

MEMORANDUM

DATE: 8/26/05

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

TO: NDA 21-045, S-011

SUBJECT: Plan B

I. Introduction

Barr previously filed a supplement seeking OTC status for all post-menarche women on April 22, 2003. I issued a not approvable letter for that supplement on May 6, 2004, 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 Laboratories (Barr or the sponsor) resubmitted its supplement to NDA 21-045, S-011 seeking to switch Plan B's prescription (Rx) status to non-prescription (OTC) for women 16 years of age and older, and to have Plan B remain Rx for women under 16 years of age. I find that the data provided support approval for OTC use for women 17 and older, but I am unable to conclude based on the data presented that women age 16 or less can use OTC Plan B safely and effectively. The data analyses submitted with S-011 stratify the data by age groups as follows: 12-16, 17-25, and older. Because the 16 year olds are grouped in these analyses with the younger adolescents, I would approve Plan B for OTC use for women 17 and older, not 16 and older as Barr requests.

Although Barr did not propose to switch the Rx status of Plan B for women under 16 years of age in its July 21, 2004 resubmission, the CDER reviewers in the Divisions of Reproductive and Urologic Drug Products and the Division of Over-the-Counter Drug Products (the review divisions), the Deputy Directors of the Offices of Drug Evaluation (ODE) III and V, and the Director of the Office of New Drugs recommended that Plan B should be switched OTC for the entire population of women who might use the product, including women under age 16. For the reasons described below, I do not agree with these recommendations.

Two citizen petitions have been submitted to FDA regarding the Rx status of emergency contraception. One petition, submitted on February 14, 2001, by the Center for Reproductive Law and Policy (CRLP) (now the Center for Reproductive Rights) on behalf of several organizations and supplemented August 7, 2001 and February 13, 2002, urged FDA to exempt from the Rx dispensing requirement both Plan B and Preven, an emergency contraceptive marketed by Gynetics, as well as any equivalent drugs (Docket 01P-0075/CP1). The second petition, submitted by the Pharmacists Planning Service, Inc. on May 12, 2004, urged FDA, by regulation, to switch Plan B from Rx to a "pharmacist-only" status (Docket 01P-0075/CP2) (i.e., to allow sales by pharmacists to consumers without a prescription, but not to allow the product to be sold by retail outlets on the shelves for consumers to pick up and purchase). To the extent these petitions raise issues that are relevant to this review, my views on these issues at this point in time are addressed below.

In addition, my office has received many calls, letters, and e-mails from interested members of the public both supporting and opposing the switch to OTC status of Plan B, and some of which have supported Barr's July 2004 proposal to market Plan B OTC for women 16 and over, and Rx for women under 16. While these calls and e-mails have not raised arguments not already raised in the reviews and the petitions, they are indicative of the high level and divided nature of public interest in FDA's decision on this matter.

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."¹ 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.²

Such switch applications 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.³

III. Findings

A. Data on Plan B Use by Women 17 and Older

Plan B provided pursuant to a prescription has previously been proven to be effective for emergency contraception and has a well-documented safety profile. In a label comprehension study and in an actual use study submitted with the supplemental NDA, the sponsor has demonstrated that women of childbearing-potential age 17 and older can use Plan B safely and effectively for emergency contraception in the OTC setting. The data submitted by Barr demonstrate that Plan B is safe and effective without the supervision of a practitioner licensed by law for women ages 17 and older in self-medication as directed in the proposed labeling. The CRLP petition and many of the comments on that petition also support this view.

¹ 21 U.S.C. § 353(b)(1).

² 21 C.F.R. § 310.200(b).

³ See 21 U.S.C. § 355(d).

B. Data on Plan B use by Women 16 and Younger

In reviewing a proposed switch from Rx to OTC status, FDA assesses the actual use and labeling comprehension studies submitted by the applicant to support the switch. As described in my May 6, 2004 Not Approvable letter, the April 2003 supplement contained very limited actual use data on women ages 14 and 15, and no actual use data on women under age 14. Similarly, the label comprehension study also included few women ages 16 and under (n=76).⁴ Moreover, as described below, what little data were in the supplement raised questions about whether the product can be used safely and effectively by younger adolescents.

Although in NDA 21-045, supplement S-011 Barr proposed to switch Plan B to OTC for women 16 years and older, the data in S-011 are stratified by age in the following categories: 12-16 years, 17-25 years, and 26 years and older. There were no analyses in the supplement that distinguished 16 year olds from younger women in the 12-15 year old category. Accordingly, I find that although the safety and efficacy of Plan B as an OTC drug product in women 17 years of age and older have been established by data submitted by Barr in NDA 21-045, S-O11, Barr has not met the statutory burden of demonstrating that the product is safe for use without the supervision of a practitioner licensed by law for women under age 17.

First, when compared to older adolescents (>17 years) and adults, early adolescents (ages 12-16 years) were less likely to specifically comprehend Plan B's labeling instructions. In the label comprehension study (N=656), adolescents (ages 12-16 years, n=76) did not understand certain key directions in the labeling. For example, women ages 12-16 did not understand as often as women 17 years and older that Plan B's indication is to prevent pregnancy after unprotected sex (86% for ages 12-16, 93% for ages 17-25, 95% for ages 26-50), that Plan B is not for routine use (57% for ages 12-16, 67% for ages 17-25, 71% for ages 26-50), that the first pill should be taken within 72 hours after intercourse (77% for ages 12-16, 86% for ages 17-25, 87% for ages 26-50), and that the second pill should be taken 12 hours after the first pill (77% for ages 12-16, 90% for ages 17-25, and 82% for ages 26-50).⁵

Second, the data from the actual use study, which enrolled very few women under 17 years, also raise concern about the safety of OTC Plan B for young women. For instance, they show that adolescents under age 17 were less compliant with the 4 week follow-up period specified in the study protocol when compared to the older women (ages ≥ 17 years). Fifty-five percent of the subjects aged 14-16 had two or more follow-up contacts, while 89% of the older subjects (ages 17-44) had two or more follow-up contacts.⁶ These differences in follow-up undermine the ability of the actual use study to support safe use of OTC Plan B in this age group.⁷ Furthermore, of the 29 14-16 year olds enrolled, most of them were 16 year olds (20 of 29 or 69%).⁸

⁴ Plan B, Label Comprehension Study, Table 9, page 31.

⁵ Id.

⁶ Plan B, Actual Use Study, Final Report Tables, Table 1.4c, page. 16.

⁷ See also, page 23 of January 12, 2004 sNDA review by OTC Division (Jin Chen).

⁸ January 11, 2005 email from Joseph Carrado to Tia Frazier.

The OND reviews both before and after issuance of the not approvable letter state that the safety and efficacy of Plan B as an OTC drug product have been established for women of all ages. Several of the Office of New Drugs reviews cite studies that they believe demonstrate that Plan B can be used safely and effectively in women under 16.

First, some of the reviews discuss the literature review submitted by the applicant, which included studies that addressed questions of important potential behavioral changes associated with the availability of an emergency contraceptive (e.g., substitution of the product for routine and more effective contraception, or increased medically risky behavior).⁹ One reviewer cites studies evaluating the use of emergency contraception in a variety of clinical settings that enrolled over 1,000 adolescent women age 16 years or less.¹⁰ Although these studies are relevant, they do not, in my view, sufficiently approximate actual OTC use by adolescents under age 17 enough to support OTC approval. None test the hypothesis that typical adolescent consumers will use the product correctly without physician intervention, as the studies either were not conducted in the general population or provided product education assistance beyond what adolescents would receive in an OTC situation, where no contact with a health care professional is expected. One review states that there was no suggestion based on the data from the sponsor's studies that younger women were less able to use the product correctly in a simulated OTC setting than older women.¹¹ Based on the data cited previously from the actual use and label comprehension studies, I disagree with this assessment.

Furthermore, neither the CRLP petition nor the comments supporting that petition have provided any additional data on which I could rely to make the finding that Plan B will be used safely and effectively by adolescents under the age of 17. Some of the outside comments opposing the petition also noted the lack of data about what effect switching Plan B to OTC status would have on the sexual behavior of adolescents and the impact on adolescent health (such as increasing the incidence of sexually transmitted diseases).¹²

In conclusion, neither the original supplement nor the resubmission contain adequate data to demonstrate that prescription dispensing is no longer necessary for women under age 17. The data submitted do not demonstrate that women under age 17 can be expected to use Plan B appropriately in self-medication as directed in the proposed labeling. As discussed above, the inappropriate use of Plan B can have several significant adverse clinical consequences. In the absence of these data, and absent persuasive data from other relevant patient populations (see below), the statutory and regulatory standards for approving a supplement to switch Plan B from Rx to OTC for this population are not met.

C. Inability to Extrapolate From Adult Data

⁹ See e.g., Jenkins review, dated April 22, 2004, signed April 18, 2004, at 2; Rosebraugh review, dated March 23, 2004, signed March 30, 2004, at 4.

¹⁰ Beitz review, January 12, 2005, at 1.

¹¹ Jenkins review, dated January 14, 2005, signed January 18, 2005, at 2-3.

¹² The commenters themselves failed to provide data to support their other concerns about, for example, whether OTC availability would increase the potential for misuse and adolescent promiscuity.

In making decisions about pediatric pharmaceutical use, it is often possible to extrapolate data from one age group to another. For example, we have extrapolated safety and efficacy data from adults to children for the approval of drugs to treat seasonal allergic rhinitis and symptomatic gastroesophageal reflux disease, where the disease course and pathophysiology, as well as the drugs' effects, are similar in adult and pediatric populations.

In this instance, it would be inappropriate to extrapolate the existing data from the 17 and older population to the under 17 population based on the nature of the product itself (i.e., a hormonal contraceptive), the risks associated with its inappropriate use, and the characteristics of the population of young women to whom the data would be extrapolated.

With regard to the risks associated with inappropriate use of Plan B, if a young woman did not understand that Plan B was for emergency contraception and non-routine use, and instead, used the product routinely (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 use of other contraceptives. Reflecting these risks, non-emergency hormonal contraceptives are now available only by prescription because the intervention of a learned intermediary is thought to be necessary to minimize the risks of the serious side effects that may be associated with long-term regular use.

Further, younger adolescents may believe that Plan B could be substituted for other forms of birth control (e.g., barrier methods), placing them at greater risk of infection from HIV or other sexually transmitted diseases. This concern is heightened by the data from the label comprehension study (discussed above), which found that women ages 12-16 did not understand as often as women 17 years and older that Plan B is not for routine use (57% for ages 12-16, 67% for ages 17-25, 71% for ages 26-50).¹³ The actual use study did not contain enough data to demonstrate that younger women would not engage in this form of dangerous substitution.

In addition, if a young adolescent does not understand that the first dose of Plan B should be taken within 72 hours of unprotected intercourse, and the second pill 12 hours later, the effectiveness of the product will be compromised, and she may be at greater risk of having an unwanted pregnancy. As previously discussed, younger women were less able to understand that the first pill should be taken within 72 hours after intercourse (77% for ages 12-16, 86%, for ages 17-25, 87% for ages 26-50), and that the second pill should be taken 12 hours after the first pill (77% for ages 12-16, 90% for ages 17-25, and 82% for ages 26-50).¹⁴

Finally, with regard to the characteristics of a younger population in general, extrapolation of the actual use and labeling comprehension data to this group could be inappropriate because data in the pediatric literature on younger age groups suggest potentially significant differences from older adolescents with regard to cognitive abilities and risk taking behaviors.¹⁵ The less developed cognitive abilities of women under age 17 could

¹³ Plan B Label Comprehension Study, Table 9, page 31.

¹⁴ Id.

¹⁵ Chambers R, Taylor J, Potenza MN. "Developmental Neurocircuitry of Motivation in Adolescence: A Critical Period of Addiction Vulnerability" *Am J Psychiatry* 160: 1041-1052, June 2003; Dahl R. "Adolescent Brain Development: A Period of Vulnerabilities and Opportunities. Keynote Address" *Ann NY Acad Sci* Vol 1021: 2004; 1-22; Steinberg L. "Risk Taking in Adolescence" *Ann NY Acad Sci* Vol 1021: 2004, 51-58.

lead to inappropriate use of Plan B and the potential for younger women engaging in risky sexual behavior, behaviors which carry significant safety and efficacy concerns.

To conclude, it is inappropriate to extrapolate from adult data to younger women to support the safety of OTC Plan B. This, coupled with the lack of adequate data in the under 17 population demonstrating that these young women understand the indication and proper use of the product and the risks associated with having unprotected sexual intercourse, mean that safe use of OTC Plan B in this age group cannot be assured. I conclude that retaining the Rx status for Plan B for women under 17 years of age is appropriate. Such an outcome addresses the concerns about potential improper use by the under 17 population by providing for the involvement of a learned intermediary to counsel young women who may engage in sexual intercourse about how to use Plan B and other contraceptives appropriately, and about the risks associated with engaging in unprotected sexual intercourse.

D. Effect of having both Rx and OTC versions of Plan B

The OND reviewers and the CRLP petition argue that labeling Plan B to be sold without a prescription to women 16 and over, and with a prescription for women under 16, could have the unintended public health consequence of limiting access to women of all ages.¹⁶ This is not a factor FDA would normally consider in making a switch decision, as it is not in the criteria for non-prescription status in the statute or FDA's implementing regulations. FDA's approval decisions are based on whether products can be safely and effectively used by the population for whom they are indicated. In the case of Plan B, I have concluded that the Rx designation for women under age 17 is necessary for the safe and effective use of the drug by that age group. Furthermore, I believe that Plan B has been shown to be safe and effective without a prescription for women 17 and older. I believe that if Plan B is made available OTC to women 17 years and older, this will significantly expand access for most women and will enhance the public health by reducing the risks of unintended pregnancies and the number of abortions. However, my view with respect to Plan B's approvability for OTC use for women age 17 and older and for women under age 17 rest on whether the data demonstrate that the product is safe and effective for each group.

IV. Precedent

Decisions on whether a drug should be switched from Rx to OTC status involve a case-by-case risk/benefit analysis that considers the drug at issue, the indication, and the population for whom OTC use is proposed. As described below, my views regarding Plan B are readily distinguishable from prior decisions made about other contraceptive OTC products and non-contraceptive OTC products.

For example, some OND reviews question whether having both Rx and OTC versions of the same drug for different populations parts from precedent in that other non-prescription forms of birth control are available OTC to women of all ages. I do not dispute that such products are available OTC, but submit that both the inherent risks of Plan B as a systemically absorbed hormonal product, which carries significant risks if used improperly, and the absence of demonstrated safe OTC use distinguish Plan B from other contraceptives available OTC to women under age 17. Other forms of contraception such as condoms and spermicides, including Nonoxynol-9 (N-9), have been available OTC for

¹⁶ These reviewers based their analysis on Barr's proposal which used age 16 as the cutoff for OTC use.

many years, and have a record of decades of safe use with OTC availability. In addition to their record of safe OTC use, they do not represent the same level of potential risk as oral hormonal contraceptive products because they do not involve systemic absorption of appreciable quantities of pharmacologically active substances. FDA recently proposed to add warnings to products containing N-9 to caution consumers that frequent use may increase the risk of transmission of sexually-transmitted diseases. FDA has determined that, with these warnings, such products remain generally recognized as safe and effective for OTC use. In contrast, however, Plan B does not have a record of safe OTC use, and the supplement did not provide the data necessary to support an OTC switch for women under age 17 (either with or without specific warnings on the label).

In addition, some of the OND reviews point out that other non-contraceptive OTC drug products have been approved as safe and effective for a wide range of ages in the absence of data in young people. These reviews also cite the lack of precedent for distinguishing between Rx and OTC status based on age. One reviewer raises the concern that keeping Plan B Rx for women ages 15 and under might have ramifications for how we regulate other OTC drugs where there is known abuse by adolescents, such as dextromethorphan, laxatives, and analgesics.¹⁷

In my judgment, all of these criticisms overlook several critical facts. First, FDA consistently considers age-related data (or the absence of such data) when making regulatory judgments about how OTC drug products should be labeled. The key distinction between Plan B and most other OTC drugs relates to the degree to which data submitted for one population may be extrapolated to another. Second, my request for more data related to women under the age of 17 is grounded in the previously described difficulties associated with trying to extrapolate safety and effectiveness for this population from data submitted about women 17 years of age and older. Finally as discussed above, adolescent women under the age of 17 are cognitively less mature than women 17 and older, and they are also prone to a higher incidence of risk-taking behavior. These realities raise important questions about whether women under the age of 17 can use Plan B safely and effectively without the involvement of a learned intermediary.

Third, the need for additional data is also compelled by the specific risks associated with Plan B, which differ from most other OTC drug products. Plan B is a form of oral hormonal contraceptive that is currently available Rx-only because of the serious side effects that may be associated with long-term regular use. The approved indication for Plan B is for use after unprotected sex, e.g., when other birth control was not used or when physical barrier methods have obviously failed. Other non-contraceptive, OTC products, such as antacids, are indicated for uses that are normally associated with risks much less serious than unprotected sexual intercourse, unwanted pregnancy, and the risk of stroke. Before approving a drug for OTC use, FDA has a statutory obligation to assess whether that drug is safe and effective when used as directed by its target population. More information are needed demonstrating whether OTC use of Plan B by women under the age of 17 would increase their potential for harm from already risky behavior (e.g., by increasing the frequency of unprotected sex) or present serious health risks (e.g., stroke and blood clots) from frequent use of a high-dose oral contraceptive. Non-hormonal contraceptive OTC products do not pose such risks.

¹⁷ Rosebraugh, review, January 12, 2005, at 1.

The question has been raised whether it is more reasonable to limit the use of Plan B to young adolescents through OTC labeling.¹⁸ For example, some OTC products contain dosing information for a defined age range and advise the user to seek advice from a physician before using in children younger than the defined age. Some suggest that this approach should be adopted for Plan B, asserting that the best way to address any lack of data for women under age 16 would be to make the product available OTC only and to label the product “not for use under age 16,” or “for children under the age of 16, consult a physician.”

I have considered this. However, while there are many such labels, most such warnings are the result of recommendations made by expert panels that were first convened when FDA began the OTC Drug Review in the early 1970s. Among other things, these panels helped FDA determine on a drug-by-drug basis what safety and effectiveness data, if any, could be extrapolated to children. These panels made recommendations to FDA about whether the adult doses were appropriate for children, how doses should be modified based on age, or whether the product should not be used at all (or only on the advice of a physician) for certain age groups. Based on these analyses, FDA promulgated OTC drug monographs that set forth the conditions under which certain OTC drugs are generally recognized as safe and effective for certain uses. Several of these monographs include age-related warnings to clarify that, based on what we know about the drugs, they are not generally recognized as safe and effective for OTC use for certain age groups (e.g., 21 CFR 332.30; 333.250; 341.72). This approach makes sense in the context of most OTC drugs because the populations to which the warnings generally apply -- children ages 6 and under -- do not self-diagnose and do not purchase OTC drug themselves. Instead, the warnings target adults who purchase the products and for whom the products are intended. Similarly, many such OTC products are also sold in child-proof packaging. In the case of Plan B, however, the population for whom the drug is Rx-only includes persons who are old enough to visit pharmacies and purchase OTC drug products for their own use. Because the data are not adequate to show that adolescents under the age of 17 are able to understand the instructions for use and would use the product as intended in the label, it would be inappropriate to rely solely on labeling to limit inappropriate use by younger women.

Finally, I do not believe that this position sets a precedent for requiring more data in younger age groups for prescription, non-emergency use, oral contraceptives. As indicated previously, these oral contraceptives are available at this time only by prescription. Experience has shown that with the involvement of a learned intermediary, prescription oral contraceptives can be used safely and effectively by women post-menarche under all conditions in the approved labeling.

V. Other Issues Raised in the Citizen Petitions

A. Whether Plan B is an abortifacient

Two of the comments on the CRLP petition allege that Plan B is an abortifacient. One of these comments suggests that marketing it as a contraceptive would be misleading. The second comment suggests that because it is an abortifacient, informed consent and the intervention of a physician are necessary.

¹⁸ Rosebraugh, et. al. review, January 12, 2005, at 2.

There are three theoretical mechanisms by which progestin-only, emergency contraceptive, drug products (e.g., Plan B) may prevent pregnancy. These include (1) prevention of ovulation or disruption of the normal peri-ovulatory events resulting in ovulatory dysfunction, (2) interference with the actual process of fertilization by impeding the migration of sperm into the distal portion of the fallopian tubes/abdominal cavity or disrupting the processes that sperm undergo prior to fertilization of an ovum, and (3) prevention of implantation by a direct effect on the endometrium of the uterus. Data from studies in women on the mechanism of action of progestin-only drug products conclusively demonstrate that these products prevent ovulation and/or disrupt normal peri-ovulatory events resulting in ovulatory dysfunction. It is generally believed that this mechanism is responsible for most, if not all, instances in which emergency contraception prevents pregnancy. However, available clinical data do not exclude the possibility that these drug products, in a small percentage of women, also may prevent pregnancy by impeding fertilization of a released ovum or implantation. There are no clinical data that indicate that emergency contraceptive drug products will disrupt a fertilized egg that has already implanted.

Because of the possibility that Plan B may, in some instances, prevent pregnancy by a mechanism other than prevention of ovulation or disruption of the normal peri-ovulatory events, proposed product labeling for Plan B contains the following wording in the Section "How does plan B work?"

"Plan B works like a birth control pill to prevent pregnancy mainly by stopping the release of an egg from the ovary. It is possible that Plan B may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb), which usually occurs beginning 7 days after release of an egg from the ovary. Plan B will not do anything to a fertilized egg already attached to the uterus. The pregnancy will continue."

This labeling adequately informs women that in some cases Plan B could prevent attachment of a fertilized egg to the uterus. Thus, women are provided appropriate information for making an informed choices about its use.

Under DHHS regulations, "Pregnancy encompasses the period of time from implantation until delivery."¹⁹ Therefore, because the product does not work by interrupting an established pregnancy, it is not considered an abortifacient.

B. Whether OTC availability of Plan B would increase the risks of ectopic pregnancy

One of the comments opposing the petition raises the concern that OTC availability eliminates necessary clinical monitoring to address the risk of ectopic pregnancy. In the United States, ectopic pregnancies account for approximately 2% of reported pregnancies in the general population. Among women using progestin-only, oral contraceptives for routine contraception, 50 out of 1,000 women will get pregnant, and approximately 5 out of these 50 women (10%) will have an ectopic pregnancy over the course of one year for an

¹⁹ 45 CFR 46.202(f).

overall rate of ectopic pregnancy in women using progestin-only, oral contraceptives for routine contraception of 0.5%. Therefore, the absolute risk of a woman having an ectopic pregnancy while using a progestin-only, oral contraceptive (approximately 0.5%) is less than the 2% overall ectopic pregnancy rate reported for women in the U.S.

The issue of the risk of ectopic pregnancy in women using progestin-only, emergency, contraception (e.g., Plan B) was thoroughly reviewed by Dr. Davis in his March 25, 2004 safety review of the original submission for the change from prescription status to OTC status for Plan B. In his review, Dr. Davis noted that there were 28 unduplicated cases of ectopic pregnancy in the FDA's AERS database. None of the reports was from the U.S., and there were no deaths among these 28 reports. The absence of any reported ectopic pregnancies in U.S. users of Plan B is reassuring as to its safety in this regard. However, it is not possible to fully estimate the risk of an ectopic pregnancy in users of Plan B from these data because of under-reporting of post marketing safety data. The risk of ectopic pregnancy in users of Plan B can be better assessed from clinical trial data. In his review, Dr. Davis states the following:

*"Six large randomized clinical trials (RCTs) published in the medical literature in which levonorgestrel was used for emergency contraception were reviewed (see Table 5). Among these 6 trials, there were 7,889 evaluable subjects for whom 133 pregnancies and 2 ectopic pregnancies were reported (an incidence of 1.5% ectopic pregnancies among total pregnancies). The 1.5% incidence is consistent with the reported national rates of 12.4 and 19.7 per 1000 pregnancies in the U.K. (1.24%) and the U.S. (2.0%), respectively. These 6 trials provide good clinical evidence that levonorgestrel-only emergency contraception does not increase the chance that a pregnancy will be ectopic. Moreover, because emergency contraception is at least 75% effective in preventing a pregnancy, emergency contraception also reduces a woman's absolute risk of an ectopic pregnancy."*²⁰

Although ectopic pregnancies have been reported in women who have used progestin-only, emergency contraception, the available data do not indicate that these women are at a greater risk for an ectopic pregnancy should Plan B be ineffective in preventing a pregnancy. Consequently, it is not necessary to require a prescription for Plan B in order to have the topic of ectopic pregnancy discussed by a physician with a woman who may use the product.

C. Whether FDA should establish a pharmacy or pharmacist-only class of drugs
The Pharmacists Planning Service petition urges FDA, by regulation, to switch Plan B from Rx to a "pharmacist-only" status. FDA has stated in the past that "[T]he agency believes it is questionable whether the distribution of lawfully marketed OTC drugs can be restricted [to a pharmacist only class of drugs] under current statutory provisions. Under the Federal Food, Drug and Cosmetic Act (the act) there is no provision for an intermediate class of drugs between OTC and prescription products. The statutory requirement that a drug either be limited to prescription dispensing or available OTC with adequate directions for use seems to preclude the agency from establishing a class of drugs

²⁰ Davis and Monroe Review, dated March 17, 2004, signed March 25, 2004, at page 22.

whose labeling would need to be supplemented by a pharmacist's instructions."²¹ In addition, the GAO concluded in its report titled "Nonprescription Drugs: Value of a Pharmacist-Controlled Class Has Yet to Be Demonstrated" that "[l]ittle evidence supports the establishment of a pharmacy or pharmacist class of drugs in the United States at this time. . . ." ²² The recommendation that I am making that Plan B be OTC for women 17 years and older and prescription for women under 17 does not establish a new class of drugs, but rather preserves the existing statutory distinction between OTC and prescription drugs.

VI. Proposed Labeling and Educational Program

In the July 21, 2004 resubmission, Barr has proposed to package Plan B in a single package for both the Rx and OTC indications. Barr proposed that the package would say, "Rx only for women age 16 and younger." Based on the data in the supplement, the labeling would need to be amended to say "Rx only for persons age 16 and younger." I find that the proposed labeling includes adequate directions for use in self medication for women ages 17 and older, and if amended to change age 16 to 17, would clearly convey that the product remains Rx for women under age 17. Although FDA has not previously approved a product with a single package for both prescription and OTC use, I find this packaging configuration to be adequate.

Barr Laboratories' proposed labeling was reviewed by the Division of Over-The-Counter Drug Products on November 15, 2004, and the Division requested changes to the labeling on December 22, 2004, and January 14 and 19, 2005. Barr submitted revised proposed draft labeling on January 12, 18, and 19, 2005. The revised labeling was reviewed and found acceptable by the Division on February 7, 2005.

The proposed labeling includes 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 has proposed an educational program (Convenient Access Responsible Education Program, CARE) 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.

While Barr's proposed labeling and educational program provides additional information to help women ages 17 and older use Plan B safely and effectively, it does not serve as a substitute for the data necessary to support a switch to OTC use for women under age 17, and it does not constitute the same level of supervision that a learned intermediary provides when writing a prescription.

VII. Pediatric Research Equity Act of 2003 (PREA) Requirements

²¹ Response to Citizen Petition submitted by D.C. Huffman, Jr., American College of Apothecaries, Dec. 3, 1984-page 3.

²² GAO/PEMD-95-12.

PREA requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. The Division of Pediatric Drug Development (DPDD) conducted a review of the supplemental application to switch Plan B to OTC status for women 16 years and older and concluded the sponsor's submission meets PREA requirements for post-menarchal females, and that studies in males and premenarchal females should be waived.

I agree that the proposed switch meets the requirements of PREA but use a somewhat different analysis than DPDD. First, I believe that only the switch of Plan B to OTC status for women 17 and older triggers the PREA requirements. As the DPDD notes, the original NDA for prescription Plan B was submitted on January 29, 1999 and approved on July 28, 1999. Therefore, PREA did not apply to the original application because it was submitted before PREA's effective date of April 1, 1999. The only change from the original application proposed by Barr for Plan B is to switch Plan B to OTC status for women 16 years of age and older. I have found that the data only support switching Plan B to OTC status for women 17 years of age and older. Therefore, the only relevant pediatric population at issue is the population of women 17 to 18 years of age who would be using Plan B OTC.

The safety and effectiveness of Plan B in all women age 17 years of age and older has been demonstrated in the actual use and labeling comprehension studies submitted with this supplemental application. I find, therefore, as did DPDD, that the safety and effectiveness of Plan B in the relevant pediatric population (ages 17-18) has been demonstrated, and the requirements of PREA have been met.

VIII. Conclusion

In conclusion, I find that as a matter of science, Barr's July 21, 2004 proposal to switch Plan B to OTC status meets the statutory standards for approval of an NDA supplement set forth in 21 U.S.C. 355(d) for women age 17 and older, but does not meet the statutory standards for women under age 17. If additional data on actual use and labeling comprehension in women under 17 are provided, or Barr is able to demonstrate that women age 16 can be differentiated from younger women in the actual use and label comprehension studies, I am prepared to reevaluate my conclusions.

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/s/

David Hilfiker
8/26/2005 11:01:36 AM
CSO

My assistance in the finalization of this memo does not indicate my agreement with its content or recommendations. I am participating at the request of D.Throckmorton, CDER, and I am not acting on behalf of the Office of Nonprescription Products or OND.

Steven Galson
8/26/2005 02:36:45 PM
MEDICAL OFFICER