electronic signature page)

Steven Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
 Steven Galson
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Appendix III: Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
February 25, 1997	A notice in the <i>Federal Register</i> stated that the FDA Commissioner had concluded that certain combined oral contraceptives are safe and effective for use as emergency contraception and requested submission of a new drug application (NDA) for this use.
July 28, 1999	FDA approved Plan B as a prescription form of emergency contraception.
February 14, 2001	A citizens' petition for direct over-the-counter (OTC) access to Plan B was filed, requesting that FDA grant Plan B OTC status.
April 18, 2002	FDA review staff within the Office of Drug Evaluation III sent Women's Capital Corporation (WCC) a letter, denying its proposal that FDA request that it conduct pediatric studies on the use of prescription Plan B as an emergency contraceptive in exchange for extending the drug's marketing exclusivity for 6 months, as permitted under the Federal Food, Drug, and Cosmetic Act. ⁴ According to the letter to WCC and a memorandum by review staff within the Office of Drug Evaluation III, the proposed studies would have included a pharmacokinetic study and a safety study and would have used Plan B as an emergency contraceptive in subjects as young as 12 years of age. According to review staff within the Office of Drug Evaluation III, once a young female reached menarche, she was considered an adult for contraceptives and the condition for using an emergency contraceptive is not unique to the pediatric population. The letter concluded that trials could be conducted in the adult population and then extrapolated to the pediatric population.
May 28, 2002	A Center Director Informational Briefing was held in response to the citizens' petition, filed on February 14, 2001. Meeting attendees included the Center for Drug Evaluation and Research (CDER) Director and Deputy Director, the Director of Office of New Drugs, and review staff from the Offices of Drug Evaluation III and V.
June 5, 2002	A briefing for the Office of the Commissioner was held to discuss the expected application to switch Plan B to OTC. Attendees included the Deputy Commissioner, ⁵ the agency's Chief Counsel, the then Director of CDER, the Director of the Office of New Drugs, and review staff from the Offices of Drug Evaluation III and V. According to the executive summary of the briefing, issues discussed included (1) the political sensitivity of the application, (2) consumer understanding of the proposed nonprescription product label, (3) the results of actual use studies to adequately address safety issues, (4) the review status of the supplemental new drug application (sNDA) upon submission, and (5) regulatory issues.
July 10, 2002	The Director of CDER provided the Deputy Commissioner and FDA's Chief Counsel with materials on the safety of emergency contraception and its mechanism of action, which were requested at the June 5, 2002, briefing.
September 23, 2002	FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and the sponsor held a meeting in which FDA provided guidance on the Plan B OTC switch application, which was to be submitted. According to meeting minutes, agency officials and the sponsor discussed behavioral issues in adolescents and the possibility of a behind-the-counter option or a possible age restriction. ⁶
April 16, 2003	WCC submitted an sNDA to FDA to allow Plan B to be sold OTC.
June 9, 2003	FDA review staff from the Office of Drug Evaluation III determined that the sNDA was fileable and accepted it for review. FDA set a Prescription Drug User Fee Act (PDUFA) goal date of February 22, 2004, to reach a decision on the application. ⁷

Appendix III: Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
August 22, 2003	A teleconference was held between review staff within Offices of Drug Evaluation III and V and the sponsor. According to minutes of this teleconference, review staff began working with the sponsor to prepare for the meeting of the joint advisory committee in December. Minutes also noted that FDA review staff suggested that the sponsor plan to address issues of age, literacy, or label comprehension regarding the administration of Plan B.
September 11, 2003	Review within the Office of Drug Evaluation V requested additional information on the label comprehension study results from WCC. According to the official request, review staff asked for information including results for each question asked in the label comprehension study based on literacy levels; details on what criteria were used to determine if a communication objective was met; and other specific points of clarification on how responses were scored.
September 26, 2003	A teleconference was held in which review staff within the Offices of Drug Evaluation III and V discussed the upcoming December 16, 2003, public meeting of its two advisory committees with WCC. According to teleconference minutes, review staff requested additional information on the labels used for the label comprehension and the actual use studies and on the label proposed for approval in the sNDA. Minutes also noted that WCC informed FDA that on September 23, 2003, a majority of its board voted to sell the marketing rights of Plan B to Barr Pharmaceuticals, Inc.
October 2003	Barr Pharmaceuticals, Inc., was finalizing the purchase of the marketing rights for Plan B from WCC and began to act as the agent for WCC for Plan B.
October 9, 2003	At the request of Barr Pharmaceuticals, Inc., a teleconference was held to discuss the upcoming joint public meeting of FDA's advisory committees. Meeting participants from FDA included review staff within the Offices of Drug Evaluation III and V. According to teleconference minutes, review staff asked Barr Pharmaceuticals, Inc., about possible age restrictions for use of Plan B. Minutes also noted that Barr Pharmaceuticals, Inc., said that it intended to offer its product to women as young as 15 years of age. Also, Barr Pharmaceuticals, Inc., agreed to explore and report back to FDA on behind-the-counter marketing and the implementation of age limitations on the sale of Plan B.
November 5, 2003	A reviewer within the Office of Drug Safety completed her review of the Plan B label comprehension study, which was initially submitted to review staff within the Office of Drug Evaluation III. According to the official memorandum on the review of the label comprehension study, the reviewer concluded that making the proposed changes to the Plan B label would likely result in acceptable levels of comprehension. Review staff within the Office of Drug Evaluation V told GAO they concurred with the reviewer's findings.
December 2, 2003	A meeting was held between FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and the sponsor. According to meeting minutes, FDA officials informed Barr Pharmaceuticals, Inc., that the agency may not be able to present a clear regulatory path for alternate OTC distribution mechanisms for Plan B in time for the December 16, 2003, public meeting.
December 10, 2003	A briefing for the Office of the Commissioner was held to discuss the upcoming public meeting of the Nonprescription Drugs Advisory Committee (NDAC) and Advisory Committee for Reproductive Health Drugs (ACRHD). FDA participants included the Commissioner, the Acting Director of CDER, the Director and Deputy Director of the Office of New Drugs, and review staff within the Office of Drug Safety and the Offices of Drug Evaluation III and V. According to the executive summary of the briefing, issues discussed included the sponsor's marketing and distribution plan and the effect making Plan B available OTC might have on consumers' behavior.
December 16, 2003	At a joint meeting of the NDAC and the ACRHD, members voted 23 to 4 to recommend approving the switch of Plan B from prescription to OTC.

Appendix III: Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
December 2003/January 2004	The Director and the Deputy Director of the Office of New Drugs told GAO they were told by the Acting Deputy Commissioner for Operations* and the Acting Director of CDER that the Plan B application could not be approved. These officials said they were told that this direction came from the Office of the Commissioner. The Acting Deputy Commissioner for Operations and the Acting Director of CDER told GAO they did not say this.
January 15, 2004	A meeting was held between officials within the Office of the CDER Director and review staff within the Offices of Drug Evaluation III and V about the Office of the Commissioner's position on the acceptability of the Plan B OTC switch application. According to meeting minutes, the Acting Director of CDER said that a not-approvable decision was recommended by the Office of the Commissioner based on the need for more data to more clearly establish appropriate use in younger adolescents, the need to develop a restricted distribution plan, or both. Meeting minutes also indicated that review staff also informed the Acting Director that their reviews were not yet completed and that there were additional data regarding adolescent use of Plan B. It was then agreed that review staff would complete their reviews and collect the additional data and present them to the Commissioner and the Acting Director of CDER some time in February.
January 16, 2004	Review staff within both Offices of Drug Evaluation III and V later noted in their completed reviews of the Plan B OTC switch application that they were told at this meeting that the decision on the Plan B application would be made at a level higher than the offices of drug evaluation.
January 16, 2004	A teleconference was held between review staff from the Office of Drug Evaluation V and the sponsor. According to meeting minutes, review staff informed the sponsor that a meeting was held with CDER management, including the Acting Director of CDER and the Director and Deputy Director of the Office of New Drugs, in which "some issues" were raised that would require review staff to "provide additional information and have additional discussions with CDER upper management." Minutes also noted that review staff told the sponsor they would not be discussing labeling revisions at that time and that they had been instructed by CDER management to complete their written reviews regarding the OTC switch application.
January 21, 2004	A memorandum from the Director of Office of Drug Evaluation V indicated that she was in agreement with the favorable assessment of review staff and the majority votes by members of the joint advisory committee. Her memorandum concluded that adequate data had been submitted to approve Plan B for OTC marketing with certain product-labeling modifications—such as strengthening the message that Plan B is not for regular contraceptive use—included to address concerns raised at the public meeting and in the agency's reviews.
January 23, 2004	A meeting was held between FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and Barr Pharmaceuticals, Inc./WCC. According to meeting minutes, FDA officials told the sponsor that the decision on the application would be made at a level higher than the Offices of Drug Evaluation. The Director of the Office of New Drugs told the sponsor that such a high-level decision was not typical of CDER's procedures for drug approvals. The minutes also noted that review staff within the Offices of Drug Evaluation were in the process of completing their reviews and would forward them with their final recommendations to high-level management. Meeting minutes also indicated that FDA officials told the sponsor that they would need to request a meeting directly with the Office of the Center Director or the Office of New Drugs to understand high-level management's concerns. In addition, meeting minutes noted that FDA officials told the sponsor that the Office of the Commissioner and the Acting Director of CDER had raised concerns as to whether there were adequate data to establish that minors (i.e., those under 18 years of age) would use Plan B appropriately in the absence of a learned intermediary. Potential options that were suggested from FDA and CDER management included the possible need to (1) collect additional data, perhaps from another actual use study targeted to minors, or (2) to impose an age restriction on the OTC sale of the product.

Appendix III: Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
February 2, 2004	Review staff within the Office of Drug Evaluation III requested that the sponsor reanalyze the adolescent data of the Plan B actual use study. According to the official request, staff asked for a "[s]ummary presentation of the Actual Use data from the participants in the less than 18 years of age subset, including comparisons to the older subset within the study."
February 13, 2004	FDA confirmed that it had extended the PDUFA goal date for a decision on the Plan B OTC switch application for 90 days due to the submission of the requested adolescent data from the actual use study by the sponsor. The extended PDUFA goal date was May 21, 2004.
February 18, 2004	A briefing was held during which review staff within Offices of Drug Evaluation III and V presented their analysis of additional summary data to the Commissioner on the use and behavior of adolescents in association with increased access to emergency contraceptive pills. Other attendees included the Acting Deputy Commissioner for Operations and the Acting Director of CDER. According to meeting minutes, included in the presentation were the review staff's recommendations that Plan B have an OTC marketing status without restriction. The meeting minutes also noted that the Commissioner raised concerns regarding adolescents, including the potential for changes in future contraceptive behaviors and the potential benefits of counseling from a learned intermediary for younger adolescents. In addition, the meeting minutes noted that CDER was directed by the Commissioner to work with the sponsor on a marketing plan to limit the availability of Plan B in an OTC setting and to consider the most appropriate ages that should have OTC access restricted. The Commissioner requested a "rapid action" on the application.
February 19, 2004	Review staff within the Offices of Drug Evaluation III and V met with the Acting Deputy Commissioner for Operations, the Acting Director of CDER, and the Director and the Deputy Director of the Office of New Drugs. According to a reviewer's memorandum, in part, during this meeting, the Acting Deputy Commissioner for Operations expressed her and the Commissioner's concerns regarding adolescents and the potential for adverse behaviors resulting from increased access to Plan B. The Acting Director of CDER concurred with these concerns.
February 22, 2004	This was the original PDUFA goal date for the initial Plan B OTC switch application.
February 26, 2004	Barr Pharmaceuticals, Inc., completed acquisition of the marketing rights for Plan B from WCC.
March 11, 2004	Barr Pharmaceuticals, Inc., submitted an amendment to its sNDA, proposing a dual-marketing strategy, making Plan B OTC for women 16 years of age and older and prescription only for women under 16 years of age.
April 2, 2004	The Deputy Director of the Office of Drug Evaluation III completed her review of the Plan B OTC switch application and recommended that Plan B be approved for use as an emergency contraceptive in the OTC setting without age restriction. The review concluded there were sufficient data on the safety and effectiveness of Plan B to approve its use in the OTC setting.
April 22, 2004	The Director of the Office of New Drugs issued his review of the Plan B application and concurred with the recommendations of the offices of drug evaluation that the sponsor had provided adequate data to demonstrate that Plan B could be safely, effectively, and appropriately used by women of childbearing potential for the indication of emergency contraception without a prescription. He recommended that this application be approved to permit availability of Plan B without a prescription and without age restriction.
May 2, 2004	The Acting Director of CDER contacted the Director of the Office of Pediatric Therapeutics, within the Office of the Commissioner, via e-mail requesting assistance on language regarding cognitive development among adolescents. According to internal FDA e-mails, the Director of the Office of Pediatric Therapeutics responded that she would consult with another official with a background in developmental pediatrics and would follow up with "behavioral science information as to why one cannot extrapolate decision making on safety issues" from older populations to younger adolescents.

Appendix III: Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
May 3, 2004	According to internal FDA e-mails, the Director of the Office of Pediatric Therapeutics provided the Acting Director of CDER with information on brain development and the maturation of higher-order thinking among adolescents 10 years to 21 years of age. In her e-mail to the Acting Director, the Director of the Office of Pediatric Therapeutics included the statement that "[d]uring early adolescence (10-13) there is an emergence of impulsive behavior without the cognitive ability to understand the etiology of their behavior."
May 5, 2004	According to teleconference minutes, the Acting Director of CDER called Barr Pharmaceuticals, Inc., officials to inform them of the not-approvable action and asked permission to release the not-approvable letter. According to FDA regulations, without consent of the sponsor, the agency cannot publicly release data or information contained in an application before an approval letter is issued. Minutes noted that the Acting Director told sponsor officials that (with their permission) he would conduct a press interview to discuss the not-approvable action and the staff's disagreement with the not-approvable action would be acknowledged publicly.
May 6, 2004	FDA issued a not-approvable letter, denying Plan B OTC marketing status, citing a lack of adequate data regarding safe use among younger adolescents. The letter also stated that FDA was not able to conduct a complete review of the dual-marketing strategy in the amendment to the sNDA because of the absence of the draft product labeling describing how Barr Pharmaceuticals, Inc., would comply with both the prescription and OTC labeling requirements in a single package.

Source: GAO analysis of FDA data.

*See 21 U.S.C. § 355a(b), (c). FDA may request that manufacturers of new or already-marketed drugs conduct studies of their drugs in pediatric populations where it believes that such studies will lead to additional health benefits. Studies completed in accordance with FDA requirements entitle the manufacturer to an additional 6 months of marketing exclusivity. In its technical comments on the draft of this report, FDA stated that it did not ask for pediatric data for the prescription version of Plan B because the product's physiological effects are the same in younger and older women, and because a health care practitioner is involved in dispensing prescription drugs.

*On September 23, 2005, the Commissioner of FDA, who was appointed on July 18, 2005, resigned from his position. He held the title of Deputy Commissioner from February 24, 2002, until March 26, 2004, when he was named Acting Commissioner. Because he was Deputy Commissioner during most of the time covered by this report—for those events associated with the initial Plan B OTC switch application through the May 6, 2004, decision—we use the title of Deputy Commissioner for him in this report.

*Behind-the-counter is defined as a classification of drug products that do not require a prescription but are also unlike OTC products in that there is a measure of clinical oversight in their use. For behind-the-counter products, pharmacists are able to intervene by advising patients on the product's proper use and associated risks and by referring them to their physicians when appropriate. See Robert I. Field, "Support Grows for a Third Class of 'Behind-the-Counter' Drugs," *Pharmacy and Therapeutics*, vol. 30, no.5 (2005): 260-261.

*FDA, in collaboration with various stakeholders, including representatives from consumer, patient, and health care provider groups and the pharmaceutical and biotechnology industries, has developed performance goals for the time to complete the review of an application submitted to the agency, which have been incorporated by reference into PDUFA.

*The Acting Deputy Commissioner for Operations was the Director of CDER when the initial Plan B OTC switch application was submitted in April 2003. She told GAO that she became the Acting Deputy Commissioner for Operations in March 2004, and that her role in the review of the initial Plan B OTC switch application was as a consultant to the Acting CDER Director.

See 21 C.F.R. § 314.430(d)(1).

Appendix IV: Acting Director of CDER's Official Memorandum Explaining His Not- Approvable Decision, May 6, 2004

The following is the official memorandum submitted to the record by the Acting Director of CDER to explain his decision on the initial Plan B OTC switch application. GAO has redacted information identifying specific persons as well as information not directly related to the review of the initial Plan B application.

Appendix IV: Acting Director of CDER's
Official Memorandum Explaining His Not-
Approvable Decision, May 6, 2004

MEMORANDUM

DATE: May 6, 2004
FROM: [Text Redacted]
Acting Director, Center for Drug Evaluation and Research
TO: NDA 21-045
SUBJECT: Review of NDA for Rx to Over the Counter Switch for Plan B

I have read and carefully considered all of the reviews in the action package for this application. I do not concur with the recommendation by the Office of New Drugs to approve Barr's application to switch Plan B to over-the-counter (OTC) status. My decision is based on the lack of available data relevant to OTC use of the product by adolescents younger than 14 and very limited data in the 14-16 age group. Without data in the application on OTC use in this age group, and lacking confidence that data from older adolescents can be confidently extrapolated to this age group, I find the proposal to switch Plan B from Rx to OTC use—thus making it available to very young adolescents—to be unsupported. Specific concerns regarding the application include the following:

- Sexual activity among 11- to 14-year-old females in the United States is well documented.¹ Despite the urgent need to prevent pregnancy in these young adolescents, the application contained no data in subjects under 14 years of age.
- In making decisions about pediatric use, it is often possible to extrapolate data from one age group to another, based on knowledge of the similarity of the condition. However, in this case, adolescence is known to be a time of rapid and profound physical and emotional change. For example, during early adolescence (10-13), this age group experiences the emergence of impulsive behavior without the cognitive ability to understand the etiology of their behavior. During mid-adolescence (14-16), youth begin to develop the capacity to think abstractly; however, their ability to integrate their emerging cognitive skills into their real-life experiences is immature and incomplete. The capacity to understand complex concepts, which develops during middle adolescence, allows adolescents to modulate their impulsive behavior.² Because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older ages to younger ages. I am uncomfortable with our current level of knowledge about the potential differential impact of OTC availability of Plan B on these age subsets.

¹"14 and Younger: The Sexual Behavior of Young Adolescents," The National Campaign to Prevent Teen Pregnancy, May 2003.

²*Burke's Psychology*, 21st edition, Chapter 31, Growth and Development, Psychological Development During Adolescence.

I also have the following concerns:

- The additional studies cited in the Office of New Drugs reviews do not approximate actual OTC use sufficiently to support approval. Although the studies are relevant, none tests the hypothesis that typical adolescent consumers with no extra information will use the product correctly. The studies are either not conducted in the general population or they provide product education assistance beyond what adolescents would receive in an OTC situation, where no contact with a health care professional is expected. Likewise, the literature review submitted to address questions of important potential behavioral changes associated with availability of an emergency contraceptive (e.g., substitution of the product for routine and more effective contraception, or increased medically risky sexual behavior) did not contain studies that mimic what would be actual OTC availability.
- The number of adolescent participants in the actual use study is too small to generalize to the U.S. population of adolescents. I do not believe the data set on this age group is large enough to reach valid conclusions from the study.

Some staff have expressed the concern that this decision is based on non-medical implications of teen sexual behavior, or judgments about the propriety of this activity. These issues are beyond the scope of our drug approval process, and I have not considered them in this decision.

The need for data on young adolescent behavior discussed in this memo does not apply to prescription contraceptive products because use of prescription products involves monitoring by health care practitioners and, most-likely in this age group, parents.

[Remaining Text Redacted]

Appendix V: Director of the Office of New Drugs' Official Memorandum on His Decision on the Plan B Application, April 22, 2004

The following is the official memorandum submitted to the record by the Director of the Office of New Drugs to explain his decision on the initial Plan B OTC switch application. GAO has redacted information identifying specific persons as well as information not directly related to the review of the initial Plan B application.

MEMORANDUM

DATE: April 22, 2004
FROM: [Text Redacted]
Director, Office of New Drugs
TO: NDA 21-045
SUBJECT: Review of NDA for Rx to OTC Switch for Plan B

This memorandum is intended to summarize my review, conclusions, and recommendations regarding the pending application submitted by Barr Laboratories proposing a switch to non-prescription status for Plan B (levonorgestrel) for emergency contraception. I have read and carefully considered the reviews in the action package written by [Text Redacted]. I also attended the December 16, 2003, joint meeting of the Non-Prescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee at which this application was presented for discussion and public input.

The drug product and indication proposed by the sponsor for non-prescription marketing (also known as over-the-counter or OTC) are identical to the approved prescription product. Plan B has previously been proven to be effective for emergency contraception, and has a well-documented safety profile. Therefore, the primary regulatory issue in considering the potential non-prescription use of this product is whether it can be used safely, effectively, and appropriately by women of child-bearing potential without need for a learned intermediary (e.g., counseling from a physician). In support of this application the sponsor submitted a label comprehension study and an actual use study, both of which have been extensively reviewed by the staff in the two divisions. In my opinion, these studies provide adequate evidence that women of childbearing potential can use Plan B safely, effectively, and appropriately for emergency contraception in the non-prescription setting. The data submitted by the sponsor in support of non-prescription use of Plan B are fully consistent with the Agency's usual standards for meeting the criteria for determining that a product is appropriate for such use. This conclusion is supported by the fact that both divisions and offices responsible for the review of this application have recommended approval and the fact that the joint Advisory Committee voted 23 to 4 in favor of recommending that Plan B be switched to non-prescription status.

Other senior officials within the Agency, including the former Commissioner [Text Redacted] and the Acting Center Director [Text Redacted], have expressed concerns about the potential for unsafe, ineffective, or inappropriate use of Plan B by adolescents if it were to be made available without a prescription. These concerns appear to have been based primarily on the limited number of adolescent women included in the sponsor's label comprehension and actual use studies. While it is true that the number of adolescents enrolled in the sponsor's studies was relatively small, these studies did not exclude adolescent women from enrollment and were conducted in settings that would be expected to capture a representative population of women who currently seek emergency contraception. Therefore, it is likely that the percentage of patients enrolled in these studies is an accurate reflection of the potential users of Plan B in an OTC setting. Furthermore, the data from these studies do not suggest that adolescent women are significantly different from older women in their comprehension of the labeling or appropriate use of the product in the OTC setting, and for some analyses the adolescent women actually performed better than older women. I, therefore, believe that the data from the studies submitted by the sponsor are sufficient and adequate on which to base a regulatory decision on whether Plan B can be used safely, effectively, and appropriately by women of childbearing potential.

regardless of age, in the OTC setting. The Agency has not heretofore distinguished the safety and efficacy of Plan B and other forms of hormonal contraception among different ages of women of childbearing potential and I am not aware of any compelling scientific reason for such a distinction in this case. I would also note that the Agency has a long history of extrapolating findings from clinical trials in older patients to adolescents in both prescription and non-prescription approvals, and this practice was recently incorporated into the Pediatric Research and Equity Act (PREA).

As detailed in the reviews prepared by [Text redacted], in addition to the studies submitted by the sponsor there exists a substantial body of data from recently completed published and unpublished studies on emergency contraception that have enrolled a substantial number of adolescent women. While none of the studies directly mimic the OTC setting for access to Plan B, I believe that these data are relevant and help to address whether adolescents can use Plan B in the OTC setting. Taken together, these additional studies do not support a concern that adolescent women are less able to understand the label directions or less likely to appropriately use the product than older women. Further, these studies found that increased access for adolescents to emergency contraception did not result in inappropriate use of Plan B as a routine form of contraception, an increase in the number of sexual partners, an increase in the frequency of unprotected intercourse, or an increase in the frequency of sexually transmitted diseases.

In summary, I concur with the recommendations from the review divisions and offices that the sponsor has provided adequate data to demonstrate that Plan B can be safely, effectively, and appropriately used by women of childbearing potential for the indication of emergency contraception without a prescription. I, therefore, recommend that this application be approved to permit availability of Plan B without a prescription and without restrictions regarding the availability of the product to adolescent women.

I am sensitive to and respect the concerns that some may have regarding non-prescription access to Plan B by adolescents. Products that are indicated for uses related to sexual activity in adolescents raise concerns for some people that go beyond a finding based on clinical trial data that the product is safe and effective for its intended use in adolescents. These concerns are derived from individual views and attitudes about the morality of adolescent sexual behavior and also overlap with concerns about the role for parents and health care professionals in decisions about contraceptive use in adolescents. While acknowledging these concerns, I believe that the available data clearly support a conclusion that Plan B meets the statutory and regulatory requirements for availability without a prescription for all age groups. Such a conclusion is consistent with how the Agency has made determinations for other OTC products, including other forms of contraception available without a prescription. Further, I believe that greater access to this drug will have a significant positive impact on the public health by reducing the number of unplanned pregnancies and the number of abortions. While OTC access to Plan B for adolescents may be controversial from a societal perspective, I cannot think of any age group where the benefit of preventing unplanned pregnancies and abortion is more important and more compelling.

The sponsor is aware of the societal issues related to OTC access for Plan B, particularly to adolescents. They initially proposed a voluntary marketing plan called CARE (Convenient Access Responsible Education), which was designed to increase awareness of appropriate use of Plan B through education while increasing availability through OTC access. The joint Advisory Committee voted 22 to 5 (with one abstention) that this program was adequate for introduction of Plan B into the OTC setting. [Remaining Text Redacted]

Appendix VI: Comments from the Food and Drug Administration

	DEPARTMENT OF HEALTH & HUMAN SERVICES	Public Health Service
		Food and Drug Administration Rockville MD 20857

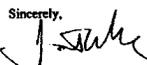
October 28, 2005

Marcia Crosse
Director, Health Care
United States Government Accountability Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Crosse:

Please find enclosed the Food and Drug Administration's general comments in response to the Government Accountability Office's draft report entitled, "*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."

We appreciate the opportunity to review and comment on this draft report before it is published, as well as the opportunity to work with your staff in its development.

Sincerely,

Janet Woodcock, M.D.
Deputy Commissioner for Operations

Enclosure

General Comments to GAO's Draft Report, Entitled, "*FOOD AND DRUG ADMINISTRATION: Decision Process to Deny Initial Application for Over-the Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual*."

We would first like to observe that the agency's opportunity to review this report was atypical. Usually, GAO provides the agency with copies of the report and gives the agency ample time for an internal review and for comment. In this case, we were not provided a copy of the report to review and discuss among ourselves. Instead, GAO offered various viewing times and required FDA personnel to sit in a room with a GAO representative in order to review the report. We were not permitted to copy portions of the report or to make telephone calls. Because of these restrictions, we have had to compile our comments based on our recollection and notes of what the report said during the limited time we had to review it. Our substantive comments are as follows:

1. One of the principal findings in the report is that the decision process for issuance of the Not-Approvable letter for Plan B in May of 2004 was unusual in that FDA high-level management was more involved in the Plan B decision than it has been in other over-the-counter (OTC) switch decisions. While it is true that management at the Center for Drug Evaluation and Research (CDER or Center) is not always involved in making decisions on OTC switch applications, the report suggests that the Center Director's involvement on the Plan B application was more unusual than it actually was. The report does not reflect the fact that Center management is ultimately responsible for all decisions made within CDER, and the Center Director is regularly apprised of, and involved in, regulatory decisions that are not routine, such as those that raise complicated scientific issues, are likely to be controversial, or those for which there is a difference of opinion in the Center. Because of the amount of public interest in the Plan B application, including the fact that two citizen petitions had been submitted regarding the OTC switch of Plan B, it was fairly typical that the Center Director was involved in the regulatory action on Plan B. In addition, the Center Director discussed the Plan B switch application with high-level management within the Office of the Commissioner. Such discussions are part of the Center Director's responsibilities (i.e., to keep his superiors within the agency apprised) and are typical for high-profile, controversial applications.
2. The report also says that the issuance of a Not-Approvable letter in May of 2004 was unusual because there were conflicting accounts about whether the decision to not approve the supplemental application was made before the reviews were completed. The report discusses at length the communications between the review divisions and the Acting Director, CDER and the Acting Deputy Commissioner for Operations in the December 2003 and January 2004 timeframes. The tone of the discussion suggests that the decision to not approve Plan B that was reflected in the May 6, 2004, letter may have been made as early as December 2003 before the reviews were completed, and that this was somehow improper. The report does not reflect that the ordinary course of making regulatory decisions in CDER almost always encompasses discussion of alternative regulatory courses of action over a period of time. A decision on an application is not considered to have been made until the chosen

alternative is documented in an action letter, with supporting rationale. In the first cycle review of Plan B, regulatory alternatives were discussed as the original user fee performance goal date of February 20, 2004, approached. It was entirely normal for the Acting Center Director and others to convey to the review divisions their concerns regarding the application so the division could determine what communications with the applicant were appropriate as the goal date approached. It is inaccurate, however, to claim that a decision to issue a Not-Approvable letter was made several months before the action letter was issued. As the report itself indicates, as late as May 2, 2004, the Acting Director, CDER consulted with the Office of Pediatrics seeking more data on cognitive development in adolescents. The information received provided support for the conclusions reflected in the letter issued on May 6, 2004, documenting the action on the first review cycle of the application.

3. The third aspect of the action on Plan B that GAO found was "unusual" was that the rationale for the decision was "novel" and did not follow traditional practices, referring to the consideration of behavioral issues such as decreased use of condoms and increased risk of sexually transmitted diseases (STDs). This conclusion reflects a fundamental misunderstanding of the issues normally considered in OTC switch applications and the Acting Director's rationale supporting his action on the first cycle review of the Plan B supplemental application. First, all OTC switch applications require consideration of "behavioral" issues, including whether the disease or condition can be self-diagnosed and whether the drug can be used safely and effectively under actual conditions of use. Most switch applications are accompanied by actual use and label comprehension studies that examine such "behavioral" issues. In addition, the "behavioral" issues with regard to this application are directly related to safe use of the product. For example, if a woman chose not to use condoms and to rely on Plan B as her only form of contraception, she may be exposing herself to risks related to acquiring STDs, and if she relies on Plan B as her routine form of birth control, she would be exposing herself to the risks of regular oral contraceptives (which are only available Rx).

In the case of Plan B, the behaviors that were appropriate for consideration included sexual behaviors such as condom use and increased risk of STDs. Furthermore, the report suggests that the Acting Director, CDER alone identified these behavioral issues as concerns in his review. In fact, the Acting Director, CDER was not the source of these issues in the review of the Plan B supplemental application. Regarding the studies that were submitted by Barr and reviewed by the Divisions, the actual use study included specific questions about condom use and the label comprehension study included data from questions that assessed women's understanding that Plan B does not protect against STDs. The Acting Director, CDER reviewing the data in the application concluded that the data on actual use and label comprehension were inadequate to allow a conclusion that Plan B could be used safely and effectively in women under 16 because women in that age group were inadequately represented in the actual use and label comprehension studies. Rather than introducing a "novel" approach to this OTC switch application, the Acting

Director, CDER reached a different conclusion than that of the review Divisions based on his view of the adequacy of the data supporting the switch.

4. The last aspect that GAO asserts was unusual (listed first in the GAO report) was that the Directors of the Offices of Drug Evaluation (ODE) III and V and the Director of the Office of New Drugs "refused to sign" the Not-Approvable letter. The Acting Director, CDER did not ask the ODE Directors or the OND Director to sign the letter, nor was the letter ever presented to them for signature. It would be more accurate to state that those FDA officials did not agree with the issuance of a Not-Approvable letter, and therefore were not asked to sign it.

Appendix VII: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7119 or crossem@gao.gov

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Cathleen Hamann; Julian Klazkin; Gay Hee Lee; and Deborah J. Miller made key contributions to this report.

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