MEMORANDUM

DATE: August 24, 2006

FROM: Steven Galson, MD, MPH
Director, Center for Drug Evaluation and Research

TO: NDA 21-045, S-011

SUBJECT: Plan B®

I. Introduction

On April 16, 2003, Barr Pharmaceuticals (Barr or the sponsor[1]) submitted a supplement to NDA 21-045 to switch Plan B®, (levonorgestrel) Tablets, 0.75 mg, to over-the-counter (OTC) status. The supplement, S-011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act), was received April 23, 2003. On May 6, 2004, I issued a Not Approvable letter because the supplement did not contain data demonstrating that the product was safe and effective for OTC use by women under age 16.

On July 21, 2004, Barr resubmitted its supplement to NDA 21-045, S-011, seeking to switch Plan B®'s prescription (Rx) status to OTC for women 16 years of age and older, and to have Plan B® remain Rx for women under 16 years of age. This resubmission of July 21, 2004, constituted a complete response to our May 6, 2004, Not Approvable letter. The resubmitted supplemental new drug application proposed to switch Plan B® to OTC status for women ages 16 years or greater and maintenance of prescription status for women under age 16.

On August 26, 2005, then Commissioner Lester M. Crawford, DVM, PhD, sent the sponsor a letter indicating that the Center for Drug Evaluation and Research (CDER) had completed its review of the application, as amended, and had concluded that the available scientific data are sufficient to support the safe use of Plan B® as an OTC product, but only for women who are 17 years of age and older.

The letter went on to state, however, that the Agency was unable, at that time, to reach a decision on the approvability of the application because of unresolved issues that related to the NDA. The letter mentioned three issues: whether the same active ingredient could be marketed both Rx and OTC based solely on the age of the individual using the drug; how, as a practical matter, an age-based distinction could be enforced; and whether the Rx and OTC versions of the same active ingredient may be marketed in a single package. The letter also stated that the agency had decided to ask for public comments on whether we should initiate a rulemaking to codify our interpretation of section 503(b) of the Federal Food, Drug, and Cosmetic Act regarding when an active ingredient can be

[1] The current applicant for the Plan B sNDA is Duramed Research Pharmaceuticals, a wholly-owned subsidiary of Barr. For ease of reference, this memo will refer to both entities as Barr.

simultaneously marketed in both a prescription drug product and an OTC drug product through an advance notice of proposed rulemaking (ANPRM) that published on September 1, 2005 (70 FR 52050). The comment period closed on November 1, 2005, and the agency received about 47,000 comments. The agency hired a contractor to summarize and categorize the comments and the contractor submitted a final report on May 19, 2006.

On July 31, 2006, Dr. Andrew von Eschenbach, Acting Commissioner of Food and Drugs, sent the sponsor a letter indicating that the agency had reviewed the comments received in response to the ANPRM and determined it was not necessary to engage in rulemaking to resolve the novel regulatory issues raised by the application and that we were now proceeding with further evaluation of the application.

CDER staff met with the sponsor on August 8, 2006, and discussed how to address the issues raised in Dr. von Eschenbach's letter regarding the restriction on OTC sales of Plan B® to ages 18 and over, the packaging of prescription and OTC Plan B® in one package, and the Convenient Access Responsible Education (CARE℠) Program.

On August 17, 18, and 23, 2006, the sponsor amended its application to propose revisions to the labeling and to the CARE℠ Program.

II. Approval Standards

FDA must require Rx dispensing of any drug that is not safe for use "except under the supervision of a practitioner licensed by law to administer such drug."[2] A drug sponsor may submit a supplemental application to "switch" a drug that FDA has already approved for Rx use to OTC status. FDA will grant a supplemental application to "switch" when it finds that Rx dispensing is:

> not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and . . . the drug is safe and effective for use in self-medication as directed in proposed labeling.[3]

Such switch applications generally include data from actual use and labeling comprehension studies to demonstrate that the product can be safely and effectively used without the supervision of a practitioner licensed by law to administer the drug. FDA may approve an NDA application only when, among other things, the investigations submitted in the application include adequate tests showing whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling and when there is sufficient information to determine from the application whether the drug is safe for use.[4]

[2] 21 U.S.C. § 353(b)(1).
[3] 21 C.F.R. § 310.200(b).
[4] See 21 U.S.C. § 355(d).

III. Findings

I have completed my review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use under the conditions set forth in the draft labeling submitted August 23, 2006. My previous memoranda on this application (May 6, 2004, and August 25, 2005) describe my reasoning for concluding that Plan B® is safe and effective for OTC use for ages 17 and older, but, in the absence of additional data demonstrating that it is safe and effective for OTC use in women under 17, it must remain Rx for this age group.[5] This memorandum addresses the three issues raised in Dr. von Eschenbach's July 31, 2006 letter: the age 18 restriction, the packaging of the product, and the CARE℠ program.

A. Restriction to Rx Use for Women Under 18

Regarding the restriction on OTC use to age 18 and older, Dr. von Eschenbach decided that this was the appropriate age for OTC use for the reasons described in his memorandum of August 23, 2006. I have read that memorandum and, although I previously concluded that OTC use should be restricted to women 17 or older, I have now determined that for the reasons Dr. von Eschenbach outlines, the approval of this application should reflect a restriction to OTC use for those age 18 and older.

B. Packaging

Regarding the packaging of the Rx and OTC products in a single package, Barr has proposed to package Plan B® in a package that is designed to satisfy both the Rx and OTC labeling requirements. On the front of the package, the statement will appear: "Rx only for age 17 and younger." In addition, the package will have the Drug Facts box required for all OTC products, and will have space for a pharmacist to apply the standard prescription drug labeling before dispensing the product pursuant to a prescription. These proposals make it clear that the product is Rx for age 17 and younger, and OTC for ages 18 and older, satisfying the requirements of section 503(b)(4)(A) of the Act that a drug that is subject to the prescription requirement in section 503(b)(1) bear the "Rx

[5] As I noted in my August 26, 2005, memo, various CDER reviewers recommended that Plan B® should be switched OTC for the entire population of women who might use the product, including women under age 18. Similar views were expressed by various CDER reviewers in this review cycle (see for example, August 22, 2006, review of the Director, Office of New Drugs, the Director, Office of Nonprescription Products (ONP), and the Acting Director, Office of Drug Evaluation III). For the same reasons described in my August 26, 2005, memo, I do not agree with those recommendations.

I would, however, like to clarify for the record a statement in my August 25, 2005 memo. On page 5, I stated that if Plan B® was used routinely for contraception (a use inconsistent with the labeling), the well-known risks associated with hormonal contraceptives, such as blood clots and stroke, are likely to be higher than with the use of other contraceptives. While it would be inappropriate to use Plan B® for routine contraception because this dose of levonorgestrel has not been shown to be safe and effective for such a use, the relationship between progestin-only oral contraceptives, such as levonorgestrel, and strokes and blood clots has not been fully defined. This clarification does not change my view that the sponsor did not establish that Plan B® can be used safely and effectively by women under 17 without the supervision of a licensed practitioner.

only" symbol. Because section 503(b)(1) applies here, section 503(b)(4)(B), does not. Section 503(b)(4)(B) states: "A drug to which paragraph (1) does not apply shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol described in subparagraph (A) [the "Rx only" symbol]."

Furthermore, there are important policy reasons for approving this packaging configuration related to implementing the restriction of the OTC product to ages 18 and over. Because the package will be labeled with the "Rx only" symbol, State and Federal law will require that the packages be dispensed only by pharmacies and other healthcare providers such as physicians and clinics authorized to dispense prescription drugs. The product will not be available through convenience stores and gas stations because they will not be authorized to sell the prescription product. As described in the CARE^{SM} program, wholesale distributors and retail chain drug stores confirmed to the sponsor that they will distribute Plan B® only to licensed pharmacies or heath care clinics. Furthermore, since Plan B® has both Rx and OTC labeling, pharmacies will keep Plan B® behind-the-counter, and either a prescription or government-issued proof of age will be presented before sale of the product.

C. The CARE^{SM} Program

In its July 2004 submission, Barr submitted proposed labeling that included a consumer information leaflet that elaborates on the information contained on the Plan B® outer carton and inner packaging. Among the important information that is included in the consumer information leaflet is information about how Plan B® works, when it is appropriate to use Plan B®, how often it should be used, side effects and warnings, and directions for use. In addition, Barr Laboratories proposed an educational program (Convenient Access Responsible Education Program, CARE^{SM}) with the following elements: (1) labeling, packaging, web site, and informational 24-hour toll-free number, (2) education initiatives for healthcare providers and pharmacists, (3) distribution plans, and (4) monitoring efforts to assess whether the Rx/OTC age distinction is understood and adhered to.

In response to Dr. von Eschenbach's letter of July 31, 2006, describing several issues that he asked be addressed concerning the enforceability of the age restriction, representatives from CDER met with Barr to discuss proposed changes to the CARE^{SM} program to address these concerns. On August 17 and 18, and 23, 2006, Barr submitted amendments to Supplement O11 proposing changes to the CARE^{SM} program.

Specifically, Barr:

- Made changes throughout the program to reflect that Plan B® would be made available only by prescription to women age 17 and younger and would be made available OTC to those age 18 and older who show a government-issued identification of their age.
- Clarified that wholesale distributors and chain drug companies will only distribute Plan B® to licensed pharmacies or other licensed healthcare clinics.
- Clarified that since Plan B® will be labeled as both Rx and OTC, pharmacies will keep the product behind the counter to effectuate the restriction of the OTC

product to ages 18 and older.

- Clarified that if violations of the age restriction are observed, the sponsor will increase its educational efforts regarding the age restriction and focus on improving the level of understanding among pharmacists and pharmacy staff, and will also report repeat violators to the relevant State Boards of Pharmacy.[6]
- Committed to report to FDA the results of its surveys to provide signals of program effectiveness and potential problems, and the point-of-purchase monitoring program to determine whether the Rx requirement for those ages 17 and younger is being adhered to at the point of purchase. These results will be reported to FDA at six-month intervals beginning 30 calendar days after the six-month interval commencing on the date of the approval of the amended sNDA.
- Made additional editorial and clarifying changes to the CARE℠ program to reflect changes in packaging.

I have determined that with the changes the sponsor has proposed, the CARE℠ program is adequate to support my finding that Plan B® can be safely distributed in the package configuration proposed by Barr.

To ensure that Plan B® will be used safely and effectively by Rx consumers age 17 and below and OTC consumers age 18 and above, the sponsor has agreed to the following activities:

- Monitor trends in the use of emergency contraception to evaluate the effectiveness of the CARE℠ program. Specifically, the sponsor agreed to conduct a market research survey or surveys of a subset of healthcare professionals annually, and when practicable, in collaboration with established professional groups. These surveys will be designed to determine whether the Rx requirement for those ages 17 and younger is being adhered to at the point of purchase and to provide signals of program effectiveness and potential problems

[6] I disagree with the recommendation by the Office of Surveillance and Epidemiology (OSE) that the CARE℠ program should require the sponsor to notify FDA instead of the State Boards of Pharmacy when pharmacists repeatedly fail to comply with the age restriction (OSE Plan B® CARE℠ Program Review Team Review, August 22, 2006). The Director, ONP, accepted OSE's recommendation (Director, ONP Review, August 22, 2006). OSE explained that it believed such a measure of monitoring the compliance with the age restriction was "overly punitive" and may have a negative impact on the availability of this product OTC. OSE states that a lack of pharmacy compliance may be reflective of an inadequate education plan and this information could be used as an opportunity to improve and/or revise the CARE℠ program. I disagree that the sponsor's proposal is overly punitive, or that it is proposed as a substitute for adequate education. The CARE℠ program states that "findings from the [point-of-purchase] study will be communicated to the pharmacy and the corporate office, if appropriate, since education and retraining will be the first course of remedial action." (CARE℠ Program, August 22, 2006, p. 11) The plan states that only in the case of repeat violators will the violator's State Board of Pharmacy be notified. (Id.) Furthermore, these reports to a State Board of Pharmacy do not mean that FDA will not be informed of violations. The CARE℠ program provides that the sponsor will report to FDA periodically the findings of the point-of-purchase monitoring program. I believe the sponsor's proposed approach to monitoring will increase the likelihood that pharmacists will dispense Plan B® appropriately, and it is within the sponsor's discretion to propose such action.

associated with consumers' understanding of the purpose and proper use of Plan B®.

- Using relevant survey data regularly collected by others (e.g., Centers for Disease Control's Behavioral Risk Factor Safety Surveillance (CDC BRFSS), Youth Risk Behavior Safety Surveillance (YRBSS)), to monitor for potential indicators that Plan B® is being used in an inappropriate manner. Potential areas of monitoring and reporting include evaluating possible correlations between increases in sexually transmitted infections (STIs) based on geographic areas and data and trends in pregnancy and/or abortion rates based on geographic areas.
- Conduct a "Point-of-Purchase Monitoring Program" to track how Plan B® is being sold at the time of purchase, including using anonymous shoppers who will be directed to visit locations where Plan B® is available and purchase the product. Using the data collected, the sponsor will document and analyze the level of comprehension of the Plan B® prescription age requirement and how it is handled at the point of purchase. The program will be conducted twice in the first year and annually thereafter. The sponsor will report repeat violators to the relevant State Boards of Pharmacy.
- Report to FDA on the results of these activities on a six-month interval beginning 30 calendar days after the six-month interval commencing on the date of the approval of the amended sNDA.

Finally, I note and agree with the other elements of the CARE℠ program described in the submission of August 23, 2006, which are designed to help ensure compliance with the approved labeling, and particularly the restriction of OTC use to ages 18 and older. The program includes the following elements:

- The sponsor and third party distributors, wholesalers, and chain drug companies will only distribute Plan B® to licensed pharmacies or other licensed healthcare clinics. As a result, Plan B® will not be sold at gas stations or convenience stores. Given that Plan B® will have both Rx and OTC labeling, the pharmacies will keep Plan B® behind-the-counter.
- The sponsor will conduct an education campaign that will focus initially on healthcare professionals (including prescribers and pharmacists) to raise awareness and knowledge levels about emergency contraception. The education campaign will clearly communicate the prescription age requirement and the appropriate use of emergency contraception. The campaign will include continuing education by certified professionals and educational materials (including websites and toll free numbers) that can be accessed easily and at any time.
- The sponsor will make available to State Boards of Pharmacy continuing education programs for use at annual meetings and other regional programs.
- The sponsor will provide to prescribers and healthcare professional associations materials for distribution to patients that will encourage patients to discuss any questions about emergency contraception with a healthcare professional.
- The sponsor plans to educate consumers, in part by targeting consumers ages 18 to 44 to convey critical awareness and educational messages as well as

information about product availability, time sensitivity of use, and the age requirements to obtain Plan B® as a prescription or OTC product.

I conclude that the CARE℠ program is sufficiently rigorous to prevent young women from obtaining Plan B® over-the-counter without the supervision of a practitioner licensed by law to prescribe the drug. Monitoring of the program's effectiveness will allow FDA to assess whether further modifications will be necessary to prevent inappropriate use of Plan B®.

IV. Conclusion

In conclusion, I find that Barr's sNDA, as amended most recently on August 23, 2006, meets the statutory standards for approval as set forth in 21 U.S.C. 355(d).

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/s/

Leah Christl
8/23/2006 07:38:08 PM
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by Dr. Steven Galson. My signture is for
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Steven Galson
8/24/2006 07:17:59 AM
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