CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-045/S011

MEDICAL REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 22, 2006

FROM: Julie Beitz, MD
Acting Office Director,
Office of Drug Evaluation III

SUBJECT: NDA 21-045 Levonorgestrel; Plan B
Duramed Research, Inc.

I have reviewed Duramed's submission dated August 17, 2006, provided in response to the Agency's letter of July 31, 2006. This submission proposes that Plan B be marketed as an OTC product with a prescription-only requirement for those aged 17 years and younger. This memo documents my view that there are sufficient data on the safety and effectiveness of Plan B to approve its use in the OTC setting without an age restriction. In the absence of new data to support an age restriction, my conclusions as stated in my previous memos of April 2, 2004, and January 12, 2005, remain unchanged.

Julie Beitz, MD
Acting Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
8/22/2006 12:34:20 PM
DIRECTOR

John Jenkins
8/22/2006 12:47:26 PM
MEDICAL OFFICER
See my review dated August 22, 2006.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office Director Memorandum

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Nonprescription Products
5901-B Ammendale Road
Beltsville, MD 20705-1266
(301) 796-2060

Date: August 22, 2006

From: Charles J. Ganley, M.D. _____
Director, Office of Nonprescription Products (HFD-560)
Office of New Drugs
Center for Drug Evaluation and Research

Subject: Plan B/ NDA 21-045/S-011

The sponsor was asked by FDA at an 8-8-06 meeting to amend their application to market Plan B over-the-counter. They were instructed that Plan B could be considered for marketing if they changed the age limit to 18 years and above for sale without a prescription, market a single package for prescription and OTC distribution and make revisions to the Convenient Access Responsible Education (CARE) plan.

The sponsor submitted changes to the labeling and CARE plan on 8-17-06. They have complied with all of the requests made to them. The sponsor is also compliant with the child resistant packaging regulations.

The Office of Safety and Epidemiology recommends three changes to the current packaging and CARE Plan:

1. If the sponsor comes out with additional tablet strengths, they will need to increase the font size of the content information on the principle display panel.
2. As part of the CARE plan, the sponsor should notify FDA of failures to comply with the plan and not the Board of Pharmacy.
3. The CARE plan should specify identification with a government issued ID.

All of these suggestions are acceptable and should be conveyed to the sponsor.

There is a single formatting issue in Drug Facts (inclusion of a period) that can be done post-marketing.

Conclusions

Previous reviews from the Division of Over-the-Counter Drug Products (DOTCDP) and Office of Drug Evaluation V (ODEV), signed by Dr. Rosebraugh and Dr. Bull, recommended sale of Plan B over-the-counter without restrictions. DOTCDP and ODEV have evolved into the Office of Nonprescription Products (ONP). No new data was provided to suggest the restriction based on age is necessary. Based on the previous findings of the DOTCDP and ODEV, ONP continues to believe that restriction on access is not necessary.

Usually OTC product advertising falls under the purview of the Federal Trade Commission. Given the single package of this product for Rx and OTC marketing, the action letter should clarify whether the sponsor is required to submit all advertising information to DDMAC.

Insert name of document and where filed in OTC

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/s/

Charles Ganley
8/22/2006 01:18:10 PM
MEDICAL OFFICER

MEMORANDUM

DATE: August 22, 2006

FROM: John K. Jenkins, MD
Director, Office of New Drugs

TO: NDA 21-045, S011

SUBJECT: Review of resubmitted NDA for Rx to OTC Switch for Plan B

The sponsor resubmitted this application on August 17, 2006, in response to a letter dated July 31, 2006, from Dr. Andrew von Eschenbach, Acting Commissioner of FDA. In his letter, Dr. von Eschenbach informed the sponsor that the Agency had determined that "it is not necessary to engage in rulemaking to resolve the novel regulatory issues raised by your application." Dr. von Eschenbach further indicated that the Agency would like to meet with the sponsor to discuss resumption of review of their sNDA for the Rx to OTC switch of Plan for emergency contraception in women 18 years of age an older. The sponsor subsequently met with the Agency on August 8, 2006. During that meeting issues related to the age cutoff for OTC marketing, the sponsor's proposed CARE Program, and other administrative issues were discussed. I did not attend that meeting but have reviewed draft meeting minutes.

The resubmitted application includes revised prescription and OTC labeling for Plan B along with a revised CARE Program. The proposed prescription (for women 17 years and younger) and OTC labeling (for women 18 years and older) have been reviewed and found to be acceptable by staff in the Division of Reproductive and Urologic Products and the Division of Non-Prescription Clinical Evaluation, respectively. The changes made by the sponsor to the CARE Program appear to respond to the recommendations made by the Agency during the August 8, 2006, meeting.

As documented in my reviews dated April 28, 2004, and January 18, 2005, I believe the available data are adequate to support a conclusion that Plan B can be safely and effectively marketed as a non-prescription product for all women of child-bearing potential in need of an emergency contraceptive. I am not aware of any new data that supports the need for an age restriction for OTC marketing of Plan B, therefore, the conclusions and recommendations of my prior reviews are unchanged. I continue to recommend that the application be approved for OTC marketing without an age restriction.

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/s/

John Jenkins
8/22/2006 05:05:32 PM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Supplemental NDA Label Changes

NDA	sNDA 21-045 / 011
Type of Application	Prescription to OTC Switch
Applicant	Duramed Research Pharmaceuticals
Drug Name	
Trade name	Plan B®
Established name	Levonorgestrel
Indication	Emergency contraception
Route of Administration	Oral
Dosage Form	0.75 mg tablet
Dosing Regimen	One tablet within 72 hours after intercourse followed by a second tablet 12 hours later
Related Submissions	NDA 21-045 (original submission) and sNDA 21-045 / 011 (SE6)
Submission Date	August 17, 2006 (Revised prescription labeling)
Review Completed	August 18, 2006
Reviewer	Daniel Davis, MD, MPH Medical Officer

Materials Reviewed: Physician Package Insert for the prescription (Rx) product submitted on August 17, 2006.

Background and Summary:

Plan B® (levonorgestrel 0.75 mg) is given in 2 doses, 12 hours apart, for Emergency Contraception. In April 2003, the sponsor submitted SE6 Efficacy Supplement #011 to market Plan B® as an over-the-counter (OTC) product. This supplement received a Not Approvable letter on May 6, 2004. In July 2004, Duramed Research Pharmaceuticals submitted a major amendment, which constituted a complete response containing additional data in support of the supplement.

The Applicant and FDA met on August 8, 2006 to discuss the status of this application and the Agency's recommendation that Plan B remain a prescription drug product for women 17 years of age and younger and become a non-prescription product for women 18 years of age and older. In response to that meeting, the Applicant submitted by e-mail on August 17, 2006 revised prescription labeling.

Review of labeling:

The proposed label for the prescription product clearly states that Plan B is not for routine contraception and that it does not protect against STIs. After reviewing the physician label that was submitted by the Applicant on August 17, 2006, the following changes are noted:

1. Throughout the label, the Applicant has made the Agency's recommended change that the prescription drug product is "for women age 17 and younger." The Indications and Usage section now reads (new text shown by underline):

   "For women age 17 and younger, Plan B® is a prescription-only emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure."

2. The Introductory section of the label now reads (new text shown by underline):

   Rx Only for women age 17 and younger

   For women age 17 and younger, Plan B® is a prescription–only emergency contraceptive. Plan B® is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

3. The Applicant replaced the 18th Edition of the Trussell table with the 17th edition of the Trussell Table as requested by the Division of Reproductive and Urologic Products (DRUP) in order to be consistent with presently approved labeling for Plan B and non-emergency contraceptive products.

4. As recommended by DRUP, the Applicant made a minor revision to the Clinical Studies section of the label. This Section now reads (deleted text shown by strikethrough):

   "….. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with Plan B®. ~~Thus, Plan B® reduced the expected number of pregnancies by 89%~~."

Recommendation:

The Applicant has made the revisions to prescription labeling for Plan B that have been necessitated largely by the Agency's decision that Plan B remain a prescription drug product for women 17 years of age and younger and become a non-prescription product for women 18 years of age and older. Based on this decision by the Agency, the changes proposed by the Applicant are acceptable and approval of labeling submitted on August 17, 2006 is recommended.

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/s/

Daniel Davis
8/18/2006 03:35:10 PM
MEDICAL OFFICER

Scott Monroe
8/22/2006 02:21:26 PM
MEDICAL OFFICER

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.

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[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-011, 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]

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[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 heath 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

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[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 gastroesophagial 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

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[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 pregancy 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

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[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

Division Director Memo-Addendum
NDA #: 21-045/S-011
Drug Name: Plan B (Levonorgestrel 0.75 mg)
Sponsor: Women's Capital Corporation
Receipt Date: July 22, 2004
PDUFA Date: January 22, 2005
Type of Document: Response to NA letter-addendum
Date: February 7, 2005

I agree with Arlene Solbeck's review, which was placed into DFS on January 21, 2004 that no further labeling revisions are requested of the sponsor. The sponsor has made all changes requested of them and their labeling is acceptable. The current label conforms with Drug Facts in style. For content extending beyond medical issues, I would point out that the legality of requiring an age restriction for OTC purchase and using a single package for both prescription and OTC marketing should be determined by the Office of Chief Counsel. There is a pending consult with the Office of Chief Counsel regarding these issues that has not been responded to at the time of this memo addendum. Also, as I stated in my last memo, I do not agree with an age restriction, but have given advice on labeling as this is the course of action that center management has indicated it is taking.

Curtis J. Rosebraugh, MD, MPH

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HFD-580/griebel/beitz
HFD-020/jenkins

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Curtis Rosebraugh
2/7/05 11:56:44 AM
MEDICAL OFFICER

MEMORANDUM

DATE: January 14, 2005

FROM: John K. Jenkins, MD
Director, Office of New Drugs

TO: NDA 21-045, S011

SUBJECT: Review of resubmitted NDA for Rx to OTC Switch for Plan B

This memorandum summarizes my review, conclusions, and recommendations regarding Barr Laboratories' complete response to the not-approvable letter issued at the end of the initial review cycle. In the original supplemental application the sponsor proposed to switch Plan B (levonorgestrel) to non-prescription status (OTC) for emergency contraception. Following my review of the original application, I agreed with the two divisions and two offices involved in the review that the sponsor had provided adequate information to support the proposed switch and recommended that the application be approved (see my review memorandum dated April 28, 2004). Dr. Galson, the Acting Center Director, did not concur with that recommendation and issued a not-approvable letter dated May 6, 2004.

In his review memorandum, Dr. Galson cited concerns about "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" as the primary basis for his decision that the application was not approvable. Dr. Galson stated that adolescence is a time of rapid and profound physical and emotional change including the emergence of impulsive behavior without the cognitive ability to understand the etiology of the impulsive behavior in early adolescence (10-13 years). He also stated that 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. He concluded that "because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older ages to younger ages." Dr. Galson concluded that the data submitted in the application as well as other published and unpublished studies reviewed by OND were inadequate to support a conclusion that adolescents could use Plan B safely in the OTC setting.

In the not-approvable letter the sponsor was informed that before the application could be approved it would be necessary for them to provide data demonstrating that Plan B can be used safely by women under 16 in the OTC setting. Alternatively, they were informed that they could supply additional information to support a revised indication to allow marketing Plan B as a prescription only product for women under the age of 16 years and a non-prescription product for women 16 years and older. The sponsor was informed that if they decided to pursue the latter approach it would be necessary for them to describe

how such an approach complied with all relevant statutory and regulatory requirements for prescription and non-prescription products.

In its response to the not-approvable letter, the sponsor requested that Plan B be approved as a non-prescription product for women 16 years and older and as a non-prescription product for women under 16 years. The sponsor proposed that the product be sold in a single package configuration for both the prescription and non-prescription age groups and provided their analysis of how such a single package meets the relevant statutory and regulatory requirements for prescription and non-prescription products.

I have read and carefully considered the reviews in the action package generated during this second review cycle written by Drs. Dan Davis, Donna Griebel, and Julie Bietz of the Office of Drug Evaluation III and the review written by Dr. Curtis Rosebraugh and co-signed by Drs. Charles Ganley and Jonca Bull of the Office of Drug Evaluation V. I have also carefully reviewed Dr. Galson's May 6, 2004, review and the not-approvable letter.

I continue to believe that the sponsor has provided adequate information to support a conclusion that Plan B can be used safely and effectively by women of child-bearing potential for emergency contraception in the OTC setting without the need for intervention by a healthcare profession. I do not concur with Dr. Galson's conclusion that the data from the label comprehension and actual use studies conducted by the sponsor, taken together with data from published and unpublished literature, are inadequate to support the same conclusion for women less than 16 years of age. I therefore support approval of Plan B as an OTC emergency contraceptive without an age restriction and believe that the sponsor's proposal for "dual marketing" of Plan B as both a prescription and non-prescription drug should not be approved. I note that the FDA's Office of Chief Counsel is currently actively reviewing the legal issues associated with the sponsor's proposal for "dual marketing." Even if the sponsor's proposal is determined to be consistent with current statutes and regulations I believe the proposal should not be approved since there is, in my opinion, no scientific basis for the differentiation in prescription and non-prescription status based on age and such an approach is inconsistent with well established FDA precedent with regard to labeling OTC products for use in adult and pediatric populations.

I will briefly expand on the bases for my conclusions.

Dr. Galson is correct in noting that a relatively small number of subjects less than 16 years of age were included in the label comprehension and actual use studies conducted by the sponsor. As I noted in my previous memorandum, given the setting in which these studies were performed it is likely that the observed age distribution is reflective of the age distribution of the population of women who will use Plan B if approved for non-prescription marketing. Further, I believe that it is entirely reasonable to extrapolate the findings from the older women in these trials to adolescents given well established agency precedent for extrapolating data from studies in adults and older adolescents to younger adolescents and the fact 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. There is no pharmacologic or safety issue for the use of levonorgestrel at the dose found in Plan B in younger adolescents compared to older women, and the approved prescription labeling for Plan B and other oral contraceptives that contain levonorgestrel make no distinction based on age.

Dr. Galson has cited developmental differences between adolescents and older women in support of his concern about extrapolation of findings from older to younger women. In my opinion, the concerns Dr. Galson raises are more applicable to the ability of adolescents to make reasoned decisions about engaging in sexual intercourse, not their ability to understand how to use Plan B safely and effectively as an emergency contraceptive should they engage in unprotected sexual intercourse. The Plan B regimen is very simple (one tablet as soon as possible after unprotected intercourse and another tablet 12 hours after the first) and in many ways easier to follow than many other OTC products that are labeled for use by adolescents and younger children (e.g., some OTC products require a decision about the proper dose to be taken based on age or weight, require frequent repeat dosing, and contain multiple warnings and "Do not use if" statements). Further, levonorgestrel, the active ingredient in Plan B, has a very high margin of safety. This high margin of safety combined with the packaging configuration, which only includes two tablets per package, makes it very unlikely that a serious adverse event would occur if an adolescent incorrectly dosed the product.

With regard to the policy precedent, the agency has not to my knowledge previously approved marketing of a drug product as both prescription and non-prescription for the same indication based solely on an age distinction. Products that are currently marketed as OTC products generally contain dosing information for a defined age range; e.g., children 6 years an older, and for children younger than the defined age range the labeling instructs the user to seek advice from a physician before using. It is not clear why a similar approach, which has been effectively utilized for many years by the agency, could not also be applied to Plan B. A decision to approve Plan B as a prescription and non-prescription product for the same indication with the only difference being the patient's age sets an important policy precedent that must be carefully considered and justified. In my opinion, such an approval for Plan B cannot be justified based on scientific data (e.g., there is no unique safety concern for the drug in women under age 16 and in my opinion the data presented by the sponsor support a conclusion that younger adolescent women can use the product safely in the OTC setting) and such an approval has the potential to raise other serious scientific and policy issues. For example, other OTC contraceptive products are not marketed under such "dual" prescription and non-prescription status. Approval of Plan B as a "dual" product based on age is likely to lead to petitions to the agency that other OTC contraceptives be similarly restricted, which could significantly alter the availability of contraceptives to sexually active adolescents, a group where pregnancy leads to serious short and long-term risks to the mother and the child. The potential policy implications on the OTC monographs, which do not currently distinguish between prescription and non-prescription status based on age, must also be carefully considered prior to approval of Plan B as a "dual" product.

As I noted in my prior memorandum on this application, I am sensitive to and respectful of 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. An agency decision to approve Plan B as a "dual" product may have the paradoxical effect of decreasing access to and use of the product if pharmacies and pharmacists choose not to stock the product due to an unwillingness to participate in verifying the age of women who present to the pharmacy requesting Plan B or based on liability concerns. The age restriction will also be difficult to enforce and easy to bypass (e.g., an adolescent girl can simply have an older friend purchase the product for her) and in the end is not likely to serve its apparent intended purpose of ensuring that younger adolescent women be guided in the use of the product by a healthcare professional.

For the reasons stated above, I believe that the proposed "dual" marketing strategy for Plan B should not be approved, and instead, the sponsor's original proposal for non-prescription marketing without restrictions based on age supported by their CARE program should be approved.

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/s/

John Jenkins
1/18/05 11:48:29 AM
MEDICAL OFFICER
Recommend approval of Plan B for non-presciption status with no age restriction. Recommend not-approval of sponsor's proposal for non-prescription status for women 16 years and over and prescription status for women under 16 years.

Division of Reproductive and Urological Drug Products

Medical Officer Review of Complete Response

Type of Submission	Complete response to Not Approvable action for prescription to OTC switch
NDA Number	21-045/S-011, [SE6]
Applicant	Duramed Pharmaceuticals, Inc (a Subsidiary of Barr)
Date of Submission	July 21, 2004
Primary Medical Reviewer	Daniel Davis, MD
Date of Review	January 12, 2005

1. RECOMMENDATION REGARDING APPROVAL AND POSTMARKETING COMMITMENTS

1.1 Recommendation regarding Approval

There are no new safety findings that would preclude the approval of changing Plan B® from prescription status to over-the-counter (OTC) status for preventing pregnancy (i.e., emergency contraception) following unprotected intercourse or a known or suspected contraceptive failure in women of any age who are at risk of becoming pregnant. Data submitted by the Applicant during the original review cycle have shown that Plan B is sufficiently safe and efficacious when used in accordance with proposed labeling that it can be distributed over-the-counter without any age or distribution restrictions and without the need for any further clinical studies.

The Applicant, however, has requested that the product remain as a prescription-only product for adolescents under age 16 years. This reviewer does not believe that this request is warranted or desirable.

Final labeling will need to be agreed to by the Applicant and the OTC Division of the FDA prior to approval. The Applicant's marketing plan and postmarketing CARE^{SM} (Convenient Access, Responsible Education) Program are designed to limit the availability of Plan B to pharmacies and clinics, and to educate health-care providers and consumers regarding the responsible use of emergency contraception, methods of routine contraception, and prevention of sexually transmitted infections (STIs).

1.2 Postmarketing Commitments

This reviewer has no specific recommendations for postmarketing studies or risk management steps.

2. REGULATORY BACKGROUND:

The Applicant submitted Supplement 011 to NDA 21-045 on April 22, 2003 for the switch from prescription status to OTC status for Plan B for the indication for emergency contraception. The original PDUFA date was February 22, 2004 and a 3-month extension was granted extending the date to May 22, 2004. On May 6, 2004 the Applicant received a Not Approvable letter from the

Agency. The primary reason for the action was that the CDER Center Director did not believe that "adequate data had been submitted 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." The Applicant was informed that before the application could be approved, Barr would need to either provide additional data demonstrating that Plan B can be used safely by women under age 16 without professional supervision or supply information in support of marketing Plan B as a prescription-only product for women under the age of 16 years and a nonprescription product for women age 16 years and older.

The current re-submission package S-011, SE6, requests that Plan B be prescription only for women under age 16 years and nonprescription (i.e., OTC) for women 16 years of age and older. **This brief clinical review discusses (1) a general over view of the submission, (2) additional safety data submitted by the Applicant and a safety update prepared by the FDA's Office of Drug Safety (ODS), (3) emergency contraception (EC) availability, (4) the Applicant's CARE (CONVENIENT ACCESS, RESPONSIBLE EDUCATION) Program, and (5) the Applicant's proposed Product Label.**

3. GENERAL OVERVIEW OF SUBMISSION

The submission dated July 21, 2004 addresses primarily the issues of 1) the dual prescription-OTC status for the identical product of two tablets of levonorgestrel 0.75 mg for the indication of emergency contraception, and 2) the associated labeling changes. The proposal is that the product will be prescription-only for adolescents under the age of 16 years, while it will be over-the-counter for women age 16 years and older. The Applicant has proposed that one package [carton] be used for both groups.

The submission dated January 7, 2005 is an update on USA pharmacy availability of Plan B, global EC availability, and an annotated bibliography of 28 articles from the medical literature relating to all aspects of EC that were not previously submitted to the Division.

There are no new safety issues that have appeared since the December 2003 Reproductive AC meeting and some additional data on the use of emergency contraception by young adolescents. New comparative data on different dosing regimens using a total of 1.50 mg of levonorgestrel have been published in the medical literature. The authors conclude that the safety and contraceptive effectiveness of a single-1.5 mg dose or two-0.75 mg dose [either 12 or 24 hours apart] regimens are comparable and can be initiated up to 120 hours after unprotected intercourse. From the medical literature submitted by the Applicant, the data on adolescents in the USA, Mexico, UK, Spain and Sweden does not demonstrate an increase in pregnancy or STI rates or a decrease in condom use rates associated with easier access to, or use of, emergency contraception.

Reviewer's comment:

- **The safety and effectiveness of a total dose of 1.5 mg levonorgestrel, either as a single or divided dose, for women of all ages remains the same as was previously determined in 2003 and early 2004.**
- **There is no new data that shows a problem or concern with easier access to, or use of, emergency contraception by adolescents or any other group of women.**

4. ADDITIONAL SAFETY DATA SINCE ORIGINAL SUBMISSION

4.1 Periodic Safety Report

Periodic Report P-016 was received on 9-08-04 and contained a total of 297 adverse events in 161 patients. There were 11 15-day reports for the reporting period. There were no serious listed initial or follow-up reports.

Reviewer's comment:

- **No safety signals of concern are found in this periodic safety report.**

4.2 Office of Drug Safety (ODS) Consultation

The ODS was consulted and reviewed the FDA adverse event reporting system (AERS) database for any reports that listed levonorgestrel products [e.g., Plan B, Postinor, Levonelle] for use as an emergency contraceptive. Special attention was paid to reports of ectopic pregnancy, bleeding requiring hospitalization, and birth defects that might be associated with the use of these products. The previous ODS report covered up to October 9, 2003. The updated report covered the period from the date of the original Plan B approval in 1999 up to January 3, 2005 and found the following information:

- There were 20 additional unduplicated cases in the AERS database [an increase from 116 to 136]; although all of the 136 reports [70 foreign, 66 USA] met the regulatory definition of serious, only 52 listed an outcome that involved hospitalization or were life-threatening
- There were 7 new reports of ectopic pregnancy; of the 35 total reports of ectopic pregnancy, none are from the USA
- Since the original approval date for Plan B, there have been only 3 AERS reports in adolescents under the age 18 [2 foreign and 1 USA]; the USA report was for a 15 year old who had a positive pregnancy test and no other AEs
- There was 1 new report of congenital anomalies; a 19 year old women in the UK gave birth to a baby with multiple anomalies who died at age 3 months
- There were no new reports of hypersensitivity to levonorgestrel
- There were no new reports of convulsions
- There have been no reported user deaths since approval

Reviewer's comment:

- **Since the extensive clinical safety review of March 25, 2004, the data here shows no new or increased safety signals. The 20 additional unduplicated AERS reports since October 9, 2003 is entirely within the expected number as use of levonorgestrel for emergency contraception continues to increase each year in the USA and globally.**

5. UPDATE ON AVAILABILITY OF PROGESTIN-ONLY EMERGENCY CONTRACEPTION

5.1 USA states with pharmacy access

To date, 6 states (Alaska, California, Hawaii, Maine, New Mexico, and Washington) have legislated pharmacy access to EC without a prescription obtained directly by the patient from a physician. Certified pharmacists in these 6 states can also dispense Plan B directly to women age 15 and younger by following the approved protocol of their state.

5.2 Global data on OTC and BTC (behind the counter) availability

EC pills are available truly OTC only in Norway (2000) and Sweden (2001). EC pills are available directly from a pharmacist without having to see a physician in 35 countries; the only countries with an age restriction are the UK and Switzerland where the pharmacy access in limited to women over age 16. Of note is that pharmacy access in the UK costs the consumer directly, whereas if the individual has a prescription from a physician, the EC is for free (covered by the National Health Plan).

There are a total of 108 countries in which levonorgestrel 0.75 mg tablets are approved for regular postcoital contraception or emergency contraception.

6. CARE^{SM} (CONVENIENT ACCESS, RESPONSIBLE EDUCATION) PROGRAM

The four core elements of the CARE Program are:

1. Label/package/informational 24-hr toll free number and Plan B web address. These items are designed to provide essential information to consumers in an accessible, easy to understand format. The proposed Plan B packaging is designed to meet both prescription and OTC requirements.

2. Education: to provide information for health care providers, pharmacists, and consumers and to provide educational materials for consumer use. All audiences will be clearly instructed on the age requirement that women age 15 and younger must have a prescription for Plan B.

3. Distribution: to ensure that Plan B will be available only in licensed drug wholesalers, retail operations with pharmacy services, and clinics; these settings will facilitate the Rx-only age requirement and will provide easy access by the consumer to a pharmacist or other healthcare professional should questions arise.

4. Monitoring: will monitor trends in the sales and use of emergency contraception to evaluate the effectiveness of the CARE program and will make adjustments as appropriate. The monitoring will also determine if the age restriction is properly being adhered to.

In the section of the NDA submission that outlines the CARE Program, the Sponsor states that the education program for consumers will begin about 6 months following product launch. The direct to consumer campaign (page 7) will be designed to target women ages 17 to 44, and media placements that appeal to teen/adolescent audiences will not be used.

Reviewer's comment:

- **DRUDP recommends that the educational program for consumers begin at the same time as the OTC product is launched.**
- **Because Plan B can safely be used by women of all ages, the direct to consumer campaign should also target women age 16 and younger and encourage them to contact their health care provider to learn about emergency contraception, routine forms of birth control, and STI/HIV if these topics are applicable.**
- **Demographic information and data from the most common questions from calls made to the 800 line might be very helpful to make future changes in the product label, patient information, and educational programs.**

Page 11 of 11: the "Point of Purchase Monitoring Program" intends to track how Plan B is being sold at the time of purchase, identify areas where more education on the prescription age restriction is needed, and make corrective measures where needed. The program will be conducted 6 and 12 months post launch and then annually.

Reviewer's comment:

- **This program is not necessary because the product can safely be used by women of all ages.**

7. PRODUCT LABELING

The proposed product labeling contains much new and accurate information on contraceptive choices and STDs, but no information on the possible mechanisms of action (MOA) of Plan B for emergency contraception. A primary concern of a few of the Advisory Committee members at the December 2003 meeting was the MOA of the product. This is also an issue for some potential users of the product because of the belief that any interference during or after the process of fertilization of the ovulated egg is not acceptable.

Reviewer's comment:

- **The DRUDP provided to the OTC Division recommendations for specific MOA language to be added to the label, package insert and carton box. The language lists all of the possible mechanisms of action, even though some are theoretical and not clearly proven. The Division agrees that Plan B will "not work if you are already pregnant."**
- **The Division recommends that "abnormal vaginal bleeding" be deleted from the list of contraindications; the AC members agreed with this change.**

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/s/

Daniel Davis
1/12/05 05:01:11 PM
MEDICAL OFFICER

Scott Monroe
1/12/05 06:19:30 PM
MEDICAL OFFICER
I concur with Dr. Davis's recommendation that Plan B, if used in accordance with proposed labeling, is sufficiently safe and effective that it should be available over-the-counter without any age restriction.

Division Director Memo-Addendum
NDA #: 21-045/S-011
Drug Name: Plan B (Levonorgestrel 0.75 mg)
Sponsor: Women's Capital Corporation
Receipt Date: July 22, 2004
PDUFA Date: January 22, 2005
Type of Document: Response to NA letter
Date: January 12, 2005

Introduction

The original application for this product was reviewed by both the Division of Reproductive and Urologic Drug Products and the Division of Over-The-Counter (OTC) Drug Products (the Division), with the delegated authority for the final regulatory decision resting within the Offices of Drug Evaluation III and V as typically practiced under the current CDER procedure governing the review of a proposed Rx-to-OTC switch (MaPP 6020.5). In the initial review of this application, both Divisions, both Offices, and the Director of the Office of New Drugs recommended approval of the application (see January 15, 2004 Rosebraugh review; January 21, 2004 Bull review; March 30, 2004, Rosebraugh/Bull review; April 1, 2004, Griebel review; April 2, 2004, Beitz review; and April 28, 2004, Jenkins review). However, the Center of Drug Evaluation and Research Immediate Office did not concur with these recommendations, removed the delegated authority, and issued a Not Approvable action to the applicant on May 6, 2004 (see May 6, 2004, Galson review). Please refer to the action letter for all the deficiencies identified by Dr. Galson, but the main concern expressed by him was that he felt there was insufficient data to support a conclusion that Plan B could be used safely by adolescent women under 16 years of age.

The applicant has responded to these deficiencies in a July 21, 2004 submission with a proposal that would allow the product to be sold OTC to consumers over the age of 16 and to be sold by prescription only to consumers under the age of 16. This amendment is the subject of the current review and pending decision.

Recommendations

In my memorandum during initial review cycle, I concluded the following:

1) Plan B adequately meets the Durham-Humphrey Amendment criteria for OTC marketing without restriction;
2) Any system placing barriers to access would defeat the purpose of the drug and lessen its public health potential; and
3) Placing age restrictions for theoretical abuse by a small segment of the population would have ramifications for how we regulate other OTC drugs where there is known abuse by the population and by adolescents such as dextromethorphan, laxatives and analgesics.

I have not been presented with data that would dissuade me from my original conclusion. I also continue to believe that adequate data was submitted to allow Plan B to be marketed without regard to age. I also believe that the sponsor's original proposal for the CARE program would ensure proper use of Plan B by women of all ages, including adolescents.

In regard to the proposal submitted by the sponsor, I have many concerns regarding the regulatory precedent that approval of this plan would set and possible unintended consequences. I am concerned that the regulatory precedent that would be set by requiring adolescents to obtain a prescription to access an otherwise OTC contraceptive product may have implications for other OTC contraceptive products that are currently marketed which do not bear age restrictions and have not submitted adolescent data for OTC marketing.

In the past when the Division has felt that there was insufficient data to warrant labeling for a particular age group, we have labeled the product with language that reflects that under a certain age, a physician should be consulted, but an age restriction for sale of the product was not part of the labeling. We have handled age restrictions by placing them in the **Do Not Use** and **Ask a Doctor Before Use If** sections of the Drug Facts Labeling. These warnings may be bolded to highlight the age restrictions (such as with stomach acid modifying agents). It should be noted that almost all OTC products are restricted from some group of the general population because of safety or efficacy concerns (e.g., restrictions by age, concomitant medications or disease severity). In previous cases, we have addressed these restrictions in labeling using the **Warnings** section of Drug Facts, but have not restricted sale of the product from these populations.

The labeling proposed for this product would include a statement to the effect that it can not be sold to anyone under the age of 16. We have not done this for other OTC products except for nicotine products, a case not applicable to Plan B because this is a requirement placed on nicotine delivery systems by the DEA. Placing an age restriction for sale may place an unacceptable legal burden on pharmacies which would have the undesired effect of limiting access. It is also unclear how an age restriction would be enforced in a pharmacy setting. Additionally, it is unclear what this new precedent would mean for those products that have statements regarding contacting a physician if under a certain age. Would they also be eligible to be prescription only for those age groups?

Finally, it is unclear what additional data could be provided on adolescent use that would be sufficient to lift the age restriction in the future.

For these reasons, I do not support a recommendation for an age restriction.

Having said the above, we have been asked to comment on the adequacy of the proposed labeling to assure that the age restriction is followed. Comments have been sent to the sponsor and to date, the applicant has not proposed new labeling in response to the

December 22, 2004 labeling comments. The legal and regulatory acceptability of the applicant's proposal is currently under review in the FDA Office of Chief Counsel.

Summary

I continue to believe an age restriction is not appropriate for this product for all the reasons stated above and in my previous reviews.

Curtis J. Rosebraugh, MD, MPH

cc: orig.

HFD-560 /frazier /cothran/solbeck/chen/leonard segal/ganley/bull
HFD-580/griebel/beitz

Attachment 1

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/s/

Curtis Rosebraugh
1/12/05 10:57:35 AM
MEDICAL OFFICER

Charles Ganley
1/12/05 11:30:34 AM
MEDICAL OFFICER

Jonca Bull
1/12/05 12:27:05 PM
MEDICAL OFFICER

Deputy Division Director Memorandum

To:	**Julie Beitz, M.D., Deputy Director ODE III**
Re:	**Approvability of NDA 21-045 SE6, N-011**
Drug:	**Plan B (levonorgestrel)**
Dosage:	**0.75 mg tablet for oral administration**
Type of Submission:	**Response to Not Approvable action**
Submission Date:	**July 21, 2004**
Memo Date:	**January 12, 2005**

Recommendation Regarding Approval

In my April 2004 Deputy Division Directory Summary Review of NDA 21-045, I concluded that the risk benefit ratio of non-prescription access to Plan B supported its switch to non-prescription status without restricted access on the basis of age. This recommendation was made after reviewing the label comprehension and actual use study data submitted by the applicant in the NDA, the data from large controlled trials on advance provision of emergency contraception, summary data from the large single arm telephone access study from North Carolina (DIAL EC) submitted by that studies investigators, the levonorgestrel safety database, the vote and minutes from the December 2003 Joint Session of the Nonprescription Advisory Committee, and medical literature addressing public health issues surrounding the impact of improved access on sexual health and behaviors. (See this document's Appendix for a copy of my Deputy Division Director Summary Review from April 2004, which documents the regulatory review history of the original Plan B NDA submission for non-prescription status.)

No new safety and efficacy data has been presented in this NDA submission or in the Division's updated review of the medical literature and post-marketing safety reports for levonorgestrel that alters my original recommendation that the risk benefit ratio of non-prescription access to Plan B supports its switch to non-prescription status without age restriction. I continue to support Plan B's switch to nonprescription status without age restrictions. I cannot support the Applicant's proposal in the current NDA submission (which was made in response to the CDER Center Director's May 6, 2004 Not Approvable letter that informed the applicant that provision of information in support of marketing Plan B as a prescription-only product for women under the age of 16 years and as a nonprescription product for women 16 years of age and older was one of two pathways to obtain approval) to restrict access to the non-prescription product through a mechanism that requires that the product be sold by prescription-only to consumers under the age of 16. I do not support this approach for two reasons:

1) Labeling the product to only be sold with a prescription to consumers under the age of 16 sets a precedent that could have negative consequences on current products sold as non-prescription products, including contraceptive products like condoms and spermicidal products. In instances where it has been believed that insufficient data exist to warrant labeling for a particular age group, the Division of Over the Counter Drug

Products has labeled the product with an age under which a physician should be consulted, using language in the package Drug Facts labeling such as "Do Not Use" or "Ask a Doctor Before Use If". (See Division of Over the Counter Drug Products Review by Dr. Curtis Rosebraugh.)

2) Labeling the product to only be sold without a prescription on the basis of age criteria could have the unintended public health consequence of limiting access to women of all ages. Enforcing the age restriction for a reproductive health drug could be considered an undesirable legal burden for pharmacies that prompts pharmacies that already carry the prescription-only product to cease carrying the product altogether. Additionally, there are multiple reported instances in the media and in the medical literature of pharmacists who refuse to fill prescriptions for the current prescription product because they believe it causes medical abortion. The public health goal of improving access of women to emergency contraception will not be achieved by the proposed age restriction if those pharmacists who object to the product on the basis of their personal beliefs remain in a position of controlling access to the product, even for those women 16 and older given that they will need to check age to allow access to the nonprescription product.

I concur with the reviews of Dr. Dan Davis and Dr. Scott Monroe from the Division of Reproductive and Urologic Drug Products that the sponsor's CARE^{SM} (Convenient Access, Responsible Education) Program is reasonable. We have discussed with the Applicant that monitoring of the adequacy of the program could be further improved by collecting and analyzing the questions consumers ask of the pharmacist in their queries to the 1-800 information call line along with demographic data collected from those consumers who request information. This information could be used to refine labeling messages, if the analyses suggest changes could be helpful. The Applicant's response is pending.

In summary, I do not recommend that this application be approved with the Applicant's proposed age restrictions for reasons listed above. I believe that the product should be approved for switch to non-prescription status without age restriction.

Donna J. Griebel, MD
Deputy Director of the Division of Reproductive and Urologic Drug Products

APPENDIX: Deputy Division Director Summary Review of New Drug Application (Dated April 1, 2004 – from first review cycle) is attached.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 12, 2005

FROM: Julie Beitz, MD
Deputy Office Director,
Office of Drug Evaluation III

SUBJECT: NDA 21-045 Levonorgestrel; Plan B
Barr Research, Inc.

This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's (DRUDP) recommendation to approve Plan B for use as an emergency contraceptive in the over-the-counter (OTC) setting without an age restriction. Plan B consists of a single levonorgestrel 0.75 mg tablet that is taken within 72 hours of unprotected sex followed by a second tablet twelve hours later.

The Plan B regimen was originally approved on July 28, 1999, with an extensive safety database that included controlled trials and an extensive literature on over 15,000 women. On April 22, 2003, the sponsor submitted an application for the OTC switch of Plan B. There were no efficacy concerns raised in this application since the proposed OTC dose was the same as that for the prescription product. In my April 2, 2004, memorandum, I concluded that this application provided adequate evidence that Plan B was "safe and effective for use in self-medication as directed in proposed labeling"[1]. This was also the conclusion reached by the majority of experts convened to discuss the merits of a switch at the December 16, 2003, Joint Meeting of the Nonprescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee. This conclusion was based upon consideration of 1) levonorgestrel's clinical trial and postmarketing safety profile, 2) the sponsor's Labeling Comprehension and Actual Use studies, and 3) findings from several studies evaluating use of emergency contraception in a variety of clinical settings that enrolled over 1000 adolescent women aged 16 years or less.

On May 6, 2004, the Agency issued a not approvable letter citing concerns regarding safe use of the product by young adolescents in the OTC setting. Barr's submission dated July 21, 2004, represents a complete response to the not approvable letter. In this submission, Barr proposed to market Plan B as a nonprescription product for women 16 years and older, and as a prescription product for women less than 16. Barr submitted (1) proposed draft product labeling, outer carton, inner carton, and patient brochure, (2) a summary of the **CARE** (**C**onvenient **A**ccess, **R**esponsible **E**ducation) Program, (3) a safety update, and (4) legal arguments in support of a dual use/single package configuration for the product. No new safety concerns have been identified since the May 6, 2004, action letter was issued. This memorandum is written with the assumption that the Agency's Office of Chief Counsel will uphold the legal arguments regarding the single package configuration, and that final product and carton labeling will adequately address the Agency's comments regarding Barr's proposed drafts.

Proposed CARE Program

The sponsor has proposed the **C**onvenient **A**ccess **R**esponsible **E**ducation Program with the following elements: (1) labeling, packaging, web site and informational 24-hour toll-free number, (2) educational initiatives for healthcare providers and pharmacists, (3) distribution plans, and (4) monitoring efforts to assess whether the age restriction is understood and adhered to.

The program's premise is that neither education nor increased product access alone will minimize delays in obtaining Plan B and ensure safe use. The outer carton will contain labeling information for consumers in Drug Facts format. The inner carton will contain a brochure with information about Plan B, routine

[1] See 21 CFR 310.200(b)

methods of contraception, and sexually transmitted diseases (STDs), as well as a "Time Reminder" card. The sponsor has proposed an educational program for healthcare providers that will precede by six months the consumer education campaign. This is to ensure that healthcare providers will be sufficiently prepared to support their patients. The direct-to-consumer campaign will target adult women rather than adolescent audiences. To the extent possible, distribution of Plan B will be limited to licensed drug wholesalers, retail operations with pharmacy services, and family planning clinics to ensure successful implementation of the Plan B prescription-only age requirement. Pharmacists in the states with Pharmacy Access Programs will be able to dispense Plan B directly to women less than 16 years by following the approved protocol in their state. Monitoring efforts will include (1) surveys of healthcare professionals to assess knowledge, attitudes, and trends among users, (2) correlation of rates of pregnancy, abortion and STDs with Plan B sales, and (3) "Point-of-Purchase" activities in which anonymous shoppers aged 15 to 18 years will periodically visit locations where Plan B is available and attempt to purchase the product. Lessons learned from these monitoring activities will inform the sponsor regarding areas in need of improved or intensified educational efforts.

Conclusions

Plan B is an effective means to prevent pregnancy. Access to Plan B and educational efforts would need to be substantially improved in order to reduce current rates of unwanted pregnancy in the US. Pharmacy Access Programs are innovative options, but are challenging to implement and do not ensure uniform access to women across the fifty states.

In my view, there are sufficient data on the safety and effectiveness of Plan B to approve its use in the OTC setting without an age restriction. Educational messages conveyed in product and carton labeling and via the sponsor's CARE Program should ensure proper use of Plan B by women of all ages, including adolescents. Healthcare providers would continue to play a critical role, on an ongoing basis, in educating women about contraceptive methods and STD prevention, and in monitoring for STDs.

The sponsor's proposal to retain prescription status for adolescents under age 16 will require that healthcare providers continue to prescribe Plan B to this age group. I have concerns regarding the regulatory precedent that would be set by requiring adolescents to obtain a prescription to access an otherwise OTC contraceptive product. In particular, an age restriction for Plan B would have implications for other OTC contraceptive products which currently do not bear age restrictions. Secondly, there are OTC products that adolescents can purchase legally today without a prescription which carry safety risks if misused that are far more serious (e.g., life-threatening overdose) than would occur with inappropriate use of Plan B. Thirdly, if implemented, the age restriction would be a challenge to enforce in the retail pharmacy setting. Fourthly, it is unclear what additional data Barr could provide on adolescent use of Plan B that would be sufficient to lift the age restriction in the future, since women less than 16 years could only access the product via prescription. For these reasons, I do not support an age restriction for this product.

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
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DIRECTOR

MEDICAL OFFICER REVIEW

Division Of Pediatric Drug Development HFD 960

SPONSORS: Barr Laboratories, originally Women's Capital Corporation

NAME: Plan B

NUMBER: 21-045

CLASS: Contraceptive

MEDICAL OFFICER: Hari Cheryl Sachs, MD, FAAP

REVIEW DATE: November 10, 2004

REVIEW SUMMARY:

Plan B (levonorgestrel), a progestin only contraceptive, was approved for emergency contraceptive (EC) use in July 1999. Levonorgestrel is thought to work by delaying or inhibiting ovulation, inhibiting fertilization or inhibiting implantation of a fertilized egg. Levonorgestrel will not interrupt an established pregnancy. A request to move this drug to nonprescription status (NDA 21-045 S-011) was received April 2003, in order to facilitate timely access. The OTC switch was denied in May 2004. Subsequently, a resubmission was filed in July 2004 which proposes an OTC switch for patients 16 and older, while continuing prescription status for those patients under 16. The pediatric division has been consulted to determine whether or not the sponsor's submission fulfills the requirements of the Pediatric Research Equity Act of 2003 (PREA).

The sponsor's submission meets PREA requirements for post-menarchal females. Studies in males and pre-menarchal females should be waived.

OUTSTANDING ISSUES:

SIGNATURES

Reviewer: *Hari Cheryl Sachs, MD, FAAP* **Date:** *11/10/04*

Acting Team Leader: *Jean Temeck, M.D.* **Date:**

Acting Division Director: *Lisa Mathis,, M.D.* **Date:**

Plan B (levonorgestrel)

Background:

Plan B (levonorgestrel), a progestin only contraceptive, was approved for emergency contraceptive (EC) use in July 1999. Levonorgestrel is thought to work by delaying or inhibiting ovulation, inhibiting fertilization or inhibiting implantation of a fertilized egg. Levonorgestrel will not interrupt an established pregnancy. A request to move this drug to nonprescription status (NDA 21-045 S-011) was received April 2003, in order to facilitate timely access. The OTC switch was denied in May 2004. Subsequently, a resubmission was filed in July 2004 which proposes an OTC switch for patients 16 and older, while continuing prescription status for those patients under 16. The pediatric division has been consulted to determine whether or not the sponsor's submission fulfills the requirements of the Pediatric Research Equity Act of 2003 (PREA).

Plan B must be taken within 72 hours of unprotected intercourse/contraceptive failure in order to be effective. Delay decreases efficacy as illustrated by pregnancy rates: unprotected- 8 %, Plan B at 24 hr 0.4 %, Plan B at 72 hr- 2.7 %. The proposed OTC package would consist of two 0.75 mg tablets along with labeling emphasizing that Plan B is for emergency and not routine contraceptive use, listing appropriate precautions (not to use if pregnant or allergic), and failure to protect against HIV or other sexually transmitted infections. In addition, a 24-hr hotline number is to be listed on the package to allow consumers to obtain guidance regarding appropriate use.

Regulatory History: The sponsor submitted the NDA for Plan B on January 29, 1999 and approval was granted July 28, 1999. PREA does not apply to the original application because the application was submitted before PREA's effective date of April 1, 1999. The submissions for OTC switch however, trigger PREA since emergency contraception is approved for use in post-menarchal females, a population which includes adolescents.

In order to fulfill the terms of PREA, a sponsor must submit sufficient data to assess the safety and efficacy of the product for its indicated use. In addition, the data should support dosing and administration of the product in the relevant pediatric subpopulations. An age-appropriate formulation must be available. Extrapolation of efficacy from well-controlled adult studies is permissible with appropriate supplemental information (e.g., pharmacokinetics, safety, etc.) The requirement may be waived if the condition does not occur in the pediatric population; studies are highly impractical; the drug is ineffective or unsafe; the drug does not represent a benefit over existing therapies; or is not likely to be used in a substantial number of pediatric patients.

Is the submitted data sufficient to assess the efficacy of Plan B for emergency contraception?

Barr has submitted sufficient data to assess the efficacy of Plan B for its intended use. Plan B is an approved product for emergency contraception in post-menarchal females. Efficacy can be extrapolated from adults to the adolescent population for the prescription product. Efficacy of other contraceptive agents has been extrapolated to adolescents as

evidenced by typical labeling of these products, "Safety and efficacy of Drug X have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users ages 16 years and older. Use of this product before menarche is not indicated." In fact, although the original sponsor submitted a PPSR in December 2001 for pK and safety studies in adolescents, ages 12-16, an inadequate letter was issued citing, "the proposed trials could be conducted in the adult population and results extrapolated to the postmenarcheal pediatric population." Thus far, the only WR that has been issued for a contraceptive agent is norgestimate (Ortho Tri-Cyclen) for increasing bone mineral density in anorexic adolescents.

Although efficacy can be extrapolated, the sponsor submitted data on over 1,000 adolescents $\leq$ 16 years of age who participated in studies conducted to support the OTC switch (see Appendix A) These studies included simulated OTC settings and a label comprehension study as well as a literature review. Five percent (29/585) of subjects enrolled in the actual use study were adolescents, ages 14 to 16 years of age. Twelve percent (76/656) of subjects enrolled in the label comprehension study were adolescents, ages 12-16 years of age (see Appendix B). Recruitment for young adolescents in these studies may have been hampered due to restricted use (<16 years in countries where EC is available over the counter) and/or IRB restrictions/parental consent issues (which deter enrollment in many U.S. studies.)

The relative distribution of adolescent data reflects the use of Plan B and EC in adolescents, as well as the relative proportions of adolescents requesting Plan B. According to Advance PCS (prescription use data found in Appendix C), the youngest adolescents (8-14 years) accounted for <0.5 % of total claims for either Plan B or Preven during 2002-2004. Teenagers, age 15-17 years, represented 5 % of total claims. Use in children under age 12 was minimal, accounting for no more than 8-12 of the over 10,000 total prescriptions per year.

Is the submitted data sufficient to assess the safety of Plan B for emergency contraception?

The safety of Plan B for its intended use in adolescents has also been sufficiently demonstrated. Labeled adverse events include: nausea, abdominal pain, fatigue, headache and menstrual changes. Initial approval was based on safety data from over 15,000 women from 29 countries (see Medical Officer Review dated July 12, 1999). The sponsor also submitted an adolescent safety study in 52 evaluable females, ages 13-16 years, who were followed for 3-5 weeks after standard dosing of Plan B. No serious adverse events occurred. The range of symptoms reflects current product labeling. During the actual use study, 22/29 adolescents experienced only minor, self-limited adverse events, such as abdominal pain, nausea, vomiting, weakness and/or headache. One pregnancy in a 17 year old also occurred. An analysis of postmarketing adverse events by ODS (June 24, 2002) and review of the published English literature do not reveal an excess of adverse events in adolescents.

Is the submitted data sufficient to support dosing and administration of Plan B in adolescents?

To address dosing, Barr compared the pharmacokinetics of a single 0.75 mg dose of Plan B administered to 16 healthy adult females, aged 19-44 years, enrolled in one study to 22 healthy adolescent females, aged 13-16 years, who were enrolled in another study. Systemic exposure was somewhat lower (AUC was ~23% lower and C_{max} was ~47% lower) in adolescent females compared to adult females. The Biopharmacutics reviewer, Dr. Myong-Jin Kim, stated that there are no inherent reasons to believe that adolescent females would have different pharmacokinetic characteristics compared to adult females and that the observed differences might be related to limitations associated with cross-study comparisons and to differences in study design between these two studies (see Dr. Kim's review dated March 12, 2004). Moreover, comparison of pharmacokinetic studies (n=7) in the published literature suggests high variability in the pharmacokinetics of Plan B in adult women as well. (see Myong-Jin Kim review 3/12/04). The review division concluded that the difference in bioavailability of Plan B between adolescent and adult females is unlikely to impact efficacy. (see Dr. Dan Davis, Medical Officer's Safety Review of Supplemental NDA, dated March 17, 2004)

According to the literature and trials submitted by the sponsor, adolescent patients used EC correctly during the trials (Glasier 1998, Raine 2000 and Raymond 2003). Adolescents also presented themselves for EC in the appropriate 72-hour window (Shawe 2001, Raymond 2003). During the actual use study, 95 % of the patients self-selected correctly; however, patients were excluded from the trial if they came to clinic for reasons other than requesting EC. In this trial, compared to older women (n = 494, ages 18-44 years), young adolescents (n= 29 ages 14-16 years) tended to time both pills better than adults (77 % vs. 72 %). All the adolescents (n=46, ages 14-17 years) took the second dose within 12 +/-2 hours of the first dose. In the large group of patients who received prescriptions directly from a dial in pharmacy number, 92 % of adolescents 18 and under (as well as adults) used EC in a timely manner. Similarly, young adolescents (age 15-17 years) given advance prescription used EC sooner than those with standard access. Moreover, both groups used correct timing of EC (Gold 2004).

In contrast, compared to the young adult group (ages ≥17 years), younger adolescents were less compliant with the 4 week follow-up period (Raymond 2003).
In the label comprehension study, adolescents (ages 12-16 years) did not understand certain key directions (indication to prevent pregnancy, not for routine use, take the first pill within 72 hours of intercourse and take 2nd pill 12 hours after the first pill) as often as adults (see the Table below). Moreover, use was contraindicated for 4.5 % of adolescents compared to 1.2 % of adults.

Table: Label comprehension study- Communication objectives by age (% of enrolled subjects) (excerpted from Table 5a in Jin Chen's 1/12/04 Plan B Clinical OTC Review *Statistically significant differences *(p<.01), #(p<.05)

Direction	Percent correct Adolescent (12-16 years) (n =76)	Percent correct Young Adult (17-25 years) (n = 355)	Percent Correct/acceptable Adult (26-50 years) (n = 255)	Percent Total Correct/acceptable (n = 656)
Indication: prevent pregnancy	86#	93	95	93
Not for routine use	57	67	71	67
Use within 72 hr	77	86	87	85
Take 2nd pill 12 hours later	77*	90	82#	86
Does not prevent STI (HIV/AIDS)	93#	96	92#	94
Side effects include nausea and vomiting*	90*	93	84*	89

Reviewer comment: Note that no adjustments for multiple statistical comparisons were made in this analysis. As mentioned above, adolescents (ages 12-16 years) did not understand certain key information (indication to prevent pregnancy, not for routine use, take the first pill within 72 hours of intercourse and take 2nd pill 12 hours after the first pill) as often as adults. Also, older adults' comprehension differed from younger adults for several objectives. Difficulty with these same objectives was observed in adults with low literacy levels (adolescents did not receive literacy assessments). The Division of Surveillance, Research, and Communication concluded that these deficiencies could be addressed by changes in labeling (e.g., bolding the statement "not for routine use") and an appropriate package insert.

Following the exact directions regarding the timing of the second pill has been problematic for adults as well as both younger and older adolescents. Using the strict definition of exactly 12 hours, only 71 % of adults took the 2nd dose appropriately. During the actual use study 28 % did not follow strict 12 hour timing. However, when a 4 hour delay in the timing of the second tablet was analyzed, incorrect use decreased to 6.6 % (Raymond 2003). Only 25 % of post-partum women over age 14 could state the correct timing of emergency contraception when interviewed (Jackson 2003). For this reason, some experts advocate the use of a single dose (1.5 mg levonorgestrel).

Should any studies be waived?

Since emergency contraception is not indicated for use in males and pre-menarchal females, studies in these populations should be waived.

Conclusion:

The sponsor's submission meets PREA requirements for post-menarchal females. Studies in males and pre-menarchal females should be waived.

Appendix A

Enrollment Data by Age for Studies Enrolling Adolescents Receiving Emergency Contraception Pills either by Advance Provision or by Standard Access (table abstracted from p. 26 of Dr. Davis' review)

Study	Age	Total N	≤16	Percent	Comment	13-15	Percent
Actual Use (Raymond)	14-44	585	29	5	Actual Use study	29	5
Gold	15-20	301	115	38	Adolescent Medicine clinic		
Jackson	14+	370	15	4	Postpartum mothers		
Raine	15-24	2090	254	12	Women at family planning clinics NOT seeking AC		
Dial EC	8-51	7756	613	8	Toll-free phone in for prescription to be filled at pharmacy of choice	202	2.6
Total		11,102	1026	9			

Appendix B (Age Distribution of Plan B OTC Label Comprehension Study)

Distribution by Age (Final Report Study Number 9728) p. 4 Karen Lechter, MD (HFD 410)

Age Range	Number	%
12-16	76	12
17-25	355	54
26-50	255	34

Appendix C: Total Claims during 2002-2004 (Advance PCS)

DRUG LABEL NAME	AGE IN YEARS	2002		2003		2004 (Jan-Jun)	
		# Claims	%	# Claims	%	# Claims	%
Preven Contraception Kit	ALL AGES	10,920	100.0%	13,130	100.0%	6,196	100.0%
	8		0.0%	1	0.0%		0.0%
	10		0.0%	1	0.0%		0.0%
	11		0.0%	2	0.0%		0.0%
	12	6	0.1%	4	0.0%	3	0.0%
	13	13	0.1%	16	0.1%	8	0.1%
	14	26	0.2%	45	0.3%	22	0.4%
	18-23 Years	3,288	30.1%	4,117	31.4%	1,752	28.3%
	24 and Over	7,039	64.5%	8,395	63.9%	4,156	67.1%
Plan B 0.75mg Tab	ALL AGES	7,772.0	100.0%	16,977.0	100.0%	14,248.0	100.0%
	8	1	0.0%	1	0.0%		0.0%
	9		0.0%		0.0%	1	0.0%
	10	1	0.0%	1	0.0%		0.0%
	11	3	0.0%	2	0.0%	4	0.0%
	12	2	0.0%	8	0.0%	6	0.0%
	13	17	0.2%	16	0.1%	22	0.2%
	14	27	0.3%	76	0.4%	58	0.4%
	18-23 Years	2,787.0	35.9%	6,054.0	35.7%	4,962.0	34.8%
	24 and over	4,423.0	56.9%	9,758.0	57.5%	8,407.0	59.0%
Ovral 21	ALL AGES	1,856	100.0%	1,398	100.0%	480	100.0%
	12	2	0.1%	1	0.1%		0.0%
	13	3	0.2%	1	0.1%	1	0.2%
	14	17	0.9%	16	1.1%	3	0.6%
	15	8	0.4%	8	0.6%	2	0.4%
	16	22	1.2%	18	1.3%	3	0.6%
	17	54	2.9%	21	1.5%	11	2.3%
	18-23 Years	243	13.1%	223	16.0%	54	11.3%
	24 and Over	1,504	81.0%	1,110	79.4%	406	84.6%
Ovral 28	ALL AGES	16,037	100.0%	10,006	100.0%	3,804	100.0%
	10	2	0.0%		0.0%		0.0%
	11	3	0.0%	3	0.0%		0.0%
	12	13	0.1%	24	0.2%	3	0.1%
	13	17	0.1%	11	0.1%	3	0.1%
	14	71	0.4%	43	0.4%	6	0.2%
	18-23 Years	2,333	14.5%	1,333	13.3%	530	13.9%
	24 and Over	13,056	81.4%	8,177	81.7%	3,090	81.2%

Source: IMS HEALTH; National Disease and Therapeutic Index, CD-ROM- Extraction Date: 9-9-04 (0409ocbydiag4.dvf)

**NOTE: DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH. Clearance must be requested from IMS HEALTH through the FDA Office of Drug Safety

References

Glasier A, Baird D. The effects of self-administering emergency contraception. *NEJM* 1998; 339(1):1-4.

Gold M, Wolford J, Smith B, Parker A The Effects of advance provision of emergency contraception on adolescent women's sexual and contraceptive behaviors *J Pediatr Adolesc Gynecol* 2004: 17; 87-96.

Jackson, R, Schwarz, E. Freedman, L, Darney P Advance supply of emergency contraception: effect on use and usual contraception- a randomized trial *Obstet Gynecol* 2003: 102(1); 8-16

Raine, T; Harper C, Leon K, Darney P Emergency contraception: advance provision in a young, high risk clinic population. Obstetrics and Gynecology Vol 96(1) July 2000, 1-7 10862832

Raymond E, Chen P and Dalebout S. "Actual Use" study of emergency contraceptive pills provided in a simulated over-the-counter manner. Emergency Contraception (July 2003) Vol 102 (1): 17-23.

Shawe, J, Ineichen, B., Lawrenson, R Emergency contraception: who are the users? The Journal of Famiily Planning and Reproductive Health Care 2001: 27 (4): 209-212

Additional Material Reviewed:

Memo:
Steven Galson (Acting Director, CDER) May 6, 2004
John K. Jenkins (Director OND) April 22, 2004
Julie Beitz (ODE III, Deputy Office Director) April 2, 2004
Curtis Rosebraugh (Division Director) March 23, 2004
Jonca Bull (Office Director ODE V) January, 21, 2004
Reviews
Donna J. Griebel MD (Deputy Division Director Division Repro and Urologic Drug Products ODE III) April 1, 2004
Attachment B Teratogenic Risk of Emergency Contraception and Hormonal Products for Prevention of Pregancy: A Review of the Literature (Daniel Davis/Scott Monroe) March 25, 2004
Medical Officer Safety Review Supplemental NDA (Daniel Davis) March 16, 2004
Clinical Pharm and Biopharmaceutics Review (Myong-Jin Kim DPE II) March 12, 2004
Addendum to Plan B Clinical OTC Review (Jin Chen) March 3, 2004
Medical Team Leader Review (Andrea Leonard-Segal HFD-560) January 6, 2004
Minutes Reproductive Health Drugs Advisory Committee and Non-prescription Drug Advisory Committee (Dec 16, 2003)
Label comprehension study (Karen Lechter HFD-410) Nov 2, 2003
Pediatric Exclusivity/Rule Letters (April 17 2002)
Attachment C ODS postmarketing Safety Review (Sarah Singer October 31, 2003)
Daniel Davis, HFD-580 Memo re: PPSR (April 15, 2002)
ODS Post marketing Safety Review (Sarah Singer/Cynthia Kornegay HFD-430) 2/1/2002, updates June 24, 2002
Nonspresciption Drugs Advisory Committee Meeting with the Advisory Committee for Reproductive Health Drugs Dec 16, 2003 (slides, transcript and minutes)
Brief literature review for additional safety information

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/s/

Hari Sachs
11/12/04 05:36:32 PM
MEDICAL OFFICER

Jean Temeck
11/12/04 05:39:49 PM
MEDICAL OFFICER

Lisa Mathis
11/16/04 05:49:37 PM
MEDICAL OFFICER
Concur with partial waiver for male and premenarchal female population; and for the postmenarchal peds population <14 years of age based on lack of patients
in this age group (<0.5% of total population).
PREA requirements for pt.s >14 yrs met.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 10, 2004

TO: NDA 21-045/S-011

FROM: Bronwyn Collier, ADRA ODE III

SUBJECT: Pediatric Team Consultation

Dr. Galson provided the attached documentation of his consultation with the Pediatric Team (OCTAP).

Collier, Bronwyn E

From: Houn, Florence
Sent: Monday, May 10, 2004 7:36 AM
To: Collier, Bronwyn E
Cc: Griebel, Donna J; Beitz, Julie G; Bull, Jonca
Subject: FW: confidential

Bronnie, pls put this into DFS for archival purposes under the Plan B OTC NDA. Thx.

F

-----Original Message-----
From: Galson, Steven
Sent: Sunday, May 09, 2004 9:07 PM
To: Houn, Florence
Cc: Murphy, Dianne; Jenkins, John K; Kweder, Sandra L; Throckmorton, Douglas C; Bull, Jonca; Cummins, Susan
Subject: FW: confidential

Hi Flo,
This is the documentation of my consultation with Dianne. We had a short conversation referred to in the earliest email at bottom. I want to be sure you realize that I had made up my mind concerning the essential contents of the letter & memo before I spoke to Dianne, but she and Susan did help me with the citation and helped flesh out the thought. Feel free to add this or a summary of it to the file if you believe it's needed.
Thanks
Steven

-----Original Message-----
From: Murphy, Dianne
Sent: Monday, May 03, 2004 5:24 PM
To: Galson, Steven
Cc: Cummins, Susan; Murphy, Dianne; Murphy, Shirley
Subject: RE: confidential

Brain development and higher order thinking matures throughout the entire adolescent period of 10-21 years. 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. During early adolescence (10-13) there is an emergence of impulsive behavior without the cognitive ability to understand the etiology of the behavior.(1)The capacity to understand complex concepts, which develops during middle adolescence, allows the adolescent to modulate their impulsive behavior.

Additional facts for you Steve:

Adolescence is usually considered to evolve in three maturational stages; early adolescence is 10-13, middle is 14-16 and late is 17-21.

Cognition is concrete in early adolescence. Abstraction begins in the middle period and is complete in late adolescence.

Sexually active adolescence occurs most often in youth 15 and older. By age 15, 24% of females and 27% of males had been sexually active. Thus limiting access to younger adolescence will probably focus on those who are in exploitive, non-voluntary first sex situations and who would most benefit and are in need of adult intervention. 7 in 10 of those who had sex before age 13 had a nonvoluntary 1st sex experience (2)

(1)Rudolph's Pediatrics -21st edition. Chapter 3.1 Growth and Development, Psychological Development during adolescence.

(2) The Allen Guttmacher Institute: http://www.agi-usa.org/pubs/fb_teen_sex.html the underscore is subsumed in the underlining: 5-3-2004 The Guttmacher Institute focus of research is reproductive health.

Let us know if you need more or something different.

Dianne and Susan

-----Original Message-----
From: Galson, Steven
Sent: Monday, May 03, 2004 4:36 PM
To: Murphy, Dianne
Subject: RE: confidential

I need to finalize my document in the next 24 hrs. Thanks

-----Original Message-----
From: Murphy, Dianne
Sent: Sunday, May 02, 2004 11:36 PM
To: Galson, Steven
Cc: Cummins, Susan
Subject: Re: confidential

Steve,
I will speak with Susan Cummins whose background is developmental pediatrics and we will provide 2 or 3 sentences that focus on the differences in behavior and judgement between the early and late adolescent period. In other words, behavioral science information as to why one cannot extrapolate decision making on safety issues from the older adolescent to the younger one.
Dianne

Dianne Murphy, MD
Director
OCTAP, CDER, FDA
301-827-7777
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Galson, Steven <GalsonS@cder.fda.gov>
To: Murphy, Dianne <MURPHYD@cder.fda.gov>
Sent: Sun May 02 20:51:36 2004
Subject: confidential

Dianne,
Below is one sentence from the memo I briefly discussed with you. I would appreciate your assistance is reforming the sentence if you think it's not accurate, and elaborating on it slightly. I don't have space for more than 2 or 3 sentences and don't want to get too technical. Just want to make sure I'm accurate. The underlying issue is whether studies of adult behavior can be extrapolated to adolescent behavior. I think not, but want to make sure my statements in this regard are correct. Thanks.

The period of early adolescence is known to be a time of rapid and profound physical and emotional change

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/s/

Bronwyn Collier
5/10/04 10:13:02 AM
CSO

MEMORANDUM

DATE: May 6, 2004

FROM: Steven Galson, MD, MPH
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] *Rudolph's Pediatrics,* 21st edition, Chapter 3.1, 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 heath 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.

I will be working toward the expeditious evaluation of Barr's proposed access plan when we receive a complete version. If it is approved, this plan would dramatically increase access of this product and will represent an important incremental step forward in contraceptive availability in the United States.

Wider availability of safe and effective contraceptives is important to public health. I look forward to supporting CDER's important continued role in ensuring improved availability of these products.

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/s/

Steven Galson
5/6/04 02:14:53 PM
MEDICAL OFFICER
NDA 21-045/S-011

MEMORANDUM

DATE: April 22, 2004

FROM: John K. Jenkins, MD
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 Dr. Jonca Bull, Dr. Julie Beitz, Dr. Donna Griebel, and Dr. Curtis Rosebraugh. 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 (Dr. McClellan) and the Acting Center Director (Dr. Galson), 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 Drs. Griebel and Rosebraugh, 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. Subsequently, in response to concerns raised by upper management within the Agency about OTC access to plan B for adolescents, the sponsor submitted a preliminary proposal for voluntary dual Rx (for women under 16 years) and OTC marketing (for women 16 and above) of Plan B. This proposal has undergone preliminary review by the Office of Regulatory Policy in CDER and it appears that it may be feasible under the current statute and regulations, however, a formal review by the Office of Chief Counsel has not be completed. While I do not believe that restrictions on OTC availability to adolescents are warranted, and I believe that such restrictions could be counterproductive to improving access to contraceptive options for this age group, this voluntary proposal from the sponsor deserves further consideration. It may serve to responsibly address the societal concerns that have been raised by some about OTC access to Plan B for adolescents while simultaneously greatly expanding access to Plan B to the vast majority of women of childbearing potential who may greatly benefit from such access.

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/s/

John Jenkins
4/28/04 08:23:43 AM
MEDICAL OFFICER

Concurrence with division and ODE recommendations that application should be approved for non-prescription marketing without restriction based on age.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 2, 2004

FROM: Julie Beitz, MD
Deputy Office Director,
Office of Drug Evaluation III

SUBJECT: NDA 21-045 Levonorgestrel; Plan B
Barr Research (on behalf of Women's Capital Corporation)

This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's (DRUDP) recommendation to approve Plan B for use as an emergency contraceptive in the over-the-counter (OTC) setting. Plan B consists of a single levonorgestrel 0.75 mg tablet that is taken within 72 hours of unprotected sex followed by a second tablet twelve hours later.

The Plan B regimen was originally approved on July 28, 1999, with an extensive safety database that included controlled trials and an extensive literature on over 15,000 women. On April 22, 2003, the sponsor submitted an application for the OTC switch of Plan B. There are no efficacy concerns raised in this application since the proposed OTC dose is the same as that for the prescription product. In my view, this application provides adequate evidence that Plan B is "safe and effective for use in self-medication as directed in proposed labeling"[1]. This, in fact, was also the conclusion reached by an overwhelming majority of experts convened to discuss the merits of a switch at the December 16, 2003, Joint Meeting of the Nonprescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee. This conclusion is based upon consideration of 1) levonorgestrel's clinical trial and postmarketing safety profile, 2) the sponsor's Labeling Comprehension and Actual Use studies, and 3) findings from several studies evaluating use of emergency contraception in a variety of clinical settings (see Table 1).

Postmarketing Safety Profile

Levonorgestrel has been available as an oral contraceptive for over 25 years and has had an acceptable safety profile. Since approval of the Plan B regimen, FDA has received 116 adverse event reports, including ten reports of allergic reactions (none requiring hospitalization), 28 reports of ectopic pregnancy and 3 reports of congenital anomalies. There have been no reports of death, cardiovascular events or overdoses. Considering that there have been approximately 2.4 million uses of Plan B in the US since approval, these postmarketing reports represent a very small number of events. In order to place the reports of ectopic pregnancy in perspective, randomized clinical trial data were reviewed. These data demonstrated an incidence of 1.5% (2 ectopic pregnancies reported out of a total of 135 pregnancies) among users of Plan B, which is consistent with the rate in the general female population.

Pharmacokinetics of Levonorgestrel

The sponsor has submitted the results of two pharmacokinetic studies, one conducted in healthy adolescents aged 13-16 years, and the other conducted in healthy adults aged 19-44 years. Cross-study comparisons show that adolescents had lower C_{max} and AUC values compared to adults. Several reviewers have discussed the limitations of performing such comparisons, given differences in subjects' ethnicity and weight, in sample collection times, and in duration of fasting and dosing times. These differences are further compounded by the high intra-individual variability (23-80%) and inter-individual variability (2- to 4-fold) in pharmacokinetic parameters that have been reported following levonorgestrel administration.

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[1] See 21 CFR 310.200(b)

Available data from the original Plan B NDA and from submitted NDAs for levonorgestrel-containing contraceptives suggest similar safety and effectiveness in adolescent and adult women.[2]

Reasons for Using Plan B

The sponsor's Labeling Comprehension study assessed whether subjects understood that Plan B was to be used for prevention of pregnancy after unprotected sex and not as regular contraception. Eighty-six percent of 76 subjects aged ≤ 16 years replied that Plan B was to be used for pregnancy prevention compared with 93% of 355 subjects aged 17-25. When asked whether Plan B was to be used as backup contraception, 57% of subjects aged ≤ 16 years replied correctly compared with 67% of subjects aged 17-25.

The sponsor's Actual Use study assessed how subjects seeking emergency contraception used Plan B, which could be purchased only one course at a time. Among enrolled subjects who actually used Plan B, reasons for use were similar among the 22 subjects aged ≤ 16 years and the 518 subjects aged ≥ 17 years. The most commonly given reasons were: condom broke or slipped; no contraception was used, or missed oral contraceptive pills. Reasons given for using Plan B were similar for women using Plan B for the first time and for those who had used EC previously under supervision of a healthcare provider.

In Raymond et al.'s Dial EC Project, 7756 women across the state of North Carolina called a hotline to obtain EC, including 2065 women aged 18 or less (613 were aged ≤ 16 years). Reasons given for requesting EC were similar for adolescents and for older women, and were identical to those noted in the sponsor's Actual Use study: condom broke, no contraception was used, or oral contraceptive pills were missed (see Figure 1).[3]

Taken together, these data support the conclusion that women regardless of age understand Plan B's intended use. First time users were similar to users who had used the drug previously under a healthcare provider's supervision, suggesting that supervision prior to use is not critical for proper self-selection. Labeling and educational messages should emphasize that Plan B is a back-up form of contraception.

Timing of Dosing

The sponsor's Labeling Comprehension study assessed whether subjects understood that the first pill of the Plan B regimen should be taken within 72 hours or ASAP after sex. Ninety-four percent of subjects aged ≤ 16 years replied correctly on this point compared with 97% of subjects aged 17-25 years. Regarding the need to take the second pill 12 hours after the first, 77% of subjects aged ≤16 years replied correctly compared with 90% of subjects aged 17-25.

The sponsor's Actual Use study assessed how subjects seeking emergency contraception timed the dosing of Plan B. In the Actual Use study, 37% of subjects began a course of Plan B within 24 hours of sex and 98% took the first dose within 72 hours. This compares favorably to the results of the WHO 92908 study upon which approval of the original NDA was based.[4] In that study, 46% of users took the first dose within 24 hours and all but 0.2% within 72 hours. The interval between the first and second pill was 12 hours or less for 84% of women in the Actual Use study versus 83% in the WHO 92908 study.[5] Timing of EC dosing was similar for women using Plan B for the first time and for those who had used EC previously under supervision of a healthcare provider, suggesting that supervision prior to use is not critical for correct timing of dosing.

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[2] *See e.g.,* pediatric class labeling in the package insert for Alesse-28 tablets: "Safety and efficacy of Alesse tablets 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."

[3] Raymond EG, Spruyt A, Bley K, Colm J, Gross S, and LA Robbins. The North Carolina DIAL EC Project: Increasing Access to Emergency Contraceptive Pills by Telephone. *Contraception* 2004, *submitted for publication.*

[4] Sponsor's analysis, Slide 42, December 16, 2003, Advisory Committee Meeting

[5] Sponsor's analysis, Slide 43, December 16, 2003, Advisory Committee Meeting

In the Actual Use study, the timing of the first pill among the 22 subjects aged ≤ 16 years was 40 ± 19 hours versus 35 ± 21 hours among the 518 subjects aged ≥ 17 years. The timing of the second pill was also similar between the two age groups (12.1 ± 0.5 hours versus 12.5 ± 3.3 hours after the first pill) respectively. Timing of the first and second pills was similar among users when age was further stratified as follows: 14-15, 16-17, 18-20, 21-25 and >25 years.[6]

Studies of advanced provision that evaluated timing of EC dosing found good compliance with recommended dosing guidelines. For example, Gold et al. enrolled 301 adolescents aged 15-20 years attending an adolescent health clinic in an urban children's hospital (187 adolescents aged 15-17 years and 114 aged 18-20 years). They found that women given EC in advance began a course of EC sooner - 11.4 hours after sex versus 21.8 hours - compared to women who had to return to the clinic to obtain it.[7] This finding held true for both 15-17 and for 18-20 year-olds given EC in advance.[8]

In a study of 1083 women (23% were aged < 20 years) attending a family planning clinic in Edinburgh, Glasier et al. requested women who used EC to notify the clinic with the time of intercourse and the time EC pills were taken. Correct timing was documented in 98% of respondents.[9] Their publication did not address whether the subject's age influenced the timing of doses.

Among 2,065 women aged ≤ 18 years who called a hotline in North Carolina to obtain EC, 22% of callers were issued a prescription within 24 hours of unprotected sex and 92% within 72 hours. Among 5,691 adult callers, 26% were issued a prescription within 24 hours of unprotected sex and 92% within 72 hours (see Figure 1). The Call Center processed information given to them by callers within at most five hours, but usually within 1 hour.[3] These data suggest that adolescent callers did not unnecessarily delay their calls to the Call Center, demonstrating proper timing and self-selection.

Frequency of Unprotected Sex

Several studies of sexual behavior indicate that women given advanced provision of EC were more likely to use EC, but not more likely to report unprotected sex. These studies include the Gold et al. study of 301 adolescents aged 15-20 years[7], a study conducted by Raine et al. of 263 high-risk women aged 16-24 years (including 64% adolescents) attending a family planning clinic[10], a study conducted by Jackson et al. of 370 inner-city, postpartum women (including 57 women under age 20) who were given EC in advance or routine counseling upon discharge from the hospital[11], and a study conducted by Belzer et al. of 160 adolescent mothers aged 14-20 years given EC in advance or EC counseling only[12]. In these studies, women reporting unprotected sex who were given an advance supply of EC were two to six times more likely to use EC than women who had unprotected sex and received counseling only. In Gold et al.'s re-analysis by age, similar rates of unprotected sex were reported by 15-17 and 18-20 year-olds on study. Among 15-17 year-olds, the frequency of unprotected sex was somewhat lower among those who had received EC in advance compared to those that did not receive an advance supply (36% vs. 42%).[8]

Taken together, these studies suggest that women, even adolescent women, understand that EC prevents pregnancy, and that having a supply on hand facilitates its use but does not result in an increase in

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[6] Based on sponsor's analysis submitted via email on January 28, 2004 and Actual Use study datasets submitted February 10, 2004

[7] Gold MA, Wolford JE, Smith KA, and AM Parker. The effects of advance provision of emergency contraception on adolescent women's sexual and contraceptive behaviors. *J. Pediatric and Adolescent Gynecology* April 2004, *in press.*

[8] Gold MA, email communication dated February 13, 2004

[9] Glasier A and DT Baird. The effects of self-administering emergency contraception. *NEJM* 1998; 339: 1-4.

[10] Raine T, Harper C, Leon K, and P Darney. Emergency contraception: Advance provision in a young, high-risk clinic population. *Obstet Gynecol* 2000; 96: 1-7.

[11] Jackson RA, Schwarz EB, Freedman L, and P Darney. Advance supply of emergency contraception: Effect on use and usual contraception – a randomized trial. *Obstet Gynecol* 2003; 102: 8-16.

[12] Belzer M, Yoshida E, Tejirian T, Tucker D, Chung K, and K Sanchez. *J Adolescent Health* 2003; 32: 5086 (abstract only).

unprotected sex. Lessons learned from condom availability programs have shown that adolescents were not more likely to engage in sexual activity if condoms were made available in their high schools.[13]

Pregnancy

In the Actual Use study, 31% of enrolled subjects had been pregnant previously. There were a total of ten confirmed pregnancies reported among Plan B users, for a pregnancy rate of 1.9%. One pregnancy occurred in a 17-year-old, while the remaining nine occurred in women aged 18-36 years. Fourteen additional subjects who did not complete follow-up were reported as having unclassifiable pregnancies. Including unclassifiable pregnancies, the overall pregnancy rate would be 4.5%, which compares favorably to the pregnancy rate of 1.1% noted in the WHO 92908 study.

In the Gold et al. study, 20% of enrolled subjects (aged 15-20 years) had been pregnant previously, a rate the authors believe to be similar to what is observed in national studies of sexually active adolescents. At the one-month follow-up, 240 women (80%) could be contacted. Three pregnancies were reported among 116 women (2.6%) given EC in advance and 9 pregnancies among 124 women (7.3%) who received education only. At the six-month follow-up, pregnancy rates of 9-12% were noted for the study population overall[7], and for the subset of 15-17 year-olds[8] regardless of intervention. Among 18-20 year-olds, the pregnancy rate was lower for those who received EC in advance compared to those who had not received an advance supply (7 vs. 19%).[8]

In the Jackson et al. study, all enrolled subjects were postpartum (with two-thirds stating their pregnancy was unplanned) and 38% reported having had a prior unwanted pregnancy. At the twelve-month follow-up, they noted 11 pregnancies among women given EC in advance and 16 pregnancies among women given routine counseling on contraception (pregnancy rates of 7% vs. 10%).[11]

In the Belzer et al. study, all enrolled subjects were adolescent mothers aged 14-20 years. At the six-month follow-up, 111 women (69%) could be contacted. Four pregnancies were reported among 57 women (7%) in the Plan B advance provision group and 10 pregnancies among 54 women (18%) who received education only.[12]

Pregnancy rates on study are somewhat lower than the baseline pregnancy rates for the high-risk women enrolled in these studies. This was true for women of all ages and in a variety of different settings. These data are difficult to assess for several reasons. Follow-up at six months or longer is often incomplete due to lost enrollee contacts. In addition, most studies provided only one course of EC at a time so the impact of EC on pregnancy in sexually active women over the long term is difficult to estimate. It should be noted that the Actual Use and Belzer et al. studies evaluated Plan B, but the Jackson et al. study predates the availability of Plan B in the US, and EC provided in the Gold et al. study was switched from the Yuzpe (estrogen + progestin) regimen to Plan B when the latter became the standard of care in that community. The impact of individual EC regimens on pregnancy rates appears generally similar in these studies.

Finally, studies of adolescent sexual behavior have found that pregnancy rates were similar for adolescents attending schools that made condoms available or schools that did not have such programs.[13]

Abortion

Little data are available on abortion rates among users of Plan B. In the Actual Use study, four of the ten confirmed pregnancies were reported to have ended in elective abortion. Information is not available on the outcomes of the 14 unclassifiable pregnancies.

In the Glasier et al. study of 1083 women (23% were aged < 20 years), 15 elective abortions were reported at the twelve-month follow-up among women given EC (Yuzpe regimen) in advance and 19 abortions were reported among women in the education only group.[9] The publication did not comment on the ages of the women who had abortions.

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[13] Blake SM, Ledsky R, Goodenow C, Sawyer R, Lohrmann D, and R Windsor. Condom availability programs in Massachusetts high schools: Relationships with condom use and sexual behavior. *Am J Public Health* 2003, 93: 955-962.

Sexually Transmitted Diseases (STDs)

The sponsor's Labeling Comprehension study assessed whether subjects understood that Plan B does not prevent STDs or HIV/AIDS. Ninety-three percent of 76 subjects aged ≤16 years replied that use of Plan B did not prevent STDs compared with 96% of 355 subjects aged 17-25.

The sponsor's Actual Use study did not capture STD data. The sponsor was not required by FDA to provide data on STDs as part of its application for OTC switch given that no form of contraception other than latex condoms is believed to reliably prevent the transmission of STDs.

In the Gold et al. study, 30% of enrolled subjects (ages 15-20 years) had had a prior STD, a rate the authors believe to be similar to what is observed in national studies of sexually active adolescents. Well over 95% of subjects, regardless of age, understood that EC use did protect against STDs.[8] At the six-month follow-up, STDs were reported by 11-13% of enrollees regardless of intervention.[7] Rates of sexually transmitted diseases were somewhat higher for 15-17 year-olds compared to 18-20 year-olds.[8]

Value of Education on Emergency Contraception

The level of awareness regarding EC and the impact of education provided in the context of a behavioral study or other clinical setting are difficult to quantify. Level of awareness is variable among women, but may be as high as 70%, even among adolescents, in settings where EC education is routinely provided.[14]

In the sponsor's Actual Use study, nearly a fifth of subjects who received Plan B spoke with the clinician or pharmacist at the initial study visit to ask additional questions about the product. Their questions covered several areas including side effects, dosing, efficacy, food effects, birth control methods, efficacy, and drug-drug interactions. Adolescents asked similar questions compared to adults, although questions about birth control methods were somewhat more common among adolescents. These observations suggest that women will seek out the information they need.

In the Gold et al. study, subjects received education consisting of a 5-8 minute session conducted either by the study coordinator (who had a BS in psychology), or by a first or second year medical student. Educational pamphlets were distributed and women were told how to dose EC. Women in this study (adolescents aged 15-20 years) had a high level of prior knowledge of EC, and questions to study personnel were minimal.[14]

In the Raymond et al. study, women called a North Carolina hotline to obtain EC. During the call, a standard set of messages was provided about EC use, efficacy, side effects, and follow-up care in case of problems.[3] Many factors likely contributed to the women's decision to initiate the call, including prior knowledge about the product's ability to prevent pregnancy. Adolescents did not appear to unnecessarily delay their calls to obtain EC.

The Jackson et al. study did not provide education on EC to subjects.[11]

Although most studies provided EC education, this was often in the form of brief didactic sessions and/or informational pamphlets provided at study initiation. It is not certain how educational messages were reinforced at follow-up visits, if at all. The overall effectiveness of these efforts is difficult to assess. Lessons learned from efforts to educate adolescents about sexual behavior and risk of HIV transmission have shown that teaching adolescents cognitive skills to assess risk-taking behavior, clarify personal values, understand external influences, and increase knowledge about AIDS-prevention resources, changes behavior when traditional didactic methods have failed.[15]

Distribution of Emergency Contraception

In the US, Plan B has been available by prescription since 1999 and in some states via pharmacy access programs. Currently, Washington, California, Alaska, New Mexico and Hawaii allow pharmacists to

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14 Gold MA, teleconference dated January 22, 2004

15 Walter H and R Vaughan. AIDS risk reduction among a multiethnic sample of urban high school students. *JAMA* 1993, 270: 725-730.

provide EC without a prescription through collaborative therapy agreements with healthcare providers. In 2003, nine states introduced fifteen bills to allow pharmacists to provide EC without a prescription.[16] No age restrictions (federal or state) have been imposed for Plan B or any other prescription contraceptive products. There are also no age restrictions on OTC contraceptive products (e.g., sponges, gels, foams, condoms). These products are currently considered safe and effective for use regardless of the user's age.

Raine studied different distribution methods among 2,090 high-risk women aged 15-24 years in the San Francisco area. Emergency contraception was made available without a prescription to 878 women via pharmacy access, while 876 women were given three EC courses in advance of need, and 336 women acquired the product at a clinic as needed. At the six-month follow-up, the frequency of pregnancies or STDs contracted among women in the three distribution groups was similar. Adolescents aged 15-17 were similar to women aged 18-24 in the frequency of pregnancy or STDs contracted.[17]

Adolescent pregnancy and abortion rates in Washington State, where a pharmacy access program has existed since 1997, have fallen in recent years. For 15-19 year-olds, pregnancy rates fell from 74.5 per 1,000 women in 1997 to 55.9 per 1,000 women in 2002. Abortion rates fell from 29.6 per 1,000 women in 1997 to 22.7 per 1,000 women in 2002. Declines were seen in both 15-17 year-olds and 18-19 year-olds.[18,19] Rates of chlamydia and gonorrhea also declined in the state over this period.[20,21] These data, taken together with the Raine study, suggest that pharmacy access without a prescription is a viable method of EC distribution for women of all ages, and appears not to adversely affect rates of pregnancy or sexually transmitted diseases.

Outside the US, emergency contraception is marketed in over 100 countries and is available without a prescription in 33 of them. An age restriction has been imposed in three of these countries: the UK, Switzerland and Finland. In the UK, where the product is available from the pharmacist "behind-the-counter", adolescents under age 16 are required to have a prescription from a physician or a clinic. In Switzerland, where a "behind-the-counter" status was created by legislation to allow EC to be marketed, use of EC is not recommended among adolescents under age 16. In Finland, an adolescent under age 15 must consult a physician before she can obtain EC. Emergency contraception is available truly over-the-counter in two countries (Norway and Sweden), both of which have no age restriction. In certain Canadian provinces, Plan B is available without prescription and without an age restriction.

Proposed CARE Program

The sponsor has proposed the **C**onvenient **A**ccess **R**esponsible **E**ducation Program with the following dual objectives: (1) increase awareness through education, and (2) increase availability of Plan B through OTC distribution. The program's premise is that neither education nor increased EC access alone will minimize delays in obtaining the product and ensure safe use. The sponsor has proposed developing consumer-oriented written materials that would be available in the offices of healthcare professionals and at points of purchase, as well as public service announcements, print media and radio announcements. A toll-free number staffed by healthcare professionals 24 hours a day and a website will be implemented. Product packaging would contain labeling information for consumers on the outside, as well as educational materials inside and a dose reminder card. Educational programs geared to healthcare professionals would also be developed.[22]

As of this writing, Barr maintains that Plan B is safe and effective for use as an OTC product by all women. Barr, however, is willing to consider retaining prescription status for women under age 16, due to the small

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16 See www.naral.org Who Decides? A State-by-State Report on the Status of Women's Reproductive Rights, January 2004, p.7

17 *See* Raine T. UCSF Study #H9738-18501-02, Provision of Emergency Contraception: Pharmacy Access and Advance Distribution Evaluation, FDA Summary Report, February 11, 2004

18 *See* www.doh.wa.gov

19 *See* Center for Health Statistics, Washington State Department of Health, October 2003

20 *See* www.cdc.gov/std/stats/tables/table3.htm

21 *See* www.cdc.gov/std/stats/tables/table13.htm

22 Sponsor's Slides 72-86, December 16, 2003, Advisory Committee Meeting

number of women under age 16 enrolled in the Actual Use study. On March 11, 2004, the sponsor proposed that Plan B be distributed as an OTC product, with all the mandatory information for an OTC product, but with several specifications. Before dispensing, the age of the patient would be ascertained and if the patient is under 16, the pharmacist would dispense Plan B only pursuant to a prescription. The package would contain a blank space on a principal display panel on which the pharmacist would place a prescription label. This label would contain the names of the prescriber and dispensing pharmacy, the prescription number and date, any directions or precautions specified in the prescription, and if stated on the prescription, the name of the patient.

Barr has also proposed to make the product available at the retail level only in stores with licensed pharmacies or with a valid wholesale license. In addition, Barr proposed that it recommend to retailers that Plan B be maintained behind the pharmacy counter, that pharmacy personnel dispense the product without a prescription only to consumers with valid identification showing that they are age 16 or older, and that consumers without such proof are required to present a prescription. This proposal is currently undergoing legal review within FDA.

Summary

The following points may be considered in the decision to switch Plan B from prescription to OTC status.

General

- There are over 3 million unwanted pregnancies in the US annually. More than a quarter of these occur in adolescent mothers.[23] In contrast, 15-19 year-olds represented only 16% of child-bearing women aged 15-44 years in the US in the year 2000.[24]
- Unwanted pregnancies continue to occur despite current efforts to educate women about contraception and EC, and despite the availability of EC by prescription or pharmacy access programs.
- Despite the availability of EC, public testimony at the December 16, 2003, Advisory Committee indicated that a knowledgeable woman continues to face numerous barriers when attempting to purchase EC in the US.
- Recent estimates indicate that only 6% of US women have ever used EC.[25] Numerous factors influence how women use EC currently, and how women might use EC if it becomes available OTC. These factors include, but are not limited to the woman's age, education level, socioeconomic status, race/ethnicity, religious beliefs, residence in an urban vs. rural setting, history of prior pregnancy, frequency of unprotected sex, and awareness of contraceptive methods, particularly awareness of EC. The interplay of these various factors is often complex and difficult to quantify in studies.

Study Findings

- Data are available on EC use from US studies enrolling over 1000 adolescents aged $\leq$ 16 years in a variety of clinical settings.
- Women of all ages understood that EC should be used if/when a condom broke or slipped, oral contraceptive pills were missed or there was unprotected sex.
- Supervision by a healthcare provider is not critical for proper self-selection or correct timing of dosing.
- Several studies of sexual behavior following advanced provision of EC show that women, including adolescents, do not report having more unprotected sex compared to baseline. Lessons learned from condom availability programs have shown that adolescents were not more likely to engage in sexual activity or become pregnant if condoms were made available in their high schools.
- The timing of EC dosing is shorter when EC is provided in advance (e.g., the Gold et al. study) as compared to studies in which the woman must purchase the product (e.g., the Actual Use study or the Raymond et al. study). In these studies, the woman's age did not play a role in the timing of EC dosing or prescription-seeking.

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23 Sponsor's Slide 6, December 16, 2003, Advisory Committee Meeting

24 *See* http://factfinder.census.gov

25 National Survey of Women on their Sexual Health, survey of US women aged 18-24 years conducted by the Kaiser Family Foundation and *SELF* Magazine, 2003

- Data on the timing of the second dose of the Plan B regimen suggest good compliance regardless of age. Available data also suggest that efficacy is not reduced if the second dose is taken shortly after or concurrent with the first dose. Efficacy may be reduced if the second dose is delayed well beyond 12 hours or omitted altogether. Incorrect timing of the second dose would not have any impact on the safety of the regimen.
- Pregnancy rates on study are somewhat lower than the baseline pregnancy rates for the high-risk women enrolled in these studies. This was true for women of all ages and in a variety of different settings. These data, while difficult to assess for several reasons, do not suggest an adverse impact on pregnancy rates with EC use.
- There does not appear to be an adverse impact on the frequency of STDs in women using EC. Most women are aware that EC is not effective in preventing STDs and that other methods are more effective (i.e., condoms). A woman using EC can only reduce her risk of STDs if her partner uses condoms.
- Evaluation of the safety profile of EC over many years has shown little cause for concern. Incorrect use could result in taking Plan B when it was not necessary. In the worst case, incorrect use could lead to an unwanted pregnancy. In that instance, no harm to the pregnancy would be anticipated.
- Improved access to EC is unlikely to reduce the number of unwanted pregnancies unless it is also accompanied by comprehensive education efforts aimed at consumers and healthcare professionals on an ongoing basis, as proposed by the CARE Program. Unlike the behavior studies reviewed for this application, the CARE Program offers the opportunity to deliver repeated educational messages in a variety of venues, including written materials, a hotline and website, and public service announcements.

Study Limitations

- No single study can adequately address all possible scenarios under which EC may be taken in an OTC setting.
- Studies impose persistent barriers to access by virtue of their design and IRB requirements. For example, the IRB required that the Gold et al. investigators enroll only sexually active women who were at least 15 years old (i.e., younger women or virginal women could not be enrolled) and that only one course of EC be provided at a time.[14] In addition, informed consents and questionnaires, routinely used in study settings, would not be encountered by women purchasing EC in an OTC setting.
- With the exception of the Raymond et al. study, most studies offered reimbursement for EC as an incentive to participation. Thus, the financial burden of obtaining EC in the OTC setting is difficult to predict, but could be decidedly less if use did not require a visit to a healthcare provider. Of note, the cost of a single course of EC is anticipated to be much higher than that for oral contraceptives or condoms, so the likelihood that EC will be used routinely would be minimized.
- Level of awareness about contraceptive methods, and about EC in particular, is variable among study subjects and among women who might use EC in an OTC setting. Although most studies provided some EC education to all subjects, the impact of the various educational messages presented on behavior and outcomes in these studies is difficult to assess. The amount of interaction that took place between women and their usual healthcare providers outside the study is also unknown.

Study Strengths

- Taken together, the sponsor's Labeling Comprehension and Actual Use studies along with the other behavioral studies described here represent a large experience on the use of EC by women at high risk for pregnancy who have been observed in a variety of clinical settings. Findings from behavioral studies that evaluated women who obtained EC in advance of need, or women who had had a prior pregnancy are very relevant to the OTC setting.
- Over a thousand adolescents aged $\leq$ 16 years have been evaluated, with over half participating in the Dial EC Project in North Carolina. Results from this study are very relevant to the OTC setting given that subject eligibility was not restricted, there was no interaction with a healthcare provider at an office/ clinic visit, and callers had to pay for their prescriptions.
- Findings regarding the use of EC, frequency of unprotected sex, and frequency of pregnancy and STDs are remarkably consistent across studies, clinical settings, and age strata.

Conclusions

Plan B is an effective means to prevent pregnancy. Access to Plan B and educational efforts would need to be substantially improved in order to reduce current rates of unwanted pregnancy in the US. Access is not likely to appreciably improve if the product remains available by prescription only, even if Barr embarks on an intensive educational campaign. Pharmacy access programs are innovative options, but are challenging to implement and do not ensure uniform access to women across the fifty states.

In my view, there are sufficient data on the safety and effectiveness of Plan B to approve its use in the OTC setting without an age restriction. Educational messages conveyed in labeling and via the sponsor's CARE Program as originally proposed would ensure proper use of Plan B by women of all ages, including adolescents. If the product were to be switched OTC, healthcare providers would no longer prescribe Plan B but would continue to play a critical role, on an ongoing basis, in educating women about contraceptive methods and STD prevention, and in monitoring for STDs.

The sponsor's recent proposal to retain prescription status for adolescents under age 16 will require that healthcare providers continue to prescribe Plan B to this age group. While the proposal may prove logistically challenging to implement or enforce at the pharmacy level, it should still achieve Barr's stated goal to improve access to Plan B since the majority of product users would not need a prescription. Barr's innovative proposal for a single package that meets both OTC and prescription requirements bears careful review from a legal and regulatory standpoint.

Administrative Note

On January 15, 2004, the DRUDP/ODEIII and DOTCDP/ODEV review teams were informed that the decision regarding the approvability of this application would occur above the ODE level. On February 13, 2004, the review clock was extended three months to review new information on adolescent EC use not submitted in the original application. At a briefing for Commissioner Mark McClellan on February 18, 2004, CDER was directed to work with the sponsor on a marketing plan to limit availability of Plan B to adolescents in the OTC setting, and to consider the most appropriate age groups that should have OTC access restricted.

Barr's March 11, 2004, proposal for dispensing via prescription to users under age 16, and without a prescription to users aged 16 and older, is currently undergoing legal review within FDA. The sponsor has requested that the FDA consider under what conditions the proposed age restriction could be removed. Discussions with the sponsor regarding the amount and kinds of data that would be needed to lift the age restriction, and the strategies for collecting such data have not yet begun. The sponsor's submission of product labeling is pending at this time.

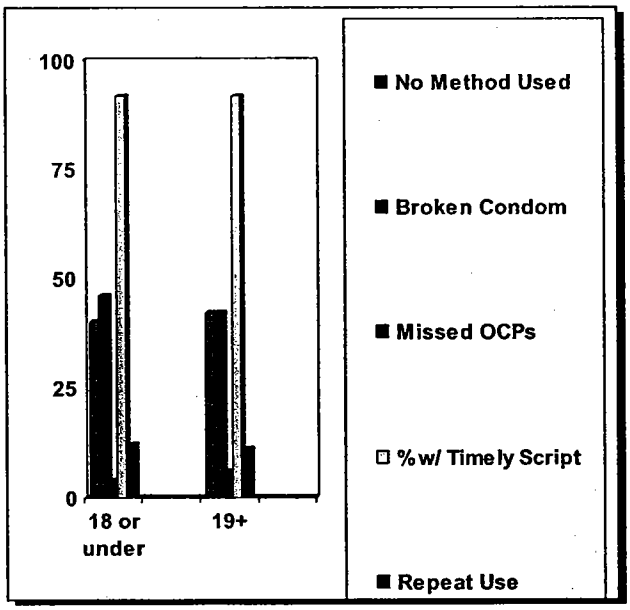
Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

Table 1. Studies Evaluating Emergency Contraception Use

Study	Age Range (years)	Total N	N ≤ 16 yr	N ≤ 17 yr	N ≥ 18 yr
Actual Use	14-44	540	22	46	494
Raymond et al[3]	8-51	7,756	613	1,225	6,531
Raine[17]	15-24	2,090	254	476	1,614
Gold et al[7]	15-20	301	115	187	114
Jackson et al[11,26]	14-?	370[a]	15	21	349
Belzer et al[12]	14-20	160[b]	NA	NA	NA
Totals	--	11,217	1,019	1,955	9,102

[a] Mean age = 26.6 years
[b] Mean age = 17 years
NA – Not available

Figure 1. Raymond et al. Dial EC Project:
Effect of Age on Reasons for Seeking EC, Percent of Subjects with a Prescription Issued within 72 Hours of Unprotected Sex, and Percent of Subjects Requesting a Second Prescription



N= 2,065 for Ages ≤ 18 years; N= 5,691 for Ages ≥ 19 years

[26] Jackson RA, email communication dated November 4, 2003

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/s/

Julie Beitz
4/2/04 10:04:08 AM
DIRECTOR

Deputy Division Director Summary Review of New Drug Application

NDA 21-045

Drug:	**Plan B (levonorgestrel)**
Dosage:	**0.75 mg tablet for oral administration**
Proposed Indication:	**Emergency contraception**
Applicant:	**Women's Capital Corporation**
Submission Date:	**April 16, 2003**
Review Complete	**April 1, 2004**

This new drug application proposes over the counter marketing of Plan B (levonorgestrel) for emergency contraception. The prescription product was originally approved in July 1999. The proposed nonprescription dose and administration schedule is identical to that found to be safe and effective for prescription use. The two major clinical trials submitted in support of this application were a single label comprehension study and a single actual use study. A literature review was 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. A pharmacokinetic study in menstruating females aged ≤ 16 was also submitted.

At the December 16, 2003 Joint Session of the Nonprescription Drug Advisory Committee and the Advisory Committee for Reproductive Health Drugs the committees voted in overwhelmingly support of approval of the nonprescription switch. However, in a January 15, 2004 meeting, senior CDER management informed the Divisions and Offices that this application is not approvable. The reason for nonapproval that was conveyed at that meeting and in subsequent meetings was that there were inadequate data to support adolescent use in the over the counter setting. The Divisions and Offices were told that the Commissioner and senior CDER management believed that the number of adolescents in the actual use study was inadequate, that there were inadequate data to show that adolescents could dose the product correctly, and that adolescents needed a learned intermediary involved in their access to emergency contraception. The Divisions presented adolescent data in an effort to address these concerns in a meeting with the Commissioner on February 18, 2004. These data, however, were considered inadequate to establish that there would be no potential for negative impact from non-prescription access to emergency contraception in the adolescent population.

This review will focus on the issues raised by senior FDA and CDER management to support their decision for nonapproval of this product for over the counter marketing and the public comments by individual advisory committee members that echoed these very same concerns. The reviewing divisions and offices have carefully examined these concerns and do not believe that scientific evidence supports nonapproval of this application. The Divisions and Offices have concluded that the risk-benefit ratio for this product supports its approval for nonprescription marketing, without an age restriction.

This review is organized as follows:

1. Summary of Label Comprehension Study Review Findings
2. Summary of Actual Use Study Review Findings
3. Summary of Studies of Impact of Access to Emergency Contraception on Behavior
4. Safety Overview
5. Summary of Pharmacokinetic Study Review Findings

6. Summary of Joint Session of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs
7. Summary Discussion of Adolescent OTC Access Issues
8. Deputy Director's Recommended Regulatory Action

1.0 Summary of Label Comprehension Study Review Findings

Label comprehension studies allow sponsors to modify product labels to enhance consumer understanding of the label prior to its ultimate test in an actual use study setting. It is the actual use study that evaluates how the consumer **acts** upon the information they read in the label. The label comprehension study presented in this NDA tested 11 communication objectives in 656 females aged 12 – 50. Twelve percent (n=79) were in the 12-16 year old age group. Fifty-four percent were aged 17-25. Data analyses by literacy level are based on the 395 women whose literacy level was tested with the REALM (Rapid Estimate of Adult Literacy in Medicine) in the study – those women who were 18 years of age or older who had not completed a college education. The REALM was not administered to participants younger than 18 because it was not considered validated in that age group. Approximately 4% (n=14) of the women tested (n=395) were found to be reading at the 6^{th} grade level or less, while approximately a third (n=122) were reading at the 7^{th} – 8^{th} grade level. The ages of untested participants less than 18 in the study correlated to 7^{th} to 12^{th} grade levels, but it is possible that the youngest participants were reading either above or below their actual grade level.

The fact that the literacy level of these younger women was not evaluated is a concern expressed by one advisory committee member, Dr. W. David Hager, M.D., in a letter to Dr. McClellan, M.D., FDA Commissioner, dated December 18, 2003. He stated that this group would be at the greatest risk for not understanding the label. "Unfortunately, literacy evaluations were not done in women 18 years of age and younger. This is the group of young women who would be greatest at risk for not understanding the package insert and directions." Dr. Hagar also expressed this concern in his public comments at the Joint Meeting of the Non-Prescription Drug Advisory and the Reproductive Health Drug Advisory Committees (afternoon of December 16) in response to FDA Question #2 to the Committees "Are the actual use study data generalizable to the overall population of potential non-Rx users of Plan B?" He stated "My answer is yes, although I still am concerned about the younger adolescent, the low numbers included in the actual use study, and the literacy information. This is a very high risk group of young women who deserve our attention as much as those who would attend family planning clinics and have college degrees. And so I'm concerned that there is not as much information both as to ability to follow the directions, effectiveness and follow-up among that population."

Reviewer Comment: The specific cause of Dr. Hager's concern about the lack of literacy testing in the younger age group of this study is not stated. The general good performance of the younger age participants in this study and the actual use study suggests that the younger age group can read and understand the label. The label comprehension study included females as young as age 12, and the literacy testing identified 395 older women who read at the 6^{th} grade level.

It is the actual use study that ultimately tests label performance, by evaluating how accurately the consumer implements the intended label message. Label comprehension studies are used by sponsors to optimize consumer performance in the subsequent actual use study by identifying where the label can be strengthened for that study. Nevertheless, Dr. McClellan and members of senior CDER management have informed both review divisions that the literacy testing limitations of the label comprehension study, and the data from that study are sources of concern

they have factored into their decision regarding approvability of the nonprescription switch. Because of these concerns, in this section I will review the communication objectives of the label comprehension study, discussing the relevance of these objectives, with a focus on performance of the lower literacy group and the younger age group relative to the rest of the study population.

Reviewer Comment: Placing a greater than usual emphasis on the label comprehension study for this product compared to the actual use study is not appropriate or usual review practice in evaluating a prescription to non-prescription switch, and is hampered by the relative strengths of the two study designs. The actual use study is a straight-forward and objective assessment of use performance, whereas the label comprehension study inserts another level of comprehension testing that is not informative to product label performance, since participants also had to understand the questions posed to them. Many of the questions used to assess label comprehension were poorly written and were easily misinterpreted. Some questions were of a higher level of complexity, and required an additional level of problem solving.

1.1 Label Comprehension Study Communication Objectives.

There were 11 communication objectives identified in the study. Of those, two (Objectives #1 and #2) related to communication of the indication. Objective #1 was that the product is indicated for prevention of pregnancy after unprotected sex. Objective #2 was that the product is a backup method, not for use as a regular contraceptive.

Three objectives (Objectives #4, #5 and #6) dealt with dosing. Two of the 3 dosing objectives focused on timing of the first dose – Objective #4 on taking the product as soon as possible after intercourse and Objective #5 that the first dose should be taken within 72 hours after intercourse.

The remaining objectives were primarily related to safety issues. Objective #3 focused on the message that the product doesn't prevent sexually transmitted infections. Objective #11 evaluated whether women understood to seek immediate medical care for severe abdominal pain (a sign of possible ectopic pregnancy). Objective #9 evaluated the message that women with allergy to product ingredients should not take the product. Among the remaining objectives, one focused on side effects (Objective #10 – nausea and vomiting) and one (Objectives #8) wasn't considered a relevant safety objective by the DRUDP reviewers.

Objective 8 evaluated instructions to not use Plan B in the presence of unexplained vaginal bleeding, a component of labeling that the DRUDP reviewers don't believe is medically warranted. Its inclusion in the prescription product labeling reflects class labeling for progestin-only contraceptives that are taken on a daily basis for months to years. The medically relevant conditions that unexplained vaginal bleeding could signal in the population of women who would take Plan B include pregnancy, cervical disease, or endometrial neoplasia (in this reproductive age group endometrial polyp or myoma). There is no evidence that Plan B would have an adverse affect on an established pregnancy, including ectopic pregnancy. There is no medically plausible affect that treatment with Plan B would have on cervical or endometrial disease, nor that it would cause a meaningful delay in its diagnosis. The merits of inclusion of this concept in labeling were weighed in discussions at the advisory committee meeting. Dr.'s Hager, Guidice and Montgomery-Rice favored retaining it in the label. Dr. Hager stated it could be a sign of ectopic pregnancy or "a symptom of other gynecological conditions that would warrant investigation", and Dr. Guidice and Dr. Cantilena concurred. Dr.'s Hewitt, Greene, Clapp and Wood all disagreed. Dr. Greene said "..it's hard for me to imagine any problem that would preclude the use of this medication or that this medication would exacerbate."

Reviewer Comment: The information in the label that could relate to ectopic pregnancy – most importantly, pain – are only relevant to the woman at the point of contact if she is already pregnant from a prior sexual encounter. As Dr. Greene stated in the meeting, signs and symptoms of ectopic pregnancy would manifest one month after start of a pregnancy. The goal with this labeling could only be to inform a woman who is already pregnant with an ectopic pregnancy to seek medical care, not that the product itself is harmful in this setting. There is no medical evidence that Plan B would impact the course of an ectopic pregnancy.

Objective 7 was not actually a safety objective. It dealt with instructions to not take Plan B if already pregnant since the product is not efficacious in the setting of an already established pregnancy. There is no evidence that levonorgestrel has an adverse impact on fetal development, which will be discussed further in the safety section of this review.

1.2 Label Comprehension Study Analyses.

The primary reviewer of the label comprehension study, Karen Lechter, J.D., Ph. D., evaluated the study data with multiple analytical approaches. She assessed the performance on each objective in the overall study population and in sub-populations grouped by literacy level (if assessed) and by age. The overall study population scored 80% or higher on all objectives except the objective that Plan B is not to be used as method for regular contraception (Objective #2 – 67%) and the objective concerning unexplained vaginal bleeding (Objective #8 - 75%). Of these two, it is a high priority to adequately deliver the message that Plan B is not for use as a regular contraceptive in an OTC label, so Objective #2 will be discussed in detail.

Objective #2 was assessed with 4 questions, and each participant had to answer 3 of 4 correctly to be scored a correct responder. Of these 4 questions, only one was a direct question that asked, "should Plan B be used as regular birth control?" The remaining 3 questions built upon scenarios and asked if the use of Plan B in the setting described was appropriate. Two of these scenario questions may have been misinterpreted by participants. One (Question #21) described a setting that could be interpreted as partner coercion – a husband who complains about using condoms, and the other (Question #25) was about a couple who wanted to use Plan B as the main contraceptive method when the husband didn't like condoms and the woman didn't want to take birth control pills. The latter question was written such that it could be interpreted as a decision at a single episode (not a continuing contraception choice). In addition, the partner component of the question could have led some participants to again project their own perceptions of women's relative power to influence birth control method decisions in the face of an unhappy male sexual partner into their answer to this question. The remaining question, Question #22 about a women who uses Plan B daily instead of her usual birth control, was answered correctly by 91% of the overall population (76% correct in the lower literate vs. 95% in the higher literate). The direct question was answered correctly by 85% of the overall population (71% correct in the lower literate vs. 93% of the higher literate). To get the overall objective correct, one of the other two, less straightforward, questions had to be answered correctly. Only 47% answered to the question about the complaining husband correctly (37% in the lower literate vs. 53% in the higher literate). The question about the couple who choose Plan B as the main form of birth control was answered correctly by 68% of the overall population (50% of the lower literate vs. 78% of the higher).

Overall, 67% met this ¾ correct criterion (46% in the lower literate vs. 78% in the higher literate group). Comparisons across age groups found similar performance on this objective despite age, including the 12-15 year old age group. This reviewer believes that the relatively poor performance on this objective compared to others tested in this study reflects a combination of issues: 1) ¾ questions had to be answered correctly 2) the scenario questions were poorly written 3) the concept being tested is challenging to succinctly deliver in a label, and it is even more

challenging to articulate a clear question that accurately tests the objective 4) lower literacy participants were challenged to not only read the label, but to read and interpret the questions. Many committee members recommended modifications to the label to strengthen the message of the importance of taking the product as soon as possible after unprotected intercourse to optimize efficacy as an emergency contraceptive, but few commented specifically on the objective that Plan B is only to be used as a back-up method, even though it was one that resulted in poorer performance in this study. Dr. Guidice did directly address this communication objective and suggested that the phrase "back up contraceptive" should be used, with the words "back up" bolded on the package. Dr. Lewis agreed with this suggestion. More emphasis was placed by advisory committee members in their discussion of clearly defining "Emergency Contraception" on the front of the product packaging. This aspect of labeling relates more to communication Objective #1 - whether potential users would understand the product's indication (Plan B is for use to prevent pregnancy after unprotected intercourse). Understanding of this concept could be linked to understanding that the product is not for use as a regular contraceptive. Ninety-three percent of the overall study population did acceptably meet this objective (84% lower literate vs. 96% of the higher literate). Although the participants in the age group 12-15 scored lower than the other age groups, they also scored well on this objective – 86%.

1.2.1 Young Age Group Performance.

The youngest age group had scores that were reportedly statistically significantly different from other age groups on 3 study objectives. These statistical analyses were not adjusted for multiple comparisons, however, and on one the youngest age group scored significantly better (side effects objective). On another (doesn't prevent HIV/AIDS), the youngest group scored similar to the oldest age group, but lower than the 17-25 year olds. In only one objective (#6), the youngest age group scored both lower than the other age groups and less than 86% - the objective evaluating understanding of timing of the second dose at 12 hours post the first. The youngest age group scored 77% on this compared to 90% in the 17-25 year olds and 82% in the 26-50 year olds. This objective was assessed with a single question, a direct question that asked when a woman should take the second tablet. The score for the overall population on this question was 86%. The literacy analysis found 82% of the lower literate and 93% of the higher literate participants answered the question correctly. The division reviewers believe the youngest age group's 77% correct score for the 12 hour dose interval is still acceptable, and as will be discussed later in this review, the younger age group performed similarly to the older age group in taking the second dose at 12 hours in the actual use study.

1.2.2 Lower Literacy Performance.

With regard to literacy, the lower level literacy group scored statistically significantly lower than the higher literacy group on nine of eleven objectives. The only exceptions were Objective #5 (importance of taking first pill as soon as possible after intercourse) and Objective #11 (abdominal pain). None of the analyses were adjusted for multiple comparisons. Scores were similar between groups on Objective #7 (should not be used by women who are already pregnant), 95% correct vs. 99% correct. Despite the differences between groups on the remaining objectives, the lower literate group scored lower than 80% in only 3 - Objectives 2, 4 and 7. Because Objective 2 (not intended to be used as a regular contraceptive) was discussed above, and the relevance of Objective #7 (should not be used by women with unexplained vaginal bleeding – 69% vs. 81%) is questionable, only Objective #4 (should be taken within 72 hours after intercourse – 71% vs. 90%) will be further described here.

Objective #4 was assessed with 4 questions, and 2 had to be answered correctly to achieve an individual correct score. One was answered with only the outer package labeling available to the participant for reference. Although 71% of the lower literate participants achieved this objective

(with 2/4 correct answers), their performance on individual questions exceeded 71%. Eighty four percent of the lower literate group correctly answered Question #29, which asked how many days was the longest a woman should wait to take the first pill. Seventy eight percent of the lower literate group answered Question #19 correctly – whether it was correct to use the product 2 days after unprotected sex. Eighty eight percent of the lower literate group answered Question #20 correctly, a question about use a week after unprotected sex. Question 10 asked what is the best time to take the first pill. Seventy-five percent of lower literate participants said "as soon as possible and within 72 hours or three days" or "within 72 hours or three days" or "as soon as possible". Participants who said only "72 hours or 3 days" in response to this question were not scored a correct response.

Although the lower literacy group performed lower on this objective, their performance on a similar objective (Objective #5) was not found to be significantly different. The overall score for Objective #5 (the first pill should be taken as soon as possible after intercourse) was 82%. The two questions in this objective addressed different components of this question. Question #10 asked the best time to take the first tablet, a straight forward dosing instructions question, while Question #26 focused on the impact of timing on efficacy – "Is Plan B more effective 1 day or 2 days after sex?" An overall correct score was obtainable with a correct answer to one of the two questions. Seventy-five percent of lower literate participants gave an acceptable answer to Question #10 (compared to 83% of the higher literate group), whereas only 64% answered the efficacy question correctly (compared to 75% of the higher literate group). The advisory committee members made many labeling suggestions to address this objective. Their discussion and overwhelming vote in favor of the nonprescription switch reflected that these modifications could be done on the basis of existing evidence, and that they did not support holding the switch to retest the label after making these changes.

2.0 Actual Use Study

The primary objectives of the actual use study were to evaluate the frequency of contraindicated and incorrect use of Plan B when dispensed under OTC-like conditions. The labeled contraindications that were used to evaluate self-selection were existing pregnancy, unexplained vaginal bleeding and allergy to the product. Correctness of use was evaluated by examining whether the labeled instructions for dosing were followed, including first dose within 72 hours of unprotected sexual intercourse and the second dose administered 12 hours after the first.

The advisory committees voted overwhelmingly in response to FDA Question #2 that the results of this **actual use** study were generalizable to the overall population of potential non-Rx users of Plan B (Yes = 27 and No = 1). FDA and CDER upper level management have expressed that they do not concur with this conclusion. Because of this, the reasons given to support a "no" vote at the meeting will be examined in this review. The single dissenting voter, Dr. Cantilena, stated that his "no" vote was cast because he shared some of the concerns that Dr.'s Hager, Crockett and Benowitz had expressed with their "yes" votes. He stated, "There were enough segments of the population studied which really did not do well," and that the study was "done in a somewhat artificial environment." Dr. Hager's comments that accompanied his "yes" vote actually focused on the "low numbers" of "younger adolescents" and the "literacy information" (presumably this comment refers to the fact that there was no literacy assessment) in the actual use study. Dr. Crockett expressed concern about "the illiterate population, that the results may not be generalizable to them," that the "off-label use potential" had not been addressed in the actual use study, and she stated that "there were a significant number of patients that did not see this as a secondary form of birth control; that intimated that they may use it as a primary method of birth control." (*Reviewer Comment: Dr. Crockett's last comment seems to refer back to the label comprehension study.*) Dr. Benewitz commented with his "yes" vote that the high percentage of

women who had some college education may not reflect the "usual user", but he believed that there were enough in the subgroups to extrapolate and say it was generalizable.

A letter to Commissioner McClellan from Dr. W. David Hagar, M.D. subsequent to the meeting, dated December 18, 2003, enumerated his concerns about the adequacy of the actual use study. He was concerned that the family planning clinics "are not a typical OTC population" and that women "were given one pack". His intermixed concerns about adolescents and literacy were included in his specific comments on the actual use study as follows, "In addition, 84% had a high school education, which also may not adequately demonstrate the educational level of women who would obtain these products. My major concern is that only 29 (4.4%) of these women were 14-16 years of age. Thus adolescents were not evaluated for literacy and very few were entered into the study." As in Dr. Hagar's comments on the label comprehension study, his concerns regarding lack of literacy assessment are not specifically defined.

The issues expressed by a minority of the advisory committee members have been reiterated in meetings by senior CDER management as concerns shared by them with the Commissioner. These will be addressed here – first addressing the "artificial" OTC setting and whether there was a potential for prompting correct and appropriate use from the actual use study, either through its design or from exposure to health professionals in the clinic setting. The issue of provision of a single pack to women on study will be addressed in the context of the "artificial" OTC setting. Subpopulation performance issues will be addressed last, in the context of the major study endpoint results.

2.1 "Artificial" OTC setting.

The study sponsor recognized that accrual would be slow under true retail OTC conditions, given the product indication. Emergency contraception product is not available OTC in the U.S. Women who are aware of emergency contraception and have had unprotected sexual intercourse are unlikely to go to an OTC setting to seek an emergency contraceptive product. The exception would be if they live in an area with an established direct pharmacy access program. Direct pharmacy access was limited at the time of initiation of the study. The study sponsor did include five pharmacy study sites in Washington State, where emergency contraception was available through the Washington State pharmacy access program. The remaining study sites were family planning clinics in Texas, Arizona, Michigan, Massachusetts and Washington.

To mimic an OTC setting as closely as possible, the following procedures were followed at enrollment:

1. A woman who identified herself as seeking emergency contraception was read a prepared script to make her aware of the study and asked if she was would answer some questions. The short script stated that the site was conducting a study for the makers of a brand of emergency contraceptive pills. It invited women to look at the package and fill out a questionnaire to give information about herself and whether she thinks she should receive the product.
2. If the woman agreed to fill out the questionnaire, she was given a sample OTC package and the questionnaire (the Screening Form). Besides collecting demographic information, this questionnaire included 4 questions that covered eligibility criteria :
   a. Did you come here today for emergency contraceptive pills?
   b. Are the pills for yourself?
   c. Do you read English?
   d. Have you ever done a mall survey about emergency contraception?

   The self-selection question was, "Do you think you should receive Plan B today?"

3. If the questionnaire indicated the woman met the study eligibility criteria and that she believed she should receive the product, she was given a consent form that provided minimal reinforcing information on the product and its use to avoid impacting the participant's actual use of the product. The consent form was examined for language that could influence a participant's use of the product and behavior on study. Only the following excerpts might be interpreted as having that potential:
   a. "..to see if women can use Plan B correctly just by reading the package without seeing a doctor."
   b. "During the calls, we will ask you how you took the pills, if you had any side effects, if you got pregnant and other information."
4. The consent form told participants they could have access to health professionals on the study:
   a. "Please let us know if you would like to speak with a pharmacist/clinician at any time during the research study."
   b. "If you have a problem, you may see the research study doctor."
5. Once consented, participants filled out a Study Background Questionnaire that asked why she wanted emergency contraception, history of use of emergency contraception (EC), contraceptive method, history of sex without a contraceptive method in the past month, menstrual and pregnancy history, concomitant medications.
6. The product was then dispensed to the participant with the Study Data Card (with an envelope to mail it in after the one week contact). There was no patient package insert. The Study Data Card collected the following information:
   a. Date of last menstrual period.
   b. Date and time of last sex act that prompted the request for EC
   c. Date and time that each pill was taken
   d. Date of a menstrual period after Plan B
   e. Date and results of pregnancy tests after Plan B
   f. Side effects experienced.

   There were no prompts on the data card regarding correct timing of administration.
7. Study staff were permitted to answer subject questions, if they had any, but were to record whether questions were asked and what those questions were.

Reviewer Comment: I disagree that this design artificially created an environment that led to correct and appropriate use by participants, as asserted by Dr. Crockett in at the advisory committee meeting in her responses to Question #1 ("they can use it with the proposed labeling in the setting of having access to education and accountability afterwards") and Question #3 ("which also have, I said before, an educational and accountability component built in which change behavior").

2.1.1 Ability to Access Additional Information

Was ability to access additional information a significant "artificial" component of this study? Reasons for not self-selecting into the study and questions asked of clinic staff were collected and presented in the NDA, and this reviewer believes that these data show that these questions could be addressed in the OTC setting through labeling or contact with professionals at the 1-800 number proposed by the sponsor. Women more comfortable with obtaining information through their health care provider still have the option to do so, and showed their ability to exercise that option in the context of this study. Six hundred sixty five women were screened. Five hundred eighty five were eligible at screening. Thirty-four didn't enroll because they were unsure or didn't want Plan B. Their reasons for not enrolling may be informative about labeling adequacy in informing and/or women's ability to self-determine whether to involve a learned intermediary.

The reasons provided by 34 subjects (5% of screened population) who were screened but did not enroll because they were unsure or didn't want Plan B are listed in Listing 5: [Subjects at Screening Who Were Not Sure or Did Not Want Plan B] (Page 143 of Volume 29). None were <18 years of age. Five were 18 yo, and 7 were 19 yo.

Reasons included:
Desires more information or needs professional input to decide – 17 (2.5% of screened)
Not sure they needed the product – 9 (1% of screened)
Wants more info on side effects – 6
Drug interaction question - 3
Impact on future child bearing question – 1
Breast feeding - 1

Another source of information on women's reaction to labeling is the record of questions asked by study participants and their requests to speak with a health care professional. Ninety-two of 585 (16%) screened subjects who did receive study product asked to speak with the clinician or pharmacist at the initial study visit. The proportion varied by site, ranging from 0% at the Boston site, to 27% at Grand Rapids and Seattle, and 29% at the pharmacy sites. The line listing, Listing 11: [Questions Asked at Treatment Assignment by Subjects Who Received Plan B] includes 93 patients who asked questions. (It is not clear why this number differs slightly from that listed in Table 1.5 Consultations with clinician at first screening, by site Enrolled Population Page 20 of Volume 2, but the difference is minimal.) The specific questions asked are recorded in Listing 11 (Page 181 Volume 29). All questions asked by an individual were recorded. Some patients asked more than one question. The most common questions were about:

Side effects (N=26; 4% study population),
Dosing (N=18; 3%),
Food effects (N=11; 2%),
Efficacy (N=9; 2%),
Birth control methods (N=6; 1%)
Drug-drug interactions (N=6, 1%).

There were 2 questions about mechanism of action, 3 questions about potential for injury to a baby if the subject was already pregnant, 3 questions trying to clarify whether the subject might already be pregnant, 3 questions about the safety of repeat doses of Plan B, and 2 questions about the safety during breastfeeding. There were two questions asking for clarification of the contraindications – one on the vaginal bleeding and the other on the allergy contraindication.

When the subset of enrollees <18 y.o. were examined, the proportion asking the questions for these qualitative categories was similar to that for the general study population, except a somewhat higher proportion of the adolescents asked birth control method questions compared to the general population –6% vs. 1%.

When the questions raised by women who self selected into the study vs. those who did not are compared, those raised by women who agreed to enter the study are more specific, and questions about side effects dominate. More of the group that self-selected out of the study indicated that they questioned whether they actually needed the product and wanted to speak to a professional to determine that. Both groups raised questions about side effects and potential drug-drug interactions.

2.1.1.1 Labeling Issues Raised by Information Sought by Actual Use Study Participants

The labeling used in the actual use study did not include information on drug-drug interactions or food effects and these were issues of clear interest to women participants in the actual use study. The prescription Plan B labeling does not contain this information, and levonorgestrel containing oral contraceptive labels do not provide information on food effects or levonorgestrel component

drug interactions. Combination oral contraceptive labels are either silent on food effects or specifically state that food effects have not been studied. Combination oral contraceptive labeling that addresses drug interactions or CYP metabolism pertains to the estrogen component. No literature reports of levonorgestrel PK studies that evaluated food effects were found by this reviewer.

Questions were raised at the advisory committee meeting regarding potential drug-drug interaction via impact on hepatic CYP enzyme systems, and whether interactions with anticonvulsants exist. No formal studies have been submitted that evaluate these pharmacokinetic questions. The labeling of levonorgestrel containing combination oral contraceptives that discuss interaction with anticonvulsants do so on the basis of known interactions with the estrogen component of the contraceptive. A literature search for interaction between anticonvulsants and levonorgestrel, and to find whether levonorgestrel has interaction with a specific hepatic CYP enzyme system revealed multiple studies that examined combination products, without isolating the levonorgestrel component. Few studies specifically address the levonorgestrel component. Fattore[1], et. al. reported that in a group of 22 women aged 18-44 years old, oxcarbazepine reduced the $AUC_{(0\text{-}24h)}$ of levonorgestrel by 47%, reduced C_{max} 25%, and reduced half-life by 45%, "presumably by stimulating CYP3A-mediated metabolism". Crawford[2], et. al. reported that carbamazepine reduced the AUC of levonorgestrel by 40%. Haukkamaa[3] reported that plasma levonorgestrel levels associated with Norplant subdermal capsules were significantly lower in 6 epileptic women taking "phenytoin alone or in combination with other anticonvulsants" compared to 10 controls who were not. Two of the women who took phenytoin concomitantly with Norplant became pregnant. These reports suggest that concomitant use of certain anticonvulsants may induce metabolism of levonorgestrel. OTC labeling could be revised to include what is and isn't known about drug-drug interactions and food effects.

2.1.2 Single Dose

The concern regarding the artificiality of a single dose expressed by Dr. Hagar presumably reflects a desire to assess repeat use when women have access to multiple packs. The product was supplied in the actual use study as single doses, but women could return to the study site and re-enroll to obtain more product. The review divisions believe that the issue of impact of access to multiple packs has been adequately assessed, particularly given the supportive data from the behavior studies submitted with this NDA. Because women did in fact have access to multiple packs through re-enrollment in the actual use study, repeat use was assessed in the study. The sponsor identified 22 subjects (4% of 540 product users on study) who received more than one study package in Listing 5 [Selected characteristics of women who received more than one Study Package] on Page 008 of Volume 29. Two of the 22 were 16 years old (4% of the 46 women under the age of 18 on study who provided data), 7 were 18 years old, the remainder were 20 years of age or older. In addition, the follow-up contacts indicated that 3 additional subjects received Plan B from another health care provider. One was 20 years old, one was 18 and the last was 17 years old. The 17 year old received it as part of her annual exam as an advanced provision prescription. Repeat use in the actual use study was similar, if not less than that observed in the behavior studies submitted to the NDA. These behavior study reports included summary data from large randomized, controlled trials that enrolled adolescents and evaluated repeat use in the setting of advanced provision (including advance provision of 3 packs of emergency contraception in one study) and a large single arm telephone access to emergency contraception conducted in North Carolina. These studies will be described in more detail in the behavioral study section of this review, with subgroup comparisons by age.

Reviewer Comment:

In this reviewer's opinion, this actual use study did mimic to a large and adequate extent, the OTC actual use setting. Although a strict adherence to an exclusively retail setting would have been ideal, I concur that it would have been difficult to accrue participants for a product with this indication in the U.S., where no OTC product exists with this indication, and women would not go to the retail setting seeking it. The questions women asked suggest potential areas to strengthen product labeling. Participants desired specific information about food effects and drug interactions. It would be important to consider including specific statements in the label regarding lack of information to suggest taking the product with food will alter its effects and to state what is known or not known about drug-drug interactions.

2.3 Contraindicated use results.

Contraindicated use was assessed on the basis of whether a user had an existing pregnancy, unexplained vaginal bleeding, or allergy to the product at the time of use. (Most of these data were collected prior to product use.) Existing pregnancy was assessed using questions regarding dates of last menstrual period in the Baseline Questionnaire, in the Study Data Card and in the phone contact follow-up Weeks 1 and 4. Similarly, at follow-up, participants were asked about diagnosis of pregnancy subsequent to taking Plan B. Participants were asked whether they had had any unexplained vaginal bleeding prior to taking Plan B during the follow-up phone contacts at Weeks 1 and 4. Similarly they were asked to provide a list of medications to which they had allergies at the phone contact follow-up.

Of the 540 participants who used the product in the study, 523 provided sufficient data to evaluate contraindicated use, and only 7 of the 523 (1.3%) had one of the contraindications assessed. Six of the 7 were unexplained vaginal bleeding, a contraindication of questionable relevance. The remaining participant had a pre-existing pregnancy when she took Plan B.

2.3.1 Age Analysis

Analysis of the contraindicated use endpoint revealed that 1 of the 7 contraindicated uses occurred in the younger age population (≤16 years of age) and that was a case of a history of unexplained vaginal bleeding. Given that there were 22/29 participants ≤16 years old who provided follow-up data in this study, the documented contraindicated use in this population was 4.5%. This proportion was somewhat higher than observed in the age group 17 and older (4.5% vs. 1%). As discussed earlier in this review, there is no underlying condition associated with vaginal bleeding that levonorgestrel would adversely impact. No participant in this age group had an allergy to Plan B. Three did not provide sufficient data to determine whether they were pregnant prior to Plan B use, but there is no known harmful fetal effect of levonorgestrel. When the dataset was evaluated using an age cut-off between 17 and 18, only one additional participant was identified for inclusion in the adolescent contraindication list. That participant, 10107-2070, reported unexplained vaginal bleeding after having stopped taking her oral contraceptive mid-cycle.

2.4 Incorrect Use Results.

The primary analysis of correctness of use was conducted by examining whether first dose was taken within 72 hours of unprotected sexual intercourse and the second dose was taken exactly 12 hours after the first. The sponsor conducted additional analyses of the time interval to second dose, since the expectation that women take a product at exactly 12 hours post the first dose could be considered excessively stringent. Since many women took the product within minutes to an hour of the 12 hour time point, these additional analyses were considered relevant.

Timing of doses was collected as follows. The study was designed with a Day 7 contact and a Day 30 contact. A study card was distributed to the participant with the study medication.

Participants were asked to fill in the times that the medication was taken on the card. At the Day 7 contact the patient was asked if she had filled in the card (Yes/No recorded in dataset Listing 23 Contact Information Week One), whether the card was in front of her at the time of the conversation (Yes/No recorded in dataset Listing 23 Contact information Week One contact), and she was asked the times that she took Plan B (recorded in Listing 24: Product Timing Week One contact, page 04 Volume 30).

The Study Data cards were intended to be the primary source of time data analyses, however, because the return rate was low (336/585 women who received study product returned the card), the first telephone contact data was used as the primary source. This reviewer found that when data recorded from Study Data cards were compared to data collected by phone, substitution of the data card data for phone data did not adversely affect outcome for this endpoint.

To be considered a per protocol correct user of the product, a participant had to have taken both doses at the correct time interval. The overall study results for this primary analysis found that 68% of participant used the product correctly. The vast majority of incorrect doses were secondary to the second dose not having been taken exactly at 12 hours after the first.

2.4.1 Age Analysis

Subgroup analyses by age, educational level and previous experience with EC did not reveal significant differences in correctness of dosing across subgroups. Comparisons of the adolescent age groups to the older age groups are summarized in the table below, with two cut points for age comparisons – between 16 and 17 years of age and between 17 and 18 years. The "N" at the head of the column is the number of participants that took the product and provided follow-up data. The 72 hour data numbers for the adolescents do not add up to the total N because a few adolescents did not provide the data on the time of first dose, but did provide the 12 hour interval data. Evaluation of the adolescents who did not take their second dose at exactly 12 hours revealed that nearly all took it within minutes of the 12 hour time point. There was one outlier that took the second dose 2 hours late. Table 1 demonstrates that correct dosing is similar across age groups.

Table 1. Age Subgroup Analyses of Correctness of Dosing in the Actual Use Study

	Age years			
	≤16 N=22	≤17 N=46	≥17 N=518	≥18 N=494
Timing for the first pill after sex act				
>72 hours	**0**	**0**	**2**	**2**
<72 hours	**19**	**40**		
Interval between the second and first pill				
At 12 hours	**18 (82%)**	**36 (78%)**	**369 (71%)**	**352 (71%)**

2.4.2 Analysis of Impact of Previous Use

The label's performance in delivering information on how to correctly use the product can be further examined in this study by comparing correct use between participants who had never used the product before and participants with a history of prior EC use. Presumably, the latter group had had a health care professional involved in providing the product to them in the past and may be expected to show superior performance in correct use if labeling was inadequate and a health care professional intervention in providing instructions on correct use was of significant value. Table 2 below summarizes the "timing performance" based on whether a subject was a new user of EC (emergency contraception) or had a history of EC use. It demonstrates that previous health

care provider intervention did not impact this element. Either the effect of health care practitioner intervention is minimal or the educational interventions included in the package had a similar effect as those of health care providers. Either way, this evidence supports a reluctance to discount the behavioral studies that will be presented in the next section of this review, merely on the basis of their educational component.

Table 2. Impact of Previous Use of Emergency Contraception on Correctness of Dosing in the Actual Use Study

	Prior EC Use	
	Previous Users N=213	First Time Users N=327
Total Correct Use	**142 (67%)**	**224 (69%)**
Timing for the first pill after sex act		
>72 hours	**4 (2%)**	**6 (2%)**
Interval between the second and first pill Exactly 12 hours		
	146 (69%)	**241 (74%)**

2.4.3 Advisory Committee Comments on Actual Use Study

FDA Question #1 to the advisory committees was "Does the actual use study demonstrate that consumers used the product as recommended in the proposed labeling?" The committee vote was yes = 27 and no = 1. The single "no" vote came from Dr. Crockett who stated that she believed that the study showed that "they can use it with the proposed labeling in the setting of having access to education and accountability afterwards." The access to education issue has been discussed at length above. Her concern regarding accountability was that a study that collects data on use, in fact reinforces correct use. It would be difficult to design an actual use study without obtaining data from patients. If the source of her concern is the Study Data card, which collected date of last menstrual period, date and time of last sex act that prompted the request and time that each pill was taken, the sponsor has proposed including a similar card in packaging to record the time of taking the first pill and second pill, mimicking the actual use study. The Divisions have discussed how this card could be designed to help women determine the recommended time of the second dose, assisting with the concept of the 12 hour dose interval.

3.0 Summary of Studies of Impact of Access to Emergency Contraception on Behavior

3.1 Advisory Committee Comments on Behavioral Studies

FDA's Question #3 to the committees at the Joint Session in December 2003 was, "Based on the data from the AUS and the review of the literature, is there evidence that non-prescription availability of Plan B leads to substitution of emergency contraception for the regular use of other contraceptive methods?" The sponsor presented analyses of behavioral endpoints from the actual use study, as well as a combination of abstracts, preliminary study reports and publications in the NDA submission to address this issue. These data were reviewed and presented by the FDA to the advisory committees both in the FDA background document and in the oral presentation at the December meeting. The committee members voted unanimously no = 28 vs. yes = 0 in response to Question #3. Dr. Crockett, however, said in her comments with her vote that "However, the actual use study, the literature review didn't lead us to think that [access to EC leads to substitution for regular use of other contraceptive methods]. However, the public testimony did, which I think is very important because those are high literacy people speaking.....I don't think that the actual use study and the literature review will accurately reflect what the true over-the –counter use would be, and I would suspect that the substitution of EC for regular use of other methods might be higher than we're led to believe in these studies, which also have, I said before, an educational and accountability component built in which

change behavior." It is unclear what Dr. Crockett heard at the open public hearing that was the basis for her comment about the open public hearing evidence. A number of women – some university students and some older professional women (none with literacy testing presented at the hearing) - testified at the open public hearing about their own personal experiences using emergency contraception. Nearly all specifically described a condom break or contraceptive failure and only one described multiple use beyond 2 – and that use was over a 10 year period. A summary of these testimonies follows. Those marked with an asterisk reported repeat use:

F. – "Plan A failed"

M - "We used condoms as our birth control method, but this time I needed [EC]"

*F; - - 23 yo; "When I needed [EC] I was a sophomore in college" One repeat use "a few years later……the condom broke."

*Ma – "I have used [EC] twice after condoms came off inside me…."

*L – 35 yo – "I used condoms, and I still do……..the condom came off inside of me…I have since taken [EC] six times over the course of ten years when my birth control did not work. It actually allows me to use condoms because it's my backup to a slipped or broken condom."

S – "I had had sex and the condom came off"

VB – "my first and only experience with [EC]. As a college freshman, I wasn't able to have a child or afford the $500 for an abortion."

G – "Last month…the condom broke"

3.2 Overview of Behavioral Studies

Of the 8 reports of randomized studies reports the sponsor submitted to the NDA to address the behavioral impact of access, 3 were conducted outside the U.S. in countries that included Africa and India. Those foreign studies were not considered relevant to the U.S. population by the review team. The remaining studies, the first five summarized in Table 3 below, evaluate advanced provision of emergency contraception (EC). The Divisions believe that advance provision studies are informative on the behavioral impact of OTC access, since the product is kept on hand at home for women to self-select use (when they deem it indicated) and, given that the product use is remote from the time it is dispensed, the woman must rely on written information to guide use.

Table 3. Effects of Emergency Contraception Advance Provision on Sexual and Contraceptive Behavior

Author & Publication	Study Design	Study Location	Subjects	Follow-up Periods	*Advance EC Access caused changes in*	
					Sexual Behavior	Contraceptive Behavior
Raine et al: *Obstet Gynecol* 2000	Non-randomized 2 groups: Advance EC (one EC course) & Control (EC education)	***USA,*** Family planning clinics	263 women age 16-24 (64% adolescents); 32% Latina & 29% AA; Excluded subjects presenting for EC	4 months	Decrease in unprotected sex in both groups vs. baseline (Control>Tx)	More likely to use less effective contraception (increased condom use) Increased EC use;
Raine et al: UCSF Study *(NDA: vol 13, p134)* Unpublished	Randomized 3 groups: Advance EC Provision (3 EC courses), Pharmacy EC Access; Standard EC Access	***USA,*** Family planning clinics	2090 women age 15-24 years; 20% Latina & 15% AA Excluded subjects presenting for EC	6 months	Decrease in unprotected sex in all 3 groups *vs.* baseline No increase in incidence of STDs compared to Stnd EC Access	Increase in OC use in all 3 groups with an offset decrease in condom use in all 3 groups
Jackson et al, *Obstet Gynecol* 2003	Randomized 2 groups by date of hospital admin: Advance EC (one EC course) & Control (***but no EC education***)	***USA,*** Inner-city hospital	370 Postpartum women age 26±6 yrs 72% Latina; 43% Married	6 months & 12 months	Increased consistent use contraception and more effective method in both groups. No increase in report of unprotected sex	No change in routine contraception and condom use; Increase in EC use.
Belzer et al: *J Adol Health* (Abstract), 2003	Randomized 2 groups: Advance EC (one EC course) & Control	***USA,*** Inner-city (unknown site)	160 adolescent mothers age 14-20 yrs; 83% Latina & 16% AA	6 months	No increase in unprotected sex (but limited data available)	No decrease in condom use and primary contraception between groups. No data provided on within group changes; (limited data available) Increase in EC use
Gold: *Unpublished Manuscript*	Randomized 2 groups: Advance EC (one EC course) & Control	***USA,*** an urban hospital-based adolescent clinic	301 adolescent women age 15-20 (17±2); 58% AA	8 months	No increase in unprotected intercourse No increase in STDs compared to control	No decrease in condom use; Other info not available

Glasier & Baird: *New Eng J Med* 1998	Randomized 2 groups by birth date: Advance EC (one EC course) & Control (EC education)	***UK,*** Family planning clinics	1083 women age 16-44 (23% age 16-20), 20%>30 y/o Post EC or Therapeutic abortion	1-year	Decrease in unprotected sex in both groups vs. baseline.	Increase in OC use in both groups with decrease in condom use similar changes between 2 groups. Increase EC use.
Lovvorn et al: *Contraception* 2000	Non-randomized 2 groups: Advance EC (one EC course) & Control (EC education)	***Africa,*** Family planning clinics	211 women (spermicide users) age 18-45 yrs	8 weeks	Decrease in unprotected sex compared to baseline in both groups (Control>AEC) Significant limitations in study design.	Increase EC use; Other info not reported. Significant flaws in study design.
Ellertson et al: *Obstet Gynecol* 2001	Randomized 2 group: Advance EC (3 EC course) & Control	***India,*** family planning clinics	411 women (condom users); age 25±4 yrs (83% 20-29 yr); Barrier method users	12 months (38% 12-month; 90% 3-month); pts off study if switched to more reliable method (23%)	Similar proportion having unprotected sex vs. the control	Increase EC use.

The Advance EC (AEC) or the Advance EC Provision (AP) or Treatment(Tx) group : Subjects received EC pills at the enrollment.
The Control or Standard EC access (SA) group: Subjects received only EC education and were advised to request EC pills from the clinics (the same sites as the advance group) by prescription when needed.
The Pharmacy EC Access (PA) group: Subjects received EC pills from pharmacy without prescription.
OC: Oral Birth Control Pills; AA: Africa American; EC: Emergency Contraception; STDs: sexually transmitted diseases;

One of the 5 U.S. study reports was published only in abstract form (Belzer, et. al[4].) and will not be discussed other than to comment that it was a study of advance provision of EC (emergency contraception) in adolescent women that followed women 8 months and found no increase in unprotected intercourse. Two of the remaining studies have been published in peer review journals, Raine[5], et. al, Obstetrics and Gynecology 2000 and Jackson[6], et. al Obstetrics and Gynecology 2003. These published studies will be presented first. The reviewing Divisions and Offices have been informed by upper level CDER and FDA management that there are concerns about the adequacy of the data to support OTC access to Plan B to adolescents, both from the standpoint of the actual numbers of adolescents studied and the impact access to the product might have on adolescent sexual behavior. These concerns were expressed despite the committees' unanimous vote in response to Question #3 regarding the scientific evidence. The applicability of each study to address these concerns in the adolescent population will be discussed here. Residual concerns in the face of this evidence are difficult to dispel if the concerns are based on personal belief systems that are weighted more heavily in regulatory decisions than clinical trial evidence.

3.2.1 Jackson, et. al.

Jackson's study evaluated advance provision of one course of EC to postpartum women, the majority of whom were Latina. Of the 370 women enrolled, 36 were less than 18 years old[7]. These women were followed 12 months. No change in routine contraception and condom use was found, nor was there an increase in unprotected intercourse in the advanced provision study arm.

3.2.2 Raine, et. al. (2000)

This study reported by Dr. Tina Raine was conducted in a high-risk inner city population of women aged 16-24 who were followed 4 months. It evaluated advance provision of one course of EC. At baseline, the advance provision group appeared to be a higher risk group compared to the control group. A higher percentage of subjects in this group presented to the clinic (at enrollment) for contraception, infection checks, had been pregnant, had given birth, had had an elective abortion, and had a new sexual partner in the past 4 months. This group was also less likely to report consistent use of condoms and oral contraceptives (OCs) at baseline than the control. Because of these imbalances at baseline, between group comparisons should be made with caution. This study found that compared to their own baseline, women aged 16-24 provided EC in advance were less likely to have unprotected sex, more likely to consistently use condoms, and were more consistent with their use of OC pills. Compared to the control group, the women provided with advance EC were more likely to switch to a less effective routine contraception method, but this reflected a higher proportional increase in condom use. Both groups had a proportional increase in those women who reported never having unprotected sex and never missing pills (proportional increase in consistent use of the their selected birth control method). These findings are summarized in Table 4 below.

Table 4. Summary of Baseline and Follow-up Contraceptive Behavior in Advance Provision (Single Dose) Study Reported by T. Raine, et. al., 2000

Contraceptive Behavior	Treatment % (n)	Control % (n)	Total % (n)	p
Initial (at Enrollment)				
Never had unprotected sex	32% (42)	34% (45)	33% (87)	0.92
Used condoms every time	**12% (10)**	**24% (18)**	18% (28)	0.08
OC users who never missed pills	**25% (11)**	**42% (19)**	34% (30)	0.08
Used emergency contraception	5% (6)	3.0 (4)	4% (10)	0.75
Follow-up				
Never had unprotected sex	50% (56)	62% (63)	56% (119)	0.42
Used condoms every time	47% (18)	50% (19)	49% (37)	0.71
OC users who never missed pills	**32% (13)**	**59% (26)**	45% (39)	0.03
Used emergency contraception	**20% (22)**	**7% (7)**	14% (29)	0.006
More effective method†	**20% (22)**	**29% (30)**	24% (52)	0.10
Less effective method‡	**28% (31)**	**17% (17)**	23% (48)	0.05
No method at enrollment and follow-up	7% (8)	7% (7)	7% (15)	0.92
Same method at enrollment and follow-up	45% (50)	47% (48)	46% (98)	0.77

Data extracted from the author's Tables 2, 4 and 5 in the publication.
† More effective methods: Depot medroxyprogesterone acetate and OC; and ‡ less effective methods: spermicides, diaphragms, and withdrawal.

Two additional large randomized, controlled trials were submitted with the NDA in early study report format (a study evaluating advance provision of 3 packs of EC to women in four family planning clinic sites in the San Francisco Bay area, a UCSF Study sponsored by Women's Capital Corporation, principal investigator Tina Raine) and as an unpublished manuscript (a study conducted in adolescent medicine clinics in Pittsburgh that evaluated advanced provision of EC, principal investigator Melanie Gold). The results of these studies have been submitted for publication. DRUDP reviewers contacted these investigators after the advisory committee meeting and asked them to provide additional detailed information, specifically a more detailed age distribution and subgroup analyses by age. The educational materials provided to the women who entered the studies were also requested. Advanced provision of the product is considered relevant to the OTC setting by the review divisions for the reasons discussed earlier – patients independently self-select use and the interval between obtaining product and its actual use necessitates that women rely on written information to guide administration and use.

3.2.3 Raine (pending publication 2004).

Dr. Raine's study in San Francisco randomized among 3 arms – advance provision of 3 packs EC, pharmacy access and standard clinic access. Six months into the study, pharmacy access was approved in the State of California and the standard clinic access arm of the study was discontinued. The study report summary that was presented in the FDA background document for the advisory committee meeting contained the data from the 3 arms up to the time of discontinuation of the 3rd arm of the study, 6 months into the study. When Dr. Raine was contacted by the DRUDP for more detailed age analyses, she provided the agency summary data for the completed study including the data analyses for all patients enrolled in the study after discontinuation of the clinic access only arm.

3.2.3.1 Summary Baseline Characteristics of Overall Study Population

This study enrolled 2090 women aged 15-24. Two hundred fifty-four were aged 15-16, while 692 were aged 17-19. Twenty percent were Latina, 15% were black and 30% were white. About half reported having had unprotected intercourse within the past 6 months. A third had a history of pregnancy. Approximately 20% had a history of sexually transmitted infection, 45% were using oral contraceptives at baseline, and 2/3 were using condoms at baseline. The study arms appeared relatively well balanced on these features, although a higher percentage in the clinic access group had had unprotected sex in the last six months, had had a history of STI, were presenting for a pregnancy test, STI check or non-reproductive health clinic visit. A higher proportion of clinic access patients were recruited from the New Generation Health Center study site (a center that serves an area of San Francisco with high poverty rates and high teen pregnancy rates) than the other arms, and a lower proportion on that arm came from the Daly City Planned Parenthood clinic.

Table 5 below summarizes the baseline characteristics of participants.

Table 5. Baseline Characteristics in the Advance Provision (3 Pack) Study Reported by T. Raine, et. al. (unpublished).

Demographics	Pharmacy Access (N = 878)	Advance Provision (N = 876)	Standard Access (N = 336)	Total (N = 2090)
Age (years)				
15-16	107 (12%)	110 (13%)	37 (11%)	254
15	34 (4%)	39 (5%)	15 (5%)	
16	73 (8%)	71 (8%)	22 (7%)	
17-19	294 (34%)	285 (33%)	113 (34%)	692
17	89 (10%)	91 (10%)	42 (13%)	
20-24	477 (54%)	481 (55%)	186 (55%)	1144
Reason for Clinic Visit				
Pregnancy Test	50 (6%)	44 (5%)	31 (9%)	125 (6%)
STD/HIV	95 (11%)	103 (12%)	52 (16%)	250 (12%)
Non-Repro Health	14 (2%)	19 (2%)	13 (4%)	46 (2%)
OCP	231 (26%)	221 (25%)	64 (19%)	518 (25%)
Unprotected sex in last six months	401 (46%)	385 (44%)	178 (53%)	964 (46%)
Ever pregnant	299 (34%)	269 (31%)	106 (32%)	674 (32%)
Ever used EC	281 (32%)	317 (36%)	121 (36%)	719 (34%)
Ever had an STD	168 (20%)	185 (22%)	85 (26%)	438 (21%)

Demographics	Pharmacy Access (N = 878)	Advance Provision (N = 876)	Standard Access (N = 336)	Total (N = 2090)
Clinical Sites (San Francisco)				
City College	53 (6%)	54 (6%)	32 (10%)	
Planned Parenthood: Daly City	268 (31%)	267 (31%)	45 (13%)	
New Generations	246 (28%)	247 (28%)	140 (42%)	
Planned Parenthood San Francisco	311 (35%)	308 (35%)	119 (35%)	

3.2.3.2 Summary Outcomes of Overall Study Population

The behavioral and sexual health outcomes observed in the study are summarized in Table 6. Use of emergency contraception was highest in the advanced provision group, as was repeat use. Despite facilitated access through advance provision or pharmacy access, however, only 10% used the product more than once. Use within 24 hours of unprotected sex (when the product is most effective) was highest in the advanced provision group.

Table 6. Sexual/Contraceptive Behaviors and Outcomes in Advance Provision (3 Pack) Study Reported by T. Raine, et. al. (unpublished).

Behavior	Pharmacy Access (N = 878)	Advance Provision (N = 876)	Standard Access (N = 336)	Total (N = 2090)
Unprotected sex in last 6 months				
At Baseline	401 (46%)	385 (44%)	178 (53%)	964 (46%)
At 6 month Follow-up	272 (34%)	326 (40%)	124 (41%)	722 (37%)
Condom Use				
At Baseline (past 6 month)				
Never	185 (21%)	202 (23%)	62 (19%)	449 (22%)
At Follow-up(≥ 6 month)				
Never	223 (28%)	231 (28%)	81 (27%)	535 (28%)
Oral Contraceptive Use				
At Baseline (past 6 month)				
Currently using	402 (46%)	413 (47%)	134 (40%)	949 (46%)
At Follow-up(≥ 6 month)				
Currently using	426 (55%)	437 (55%)	136 (44%)	448 (47%)

Behavior	Pharmacy Access N=878/812*	Advance Provision N=876/823*	Standard Access N=336/306*	Total N=2090/1940*
Unprotected Sex Every Time	26 (3%)	25 (3%)	7 (2%)	58 (3%)
EC				
Baseline use in past 6 months	140 (16%)	153 (18%)	57 (17%)	350 (17%)
Use in 6 months on study	196 (24%)	309 (38%)	63 (21%)	568 (29%)
Used >2 times on study	25 (3%)	50 (6%)	4 (1%)	79 (4%)
% of users used >2 times	13%	16%	6%	
Took EC within 24 hours	157 (81%)	264 (87%)	44 (71%)	
Pregnancy				
Prior history	299 (34%)	269 (31%)	106 (32%)	674 (32%)
On study	56 (7%)	63 (8%)	25 (8%)	144 (7%)
STI acquired on study	107 (14%)	99 (13%)	38 (13%)	244 (13%)

*First number is number enrolled; Second number is number providing data at follow-up.

There were no differences among groups in changes in contraceptive use. The proportion of participants who reported having unprotected sex during the 6 months of study declined compared to baseline in each arm. There was a similar proportion of participants in each arm who reported having had unprotected sex on study, though somewhat lower on the pharmacy access arm (34% pharmacy access vs. 40% advance provision and 41% standard access). A similar proportion reported having unprotected sex at each intercourse on each arm (3% vs. 3% vs. 2%). A similar proportion on each arm reported that they never used condoms (28% vs. 28% vs. 27%). A lower proportion of participants on the standard access arm reported oral contraceptive use – 44% vs. 55% on each of the pharmacy access and advance provision arms.

When the similar pregnancy rates and STI acquisition rates among study arms are examined in light of this information, the similar STI acquisition rates correlate with similarity in rates of condom use. Use of condoms on the arms with facilitated access to emergency contraception did not fall on this study – addressing a concern expressed by some who fear that access to EC will encourage women to abandon barrier contraceptives that are part of safer sex. The similarity of pregnancy rates among arms may reflect a number of issues. Although the study collected numbers of participants who reported any unprotected sex acts, it does not collect how many unprotected sex acts each had. Not all women who had access to EC in this study used it – 309/326 participants on the advance provision arm that reported any unprotected sex act on study used the product and 196/272 who reported any unprotected sex on the pharmacy access arm used the product. We also don't have the data at study completion on the number of oral contraceptive users who missed a pill during a cycle of oral contraceptive use. The proportion of oral contraceptive users was higher on the facilitated access arms than on the standard access arms – 55% vs. 44%. In the interim report submitted with the NDA, approximately 2/3 of study participants at 6 month follow-up had missed a pill. It is possible that participants who used oral contraceptives on study did not recognize that missing pills constituted unprotected intercourse, and that on those arms with the highest proportion of OC users – the facilitated provision EC arms – the unprotected intercourse on study was in fact higher than recognized. Certainly, the

proportional increase of OC use from the start of study to end of study was highest on the advance provision and pharmacy access arms, and new users may not have been as aware of the effectiveness issues surrounding missing pills. See further discussion of this issue below in the adolescent age group analysis of this study.

3.2.3.3 Age Group Analyses; Summary Baseline Comparisons

There were 476 adolescents aged 15-17 in this study (88 were 15 years old, 166 were 16 years old and 222 were 17 years old). The relative baseline characteristics and outcomes on study of the adolescents compared to participants older than 18 will be explored here using the data provided to the FDA by Dr. Raine. These are summarized in Table 7. The percentages shown in each column are percentages of the total number in that age group in each treatment arm.

Table 7 Relative Demographics and Outcomes by Age Group – 15-17 years of age vs. ≥ 18 years of age in the Advance Provision (3 Packs) Study Reported by T. Raine, et. al, (unpublished) (Percentages shown are the percentage of the total number within the age group in the individual treatment arm.)

Demographics	Pharmacy Access (N = 190/682)	Advance Provision (N = 201/675)	Standard Access (N = 79/259)	Total (N = 476/1616)
Baseline Clinic Visit for Pregnancy Test				
15-17 yo	19 (10%)	17 (9%)	11 (14%)	47 (10%)
≥18 yo	31 (5%)	27 (4%)	20 (8%)	78 (5%)
Baseline Clinic Visit for STD/HIV				
15-17 yo	17 (9%)	23 (11%)	10 (13%)	50 (11%)
≥18 yo	78 (11%)	80(12%)	42 (16%)	200 (12%)
Baseline Clinic Visit for OCP's				
15-17 yo	45 (23%)	37 (18%)	10 (13%)	92 (19%)
≥18 yo	186 (27%)	184 (27%)	54 (21%)	424 (26%)
Unprotected sex in last six months				
15-17 yo	95 (49%)	101 (50%)	46 (58%)	242 (51%)
≥18 yo	306 (45%)	284 (42%)	132 (51%)	722 (45%)
Ever pregnant				
15-17 yo	34 (17%)	22 (11%)	18 (23%)	74 (16%)
≥18 yo	265 (39%)	247 (37%)	88 (34%)	600 (37%)
Ever used EC				
15-17 yo	63 (32%)	58 (29%)	24 (30%)	145 (31%)
≥18 yo	218 (32%)	259 (38%)	97 (38%)	574 (36%)

Demographics	Pharmacy Access (N = 196/682*)	Advance Provision (N = 201/675*)	Standard Access (N = 79/257*)	Total (N = 476/1614)
Ever had an STD				
15-17 yo	18 (10%)	27 (14%)	13 (17%)	58 (12%)
≥18 yo	150 (22%)	290 (43%)	108 (42%)	548 (34%)

* First N is total number of 15-17 year olds in the treatment group. The second N is the total number of 18 and older participants in each group.

Compared to the older age group, a higher percentage of adolescents presented to their baseline clinic visit for a pregnancy test, a higher percentage reported having had unprotected intercourse in the previous 6 months and a lower percentage presented for oral contraceptives. A lower percentage of the adolescents had ever been pregnant or had ever had an STI. Within the adolescent age group in this study, the standard clinic access arm adolescents were more likely to be presenting for a pregnancy test and more likely to have reported unprotected sex in the past 6 months than the adolescents in the other study arms. In addition, they were more likely to have had a history of pregnancy. The pharmacy access group adolescents were more likely to be presenting to clinic for oral contraceptives than those in the other two arms.

3.2.3.4 Age Group Analyses - Outcomes

Comparisons by age group of the behavioral and sexual outcomes on study are presented in Table 8 below.

Table 8. Relative Sexual/Contraceptive Behaviors and Outcomes by Age Group – 15 to 17 years of age vs. ≥18 years of age in the Advance Provision (3 Packs) Study Reported by T. Raine, et. al, (unpublished)

Behavior	Pharmacy Access N=196/189 682/623	Advance Provision N=201/194 675/629	Standard Access N=79/72 257/234	Total N=476/455 1614/1486
Unprotected sex in last 6 months				
15-17 At Baseline	95 (49%)	101 (50%)	46 (58%)	242 (51%)
At 6 month Follow-up	71 (38%)	94 (48%)	34 (47%)	199 (44%)
≥18 At Baseline	306 (45%)	284 (42%)	132 (51%)	722 (45%)
At 6 month Follow-up	201 (32%)	232 (37%)	90 (38%)	523 (35%)
Condom Use -Never				
15-17 At Baseline (past 6 month)	24 (12%)	18 (9%)	8 (10%)	50 (11%)
At Follow-up	37 (16%)	30 (16%)	11 (15%)	449 (22%)
≥18 At Baseline (past 6 month)	161 (24%)	184 (27%)	54 (21%)	399 (25%)
At Follow-up	186 (30%)	201 (32%)	70 (30%)	457 (31%)
Oral Contraceptive Use Current Use				
15-17 At Baseline (past 6 month)	58 (30%)	44 (22%)	16 (20%)	118 (25%)
At Follow-up	75 (43%)	71 (39%)	25 (38%)	172 (41%)
≥18 At Baseline (past 6 month)	344 (50%)	369 (55%)	118 (46%0	831 (52%)
At Follow-up	351 (56%)	366 (58%)	111 (47%)	828 (56%)
Unprotected Sex Every Time at Follow-up				
15-17	6 (3%)	5 (3%)	0 (0%)	11 (2%)
≥18	20 (3%)	20 (3%)	7 (3%)	47 (3%)
EC				
15-17 Baseline use in past 6 months	51 (26%)	40 (20%)	15 (19%)	106 (22%)
Use in 6 months on study	59 (31%)	93 (48%)	22 (31%)	174 (38%)
Used > 2 times on study	7 (4%)	17 (9%)	2 (3%)	26 (6%)
% of users used > 2 times	12%	18%	9%	
≥18 Baseline use in past 6 months	89 (13%)	113 (17%)	42 (16%)	244 (15%)
Use in 6 months on study	137 (22%)	216 (34%)	41 (18%)	394 (27%)
Used >2 times on study	18 (3%)	33 (5%)	2 (1%)	53 (4%)
% of users used >2 times	13%	15%	5%	
Took EC within 24 hours				
15-17	48 (81%)	77 (86%)	14 (67%)	139 (82%)
≥18	109 (80%)	187 (87%)	30 (73%)	326

Behavior	Pharmacy Access N=196/189; 682/623	Advance Provision N=201/194; 675/629	Standard Access N=50/52; 257/234	Total N=447/455; 1614/1486
Took second dose of EC				
15-17	53 (90%)	87 (96%)	21 (100%)	161 (94%)
≥18	125 (91%)	197 (91%)	41 (100%)	363 (92%)
Pregnancy				
On study				
15-17 yo	13 (7%)	31 (16%)	9 (13%)	53 (12%)
≥18	43 (7%)	32 (5%)	16 (7%)	91 (6%)
STI acquired on study				
15-17	27 (15%)	25 (13%)	10 (14%)	62 (14%)
≥18	80 (13%)	74 (12%)	28 (12%)	182 (12%)

*First number is number of 15-17 year olds enrolled; Second number is number who provided data at follow-up.
** First number is number of 18 and older participants enrolled; Second number is number who provided data at follow-up.

Patterns of change in unprotected sex from baseline to study end in the adolescent subgroup echo those of the overall study population analyses and those of the older population subset. Proportions of adolescents reporting unprotected sex were higher than older participants both at baseline and at follow-up, but like the older age group, declined over the course of the study. Rates of unprotected sex do not increase in any group or subset after study entry, but rate of unprotected intercourse declined the least on study in the advance provision group. Only an extremely small proportion report having consistently unprotected intercourse, however, and that rate is similar across arms and subgroups. Rate of acquisition of STIs was similar across arms and age subgroups. A higher proportion reports never using condoms in all study groups and age subgroups when compared with baseline, similar across all arms. Never use of condoms is higher both at baseline and at follow-up in the older age group. Oral contraceptive use increased on study in all age groups, but more dramatically so in the adolescent groups. The exception to this general increase in oral contraceptive use on study was the standard access older age subgroup, which remained stable in proportion of oral contraceptive use from start of study to end.

In light of the higher rate of unprotected intercourse in adolescents, both at baseline and at follow-up, the higher emergency contraceptive use in this age subgroup would be expected. The adolescents on study also had a higher baseline history of EC use than the older age group. The participants in the older age group increased their use of EC on study compared to their own baseline, but mainly in the pharmacy and advanced provision arms. The adolescents on the standard clinic access arm, unlike the older participants in that arm, had a substantial increase in proportion using EC during the course of this study. Repeat use was <10% across the study, and the proportions of each subgroup that used the product more than twice on study was similar, except in the advanced provision arm. If one focuses only on the EC users in each treatment group, and examines the proportions that use the product more than twice on study, they are similar between age groups on each treatment arm. The exception is the standard clinic access arm, in which the proportion of users who use the product more than twice is nearly double in adolescents that of the older participants on that arm.

Pregnancy rates are similar across age subgroups and arms with two exceptions, the adolescents in the standard clinic access subgroup and the adolescents in the advanced provision group. The rates in these two subgroups drive a higher pregnancy rate on study in the overall adolescent population compared to the older age group. The lowest pregnancy rate on study is in the older age group provided advanced access to EC, but the rates of both of the pharmacy access subgroups and the standard access older age groups are very close to those of the lowest pregnancy rate group. The possible explanations for these findings include those discussed earlier with the discussion of the overall study findings. Ninety four adolescents on the advanced provision arm reported having unprotected intercourse during the study, and 93 reported using EC on study. Thirty four adolescents on the clinic access arm reported having unprotected sex during the study and only 22 used EC. We don't know the number of unprotected sex acts that occurred in either group. Oral contraceptive use nearly doubled in these two groups of adolescents – advanced provision and standard clinic access – from start of study to conclusion of study. It is possible that there was unrecognized unprotected intercourse in these presumably new OC users, if they either did not recognize that they had missed a pill or if they didn't know the implication of missing OC doses.

Supporting the premise that the new OC use on study could have contributed to the pregnancy finding in this study are multiple studies that have shown that adolescents are inconsistent users of oral contraceptives. A study from the late 1980s indicated adolescents miss taking about 3 pills per month.[8] One study reported that the continuity rate of an oral contraceptives in adolescents was as low as 13% at 1 year and fell to 2% at 2 years[9]. Although other studies have reported higher rates of continuity of oral contraceptives, rates in these studies are still quite low. Dinerman, et. al. reported that only 50% of adolescents in a study that enrolled 12-18 year olds continued use of an oral contraceptive at 6 months[10]. Half of those that discontinued oral contraceptives stated that they stopped them because they forgot to take them. Only 22% of the participants who started oral contraceptives reported at 6 months that they continued taking them and took them daily. Another study reported by Woods, et. al. found 59% of participants still taking the prescribed oral contraceptive at 3 months, and this fell further to 29% at 12 months.[11] The older participants in this study were more likely to be compliant at 12 months. (The mean age in this study was 17.2 +/- 2.1 years.) The study enrolled from two sites, a suburban adolescent private practice and a hospital-based city clinic. The city clinic site was found on logistic regression analyses to be the strongest predictor of noncompliance both at 3 months and 12 months, and all the pregnancies identified on study were among the non-compliant city clinic participants. The latter information further addresses the finding in Dr. Raines' study, as it enrolled predominantly from inner city clinics. Furthermore, a Swedish study conducted prior to OTC approval of emergency contraception in that country reported a Youth Clinic's experience with emergency contraception (city population 124,000) in a population that ranged in age from13-27. The authors found that despite contraceptive counseling after provision of EC for unprotected intercourse, these patients had a significantly higher pregnancy rate in the year subsequent to that request than the national average for women less than or equal to 19 year of age. None of the women who became pregnant (ages ranged 15-22) had returned for another prescription of emergency contraception, and all had received a prescription for oral contraceptives at the time they were counseled at initial provision of EC.[12].

When dosing of EC is examined in Raine's study, we find that the advance provision group had the highest proportion who took the product within 24 hours of sexual intercourse (when it is its most effective), and the proportion using the product within 24 hours on that arm was the same between age subgroups. The lowest proportion using the product within 24 hours occurred in the standard clinic access group, and within that group, a higher proportion of older participants were able to access the product within 24 hours than in the adolescent subgroup –67% adolescents vs.

73% in the older group. This relative proportion within the adolescent age group on study (able to take the product in the time frame that it is most effective, i.e. 24 hours) was lower in the standard clinic access adolescents - 67% compared to 86% in the advanced provision group. The study also collected data on whether the second dose was taken. The highest performance in the facilitated access treatment arms was in the youngest group in the advanced provision arm – 96%.

3.2.3.5 Summary

In summary, this study didn't show an increase in unprotected sexual intercourse by any group or subgroup of this study. Condom use remained essentially stable, and declines were correlated with increases in use of oral contraceptives.

3.2.4 Gold, et al (pending publication 2004).

Sexually active females aged 15-20 years were recruited from a single center, an urban hospital-based adolescent clinic in a Children's Hospital in southwestern Pennsylvania between June 1997 and October 2001. They were randomized between advance provision of EC (one pack, but told they could come back for 2 additional courses) and standard clinic access. The participants were contacted monthly by telephone for 6 months to collect the following information: sexual behavior, contraceptive behavior, pregnancy, STIs and EC use.

3.2.4.1 Baseline Characteristics of Overall Study Population

The study enrolled 49 adolescents who were 15 years olds, 66 who were 16 years old, and 72 who were 17 years old. Nearly 60% of the population were African American and 30% were Caucasian. Compared to the 15-17 year olds in the Raine 2004 unpublished study discussed above, the 15-20 year olds in this study had a slightly higher prior pregnancy rate (20% vs. 16%), but this may reflect the fact that baseline information broken out by age subgroup was not provided to the FDA in Gold's study (i.e. including 18-20 year olds in this cross-study comparison probably contributes to the apparent higher rate in Gold's study). Similarly, there was a higher rate of prior STI diagnosis in this study's 15-20 year olds – 30% vs. 13% in the 15-17 year olds in the Raine study. The proportion reporting condom use was similar between the two studies, but the OC use at study entry was lower in the Raine study – 25% vs. 38%, which may again reflect the contribution of the 18-20 year olds included as part of the younger subset in Gold's study. Table 9 summarizes the baseline characteristics of the study arms in Dr. Gold's study.

Table 9. Demographics and Baseline Sexual and Contraceptive Behaviors in Advance Provision (1 Pack) Study Reported by M. Gold, et.al. (unpublished)[*No. (%)*]

Behavior	Baseline	
	Advance EC	Standard Access
Enrolled Subjects	150	151
Age		
15-16 yo	55 (37%)	60 (39%)
17-18 yo	60 (41%)	62 (41%)
19-20 yo	33 (22%)	31 (20%)

Behavior	Baseline	
	Advance EC	Standard Access
Current Education Level		
High School	84 (57%)	93 (61%)
College/Trade	44 (30%)	41 (27%)
None/Other	20 (13%)	19 (12%)
Ever Pregnant	28 (19%)	33 (22%)
Ever STI	47 (31%)	43 (29%)
Condom User	114 (76%)	106 (70%)
OCP Use	52 (35%)	62 (41%)

3.2.4.2 Outcomes; Overall Study Population

In this study no differences between the advance provision and control group were found at the one month or 6 month follow-up for self reported unprotected intercourse over the prior month or at last intercourse. No significant difference between the two groups was found at one month in condom use or OC use. At the 6 month follow-up a significantly higher proportion of the advance provision group reported condom use in the past month compared to the control, and reflected increasing condom use compared to the first month on study. The control group had a diminished rate of condom use at 6 months compared to month 1. Oral contraceptive use was lower in the advance provision EC group compared to the control group.

EC use on study was higher in the first month in the advance provision arm – 15% vs. 8%, but at the 6 month interview it was similar – 8% vs. 6%. Repeat use was lower on the clinic access arm. Twenty-six participants on the advanced provision arm used EC 38 times on study, compared to 20 participants on the control arm who used it 24 times. Twenty-two of the advance provision arm returned for another pack of EC – 15%. Four returned twice and 1 returned 3 times. The number on the advance provision arm who used the product on study in the first month was 22, and the number who returned for another pack during the study was 20. Time interval to first dose after unprotected intercourse in the advance provision arm was shorter – 11.4 hours – compared to the control arm – 21.8 hours.

The same number of participants had a newly diagnosed STI during the conduct of this study. There were pregnancies reported on both arms of the study, but a higher number on the control arm – 18 vs. 13. These study results are summarized in Table 10 below.

Table 10. Sexual and Contraceptive Behaviors and Sexual Health Outcomes on the Advance Provision (One Pack) Study Reported by M. Gold, et. al. (unpublished)
[*No. (% of subjects who completed interview)*]

Behavior	First Month Follow-up		Sixth Month Follow-up	
	Advance EC	Std. Access	Advance EC	Std. Access
Enrolled Subjects†	150	151	150	151
Completed Interview†	123 (82%)	131 (87%)	91 (61%)	105 (70%)
EC Use‡	(15%)	(8%)	(8%)	(6%)
STDs‡			12 (13%)	12 (11%)
Pregnancy			13 (9%)	18 (12%)
In past month				
Unprotected intercourse	24 (20%)	28 (21%)	16 (18%)	19 (18%)
Used condom	73 (59%)	85 (65%)	70 (77%)	65 (62%)
Used OC pills	42 (34%)	51 (39%)	33 (36%)	50 (48%)
Used any hormonal contraception	42 (34%)	51 (39%)	40 (44%)	56 (53%)
At last intercourse				
Unprotected	21 (17%)	25 (19%)	10 (11%)	19 (18%)
Used condom	70 (57%)	80 (61%)	67 (74%)	66 (63%)
Used OC pills	35 (28%)	41 (31%)	34 (37%)	46 (44%)
Used any hormonal contraception	35 (28%)	41 (31%)	39 (43%)	50 (48%)

Data were extracted from the author's Table 2, or Figure A (†) or text (‡).

3.2.4.3 Outcomes; Age Subgroup Analyses

Table 11 below summarizes the subgroup analyses by age category – 15-17 year old vs. 18- 20 year olds. It shows that EC use on study was similar between age categories. Unprotected intercourse during the study was similar between age categories and highest in the control arm. Condom use was highest in the younger age group and similar between arms, though slightly higher in the control arm's 18-20 year old subgroup. OC use was highest in the older age group, and slightly higher in the control arms of both age groups. STI rates on study were higher in the younger age group and similar between treatment arms. During the course of study there were 13 pregnancies on the advance provision arm (9% of the entire population) and 18 on the control arm (12% of the entire population). Pregnancies broken down by age subgroup and by study arm revealed similar proportions across groups, except a higher proportion of pregnancies in the older participants in the control arm – 19% vs. 7% of the advance provision older subgroup. Pregnancy rates in both arms of the younger age subgroup appear slightly less than the control arm's old subgroup, 12% and 10% in the advance provision and control younger subgroups, respectively.

Table 11. Sexual and Contraceptive Behaviors and Sexual Health Outcomes Over the Entire Advance Provision Study (One Pack) Reported by M. Gold, et. al. (unpublished) ; Exploratory Comparison by Age Subgroup

Behavior	15-17 year olds		18-20 year olds	
	Advance EC	Std Access	Advance EC	Std Access
EC Use	17 (25%)	13 (15%)	10 (23%)	6 (13%)
Time to 1st dose Mean	16 h	20 h	14 h	18 h
Time to 1st dose Median	14h	24 h	9 h	14 h
Time to 2nd dose Mean	10 h	13 h	10 h	14 h
Time to 2nd dose Median	12 h	12 h	12 h	12 h
Unprotected intercourse	28 (36%)	37 (42%)	16 (37%)	18 (39%)
Condom Use	63 (89%)	66 (86%)	32 (80%)	38 (84%)
OC Use	28 (39%)	32 (42%)	22 (55%)	27 (60%)
Pregnancy	9 (12%)	9 (10%)	3 (7%)	10 (19%)
STI	6 (8%)	8 (9%)	2 (5%)	2 (4%)

The rate of unprotected intercourse was similar across arms and age subgroups and the relative rate of EC use between arms was the same for the two age groups. Despite this, there appears to be a trend toward a lower pregnancy rate in the 18-20 year old advance provision subgroup in this exploratory analysis compared to the same age subgroup in the control arm, but not in the 15-17 year old subgroup. If you examine when EC was used relative to when participants had unprotected intercourse, you find that in the adolescent advance provision group 71% of the users in this subgroup used the product in the first month and the number of users in that month correlates with the number of reports of unprotected intercourse. In the older age group, 60% of the advanced provision arm used the product in the first month. At the 6 month follow-up twice the number of the 15-17 year old subgroup in both the advanced provision and control arms reported having unprotected intercourse than reported using EC. Participants in this study were provided one pack of advanced EC at a time and had to return for subsequent packs. This convenience factor may have played some role in the lower aged adolescent EC use in the face of unprotected intercourse on study. The Swedish study reported by Falk, et. al., described above, found that among the women who became pregnant, none had returned to the clinic for another prescription of EC, which led the authors to conclude that clinic access structure needed to be improved to facilitate young women's re-accessing emergency contraception when needed.

3.2.4.4 Summary

The data presented above for correct timing of doses show no negative impact of age, nor any positive impact of learned intermediary intervention at the time of dispensing the product.

3.2.5 Raymond, et. al. (2004 publication pending).

After the advisory committee, an additional very large single arm study called DIAL EC was brought to the DRUDP review team's attention. The results of the study have been submitted for publication, but the principal investigator, Dr. Elizabeth Raymond, was willing to share the submitted paper and data from subgroup analyses with the FDA. The study was conducted in

North Carolina and enrolled nearly 8000 women. Follow-up extended over 25 months. Twelve hundred twenty-five were aged ≤ 17 (409 were 16 yo, 167 were 15 yo and 31 were 14 yo) and 6531 were 18 or older. These women self-selected and called this EC hotline to request EC after unprotected intercourse. Information about the study and hotline were available through leaflets left in doctor's offices and pharmacies, as well as through a media campaign. Many women reported at enrollment that they heard about the hotline from a friend. The educational intervention during the phone conversation was limited to reading the caller the points from the product label (see further discussion below in Summary Conclusions for this Section III). The study representative on the phone collected information on the time since unprotected intercourse and kept records of who called so that repeat use data is available for assessment. A study physician reviewed each participant's last menstrual period history, and a prescription was called to the pharmacy or clinic of the caller's choice.

3.2.5.1 Age Subgroup Analyses

The investigator provided the FDA with subgroup analyses by age, with a cut-off between age 18 and 19. These analyses are summarized in the Table 12 below. The majority of callers had no history of EC use in the past. The distribution of number of days between unprotected intercourse and making the call to the hotline was similar across age groups, as were the reported contraceptive problems leading to request for EC and the proportion of repeat use. Proportions who reported using no contraceptive method were similar between age groups. The proportions of callers who reported that they intended to use no contraception in the future were similar between age groups.

Table 12. Age Subgroup Comparisons in the DIAL EC Study Reported by E. Raymond, et.al, (unpublished).

	Age 8-18	Age 19-51
Days between sex act and prescription		
0	463 (22%)	1472 (26%)
1	1001 (48%)	2665 (47%)
2	427 (21%)	1101 (19%)
3	108 (5%)	249 (4%)
Missing	66 (3%)	204 (4%)
Reason for request		
Broken condom	954 (46%)	2390 (42%)
No method used	835 (40%)	2407 (42%)
Missed OC	91 (4%)	344 (6%)
Contraceptive method		
Condom only	1264 (61%)	3106 (55%)
OC only	174 (8%)	628 (11%)
Other or mixed	97 (5%)	479 (8%)
None	530 (26%)	1478 (26%)
Intended Future Contraceptive method		
Condom only	796 (39%)	1961 (34%)
OC only	519 (25%)	1623 (29%)
Other or mixed	628 (30%)	1812 (32%)
None	122 (6%)	295 (5%)

Prior EC Use		
None	1759 (85%)	4177 (73%)
1	243 (12%)	1162 (20%)
>1	54 (3%)	304 (5%)
Unknown	9 (0%)	48 (1%)
Repeat EC Use on Study		
1 Script	1700 (82%)	4795 (84%)
2 Scripts	253 (12%)	626 (11%)
3 or more Scripts	112 (5%)	270 (5%)

3.2.5.2 Summary

The strengths of this study are the very large numbers of women enrolled, the large numbers of adolescents enrolled, self-selection akin to over the counter accessibility, minimal interaction with the study representative on the phone, and the data collected on repeat use and timing of first dose (based on the timing women chose to call the hotline after unprotected intercourse).

3.3 Summary Conclusions on the Behavioral Studies.

In summary, the actual use study is supported by large randomized controlled trials and a sizeable single arm study that closely mimicked the OTC setting in terms of self-selection and minimal interaction with an intermediary. These supportive studies enrolled large numbers of adolescents, and showed no increase in unprotected intercourse. Impact on contraceptive use varied. Jackson showed no change in condom use, Raine 2004 and Gold 2004 showed an increase in condom users, while Raine 2000 showed a concomitant decrease in condom users with an increase in oral contraceptive (OC) users. Changes in OC use on the other studies also varied. It increased in the Raine 2004 study and increased relative to the control arm in the Gold 2004 study. It remained stable on the advanced provision arm of that study compared to the first month of the study, and was also stable on the Jackson study. Pregnancy rates and STI acquisition were similar between comparators in the studies that reported these endpoints. EC use was higher in the advanced provision arms of these studies and repeat use was higher in the advanced provision arms, but ranged from less than 10% to 15%. The Dial EC study showed a similar rate of repeat use.

Data specific to adolescents less than age 18 were provided in exploratory analyses in 3 of the large studies. Raine 2004 data show that the unprotected sex patterns of the adolescents echo those of the older age group on study and do not increase with advanced provision of EC. Never use of condoms also showed a similar pattern between the younger adolescents and those 18 and older in that study. Oral contraceptive use demonstrated a greater increase in the adolescent group. Gold's study also showed similar patterns of unprotected intercourse between the older and younger age groups. Condom use was highest in the youngest age group, while OC use was higher in the older age group, with a similar pattern in comparisons to control arms.

Raine (2004) showed a higher EC use in the younger age group. STI acquisition was similar between age groups. Higher pregnancy rates in the younger age group across the study compared to the older age group in the study were driven by higher pregnancy rates in the standard access and advanced provision younger adolescent subgroups. On Gold's study, EC use was similar between age categories. STI rates were somewhat higher in the younger age group than the older participants, but the same between study arms – advance access vs. standard clinic access in the younger age group. Pregnancy rates were similar between arms in the younger age group, but there was a trend to lower pregnancy rate in the advance provision arm in the older age subgroup.

The Dial EC study revealed similar proportions of EC use between younger adolescents and those women older than 18.

The Divisions do not believe these data support concern for adolescent access. They don't show substitution for regular contraceptives and incorrect timing of use in those studies that collected these data. The review divisions consider the data from the studies discussed in this section relevant and supportive for evaluation of Plan B for distribution in the over the counter setting. With the exception of the North Carolina DIAL EC study, the randomized controlled trials evaluated advance provision of emergency contraception. The Divisions believe that studies of advance provision are relevant to assessing the behavioral impact of the facilitated availability of emergency contraception through non-prescription distribution. Advance provision of EC is a form of access that makes the product more available to a woman than even OTC access, since the product is kept on hand at home for a woman to self-select when it is indicated for her. Given that the product use with advance provision is remote from the time that it is dispensed, the woman must rely on the package labeling and any written information provided to her to guide use at the time that she decides to take it. Senior CDER management has argued that the presence of an educational component in these studies, which varied amongst trials, negates the applicability of these studies to assessing the behavioral impact of improved access to EC. The Divisions disagree. They do not concur that the education provided in these trials would significantly counteract the behaviors most feared to result from easy access to an emergency contraceptive in a high risk adolescent population, a well-described age group known for risk-taking and inconsistent use of contraception. A summary of the educational component of each of the large studies discussed above follows:

Table 13. Summary of the Educational Information Provided to Participants of the Large Behavioral Studies

Study	Education
Raine, et. al. (2004)	1-page handouts x 2 + 1-page Consent form for Emergency Contraception. First Handout is an Instruction sheet for EC that states "If you have unplanned, unprotected intercourse: Take 1 Plan B pill (first dose) within 72 hours (3 days) after intercourse. Take the 2nd Plan B Pill (2nd dose) exactly 12 hours after your 1st dose. For Example: 1st dose at 10:00 AM, 2nd Dose at 10:00 PM. If you are already pregnant you should not take emergency contraception. Talk to your clinician if you think you might have become pregnant more than 3 days ago. What you should know after taking Emergency Contraception: You may have nausea and vomiting. If you vomit within 1 hour of taking your pills, call the clinic. Your next period may come earlier or later than usual. Return to the clinic for a pregnancy test if your period has not started within 3 weeks. If you have sex after using emergency contraception, you need to use a birth control method such as foam and condoms or a spermicide. Failure to do this can result in an unwanted pregnancy." Phone numbers for questions provided. 2nd Handout is the Plan B Rx product's patient package insert Consent for Emergency Contraception – Opens with the following statement "Please initial on the corresponding line after reading each statement." Ten brief statements that summarize the patient package insert messages follow in a checklist format with a line to mark for the participant to check off.

Study	Education
Gold, et. al. (2004)	EC information provided included indications for use, how and where to get EC, the toll free EC hotline number, a wallet card with the clinic phone number, risks as described in the Plan B patient package insert, a message that EC was not recommended as a primary method of contraception and that EC does not prevent STIs. In addition, participants were given three educational pamphlets about EC, abstinence, and other contraceptive options.
DIAL EC Raymond, et al (2004)	A standard set of messages about EC use was read to the caller by the phone "specialist". The PI provided a list of the content of this standard message to the FDA and it is quoted here: * Use instructions for specific type(s) of ECPs to be prescribed. * Caller should obtain and take the ECPs as soon as possible. * If she takes the ECPs more than 72 hours after her earliest act of unprotected intercourse, they may be weakly effective or ineffective for prevention of pregnancy. * ECPs may fail to prevent pregnancy no matter how soon she takes them. * If her next period is more than a week late or is irregular, she might be pregnant. * She may get any of the following symptoms after taking the ECPs: nausea, vomiting, breast tenderness, dizziness, headache, abdominal cramps, irregular bleeding, early or late next menstrual period. * The following symptoms are very unlikely but if she gets any of the following symptoms, she should come to the nearest clinic, her health care provider, or an emergency room: very bad abdominal pain, heavy vaginal bleeding, fainting, prolonged dizziness, any other worrisome symptoms. * Since unprotected intercourse may lead to STIs as well as pregnancy, caller should consider getting tested if appropriate. * Caller should use a regular precoital contraceptive method in future to prevent pregnancy and STIs.

Review of the content of the information provided at study entry in these studies revealed that it was a summary of the label points from the Plan B patient package insert. The exception was the Gold study, which provided pamphlets summarizing available contraceptive methods. The sponsor of this NDA for OTC switch also proposes to include, in addition to a patient package insert, patient information sheets on available contraceptive methods, as well as information on STIs. The sponsor also proposes a 24 hour 1-800 hotline on the package for women to access additional product information and to seek answers to any questions that arise, much like what was done in these studies.

4.0 Safety Overview

Dr. Daniel Davis, MD., conducted the safety review for this application. It included both a summary review of the safety data from the original NDA that supported the approval of the prescription product (for which he was the primary medical reviewer) and an overview of the post-marketing safety data. Important issues examined in the review include thromboembolic events, fetal effects, ectopic pregnancies, and safety of repeat use.

4.1 Prescription Product NDA Safety Data and Post-marketing Safety

Review of the safety data from the original NDA and the post-marketing safety reporting revealed no evidence of thrombotic events, except for one foreign report of phlebitis. This is consistent with what would be expected for a progestin-only product, even if used chronically.

4.1.1 Ectopic Pregnancy

Ectopic pregnancies reported in the post-marketing database were examined closely because progestin-only contraceptives, including levonorgestrel implants, have been associated with a higher rate of ectopic pregnancies. There were 28 cases of ectopic pregnancy identified in the FDA AERs database, and none occurred in the United States. The sponsor reported that of 266 pregnancies reported to the sponsor worldwide, 21 were ectopic (8%). Given that an ectopic pregnancy is more likely to be reported as an adverse event than a pregnancy, this 8% is considered an inflated rate of ectopic pregnancy. When the safety data from the randomized controlled trials that established the efficacy of levonorgestrel as an Rx emergency contraceptive were evaluated, the incidence of ectopic pregnancy of 1.5%. These data are particularly useful because in the controlled setting of the study you are more likely to capture the events and you have a total denominator to facilitate assessing incidence. This observed rate of ectopic pregnancy (1.5%) is similar to that reported as the background rate of ectopic pregnancy in the U.S. population – 2%.

4.1.2 Fetal Effects

The post marketing safety data consultation from ODS identified 3 spontaneous abortions, 1 missed abortion, 1 inevitable abortion and 3 European cases of congenital anomalies in women who had used levonorgestrel for emergency contraception. The spontaneous abortion rate that is reported associated with recognized pregnancies is 10-15%, these reports do not show a negative fetal impact of this product. Similarly, the congenital anomaly incidence is reportedly 0.85% across the population, and these few cases are well within that rate. DRUDP has previously reviewed the teratogenic risk of contraceptive hormones in early pregnancy and have concluded there is no association between accidental use of these hormones and adverse fetal outcomes. Dr. Davis' review includes details of this analysis and this information was provided in the FDA background document for the advisory committee meeting.

4.2 Long Term Exposure/Repeat Dosing

The Advisory Committees' votes in response to FDA Question #4 at the committee meeting, "Do the data presented in the NDA demonstrate that Plan B is safe for use in the non-prescription setting?" were a unanimous "Yes" (N=28). Dr. W. David Hager, M.D., in his December 18 letter to Commissioner McClellan after the meeting, states that, "We need longer term data among those who repetitively dose the medication." This statement presumably reflects a concern about the safety of repeat dosing of levonorgestrel 1.5 mg. Most of the data on repeat doses of levonorgestrel is at the low doses used in oral contraceptives or with levonorgestrel contraceptive implants. Some information on repeat doses at higher dose levels can be found in the post-coital contraception literature. Larranaga[13], et. al. (1975) reported on a clinical trial that evaluated use of 1.0 mg levonorgestrel as a post-coital contraceptive. Two hundred ninety-eight women aged 16-45 were followed on the study, which extended over a 16 month period, and the average follow-up per patient was 8.6 months. In a quarter of the months on study >10 tabs were taken. In half the study months 7 or fewer tabs were ingested. No serious adverse events were identified, and the common symptoms included headache, dysmenorrhea, nausea, dizziness, acne, bloating, and breast pain. Another post-coital contraception study reported by Chang-hai[14], et. al. evaluated postcoital use of 0.75 mg levonorgestrel administered followed by a repeat dose 24 hours later. Single 0.75 mg doses were repeated after each further sexual intercourse, not to exceed 0.75 mg/24 hours. The study was conducted in China and enrolled 514 women aged 21-

40. The average number of levonorgestrel tablets taken in a treatment cycle (approximately 28 days in length) was 4, with a range of 2 to 7. No serious adverse event was noted. The most common side effects were nausea and dizziness.

A publication on levonorgestrel two-rod implants written by Wan[15], et. al., observed 249 women for 5 years. Women who entered the study ranged in age from 18-40 years. No serious adverse effect was observed in the study. This implant system releases levonorgestrel 80 micrograms per day x 1 month (2.4 mg in first month), with a gradual decrease to 50 micrograms per day at the end of 9 months (Mean between 80 and 50 micrograms is 65 micrograms/day or 1.95 mg/month). Subsequent to 9 months the release rate is 25-30 micrograms per day (approximately 0.9 mg/month). The cumulative exposure to levonorgestrel in the first 6-9 months of treatment with this implant system seems comparable to what would be expected with monthly dosing with a single courses of Plan B 1.5 mg. After 9 months, the cumulative exposure with the implant system would be similar to every other month dosing with Plan B.

4.3 Adolescent Safety

An adolescent safety study that enrolled 60 females aged 13-16 was submitted in the NDA. Fifty-two were considered evaluable for safety. Participants took the standard dose of Plan B and recorded AE's in a diary. They were followed for 3-5 weeks after dosing. Over half the population enrolled were African American, and 13% had a history of prior use of emergency contraception. There were no serious AEs in this study and the range of symptoms reported were similar to those currently in the current product label. A higher percentage of adolescents, however, reported individual symptoms. Interpretation of this relative difference is hampered by the fact that these are cross-study comparisons. Dr. Davis pointed out in his review, as well, that a number of the adolescents reported their abdominal pain, fatigue and headache in the second week on study, when adolescent PK data suggest that the product should have been cleared. Impact of Plan B on menses in this study included 22% reporting lighter menses, 23% heavier menses, 36% early menses and 9% delayed menses. These patterns are similar to the prescription product's labeled information on effects on menses. The Rx label states that 12-13% had heavier menses, 12% had lighter menses, 13% had a delay of more than a week. Most women had their menstrual period within a one week window – either earlier or later – of what was normal for them.

Table 14. Summary Cross-Study Comparison of Common Adverse Events Reported in a Study of Adolescent Females and Studies of Older Females

Symptom Reported	Adolescent Safety Study	Plan B Label
Headache	50%	18%
Fatigue	40%	17%
Nausea	39%	23%
Dizziness	27%	11%
Lower abdominal pain	25%	18%
Breast Tenderness	14%	11%
Vomiting	12%	6%

The review divisions concur with the Advisory Committees' vote endorsing the safety of Plan B for non-prescription use. Long term pre-approval studies are not warranted.

5.0 Summary of Pharmacokinetic Study Review Findings

A pharmacokinetic study conducted in 22 females aged 12 to 16 years was submitted with this NDA. Pharmacokinetic studies in this age group were not requested by the FDA. The study evaluated a single oral administration of 0.75 mg levonorgestrel tablet. PK data from another study conducted in 18 to 45 year old females, again following a single oral administration of 0.75 mg, part of the original Plan B NDA for Rx approval, was also submitted to facilitate cross-study comparisons of these age groups.

5.1 Study Results

Dr. Myong-Jin Kim, Ph. D.'s review of these data found levonorgestrel pharmacokinetic differences between adolescent and adult females in these cross study comparisons. The mean levonorgestrel C_{max} and $AUC_{0-\infty}$ were approximately 47 % and 23 % lower, respectively, in adolescents than adults. The adolescents' C_{max} was 6.72 ng/mL (CV 45.8%), while in adults C_{max} was 12.8 ng/mL (CV 43.7%). The $AUC_{0-\infty}$ in adolescents was 86.14 ng*hr/mL (CV 42.9%), compared to 112.5 ng*hr/mL (CV 40.0%) in adults.

Dr. Kim summarized what she found in a literature review of levonorgestrel pharmacokinetics. She identified 7 studies that were conducted in the U.S., South Africa (study population was Caucasian), Sweden, Dominican Republic and China. She noted that the published literature indicates that levonorgestrel's pharmacokinetics following a single oral dose (0.75 mg) in adult females demonstrate high variability. She stated in her review that, "The mean values of C_{max} and $AUC_{0-\infty}$ LNG ranged from 5-14 ng/mL and 116-164 ng*hr/mL, respectively." She found that there are data in the literature that show marked intra-subject variability (23 – 80%) and inter-subject variability (2- to 4-fold) in levonorgestrel pharmacokinetics. The reason(s) for this variability is unknown. Given levonorgestrel's known highly variable pharmacokinetics, the differences observed between the adolescents and adults in the two studies submitted in this NDA should be interpreted with particular caution, especially because the comparisons are not being made within a single study setting.

To emphasize the limiting issues inherent to cross-study comparisons, the differences in the study designs of the adolescent and adult PK studies are summarized here. In the adolescent study, participants were only fasted for 4 hours before dosing compared to 8 hours in the adult study, and doses were administered between 4PM and 7 PM to accommodate school schedules in the adolescent study (compared to 8AM in the adult study). Fasting prior to dosing was not monitored in the adolescent study. The post-dose fast lasted for 3 hours in the adolescent study, instead of 4 hours in the adult study. The duration of blood sampling was the same in both studies and the same analytical laboratory and assay methods were used, but fewer blood samples were obtained (14 vs. 19). In terms of population differences across studies, the adolescents were lower in weight, but had a similar BMI. A higher proportion of participants in the adolescent study were African American (54% vs. 38%). There were no Latinas reported in the population of the adult study (compared to 18% in the adolescent study), and there were no White participants reported in the adolescent study (compared to 56% of the adult study).

The possible contributions of food intake (with altered bioavailability - given the cross study differences in controlled fasting), ethnicity/race, time of dose, and differences in SHBG levels to the observed differences in the PK data from these studies were evaluated by Dr. Kim through review of the published literature and analysis of the data from the two studies, but she found no clear explanation for the differences observed. Many of the questions raised have not been studied, including food-effects. Table 15 below is taken from Dr. Kim's review and summarizes her exploration of variability on the basis of race. The relative levels of C_{max} and AUC among races observed in the adult population studies is maintained within the adolescent study.

Table 15. Mean pharmacokinetic parameters of LNG following a single oral dose of 0.75 mg LNG tablet (arithmetic mean ±SD, range) Table taken from FDA Biopharmaceutics Review by Dr. Myong-Jin Kim, Ph.D.

	PK-001 (Adult females)			PK-002 (Adolescent females)				Adult females	Adult females	Adult females
								Landgren et al	He et al	Shi et al
	Plan B			Plan B				Gideon Richter	Postinor	Gideon Richter
Mean±SD (range)	Caucasian (U.S.) (n=9)	Black (U.S) (n=6)	Asian (U.S.) (n=1)	Black (U.S.) (n=12)	Multiracial (U.S.) (n=5)	Latina (U.S.) (n=4)	Asian (U.S.) (n=1)	Swedish (Sweden) (n=10)	Chinese (China) (n=10)	Chinese (China) (n=6)
C_{max} (ng/mL)	15.9±9.3 (6.7-39)	12.2±4.9 (7.4-20.5)	9.4	7.0±3.2 (3.8-12.9)	9.0±5.7 (4.1-16.8)	7.6±3.8 (4.1-12.9)	5.5	16nmol/L	11.2±3.4 (8.1-18.4)	8.6±2.0 (5.3-10.1)
T_{max} (hr)	1.8±0.9 (1-4)	1.4±0.4 (1-1.8)	1.3	1.4±0.3 (1-1.8)	1.9±1.2 (1-4)	1.6±0.5 (1-2)	1.3	2	1.9±0.6 (1-2.7)	3.3±1.0 (2-4)
$AUC_{0-\infty}$ (ng*hr/mL)	129±51 (81-219)	119.3±48 (65-176)	62.5	93.8±33.8 (60-184)	114.4±70 (44-224)	80.2±49.2 (47-151)	61.1	NR	124±42.8 (66.8-177)	116.2±41 (67-160)
Assay	GC/MS/MS							Radioimmunoassay		

NR: Not reported, 1 nmol/L ≈ 0.312 ng/mL

Landgren et al *1989 Contraception 39:275-89, He C* et al *1990 Contraception 41:557-67, Shi* et al *1988 Contraception 37:359-69*

5.2 Summary Conclusions – Pharmacokinetic Study

After discussion of the findings of the two sets of pharmacokinetic data submitted in this NDA, the review divisions concluded that these cross study comparisons were invalid, particularly in view of the significant differences in study design between the studies. The FDA did not request this study as there is no known physiological reason to expect age based differences in the pharmacokinetics of this hormonal drug within menstruating females. The dose and administration schedule of levonorgestrel for emergency contraception were not based on dose finding studies during clinical development. A lowest effective dose has not been established to allow comparisons of the C_{max} and AUC in this study to those associated with a lowest effective dose. The current approved dose of Plan B may far exceed the levels necessary to achieve efficacy.

To further address this PK/PD efficacy issue, DRUDP medical reviewer Dan Davis, M.D. contacted the principal investigator of a WHO study that evaluated levonorgestrel emergency contraception administered as a 1.5 mg single dose vs. the standard dose schedule of 0.75 mg x 2 doses at a 12 hour interval. This study entered 165 women under the age of 18. Dr. Helena von Hertzen[16] reported to Dr. Davis that there was only 1 pregnancy among the 165 participants <18 years old in the study. This pregnancy rate is lower than the 13 pregnancies that would have been anticipated without emergency contraception. When the two age groups on study were compared (combining the two treatment arms), the pregnancy rate in the group 18 years of age and older was 1.66% (43/2594), compared to the 0.61% observed in the younger age group. This argues that the levonorgestrel levels achieved in the younger age group were adequate to achieve product efficacy.

There is no evidence that levonorgestrel-only oral contraceptives, which contain a lower dose of levonorgestrel than Plan B, are less effective in adolescents. A prospective longitudinal study reported by Dinerman, et. al.[17] evaluated efficacy and other outcomes in adolescents who used levonorgestrel implants vs. oral contraceptives. Participants, who ranged in age from 12 to 18 years old, were followed 6 months. In that period there was a significantly lower pregnancy rate on the levonorgestrel arm –13 pregnancies on oral contraceptives vs. 1 on levonorgestrel implant, $p<0.01$. The single pregnancy in the 61 participants who were on the levonorgestrel arm was in a participant who had had her implant removed. This supports that levels achieved with levonorgestrel implants in adolescents are effective for preventing pregnancy. Brache, et. al. reported in a PK/PD study of Norplant levonorgestrel contraceptive implants that if inserted in the advanced follicular phase (days 8-13) ovulation was inhibited in 60% of users in the first cycle,

when peak plasma levels are only 3 nmol/l 24-72 hours after insertion[18]. Johansson et. al. in a discussion of the relative pharmacokinetics of levonorgestrel emergency contraception administered by 3 different schedules (both doses concomitantly vs.12 hour dose interval vs. 24 hours) reported that the C_{max} achieved after the 12 hour dose is further increased from 29 nmol/l after the first dose to 32.8 nmol/l after the second. By 48 hours the levonorgestrel levels are approximately 6 nmol/l. Serum levonorgestrel levels >1.3 nmol/l were present at 5 days post first dose, and levels of 0.6 nmol/l were observed at one week post dose[19].

6.0 Summary of Joint Session of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs

The Committees voted overwhelmingly in support of the switch of Plan B from prescription to non-prescription status. A summary of the vote tabulation associated with each question follows. Many of these questions and the associated discussion of individual committee members have been discussed in more detail in the relevant sections of this review.

Question #1: Does the Actual Use Study (AUS) demonstrate that consumers used the product as recommended in the proposed labeling?

Yes-27 No-1

Question #2. Are the AUS data generalizable to the overall population of potential non-Rx users of Plan B?

Yes-27 No-1

Question #3: Based on the AUS and literature review, is there evidence that non-Rx availability of Plan B leads to substitution of emergency contraception for the regular use of other methods of contraception?

Yes-0 No-28

Question #4: Do the data demonstrate that Plan B is safe for use in the non-prescription setting?

Yes-28 No-0

Question #5: Are the plans for introduction of Plan B into the non-Rx setting with respect to consumer access and safe use? If no, what other options would you recommend?

Yes-22 No-5 Abstain-1

Question #6: Do you recommend Plan B be switched from prescription to non-prescription status?

Yes-23 No-4 (one member left before the vote)

7.0 Summary Discussion of Adolescent OTC Access Issues

The members of the two advisory committees voted in overwhelming support of the OTC switch of Plan B. Subsequent to the advisory committee meeting the Divisions were informed by senior CDER management that the Commissioner had concerns about the adequacy of the data to support adolescent use in the OTC setting. CDER management suggested that the basis of concerns were beliefs that the number of adolescents in the actual use study was inadequate, that data were not convincing that adolescents could dose the product correctly, and that adolescents needed a learned intermediary involved in their access to emergency contraception.

7.1 Adequacy of Numbers of Adolescents Studied

The issues of adequacy of numbers of adolescent numbers and data to support that adolescents can dose correctly have been discussed earlier in sections of this review that summarized the actual use study and the studies that have addressed impact of access on behavior. The Divisions and Offices pointed out, in a meeting with the Commissioner on February 18, 2004, that the adolescent numbers in the actual use study referred to by Dr. W. David Hager, M.D. in his December 18, 2003 letter to the Commissioner, were those with the age break between 16 and 17. When the 17 year olds are added, the number of adolescents increased to 46, and the body of evidence available on this age group is tremendously augmented by the data available in behavioral studies cited in this NDA and the additional phone access study from North Carolina, DIAL EC. The following table, which was presented to the Commissioner, summarizes the large numbers of adolescents that make up the body of evidence from these studies.

Table 16. Studies Assessing Patient Behavior in Response to Facilitated Access to Plan B

Study	Age Range	Total N	Age		
			≤16 years	≤17 years	≥18 years
Actual Use	14-44	540	22	46	494
DIAL EC	8-51	7756	613	1225	6531
Gold	15-20	301	115	187	114
Raine*	15-24	2090	254	476	1614
Jackson	14-?	370	15	21	349
Belzer	14-20	160	NA	NA	NA
Total		11,217	1019	1955	9102
* 2004, unpublished study					

7.2 Issue of Correct Dosing in Adolescents

As discussed earlier in this review, accuracy of adolescent dosing within the actual use study was comparable to the older women within that study (see age group analysis of dosing in the Summary of Actual Use Study Review Findings). The behavior studies that collected dosing data also showed adolescent dosing was comparable to that of older participants (see M. Gold's study and B. Raymond's study summaries in Summary of Studies of Impact of Access to EC on Behavior). These data were also presented to the Commissioner in his meeting with the Divisions and Offices on February 18, 2004 .

7.3 Issue of Value of Learned Intermediary in Adolescent Access

7.3.1 Advisory Committee

With regard to the concern that access of adolescents to Plan B should be restricted to assure involvement of a learned intermediary/health care provider in adolescents' use of the product, the Advisory Committees made it clear in the December Joint Session that they could not justify such a restriction. There was a frank discussion by the advisory committee members at the meeting regarding age restriction, and the majority of members indicated that they did not believe age restriction was justified. One member who voted against the switch, Dr. Joseph Stanford, M.D. said he would have voted in the affirmative to Question #5, a question aimed at adequacy of the sponsor's proposed distribution plan (see Questions above), if labeling on mechanism of action and efficacy were adequate. He expressed no concerns about age. During the meeting, in preparation for voting on Question #5, after a public discussion with Dr. Kweder about mechanisms for age restriction that might be available to the FDA and how these mechanisms might differ from the behind the counter pharmacy mechanism in Canada, the Chairman invited

the members to comment in conjunction with their votes "about how you feel about the age for sale, whether it's an option..."

The following summarizes those statements made by members who voiced concerns about adolescent access:

Dr. Hager commented "I don't think that the actual use study gives us adequate information for that younger adolescent population and for me, that is enough of a concern .....if it is going to be generalizably available to a nine year old regardless, a ten year old regardless of, you know; there's no restriction."

Dr. Crockett indicated she did not support OTC availability for women of any age.

Dr. Cantilena voted "no", and did not say that he would favor approval with age restriction. He did say "...we have extremely little information on the adolescents, ...and a study could be done to assess their behaviors and the information that these individuals will need to use the product correctly."

The following are those members who specifically stated that they did <u>not</u> support restrictions:

Dr. Johnson, "I'm not an OB-GYN, but I can't imagine that I would prefer a 10 or 11 year old to be pregnant over some hypothetical risk that there might b e with a 10 or 11 year old taking this product. So I guess I would feel pretty strongly about not having any age restrictions."

Dr. Patten, "And I would concur that there should be no age restrictions."

Dr. Guidice, "I actually vote not to specify an age restriction."

Dr. Tinetti: "I vote to not have any age restriction."

Dr. Hewitt gave the following comments against age restriction, "...and I see no reason that medically a young, adolescent woman would not use Plan B safely.....and they need access to emergency contraception...I think it's very important that they do not have to ask a pharmacist to open up a cabinet or to hand them physically the emergency contraception. I think it's important that it's out in the open; it's easy for them to identify....So I like the idea of a pharmacist being available, but I don't want that to be a burden or an obstacle for them obtaining emergency contraception"

Dr. Greene, "...when adolescent women agree to proof of age to a pharmacist before they have intercourse, then that would be the time that they should prove their age before obtaining the product."

Dr. Clapp, "...if you are a sexually active 10 year old or 11 year old, it's certainly a bad situation, and I've had patients who are 10 and 11 and pregnant, and I think their families and they would have far preferred this option than pregnancy, and it would have been safer. We know that the morbidity and mortality associated with teen pregnancies is quite high. So there's no question that this is a safer option than the alternative, and that's a term pregnancy. As a physician, I don't ....think that I should act as the gate keeper or barrier to women, teenagers or whatever age accessing medical care for themselves, and this is a circumstance that I think that we need to

promote independence of the women and even teenagers accessing something that can prevent or make a determination of their future that they want to determine."

Dr. Snodgrass, "I think it's crucial for reasons that have already been stated that this not be behind the counter, but needs to be on the shelf or true OTC."

Dr. Lewis, "I'd like to see plans to enhance access and understandability of the product...for adolescents...."

Dr. Wood, "I...would advocate strongly against introducing subtle barriers to access, such as raising flags about age and raising issues about behind the counter use."

Dr. Emerson, "I also would be very strongly against the idea that there would be any behind the counter or things. I think that it being readily available on the shelf is very important."

Dr. Berenson, " I think it is very important that the method if placed over the counter is its accessible to all women at risk of unintended pregnancy. Any placement of the drug behind the counter....is just creating barriers to its use, ultimately its just going to result in unintended pregnancies....the adolescent female is very embarrassed about her sexuality....it would even be helpful if we could make sure that – this is being said facetiously – that there is a woman at the checkout counter....

7.3.2 Context of Benefit of Access to Emergency Contraception in Adolescent Population

The benefit of non-prescription access to emergency contraception is the improved efficacy that comes with improved timeliness of product administration. The sooner the product is taken after unprotected intercourse, the more effective it is. This product is effective if taken within 72 hours after unprotected intercourse. Women who use this product avoid an unplanned pregnancy and avoid a decision regarding abortion. A proposal to restrict access of adolescents to the product is a proposal to obstruct access of a subgroup of females to a product with a clear benefit. A paper summarizing the findings of surveys distributed in pharmacies participating in the Washington State pharmacy access program found that of the responders (about half of the surveys actually distributed), 22 % of adolescents reported that if they did not have access to emergency contraception from a pharmacist that they would wait to see if they got pregnant and another 20% said they didn't know what they would do.[20] The latter situation lends itself to time lost and diminished efficacy while seeking access. About a third of adolescent responders stated that the reason they went to the pharmacy to obtain emergency contraception was that it was the only place they knew to get the product. The review that follows will summarize adolescents' need for access to the benefit of emergency contraception and improved access. It is particularly important in this population that that benefit be maximized, i.e. that the product be accessible as soon as possible after unprotected intercourse to assure maximum efficacy.

In a 2001 CDC Youth Risk Behavior survey of high school students, 1/3 of 9th graders indicated that they were sexually active. The number of students that report they are sexually active progressively increases over the high school years, until 12th grade, when nearly 2/3 report they are sexually active. Four percent of high school females report they initiated sexual intercourse before they were 13 years old, and this proportion increased if subpopulations were examined, e.g. 8% of black female students reported initiating sexual activity before age 13. Only a third of adolescent females report that they use a contraceptive method at the time of their first sexual intercourse. [21] Half of the high school females who said they were sexually active in the Youth Risk Survey reported condom use and 21% reported oral contraceptive use[22]. White students

were more likely to report use of oral contraceptives than either black or Hispanic students (23% vs. 10% and 8%).

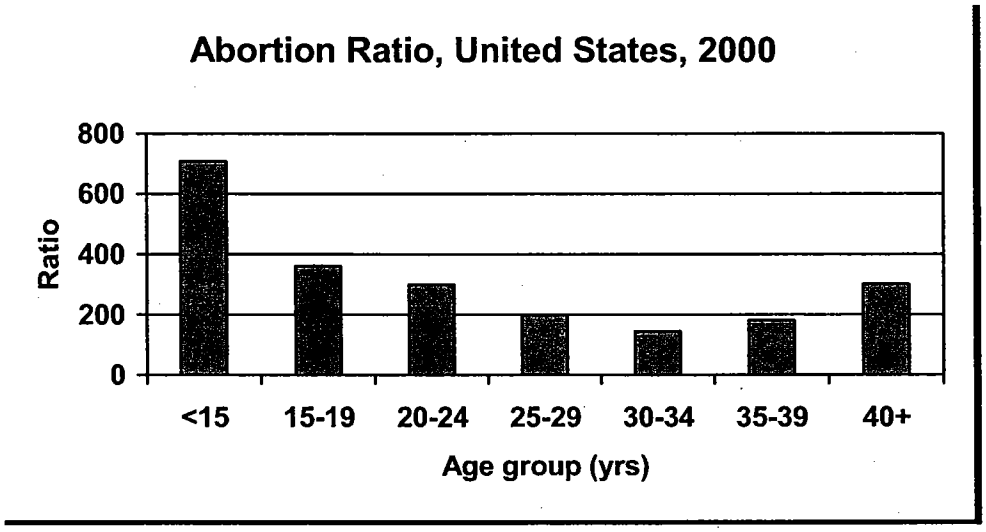
Studies of contraceptive patterns in adolescents have documented that adolescents are inconsistent users of oral contraceptives. One study reported that the continuity rate on an oral contraceptive in adolescents was as low as 13% at 1 year and fell to 2% at 2 years[23]. Although other studies have reported higher rates of continuity of oral contraceptives, the rates in these studies are still quite low. Dinerman, et. al. reported that only 50% of adolescents in a study that enrolled 12-18 year olds continued use of an oral contraceptive at 6 months[24]. Half of those that discontinued oral contraceptives stated that they stopped them because they forgot to take them. Only 22% of the participants who started oral contraceptives reported at 6 months that they continued taking them and took them daily. Another study reported by Woods, et. al. found 59% of participants still taking the prescribed oral contraceptive at 3 months, and this fell further to 29% at 12 months.[25] The older participants in this study more likely to be compliant at 12 months. (The mean age in this study was 17.2 +/- 2.1 years.) The study enrolled from two sites, a suburban adolescent private practice and a hospital-based city clinic. The city clinic site was found on logistic regression analyses to be the strongest predictor of noncompliance both at 3 months and 12 months, and all pregnancies identified on study were among non-compliant city clinic participants.

The time between initiating sexual activity and seeking health care services for contraception in adolescent females has been reported to be one year, with about half of teen pregnancies occurring in the first 6 months after first sexual intercourse.[26] There are 94 pregnancies/1000 females aged 15-19 in the United States.[27] The adolescent maternal mortality rate is reportedly twice that of adult pregnant women. [28] Pregnancies in the teen years are complicated by a higher risk of pre-term birth, higher risk of low birth weight babies and higher risk of small for gestational age babies. A Swedish paper reported that the risk of very early preterm birth in 13-15 year olds was nearly 5 times that of women aged 20-24.[29] A U.S. study of a white population of married teens in Utah, with age appropriate educational level and adequate prenatal care, found that there was a statistically significant higher risk of preterm birth (less than 37 weeks gestation; RR=1.9), low birth weight (<2500g, RR=1.7) and small for gestational age babies (below the 10th percentile, RR = 1.3).[30] A study summarizing the Parkland Hospital experience reported that preterm birth, defined as delivery of an infant weighing ≤1500 gm (very low birth weight) significantly increased, nearly doubling, in the middle school age. Significantly increased special care nursery admissions were associated with these mothers.[31]

Akinbami, et. al. reported that they evaluated the risk of preterm birth in teenage multiparas, given that adolescents are at high risk for repeat pregnancies, rates that range 17-25% in the first 12 months after the previous pregnancy.[32] They defined moderate preterm as 33-36 weeks gestational age and very preterm as less than 33 weeks gestational age in their study of data from the 1990-1996 US Natality Files. They found that, compared to 25 year old multiparas of the same race, 13-14 year old white multiparas had a higher risk of both moderate and very preterm births (OR =3.2 and OR = 9.0) as did white 15-17 year old multiparas (OR=2.2 and OR=3.8). Hispanic 13-14 year old multiparas had an OR of 2.4 for moderate preterm birth and 5.5 for very preterm birth, while 15-17 year olds' ORs were 2.3 and 2.7, respectively. Black 13 and 14 year old multiparas ORs were 2.4 for moderate preterm birth and 3.34 for very preterm birth, while the 15-17 year old ORs were 1.8 and 1.8, respectively, compared to 25 year old black multiparas.

Adolescents, particularly young adolescents, are more likely to choose termination of an unplanned pregnancy. The ratio of abortion to live births is highest in adolescents younger than 15 years of age (700 abortions/1000 live births) as summarized in the graph below[33].

Graph 1. Abortion Ratio as a Function of Age. (Abortion Ratio is the number of abortions per 1000 live births).



Clearly adolescents are at significant risk for unintended pregnancies, those pregnancies are at greater risk of complications of preterm birth, and a much higher proportion of adolescents choose to terminate these pregnancies with abortion. CDER upper management asked for evidence that availability of improved access to emergency contraception would have an impact on abortion. This was explored by the Divisions by examining the abortion statistics of countries where the product is available through full OTC access, Sweden and Norway. Plan B received full OTC approval in Sweden in 2001, and teenage abortions were reduced by approximately five per cent in the first 6 months of 2003, the first drop in a dramatic climb in abortions in this age group that had started in the 1990's.[34] Plan B was approved OTC in Norway in the second half of 2000. In 2002, the abortion ratios reported for the 15-19 year old age group in Norway had dropped to 16.9/1000 from 20.1/1000 live births in 2000. This was reported to be the lowest teen abortion rate registered since the law of self-determination for women was implemented in Norway in 1979.[35]

A similar approach to evaluating the impact of improved access to emergency contraception on abortion rates in the United States can be taken by examining abortion and teen birth rate trends in States with pharmacy access programs. The oldest such program is Washington State's, initiated in 1997. Adolescent pregnancy and abortion rates there have fallen consistently since 1997, and the number of abortions per 1000 live births in women of all age groups has decreased from 346 in 1997 to 322 in 2002.[36] [37] These data are summarized in Table 17 below.

Table 17. Teenage Pregnancy Rates by Age in Washington State (per 1,000 women) Between 1997 - 2002

	Age 15-19		Age 15-17		Age 18-19	
Year	Pregnancy Rate	Abortion Rate	Pregnancy Rate	Abortion Rate	Pregnancy Rate	Abortion Rate
1997	74.5	29.6	45.7	20.2	122	45
1998	71.2	26.9	42.6	18.4	116.8	40.4
1999	66.5	25.5	38.0	16.1	109.6	39.6
2000	64.3	25.0	36.3	15.7	107.0	39.0
2001	59.6	23.8	32.9	15.1	100.3	37.1
2002	55.9	22.7	30.9	14.0	93.8	35.8

The following table of data obtained from the CDC shows that the absolute number of legal abortions decreased for adolescents in Washington State from 1997-2000 (last year data available from the CDC)[38].

Table 18. Number of Legal Abortions in Washington State by Year and Age Group

	Age				
Year	<15 y/o	15 y/o	16 y/o	17 y/o	≤19 y/o
1997	191	385	789	1195	5728
1998	137	350	689	1129	5312
1999	143	328	659	1016	5369
2000	122	303	658	979	5231

7.3.3 Context of Risk - Issues in Adolescent Population

What does a health care provider bring to the table to justify restricting product access to adolescents in light of the benefit that is just as relevant to this population as it is to older females? Improved accuracy of dosing has not been established and as discussed in the Safety Overview section of this review, no safety issues associated with taking this product support the need for involvement of a health care provider. This leaves public health concerns that are based on presumptions about the impact of the product on sexual behaviors and sexual health. The Divisions and Offices believe that these concerns have been adequately addressed based on their review of the clinical trials summarized in this review, however, the concerns expressed to the Commissioner by Dr. W. David Hager, M.D. and some members of Congress will be further examined here.

7.3.3.1 STI Screening

Dr. Hager expressed concerns in his December letter to the Commissioner about the missed opportunity to screen for STIs if women, particularly adolescents, no longer have to see a health care provider to obtain emergency contraception. He cited the CDC recommendation to screen sexually active adolescents for STIs and said, "One of the major reasons why they have seen us for such screening has been contraception. Now, these young people will have no incentive for annual screening." His statement, "no incentive for annual screening," implies that access to emergency contraception will lead adolescents to give up contraception (the behavior studies in this review argue that this is not the case). His comment also indicates his concern that the 'opportunity' to capture young women for screening at the appointment for emergency contraception will be lost. The Washington State pharmacy access study report indicates this approach to ensuring access to adolescents for STI screening can result in a significant proportion of teens who need emergency contraception waiting to see if they are pregnant before seeking medical attention. This public health approach will result in screening that will be done either at the time of pregnancy diagnosis, or in preparation for an abortion. Furthermore, as stated earlier

in this review, it has been reported that adolescents wait an average of 1 year after onset of intercourse to seek medical consultation on contraception. The half of teens that reportedly become pregnant in the first six months after initiating intercourse can be screened for STI when they present to the clinic pregnant, but the remaining teens will have an additional 6 months that they are at risk for pregnancy before they present for contraception consultation and the opportunity for STI screening.

The chlamydia infection rates in the 15-19 year old age group (2619/100,000), a subgroup targeted for restricted access to emergency contraception to ensure they are screened for STIs, is the same as that for the 20-24 year old age group (2570/100,000)[39]. Gonorrhea rates are also similar between these two age groupings. of 676/100,000 for 15-19 y/o compared to 650/100,000 for 20-24 y/o and 251/100,000 for 25-29 y/o.[40] Restricting access to assure STI screening could be used to justify extending the age restriction to 24 years of age and under. Agreement to use of restrictions to ensure screening entails agreement with the validity of the risk/benefit analysis of the following public health policy: increasing young women's chances of presenting to a clinic pregnant is worthwhile if that will ensure that sexually active women are captured for STI screening .

A Congressional letter and the December letter from Dr. Hager to the Commissioner state that England, where pharmacy access has been approved since 2001, has experienced an increase in sexually transmitted infections. The most recent data on Great Britain's STI rates found by this reviewer were in a joint publication of the Public Health Laboratory Service (England, Wales and Northern Ireland)O, DHSS&PS (Northern Ireland),and the Scottish ISD(D)5 Collaborative Group (ISD, SCIEH &MSSVD) called Sexually Transmitted Infections in the UK: New episodes seen at Genitourinary Medicine Clinics, 1995-2000. During that period, when there was an increase in consultations at the GU clinics, a period that actually predates approval of pharmacy access in Great Britain, emergency contraception was available on the National Health Service, through contact with a learned intermediary. The authors of the PHLS report stated that there were a number of underlying reasons for the increases they observed over that period. These included "increased transmission, improved acceptability of GUM clinic services, greater public and professional awareness of certain STIs, and developments in diagnostic test sensitivity." Dr. Hager did not provide his references supporting his concern. The references cited in the Congressional letter were journalist reports in the London Daily Mail.

The impact of improved access to emergency contraception through pharmacy access programs in the U.S. on sexual behaviors that result in STIs can be explored by examining the trends in STIs in Washington State, where a pharmacy access program has been approved since 1997. In 2002, the last year data is available, Washington State ranked 40th (ranked 39th in 1996) in gonorrhea rates (49.6/100,000 compared to a national average of 125/100,000)[41] and 35th (ranked 31st in 1996) in chlamydia rates (253.4/100,000 compared to the national average of 296.5/100,000).[42] Washington's chlamydia rates approximated the national averages in 1994, but fell below the national average in subsequent years. They track with, but are below the national average. In the city of Seattle, where pharmacy access would be expected to be greatest, rates are comparable to the State rate.

7.3.3.2 Sexual Health and Contraception Education in Adolescents

The loss of the opportunity for healthcare provider intervention in sexual health behaviors and contraceptive education in adolescents who have OTC access to Plan B has also been raised as a significant concern that supports age restriction. Dr. Hager points to the published paper on the Washington State pharmacists' experience with adolescent use of emergency contraception[43] in his letter to the Commissioner, "we find that 81% of those subjects were felt to need medical

follow-up. We are not told how many of them obtained medical follow-up" to support concerns about loss of the healthcare provider in the process. The same study was referenced earlier in this review, citing its findings that a large proportion of adolescents in the study reported that they either would have waited to see if they were pregnant or would not have known what to do if they had not had pharmacy access to emergency contraception. It was a survey study in which, not only did not all recipients of the questionnaire return it (one source of bias), but pharmacists did not distribute the questionnaire to all the women eligible for participation (another, and different, type of bias). Of 838 EC prescriptions dispensed, pharmacists distributed less than 630 surveys. The specific study findings that Dr. Hager has drawn to the Commissioner's attention will be discussed further here.

Only one of the actual questionnaire questions was provided in the study's publication. We are not told the specific question wording of those that "were designed to ascertain whether adolescents would benefit from additional medical evaluation, and if so, whether they were at risk for not receiving this additional medical care". It appears, however, that this assessment was made in part on the basis of whether adolescents reported that they were not using birth control (30% of responders) or that they were "not happy with" their current method of birth control (31% of responders). The specific meaning of the latter is unclear, from a medical need standpoint, without seeing the question asked. Twenty percent "in need of a new birth control method" indicated they had no intention of seeing a doctor in the coming month, while 6% said they had no source of medical care. This latter group would arguably not be helped by having to seek EC from a health care provider, and would presumably experience a substantial delay in finding a source of either EC or prenatal care. Another criterion for designating an adolescent as having "additional medical needs" was if they reported they had a new sexual partner or if their partner was "possibly" not monogamous. Forty percent met this criterion and 40% of those said they would not see a doctor in the coming month, while 4% said they had no health care provider.

Taken together ("need birth control or STD evaluation"), 81% of the adolescents who were selected by the pharmacist to fill out a questionnaire and who, in turn, filled it out and returned it, met the criteria for being designated to have "additional medical needs". Of those "over 1/3 of them were at high risk for not receiving follow-up medical care". The latter group was made up of the 31% who said that they "had no intention of seeing a doctor in the next month", the 3% who had "no source for medical care" and the 2% who answered that both applied to them. The authors concluded that if pharmacy access were not available to these young women, many would have not received medical intervention to prevent an unplanned pregnancy. They did not conclude that these adolescents should be denied timely access to emergency contraception. Actions were taken to provide medical referral lists to help adolescents link with reproductive health care services.

Although participants were asked whether they had a "regular doctor or other source for routine medical care," this publication didn't report how many responders indicated that they did. The proportion for those participants whose answers were interpreted that they needed contraceptive or STI evaluation, who also said that they did not have a regular source of care was reported, and it was relatively low – 3%. Do we need to assure that adolescents have healthcare provider appointments specifically made for contraception, as referred to by Dr. Hager in his letter, in order to ensure health care provider intervention (including screening) and education in adolescent sexual health? The American Academy of Pediatrics, in their updated policy statement on contraception and adolescents from 1999, stated that the role of pediatricians should include "family planning services for the sexually active patient". In their statement on adolescent pregnancy, they state that pediatricians should "be prepared to take a developmentally appropriate sexual history on all adolescent patients". (Emphasis added.) They provide

recommendations for frequent follow-up to optimize compliance with contraception (quarterly appointments) and to screen for risk-taking behaviors and STIs (STI screen every 6 months).[44] A 2003 report published by the CDC in the journal Pediatrics cites the AMA Guidelines for Adolescent Preventive Services, the US Preventive Services Task Force Guide to Clinical Preventive Service, the National Center for Education in Maternal and Child Health Guidelines for Health Supervision of Infants, Children and Adolescents and the American Academy of Pediatrics Committee on Practice and Ambulatory Medicine Recommendations for Preventive Pediatric Health Care to support a statement that in their primary care visits, adolescents should be screened for sexual activity. (Emphasis added.) They recommend that sexually active patients should in turn be offered contraception and STI screening[45].

The latter study's authors evaluated the data from the 1999 Youth Risk Behavior Surveillance survey to determine the proportion of high school aged adolescents who actually have an annual health care visit. They then assessed whether those visits were utilized to provide the counseling and screening recommended by the various professional groups. The survey questions used to explore these issues were 1) "When was the last time you saw a doctor or nurse for a check-up or physical examination when you were not sick or injured?" and 2) "During your last check-up, did your doctor or nurse discuss ways to prevent pregnancy, acquired immune deficiency syndrome (AIDS), or other STDs?" Sixty percent of females indicated that they had had a "preventative" health care visit in the prior 12 months. Sexual experience was positively associated with having had such a visit (OR=1.3). Sixty-four percent of sexually experienced females had had a preventive health visit in the past 12 months. Forty-three percent of all female students who had had a preventive health visit reported that they had discussed STIs or pregnancy prevention in those visits. Sixty-one percent of the sexually experienced females who reported having had a preventive health care visit in the past 12 months reported that they had discussed STIs or pregnancy prevention during the visit.

Another study by Newacheck, et. al.[46] examined data from the 1995 National Health Interview Survey supplemental questionnaires on access to health care to determine whether adolescents had access to and were receiving primary healthcare. They reported that 92% of adolescents had a usual source or site of health care, and among those adolescents, 86% identified a regular physician. Most (77%) were seen in physician's offices or HMOs. Sixteen percent went to community health centers for their care. Urgent care centers or ERs were identified as the primary source of health care by only 2%. Fourteen percent of adolescent females had no health insurance or other public coverage of health care costs. Uninsured adolescents in the survey were more likely to get their care in community health centers (26%) or urgent care centers (6%). Nearly ¾ of adolescents had had at least one physician contact in the year prior to the survey. The average number of contacts reported was 2.5/year. The average number of physician contacts per year for the uninsured adolescents was 1.5/year. Seventy five percent of uninsured adolescents had at least one physician contact in the prior year. The authors of the 2003 CDC report in Pediatrics cited Newacheck's study and concluded that since the vast majority of adolescents in the U.S. have a source of primary health care, these primary care providers have the opportunity to provide STI prevention counseling and screening, as well as pregnancy prevention counseling and contraception services.

7.3.4 Summary of Senior Management Recommendation to Address Adolescent Issues

The data and literature review discussed in this review were presented by the Divisions and Offices to CDER Senior management and Commissioner McClellan on February 18, 2004 to address the adolescent concerns that had been conveyed to us. The Divisions and Offices in that meeting shared their conclusions that the non-prescription switch of Plan B should be approved without age restriction because the benefit of this product outweighs risk in all age groups. We

were informed that Commissioner McClellan and CDER Senior management do not concur with this risk benefit assessment and cannot support the non-prescription switch of Plan B. They have asked the sponsor to provide a restricted distribution plan that will exclude access of adolescents to the product without a prescription. FDA legal counsel was asked to assess whether the restrictions outlined are feasible within the current regulatory framework prior to taking the non-approval action on this NDA so that this distribution plan can be requested by the FDA within the non-approval letter for future consideration in a re-submission of the NDA. Dr. McClellan indicated on February 18th that any restricted distribution program would need to be reviewed in an open public hearing. In response to Division and Office review staff concerns that the Advisory Committees had already clearly stated that the Committees did not support restricted distribution, including on the basis of age, Senior CDER management indicated that the committee assembled to discuss distribution restrictions would not have to consist of the same members as those who considered this NDA at the December meeting. Barr Pharmaceuticals has responded to the age restricted distribution plan request and has submitted that plan for review, presumably with the belief that this would be incorporated into a first cycle approval of this NDA.

9.0 Deputy Director's Recommended Regulatory Action

After thorough review of the label comprehension and actual use study data submitted in this NDA, the data from the large randomized controlled trials on advance provision of emergency contraception, the large single arm telephone access study from North Carolina (DIAL EC), the levonorgestrel safety database, the vote and the minutes of the December Joint Session of the Nonprescription, and the literature addressing the public health issues surrounding the impact of improved access on sexual health and behaviors, I conclude that the risk benefit ratio of the non-prescription access to Plan B supports its approval for switch to non-prescription status. I have also concluded that it is unjustified to restrict access to the benefit of this product on the basis of age.

Donna J. Griebel, M.D.
Deputy Division Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III

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/s/

Donna Griebel
4/1/04 05:18:40 PM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Safety Review of Supplemental NDA

NDA	sNDA 21-045 / 011 (SE6)
Type of Application	Prescription to OTC Switch
Applicant	Woman's Capital Corporation 1990 M Street, Suite 250 Washington, DC 20036
Drug Name	
Trade name	Plan B®
Established name	Levonorgestrel
Indication	Emergency contraception
Route of Administration	Oral
Dosage Form	0.75 mg tablet
Dosing Regimen	One tablet within 72 hours after intercourse followed by a second tablet 12 hours later
Related Submission	NDA 21-045 (original submission)
Submission Date	April 16, 2003
Stamp Date	April 22, 2003
PDUFA Date	February 22, 2004 (original) May 22, 2004 (3-month extension)
Review Completed	March 17, 2004
Safety Reviewer	Daniel Davis, MD, MPH Medical Officer

FINAL

March 25, 2004

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EXECUTIVE SUMMARY OF THE CLINICAL REVIEW

CLINICAL REVIEW

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Executive Summary of the Clinical Safety Review

1. RECOMMENDATIONS

1.1 Recommendation on Approvability

This reviewer recommends approval of the supplemental NDA, sNDA 21-045/011 (Plan B), for the change from prescription status to over-the-counter (OTC) status for emergency contraception (EC) without any age or distribution restrictions. This recommendation is based on this reviewer's determination that the Applicant has provided sufficient information regarding the safe and proper use of Plan B, as required under 21 CFR 310.200, to exempt Plan B from prescription-dispensing requirements. This reviewer's recommendation is further supported by the findings of the joint Advisory Committee Meeting of December 16, 2003 (Reproductive Health Drugs Advisory Committee and Over-the-Counter Advisory Committee) that recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over-the-counter without any age or distribution restrictions and without any further studies before approval.

1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps

This reviewer has no specific recommendations for postmarketing studies or risk management steps. The Applicant's marketing plan and postmarketing CARE^{SM} (Convenient Access, Responsible Education) Program are designed to limit the availability of Plan B to pharmacies and clinics, and to educate health-care providers and consumers regarding the responsible use of emergency contraception, methods of routine contraception, and prevention of sexually transmitted infections (STIs).

Three members of the joint Advisory Committee did suggest the need for an age restriction and/or risk management steps to evaluate the impact of OTC availability of emergency contraceptive pills (ECPs) on sexual behavior, especially in the adolescent group (under age 18). Of concern was a potential increase in "risky" behavior such as decreased use of condoms, an increase in STIs, and a change to less reliable methods of contraception. This reviewer (DD) did an extensive review of the medical literature and unpublished primary data on adolescent behavior associated with increased availability of emergency contraception. The weight of the evidence does not support the concern that adolescents will engage in riskier behavior if emergency contraception is readily available OTC. The proposed label for the OTC product clearly states that Plan B is not for routine contraception and that it does not protect against STIs. The sponsor's proposed postmarketing CARE program is aimed at health-care provider and consumer education, especially in the areas of responsible behavior, reliable methods of regular contraception, and prevention of STIs. It is this reviewer's opinion that several investigator-initiated on-going EC studies will provide additional information about both potential public health risks and benefits for women of all ages associated with wider availability of emergency contraception.

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

Plan B® (levonorgestrel 0.75 mg tablets) was approved for prescription use in July 1999. It is marketed for a single use with two 0.75-mg tablets packaged together. The dosing regimen is to take the first tablet as soon as possible, but no later than 72 hours, after unprotected intercourse (e.g., sexual assault, no contraception) or a "contraception accident" (e.g., condom breakage, missed OC pills) and the second tablet 12 hours later. Based on the data submitted in the original NDA, Plan B was determined to be safe and effective for emergency contraception. The currently listed contraindications in the prescription label are pregnancy, unexplained vaginal bleeding, and allergy to any of the ingredients in the tablet.

2.1.1 Original NDA Safety Data

The Applicant in the original Plan B NDA presented clinical trial safety results from four general trial categories. These provided a large database of clinical information in over 15,000 women and included the following:

1. Single dose and multiple dose clinical pharmacology studies
2. Two World Health Organization (WHO/HRP) sponsored comparative trials that were the main studies supporting efficacy and safety. The trials compared levonorgestrel (0.75 mg) to the Yuzpe regimen [levonorgestrel + ethinyl estradiol] for emergency contraception.
   - WHO/HRP Study 92908 (1998) – the pivotal study for the NDA, N = 1,955
   - WHO/HRP Study 81107 (Ho and Kwan, 1993) – supportive study for the NDA, N = 834
3. Three WHO/HRP-sponsored trials of routine postcoital contraception with the levonorgestrel 0.75 mg formulation manufactured by Gedeon Richter (the manufacturer of Plan B drug product)
   - WHO/HRP Study 82906 (1987)
   - WHO/HRP Study 87908 (1993)
   - WHO/HRP Study 84902 (He, 1991)
4. Fifteen small studies of oral levonorgestrel for routine or occasional postcoital contraceptive use, using a variety of regimens, doses, and formulations

2.1.2 New Clinical Data Reviewed for the Present Supplemental NDA

Clinical data that were the focus in this safety review were provided by the Applicant or were obtained from other sources and included the following: (1) postmarketing safety data for Plan B provided by the Applicant; (2) data provided by the Applicant from published studies in which levonorgestrel was used for emergency contraception or postcoital contraception; (3) Periodic Safety Reports and MedWatch reports for Plan B previously sent to the FDA; (4) other published and unpublished studies by individual investigators not provided by the Applicant; and (5) an open-label safety-only study in 60 adolescent girls aged 13-16 who took two 0.75 mg levonorgestrel tablets. Data from 3 previously unreported clinical trials sponsored by the Applicant also were provided in the present submission and are reviewed primarily by other reviewers. These studies were: (1) Study 9728 – a label comprehension study that enrolled 656 women; (2) Study 9727 – an Actual Use Study in which 540 subjects, 14-44 yr. of age, received Plan B; and (3) Study PK-002 – a single-period pharmacokinetic study to determine the pharmacokinetics of oral levonorgestrel in healthy adolescent females, 13-16 yr. of age.

2.2 Efficacy Findings

The primary objective of the review by this Medical Officer was to review the overall safety data for Plan B and identical levonorgestrel products used for emergency contraception.

2.3 Safety Findings

2.3.1 Postmarketing (PM) Safety Data

Patient use data (Applicant's estimates). Since the approval of Plan B for prescription use, there has been extensive use of levonorgestrel for emergency contraception in the U.S. and abroad. The Applicant estimates that 2.4 million women in the United States have used Plan B since its launch in August 1999, and that in Canada 72,000 women used Plan B® in the year from July 2002 to July 2003. In the U.K., the Applicant estimates that 2.1 million women have taken Levonelle (identical to Plan B) since February 2000, while exposure in France is estimated to be 1.8 million

uses. Levonorgestrel for emergency contraception is available in 101 countries and is available without a prescription at the pharmacy in 33 of these 101 countries [data from the International Consortium for Emergency Contraception].

Postmarketing safety data (provided by Applicant). The Applicant compiled safety data up to January 2003 from a number of USA and global sources, including key European countries, Canada, and the WHO Drug Monitoring Program, to provide an assessment of the postmarketing safety profile of levonorgestrel 0.75 mg tablets. Based on information provided by the Applicant, there have been no reported deaths; most of the adverse events (AEs) attributed to the drug were mild and of short-duration. The most commonly reported AEs were nausea, abdominal pain, fatigue, headache, changes in menstrual bleeding, and metrorrhagia (heavy bleeding). Pregnancy was also a commonly reported AE, but it is not an adverse event. All of these events are consistent with both the presently approved Plan B label for prescription use and the proposed Plan B OTC label.

Postmarketing safety data (FDA findings). The FDA's Office of Drug Safety (ODS) was consulted. Their review focused on adverse events reported to the FDA Adverse Event Reporting System (AERS) and United Kingdom (U.K.) databases through October 9, 2003. There were no reports of death in women using postcoital levonorgestrel in either the AERS or the U.K. database. The AERS database search identified 116 unduplicated cases; most of the reports involved non-serious expected (labeled) events. The most common non-serious events (and number of reports for each) were the following: vaginal bleeding (26), unintended pregnancy (21), cramps/pain (11), and nausea/vomiting (11). There were 28 cases of unduplicated ectopic pregnancies (none occurred in the USA) that are discussed in Section 2.3.2. There were 3 cases of convulsion, 10 cases of hypersensitivity, and 8 cases of possible pregnancy/fetal effects. All these events are discussed in the ODS safety review (Attachment C) and are not considered to be a significant safety concern.

Postmarketing data and surveillance since July 1999 shows extensive exposure to levonorgestrel used for emergency contraception with over 6 million estimated uses. There have been **no** deaths, heart attacks, no strokes or thromboembolic events reported with levonorgestrel emergency contraception in the medical literature or postmarketing surveillance (NDA Volume 9, pg. 110-15). There has been only one reported case of phlebitis (NDA Volume 9, pg. 115); this was in a 22-year old woman in France (further details are not available).

2.3.2 Ectopic Pregnancy

Ectopic pregnancy is a potential concern with the use of progestin-only pills (POPs) taken continuously, once a day, for routine contraception. Three different sources were used to evaluate the risk of an ectopic pregnancy associated with the use of Plan B (a progestin-only product):

1. FDA Office of Drug Safety (ODS) consultation
2. Applicant's reported postmarketing safety based on data from the U.K. Medicines Control Agency, the French Health Authority, and U.S. reports sent to the Applicant
3. Randomized clinical trials (RCTs) found in the medical literature

The FDA ODS analysis found 28 unduplicated reports of ectopic pregnancy in users of levonorgestrel 0.75 mg for emergency contraception. None of the reports occurred in the U.S. despite the Applicant's estimate of over 2 million uses of Plan B in the U.S. In the Applicant's postmarketing safety data, which was based on the use of levonorgestrel 0.75 mg for emergency contraception, there were 340 pregnancies and 21 ectopic pregnancies reported up to February 2003. Data were provided from six large randomized clinical trials reported in the medical literature with 7,889 evaluable subjects reporting 133 pregnancies and 2 ectopic pregnancies, for an incidence of 1.5% ectopic pregnancies among total pregnancies. The 1.5% incidence is consistent with the reported national rates of 1.24 and 1.97 per 100 pregnancies [range 1.2% to 2.0%] in the U.K. and in the U.S., respectively. These

6 randomized clinical trials provide the best clinical estimates for the incidence of ectopic pregnancy in users of levonorgestrel emergency contraception since they provide an accurate assessment of the number of ectopic pregnancies as well as the number of total pregnancies. Based on the data from these randomized clinical trials, levonorgestrel-only emergency contraception does not increase the chance that a pregnancy will be ectopic.

The prescription label for Plan B does have a subsection titled **Ectopic Pregnancy** in the WARNINGS Section which states that health-care providers should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B. The label for prescription Plan B also states that "history of a (previous) ectopic pregnancy need not be considered a contraindication to the use of Plan B." The proposed OTC label for Plan B cautions women to be alert for symptoms that could be indicative of an ectopic pregnancy.

2.3.3 Misuse and Abuse

For a prescription product to switch to OTC status, the product must be shown to have an acceptably low potential for misuse and abuse. This reviewer has concluded that Plan B meets these criteria based on the following findings:

1. Overdose. There are no reported cases associated with levonorgestrel ECPs; if a large dose of levonorgestrel were ingested, the margin of safety appears to be high based on several large studies using levonorgestrel for routine postcoital contraception in the 1970's.
2. Addiction potential. There are no reported cases of addiction to levonorgestrel since the 1969 approval of the first of many levonorgestrel-containing products.
3. Safety of higher doses of levonorgestrel and/or repeated use of levonorgestrel emergency contraception.

   –In clinical trials of levonorgestrel for regular postcoital contraception, average monthly doses of 3.2-6.0 mg were taken by >8,800 women for an average of 6-8 months without reports of serious adverse effects.

   –Many national professional organizations clearly state that although frequent use of ECPs is not recommended, repeat use may be offered. However, the proposed label states that Plan B is not intended for routine contraception.
4. Use in pregnancy. There is no evidence that emergency contraception will interrupt an already-established pregnancy or cause any damage to the fetus.
5. Advance provision and pharmacy access. Advance provision of up to 5 packs of ECPs to approximately 18,000 women (Scotland) and pharmacy availability in 33 countries and 2 U.S. states (WA and CA) have demonstrated no safety, misuse, or abuse problems.
6. Adolescent use. Based on a limited amount of data from several studies, repeat use or reliance on emergency contraception for routine contraception does not appear to be common in adolescents and is comparable to that in older women.

2.4 DOSING, REGIMEN, AND ADMINISTRATION

The approved prescription dosing regimen is two 0.75 mg tablets taken 12-hour apart with the first dose taken as soon as possible, and no later than 72 hours, after unprotected intercourse. The Applicant is proposing the same dose and dosing regimen for the OTC product. Clinical trial data clearly indicates that the product is most effective if taken within the first 24 hours and generally more effective the sooner it is started after unprotected sex. There is data in the medical literature that indicates that a single dose of 1.5 mg of levonorgestrel is equally effective as the presently approved

dosing regimen. There also is data that supports the use of the product between 72-120 hours (4 and 5 days) after unprotected intercourse, although the effectiveness is reduced.

2.5 SPECIAL POPULATIONS

Gender. The product is intended for use only in women. No studies in men have been conducted.

Age. The product is intended only for use in reproductive-aged females at risk for pregnancy. It is not intended for use in geriatric (age 65 yr. or older) populations or in premenarchal pediatric populations. As with other hormonal products for prevention of pregnancy, the Division of Reproductive and Urologic Drug Products (DRUDP) believes that the safety and efficacy of Plan B in postmenarchal adolescents are comparable to those in older reproductive-aged women. Limited efficacy and safety data initially were provided by the Applicant from subjects ≤ 18 yr. of age and additional safety data from adolescents subjects were provided during the review process.

Race. No formal studies have evaluated the effect of race. However, clinical trials have demonstrated a higher pregnancy rate in the Chinese population with Plan B. The reason for this apparent increase in the pregnancy rate of Plan B in Chinese women is unknown. The prescription product indicates this finding in the present labeling.

Pregnancy. Use in pregnancy is not indicated because the product is not effective once a pregnancy is established. Based on a large base of data from other levonorgestrel containing products, there is no evidence that the ingestion of 1.5 mg of levonorgestrel is harmful to either the woman or the fetus in instances in which the product my be inadvertently used in the presence of an established pregnancy.

CLINICAL REVIEW

1. BACKGROUND

Plan B was approved for use as an emergency contraceptive (EC) on July 28, 1999 and launched for marketing in the U.S. in August 1999. The product contains only a progestin, levonorgestrel, in 2 single-dose tablets (each containing 0.75 mg of levonorgestrel). This product differs from the first approved emergency contraceptive in the U.S. (Preven ™), which consists of 4 tablets, each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol. The approved dosing regimen for Plan B is two 0.75-mg doses taken 12 hours apart. It should be started within 72 hours of unprotected intercourse.

In April 2003, the Applicant (Woman's Capital Corporation) submitted a supplemental NDA (NDA 21-045/011) for the switch of Plan B from a prescription drug product to a non-prescription drug product (i.e., prescription to over-the-counter [OTC] switch). Several questions must be answered in order to determine whether a product is suitable for a prescription to OTC switch. From a safety perspective, a non-prescription drug should have an acceptable safety profile based upon prior marketing experience, low abuse and misuse potential, and a reasonable therapeutic index of safety. In addition, consumers should be able to self-diagnose the condition for which the drug is indicated, and should be able to self-administer the drug properly and safely based upon the proposed product label.

On December 16, 2003, supplemental NDA 21-045/011 and a set of 6 questions to be answered were presented to a Joint Advisory Committee (Reproductive Health Drugs Advisory Committee and Over-the-Counter Advisory Committee). The recommendations of the Joint Advisory Committee were based on information provided in the FDA's and the Applicant's Briefing Packages, FDA and Applicant presentations, public testimony, and a full discussion. At the end of the meeting, the members of the Committee recommended by a vote of 23 to 4 that Plan B be switched from prescription status to non-prescription status (i.e., over-the-counter) without any age or distribution restrictions and without any further studies prior to the approval.

Subsequent to the December 2003 Advisory Committee meeting, the two reviewing Divisions received additional literature articles, information, and data from the Applicant and other sources that have been analyzed and reviewed. This supplemental information has been incorporated into the respective reviews and final recommendations.

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

There were no new chemistry, animal, or microbiology data submitted with the application or new issues that were raised during the course of the review process.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1 Pharmacokinetic (PK) Findings

The Applicant submitted data from a PK study (Study PK-002) conducted in 22 females, aged 13-16 yr., following the oral administration of a single 0.75 mg levonorgestrel (LNG) tablet. In addition, the Applicant resubmitted PK data from Study PK-001 conducted in 16 healthy females, aged 18-45 yr., after the oral administration of a single 0.75 mg LNG tablet. The Applicant also submitted copies of published literature concerning PK studies of alternative LNG dosing regimens (one single 1.5-mg dose of LNG or two separate administrations of 0.75 mg LNG at either 12- or 24-hour time intervals).

Pharmacokinetic findings from studies PK-001 and PK-002 are listed in Table 1. The mean maximal concentration (C_{max}) and the $AUC_{(0-\infty)}$ values for levonorgestrel in the adolescents were lower than those in the adult women.

- C_{max} mean ratio of adolescents/adults = 0.53 (90% CI of 0.41, 0.68)
- $AUC_{(0-\infty)}$ mean ratio adolescents/adults = 0.77 (90% CI of 0.61, 0.98)

Table 1 Pharmacokinetic Findings from Studies PK-001 and PK-002

Study No.	Subjects	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng*hr/mL)
PK-001	Healthy adult females (n=16)	14.1 ± 7.7	1.6 ± 0.7	24.4 ± 5.3	123.1 ± 50.1
PK-002	Healthy adolescent females (n=22)	7.5 ± 3.8	1.5 ± 0.7	22.2 ± 6.8	94.5 ± 45.4

Source: FDA Biopharmaceutical Review (February 2004).

A comparison of the design of each of the studies is provided in Table 2. The designs of Studies PK-001 and PK-002 were similar except for the following differences. In adolescent Study PK-002, fasting occurred for 4 hours before dosing instead of 8 hours, and lasted for 3 hours post-dose instead of 4 hours. In Study PK-002, dosing occurred between 4 PM and 7 PM instead of at 8 AM, and fewer blood samples were taken (i.e., 14 versus 19 samples).

Table 2 Comparison of Designs of Study PK-001 and Study PK-002

Study	PK-001	PK-002
Subjects	Healthy adult females (n=16)	Healthy adolescent females (n=22)
Study Design	A prospective, single-period, single-center, open-label, single dose study	A prospective, single-period, single-center, open-label, single dose PK study
Age (yr.)	28 ± 9 (19 – 44)	15 ± 1 (13 – 16)
Weight (kg)	65.3 ± 9.9 (51 – 79.5)	59.5 ± 9.4 (41.8 – 77.3)
Race	9 White (56%), 6 Black (38%), 1 Asian/Pacific Islander (6%)	12 Black (54%), 5 Multiracial (23%), 4 Latina (18%), 1 Asian (5%)
Fasting	Overnight 8 hr fasting pre-dose, 4 hr fasting post-dose	4 hr fasting pre-dose, 3 hr fasting post-dose
Dosing time	8 AM	Between 4 PM and 7 PM
Blood draw times	72 hrs post-dose: 19 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, **6**, 8, 10, 12, **15**, **18**, 24, **30**, **36**, 48, 72 hr)	72 hrs post-dose: 14 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, 72 hr)

Source: FDA Biopharmaceutical Review (February 2004).

Medical Officer's Comments

- *Based on the data provided in this Application, it cannot be determined if the PK differences reflect a true difference in the PK of levonorgestrel in young adolescents compared to adults or are a reflection of differences in study designs.*

- *The effects of food and time-of-dosing on levonorgestrel pharmacokinetics have not been studied. Since adolescents fasted for 4 hours (vs. 8 hours for adults) and were dosed in the evening (vs. morning for adults), either of these differences may have affected the observed PK parameters.*
- *Given that levonorgestrel pharmacokinetics are known to be highly variable, there is uncertainty if the apparent differences across the 2 studies represent a true difference.*
- *Since the unbound concentrations of levonorgestrel were not measured in the adolescent study, it is not known if the more physiologically relevant unbound concentrations of levonorgestrel are different in the adolescent and adult female groups.*

3.1.1 Clinical Significance of Pharmacokinetic Findings

He et al[1] conducted a randomized single-dose, crossover, relative-bioavailability study of 2 marketed formulations of 0.75 mg LNG (Hungarian and Chinese formulations, respectively) in 10 healthy Chinese adult females. Blood samples were obtained up to 24 hours post-dose and the plasma samples were analyzed for levonorgestrel by radioimmunoassay. Compared to a Postinor tablet of LNG (Hungarian formulation, similar to Plan B formulation), the Chinese tablet showed lower relative bioavailability both in terms of C_{max} and AUC as shown in Table 3.

Table 3 PK Parameters (Hungarian and Chinese Formulations of Levonorgestrel)

PK Parameter	Hungarian Formulation LNG 0.75 mg tablet (Postinor)[1]	Chinese Formulation LNG 0.75 mg tablet
Cmax (ng/mL)	11.2 ± 3.4 (8.1 – 18.4)	5.9 ± 1.7 (3.4 – 8.2)
AUC_{0-24} (ng•hr/mL)	92.2 ± 34.3 (54.0 – 152)	64.4 ± 21.9 (33.1 – 99.1)
$AUC_{0-\infty}$ (ng•hr/mL)	124.0 ± 42.8 (66.8 – 176.6)	92.3 ± 28.8 (42.7 – 121.8)

[1] LNG = levonorgestrel.
Source: FDA Biopharmaceutical Review (February 2004).

Medical Officer's Comments

- *Both the Hungarian and Chinese formulations have also been studied in a clinical trial and shown to have a similar method failure rate of 1.1 % per treated cycle when used for postcoital contraception[2]. The investigators concluded that despite the previously documented[1] marked difference between the formulations in terms of their relative pharmacokinetics there was no significant difference between the two LNG formulations in terms of contraceptive efficacy. Of note, is the observation that the reported pharmacokinetic parameters for the Chinese formulation (lower C_{max} and AUC values) are similar to those observed for adolescents in Study PK-002 following administration of the Plan B formulation of levonorgestrel.*
- *Even if the bioavailability of Plan B is lower in adolescents than adults, as suggested by the cross study comparison described above, efficacy data from a 2002 WHO study[3] indicate that levonorgestrel emergency contraception in women <18 yr. of age is at least as effective as comparable doses in women ≥18 yr. of age. In the WHO study, levonorgestrel was given as either a single-dose (1.5 mg) or as 2 standard doses (0.75 mg/dose) 12-hours apart. Among subjects <18 yr. (data from single- and 2-dose groups combined), there was only one pregnancy in 165 subjects, while 13 pregnancies would be expected if no contraception were used. For those <18 yr., the combined pregnancy rate was 0.61% (1/165), while for those ≥18 yr. the pregnancy rate was 1.66% (43/2594).* ***From these efficacy data, there is no evidence that the standard total dose of levonorgestrel (1.5 mg) was less effective in the younger age group.***

3.2 Pharmacodynamics

No pharmacodynamic data were submitted with the application.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

Clinical data were obtained from the following sources and used in this review and/or in making recommendations regarding (1) approvability of the Prescription to OTC switch and (2) Phase IV commitments:

- Data used primarily by this reviewer in this safety review:
  - Postmarketing safety data for Plan B provided by the Applicant in sNDA 21-045/011
  - Data provided by the Applicant in NDA 21-045/011 from published studies in which levonorgestrel was used for emergency contraception or postcoital contraception
  - Periodic Safety Reports and MedWatch reports for Plan B sent to the FDA
  - Other published and unpublished studies by individual investigators
  - The original NDA application and the 1999 review of the application
  - An open-label safety study (WCC-PED-001) in 60 adolescent girls aged 13-16 yr.who took levonorgestrel emergency contraception (two 0.75 mg tablets separated by 12 hours)
- Data reviewed primarily in other divisions:
  - The Label Comprehension Study (Study 9728) that was reviewed primarily by Karen Lechter, JD, Ph.D., a social scientist in the Division of Surveillance, Research, and Communication Support (DSRCS)
  - The Actual Use Study (Study 9727) that was reviewed in detail by Jin Chen, MD, Ph.D., MPH, Division of Over-the-Counter Drug Products (DOCDP)
  - Eight articles that assessed contraceptive and sexual behavior in adolescents and/or adult women following advanced provision of emergency contraception that were reviewed primarily by Dr. Chen and other members of DOCDP

4.2 Overview of Clinical Trials

Detailed information about the designs and findings of Study 9728 (Label Comprehension Study), Study 9727 (Actual Use Study [AUS]), and Study PK-002 are provided in their respective primary reviews.

- Study 9728 (Label Comprehension Study) enrolled 656 women, the majority of whom were enrolled from shopping malls. This study tested 11 communication objectives that were felt to be important for the safe and effective use of the product. Findings from the study are not included in this review.
- Study 9727 (AUS) was a 4-week, open-label, single-arm, multi-center study to evaluate self-selection and self-administration of Plan B in an OTC-like setting. The study was conducted in 5 family planning clinics across 5 states and 5 pharmacy stores in the state of Washington. A total of 585 subjects, ages 14-44 yr., were enrolled from family planning clinics (94%) and pharmacy stores (6%). A total of 540 enrollees took Plan B. Subjects were not given any educational intervention other than what they could obtain from the package containing the medication. A limited assessment of the safety and efficacy findings from the study is provided in this review.

- Study PK-002 was a single-period, single-center, open-label pharmacokinetic study conducted to determine the pharmacokinetics of levonorgestrel following oral administration of a single 0.75 mg levonorgestrel tablet (Plan B) to healthy adolescent females aged 13-16 yr.
- Among the several studies not specifically sponsored or supported financially by the Applicant that were included in the NDA were randomized, controlled trials (RCTs), some of which were blinded. The smaller of these studies were usually single-center, and the larger ones were usually multicenter.

4.3 Postmarketing Experience

There has been extensive global postmarketing experience with levonorgestrel used for emergency contraception over the past 5 years. The largest databases are from the U.S., U.K., France, and the World Health Organization (WHO) Safety Monitoring Program. A consultation was requested by DRUDP of the Office of Drug Safety (ODS) for a review of the FDA's Adverse Event Reporting System (AERS) database and other databases available to the ODS. The Applicant also submitted postmarketing safety data from other sources as noted later in this review.

4.4 Literature Review

In their April 2003 submission, the Applicant included 14 volumes (approximately 4,000 pages) of references from the medical literature. The Annual Report for Y-004, dated October 8, 2003, and the Applicant's submission of October 20, 2003 (background document for the December 16, 2003 Joint Advisory Committee Meeting) included >30 literature references and >150 pages of articles that were not previously submitted with the original Plan B prescription-to-OTC switch application. This reviewer (DD) also searched the medical literature and found additional articles that were pertinent to issues raised after the December 2003 Advisory Committee Meeting.

5. CLINICAL REVIEW METHODS

5.1 Describe How Review was Conducted

There were three separate primary reviews of this supplemental NDA.

1. Jin Chen, MD, Ph.D., MPH, Division of Over-the-Counter Drug Products (DOCDP), did the primary review of the Actual Use Study (Study 9727) and the 8 behavioral studies that were included in the submission (2 interim reports and 6 articles published in the medical literature).
2. Karen Lechter, JD, Ph.D., Division of Surveillance, Research, and Communication Support (DSRCS) did the primary review of the Label Comprehension Study.
3. Daniel Davis, MD, MPH (this reviewer), Division of Reproductive and Urologic Drug Products (DRUDP) and primary medical reviewer for the original NDA for Plan B, reviewed the overall postmarketing safety data for Plan B and many of the issues relating to the safe use of Plan B in an OTC setting, particularly by adolescents <18 yr. of age.

5.2 Overview of Materials Consulted in Review

In addition to the clinical materials listed in Section 4.1 above, other materials that were consulted during this review included:

1. Professional publications from several national organizations, including the American College of Obstetrics and Gynecology (ACOG), American Society for Emergency Contraception, Advocates for Youth, and Reproductive Health Technologies Project
2. Transcripts from the December 16, 2003 Joint Advisory Committee Meeting

3. Numerous personal communications with several experts in the field of EC research that are referenced in the relevant sections of this review
4. Attendance at, and materials from, the annual meetings for the International Consortium for Emergency Contraception (ICEC) and the American Society for Emergency Contraception (ASEC) held in New York City in October 2003

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

The sites for Study 9727 (AUS) that were inspected by the Agency's Division of Scientific Investigations were found to be in compliance with FDA standards. Other data used in the review were predominantly from peer-reviewed articles in the medical literature or directly from leading researchers in the fields of emergency contraception and/or adolescent gynecology and family planning.

5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

The 3 new clinical trials submitted in support of the NDA (Studies PK-002, Study 9727, and Study 9728) were approved by appropriate IRBs and were conducted with accepted ethical standards.

5.5 Evaluation of Financial Disclosure

The submission included a statement that there were no financial conflicts of interest[4].

6. INTEGRATED REVIEW OF EFFICACY

The proposed population and dosing regimen for OTC Plan B is identical to that of the presently approved prescription product (i.e., two 0.75 mg doses taken 12 hours apart with the first dose taken as soon after, but no later than 72 hours after unprotected intercourse). Therefore, if the user takes the product in accordance with recommended labeling, OTC efficacy should be comparable to that of the prescription product. To assess whether the adequacy of proposed OTC labeling and whether women were likely to use Plan B in an OTC setting in accordance with labeling, the Applicant conducted an Actual Use Study (Study 9727).

6.1 Actual Use Study (Study 9727): Efficacy Issues

6.1.1 All subjects

This study is reviewed in detail elsewhere in a separate primary review by Dr. Jin Chen, DOCDP and in secondary reviews by Drs. Andrea Leonard-Segal and Curtis Rosebraugh, also in the DOCDP. The following text and comments focus only on efficacy-related issues.

This was a 4-week, open-label, single-arm, multi-center study to evaluate self-selection and self-administration of Plan B in an OTC-like setting. This study was conducted in five family planning clinics across five states and five pharmacy locations in the state of Washington. A total of 585 subjects ages 14-44 yr. old were enrolled from family planning clinics (94%) and pharmacy stores (6%) in the United States. Subjects were not given any educational intervention other than what they could obtain from the package containing the medication.

Five hundred forty (540) enrollees took Plan B and 95% of them did so for correct reasons. Three percent (3%) of the enrollees did not provide specific reasons why they self-selected. The remaining nine who erred in self-selection did so because of unexplained vaginal bleeding (n= 6), pregnancy (n=1), or took Plan B before having unprotected sexual intercourse (n=2).

Medical Officer's Comment

- *These finding indicate that a very high percentage of enrollees correctly self-selected for the use of Plan B in an OTC-like setting. Although vaginal bleeding was listed as a contraindication to*

use of Plan B in Study 9727 and is presently a contraindication for use of the prescription product as well, the basis for this contraindication is actually a carryover from labeling for progestin-only contraceptive products that are intended to be used chronically (e.g., daily for months to years). It is likely that unexplained vaginal bleeding will be removed as a contraindication to use of Plan B in revised labeling (see Section 7.4).

Ninety-two percent (92%) timed the first pill correctly (within 72 hours of unprotected intercourse) Seventy-two percent (72%) took the second pill exactly 12 hours following the first and 93% took the second pill between 6 to 18 hours following the first pill.

Medical Officer's Comments

- *These findings demonstrate a high rate of correct timing of dosing with Plan B both for the first dose (92%) and the second dose (93%) using the slightly relaxed definition of correct use of "6 to 18 hours after the first dose.*
- *Recent studies have shown that the efficacy of Plan B does not appear to be reduced if both of the 0.75-mg tablets of levonorgestrel are taken at the same time. In additional, the Cmax and AUC values for levonorgestrel are very similar when the second pill is taken either 12 or 24 hours after the first pill. It is therefore unlikely that the effectiveness of Plan B will be reduced if the second tablet is taken 6 to 18 hours, instead of exactly 12 hours, after the first dose.*
- *The most important factor concerning timing of doing and effectiveness is the interval between the first dose and unprotected intercourse. In Study 9727, 92% of enrollees took the first dose of Plan B within 72 hours of unprotected intercourse, in accordance with labeling for the product.*

Pregnancies were confirmed in 10 participants who took Plan B, and the pregnancy status of another 14 subjects was unknown at the end of the study. This represents a documented failure rate of 1.9% and a "worst case" (but unlikely) failure rate of 4.4%.

Medical Officer's Comment

- *The estimated pregnancy rate for a single random act of unprotected intercourse during one menstrual cycle is about 8%. A pregnancy rate of 1.9% would be a significant reduction. It is highly unlikely that more than an occasional woman, among the 14 for whom final pregnancy status was unknown, had become pregnant during their participation in Study 9727.*

6.1.2 Subjects Less than 18 Years of Age

Fifty-seven (57) adolescents under age 18 were enrolled. Times of dosing with Plan B from 46 of these subjects were available. Of these 46 subjects, 22 were 16 yr. of age or younger and 24 were 17 yr. of age. Of these 46 subjects, first dose data were not available for 4; of the 42 subjects under age 18 for whom time of first dose was known, ***all*** took the first dose within 72 hours of unprotected intercourse in accordance with the label. Of these 42 users, the first dose was taken within 24 hours of intercourse by 37% of subjects, within 24-48 hours by 46% of subjects, and within the 48-72 hours by the remaining 17% of subjects.

Second dose data were available for all 46 of these adolescent subjects. For the • •16-year old age group, 20/22 took the second pill at exactly 12 hours after the first dose (per label), and the remaining 2 adolescents took the dose within 10-14 hours after the first dose (i.e., within 1-2 hours of the prescribed time). For the 17-year old age group, 17/24 took the second pill at exactly 12 hours after the first dose, and the remaining 7 took the second pill within 11-13 hours after the first dose (i.e., within 1 hour of the prescribed time). The combined results show that all 46 adolescent users took the second dose within 12± 2 hours of the first dose.

Among the 46 subjects < 18 yr. of age, there was ***one*** report of a pregnancy (a 17-year old).

Medical Officer's Comment

- *There was excellent compliance with the labeled dosing regimen among subjects < 18 yr. of age. Compliance was at least as good as that in the subjects 18 yr. and older.*

7. SAFETY DATA

7.1 Original NDA Safety Data

The Applicant in their original Plan B NDA presented clinical trial safety results from 4 different trial categories. These provided a large database of clinical information in over 15,000 women and included the following:

1. Single dose and multiple dose clinical pharmacology studies
2. Two World Health Organization (WHO/HRP)-sponsored comparative studies that were the primary studies supporting the efficacy and safety of Plan B. The trials compared levonorgestrel (two 0.75 mg doses separated by 12 hours) to the Yuzpe regimen [levonorgestrel plus ethinyl estradiol] for emergency contraception. These studies were:
   - WHO/HRP Study 92908 (1998): the pivotal study for the NDA, (N = 1,955)
   - WHO/HRP Study 81107 (Ho and Kwan, 1993): principal supportive study for the NDA, (N = 834)
3. Three WHO/HRP-sponsored trials of routine postcoital contraception using the 0.75-mg levonorgestrel formulation manufactured by Gedeon Richter (the manufacturer of the levonorgestrel used in Plan B):
   - WHO/HRP Study 82906 (1987)
   - WHO/HRP Study 84902 (He, 1991)
   - WHO/HRP Study 87908 (1993)
4. Fifteen small studies of oral levonorgestrel for routine or occasional postcoital contraceptive use, using a variety of regimens, doses, and formulations. (See Attachment A for a partial listing of postcoital contraception studies using levonorgestrel.)

Levonorgestrel, taken for emergency contraception, is well tolerated and safe as shown by the extensive safety data from more than 15,000 women in the above studies using various levonorgestrel doses (ranging from 0.15 to 1.0 mg) for emergency contraception, occasional postcoital contraception (up to 4 times a month), or routine postcoital contraception (no limit on the number of uses). The data in the original NDA represented the majority of both literature articles and unpublished study reports found as a result of an extensive literature search by the Applicant through 1998. The search did not uncover any serious adverse events associated with the use of levonorgestrel for emergency contraception, and the side effects reported were consistent across the many studies. In addition, during the 1999 NDA review for Plan B, no serious adverse events were reported from 3 ongoing studies of levonorgestrel for emergency contraception or from the introductory postmarketing safety data for Postinor-2 (an identical product containing levonorgestrel 0.75 mg) in 3 European countries. No reports of thromboembolic adverse events and only one report of an ectopic pregnancy were noted in all of the information reviewed by DRUDP for the original Plan B NDA. One safety finding of note was that levonorgestrel-alone emergency contraception was superior to the Yuzpe emergency contraception regimen [levonorgestrel + ethinyl estradiol] with significantly less nausea and vomiting; present labeling for Plan B includes this comparative information.

7.2 Postmarketing Safety Data

7.2.1 Extent of Patient Use

Since the launch of Plan B in August 1999, the Applicant estimates that 2.4 million women in the United States have used Plan B. From July 28, 2002 to July 27, 2003, the Applicant estimates that of the 1,458,536 units of Plan B sold in the U.S., 80% have been used (i.e., 1.2 million users). Marketing of Plan B began in Canada in June 2000; in the most recent reported 12 months, the Applicant estimates that 72,000 women used Plan B in Canada. In the U.K., the Applicant estimates that 2.1 million women have taken Levonelle (a product identical to Plan B) since February 2000. Patient exposure to levonorgestrel for emergency contraception in France is estimated by the Applicant to be 1.8 million uses. Levonorgestrel for emergency contraception is available in 101 countries and is available without a prescription at the pharmacy in 33 of these 101 countries[5].

7.2.2 Postmarketing Safety Data (Provided by Applicant)

The Applicant compiled postmarketing safety data from a number of U.S. and global sources, including from key European countries, Canada, and the WHO Drug Monitoring Program, to provide an assessment of the postmarketing safety profile of levonorgestrel 0.75 mg tablets up to January 2003. Based on these data provided by the Applicant, there have been no reported deaths; most of the adverse events (AEs) attributed to the drug were mild and of short duration. The most common AEs were nausea, abdominal pain, fatigue, headache, and changes in menstrual bleeding. In the 3-year period covered by the Applicant's required quarterly Periodic Safety Updates to the FDA and in their subsequent additional updates to January 6, 2003[6], there have been 328 reported AEs. Pregnancy (123/328) and metrorrhagia (heavy bleeding, 64/328) were the two events most frequently reported. All of these events are consistent with the presently approved Plan B label and the proposed Plan B OTC label.

7.2.3 Postmarketing Safety Data (FDA Data Sources)

AERS Database. The Office of Drug Safety (ODS) was consulted to review postmarketing safety reports for Plan B. The ODS review focused on adverse events reported to the FDA Adverse Event Reporting System (AERS) through October 9, 2003.[7] The AERS database was searched using the U.S. trade name Plan B and foreign trade names for similar levonorgestrel emergency contraceptive products (Levonelle, Levonelle-2, Postinor, and Postinor-2). The search identified 116 unduplicated cases in the AERS database; most of the reports involved non-serious and labeled events. The most common non-serious events (and number of reports for each) were vaginal bleeding (26), unintended pregnancy (21), cramps/pain (11), and nausea/vomiting (11). Adverse events classified as serious included 28 cases of ectopic pregnancy (none of which occurred in the U.S.), 10 cases of hypersensitivity reaction, 8 cases of possible pregnancy/fetal effects, and 3 cases of convulsion. Cases of reported hypersensitivity reactions and possible adverse effects on the fetus are discussed in Section 7.2.3.2 and Section 7.2.3.3, respectively. Ectopic pregnancies reported in users of levonorgestrel for emergency contraception, based on data from several sources, are reviewed in Section 7.2.4.

MHRA Database. The Medicines and Health-care Products Regulatory Agency (MHRA) also sent printouts to ODS from the U.K. Adverse Drug Reactions Online Information Tracking (ADROIT) database of all adverse events reported for Levonelle and Levonelle-2 since their approval in the U. K. There were 45 total reports for Levonelle and 243 for Levonelle-2. Among these were 5 reports of ectopic pregnancy with Levonelle and 16 with Levonelle-2, of which some may have been duplicate reports. These two products are identical except that one is available by prescription and the other by pharmacy access without a prescription in the U.K.

7.2.3.1 Deaths

There were ***no reports of death*** in women using postcoital levonorgestrel ***in either the AERS or the U.K. databases.***

7.2.3.2 Hypersensitivity (Allergic) Reactions

The ODS consultation for levonorgestrel emergency contraception identified 10 unduplicated cases of hypersensitivity reactions, of which 3 occurred in the United States. The time of onset of the adverse event was stated in 8 of the 10 reports and ranged from 4 hours to 2 days after taking the drug. Events ranged from minor localized rashes to urticaria, from localized edema to systemic edema, and difficulty with breathing (2 cases). Although 7 cases were marked "life-threatening," none of these women stayed overnight in the hospital and the narratives provided in the reports did not reflect a life-threatening event. Four of the women had taken concomitant medications, including 2 women on antibiotics, that could have been responsible for the reported reactions.

Medical Officer's Comments

- *One of the 2 cases that included difficulty with breathing occurred in a woman who appeared to have had an underlying pulmonary disorder as suggested by her list of concomitant medications (Buspar, Flovent, Singulaire, Seravent); it is therefore unclear if the reported episode of difficulty with breathing was related to using levonorgestrel.*
- *In this reviewer's opinion, none of these 10 cases was a serious adverse event.*

7.2.3.3 Adverse Unintended Effects of Levonorgestrel on Pregnancy (Potential for Congenital Abnormalities)

In the original NDA for plan B, there were no reports of congenital abnormalities among women for whom the treatment failed or among women mistakenly enrolled in studies who received the treatment after they were already pregnant. The ODS consultation [see Attachment C] found 3 cases of spontaneous abortion, 1 missed abortion, 1 inevitable abortion, and 3 reported European cases of congenital anomalies in pregnancies of women who had taken levonorgestrel for emergency contraception. Given that spontaneous abortions have been documented to occur in 10-15% of clinically recognized pregnancies[8], the number of these reported events is below the expected rate in the general population. In one congenital anomaly case, the woman also received abdominal X-rays at gestational Week 12. With the Applicant's estimated patient use of Plan B in 2.4 million USA and 2.1 million U.K. women and a given risk of pregnancy of 1.1% in these women, one would expect approximately 49,500 unplanned pregnancies. Three reported cases of congenital anomalies are well below the expected 0.85% incidence of congenital anomalies.[9] It is highly unlikely, even with significant underreporting, that exposure to Plan B is associated with the development of congenital abnormalities.

Medical Officer's Comment

- *Levonorgestrel has been used in several combination oral contraceptives for over 35 years. The DRUDP did a thorough review of the teratogenic risk associated with the accidental use of contraceptive hormones early in pregnancy (See Attachment B). The DRUDP concluded from this review that there is not an association between the accidental use of contraceptive hormones early in pregnancy and adverse fetal or pregnancy outcomes. Observations that there is no apparent increase in birth defects among pregnancies exposed to daily use of combination oral contraceptives (many of which contain levonorgestrel) are reassuring.*[10]

7.2.4 Ectopic Pregnancies

The literature suggests an increased relative risk, but not an increased absolute risk, of an ectopic pregnancy with progestin-only oral contraceptive pills that are taken on a regular daily basis. Thus, if a woman becomes pregnant while taking daily progestin-only oral contraceptive pills, the likelihood of the pregnancy being an ectopic pregnancy is greater than 1-2 per 100 pregnancies, the generally accepted incidence of ectopic pregnancies in women using no contraception. However, since progestin-only oral contraceptives are highly effective in preventing pregnancy, the absolute risk of such a woman having an ectopic pregnancy is significantly reduced, relative to sexually active women using no contraception or a less effective method (e.g., spermicide or condoms).

Medical Officer's Comment

- *Based on the data from the sources and reviews presented in the following sections, there does not appear to be an increased risk of ectopic pregnancy with the use of levonorgestrel for emergency contraception.*

7.2.4.1 Office of Drug Safety Review of AERS Database for Ectopic Pregnancies

There were 28 unduplicated cases of ectopic pregnancy in the FDA's AERS database; none of the reports was from the U.S. Among these 28 reports, there were no deaths, 15 instances in which patients were reported to have been hospitalized, and only 10 instances in which patients were reported to have had surgery. Of these 28 cases of ectopic pregnancy, 13 were reported by Gideon Richter (the Hungarian manufacturer of levonorgestrel) without information on the country of origin. Of the cases of ectopic pregnancy, 10 were from the U.K., 3 were from Israel, and 1 each were from Sweden and China.

7.2.4.2 Applicant's Review of Postmarketing Safety Data for Ectopic Pregnancies

The Applicant submitted their own assessment of postmarketing safety for levonorgestrel drug products used for emergency contraception. According to the Applicant, their review was based on postmarketing safety reports submitted to the U.K. Medicines Control Agency and the French Health Authority as well as U.S. postmarketing safety reports available to them. The Applicant listed a total of 340 pregnancies and 21 ectopic pregnancies from these sources through February 2003.[11] The numbers of pregnancies and ectopic pregnancies reported by the Applicant from each of these data sources are listed in Table 4.

Table 4 Number of total pregnancies and ectopic pregnancies (Applicant's review of postmarketing safety data)

Country	Pregnancy (N)	Ectopic pregnancy (N)	% Ectopic pregnancies (Ectopic preg)/(total preg)
France (Feb 03)*	29	8	21.6%
United Kingdom (Jan 03)	201	12	5.6%
United States (Feb 03)	110	1**	0.0%
TOTAL* **	**340[12]**	**21**	**6.2%**

* The cutoff dates for the safety data are shown the parentheses.

** Applicant stated that this report was obtained from the WHO database. It does not appear in the FDA's AERS database.

*** See the first and third bullets under the Medical Officer's Comments that follow.

Medical Officer's Comments

- *Upon DRUDP's request, the Applicant reviewed the sources for the data in this table and provided clarification in a FAX dated February 13, 2004. The corrected number of unintended pregnancies reported to WCC for women taking Plan B in the U.S. was 36 and not 110 [the other 74 listed in Table 4 were from foreign sources]. The single ectopic pregnancy in the U.S. listed in Table 4 actually occurred in a woman using Levonelle-2 in the U.K. (The correct number of U.S. ectopic pregnancies therefore should be 0 and the number in the U.K. should be increased to 13, leaving the total unchanged at 21). The correct percentage of reported pregnancies that were ectopic, based on these revised data, is 7.9% (21/266) and not 6.2% as previously reported.*

- *From postmarketing databases, it generally is not possible to accurately determine the incidence of an adverse event among users of a drug product because the number of drug exposures (total number of women who have taken the drug) can only be estimated and there is considerable underreporting of adverse events in general. However, even with considerable underreporting of adverse events, based on the Applicant's estimated use of Plan B in the U.S. one would expect at least several reports of ectopic pregnancy in the AERS database for users of Plan B. Based on the Applicant's estimated 2.4 million uses of Plan B in the U.S. since its approval and a pregnancy rate of 1%, one would expect about 24,000 pregnancies in these users. Based on the generally accepted estimate of 1-2 percent of pregnancies being an ectopic pregnancy, as many as 240-480 of these users of Plan B in the U.S. could be expected to have had an ectopic pregnancy. However, the AERS database contained no reports of ectopic pregnancy in women who used Plan B in the U.S.*

- *The "apparent" ectopic pregnancy rate reported by the Applicant, based on the ratio of reported ectopic pregnancies and reported pregnancies of all types among users of levonorgestrel emergency contraception in the U.K., France, and the U.S. (Table 4), is most likely greater than the true rate. Pregnancy, per se, is a known possible outcome with the use of emergency contraception because emergency contraception is not 100% effective; therefore, one would not expect an intrauterine pregnancy to be routinely reported as an adverse event. Ectopic pregnancy, however, is a serious adverse event, and one would expect a greater percentage of these events, relative to intrauterine pregnancies, to be reported. Assuming this to be the case, the result will be an apparent rate of ectopic pregnancy in users of levonorgestrel emergency contraception that is higher than the true rate. Based on these considerations, an "apparent" ectopic pregnancy rate of 6.2% (or the corrected rate of 7.9%) is not of concern.*

- *Randomized clinical trials, as described in the Section that follows (Section 7.2.4.3) are likely to provide the best estimates of the true rate of ectopic pregnancy in users of levonorgestrel emergency contraception.*

7.2.4.3 Ectopic Pregnancies in Randomized Clinical Trials of Emergency Contraception

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.[13,14] 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 reduce a woman's absolute risk of an ectopic pregnancy.

Table 5 Number of total pregnancies and ectopic pregnancies in randomized clinical trials.

Randomized Clinical Trial	Evaluable (n)	Pregnancies (n)	Ectopic pregnancies (n)	Levonorgestrel dose (mg)
WHO 2002[15]	1356	24	1	0.75 - 2 doses
	1356	20	0	1.5 - single dose
Arowojolu et al. 2002[16]	545	7	0	0.75 - 2 doses
	573	4	0	1.5 - single dose
WHO 1998[17]	976	11	0	0.75 - 2 doses
Wu et al. 2003[18]	643	20	0	0.75 - 2 doses
Ho and Kwan 1993 [19]	410	12	0	0.75 - 2 doses
Ho et al. 2003[20]	2,030	35	1	0.75 - 2 doses
TOTAL	**7,889**	**133**	**2**	

Medical Officer's Comments

- *Data from clinical trials are generally considered more reliable than that obtained from other sources (e.g., spontaneous postmarketing safety reports). Randomized clinical trials are the "gold standard" for estimating the frequency of events that are not "rare" in that such trials provide accurate information on the number of specific adverse events and the number of subjects at risk for them.*
- *The 1.5% incidence of ectopic pregnancy from these randomized clinical trials enrolling almost 8,000 women provides strong evidence that the use of levonorgestrel for emergency contraception does not increase the likelihood that a woman will have an ectopic pregnancy should she become pregnant.*
- *Moreover, because emergency contraceptives are at least 75% effective in preventing a pregnancy, they should reduce a woman's absolute risk of experiencing an ectopic pregnancy.*

7.2.4.4 Ectopic Pregnancies and Labeling

The prescription label for Plan B has a subsection titled **Ectopic Pregnancy** in the WARNINGS Section. The following text is found in this section:

> "Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B®."

Medical Officer's Comment

- *The proposed OTC label for Plan B cautions women to be alert for symptoms that could be indicative of an ectopic pregnancy. There is no evidence that a history of a previous ectopic pregnancy or tubal disease increases the risk of an ectopic pregnancy in women who use levonorgestrel emergency contraception.*

7.3 Misuse and Abuse

7.3.1 Overdosing with Levonorgestrel for Emergency Contraception

According to the Applicant, there are no reports of intentional overdose with levonorgestrel for emergency contraception. Overdosing is unlikely with Plan B since it is packaged as a single course of treatment and is likely to be relatively expensive. The Applicant's review of the Toxic Exposure Surveillance System (TESS) found 24 reports concerning Plan B and none that resulted in death or serious illness.

Medical Officer's Comment

- *There is no reason to expect overdosing with Plan B in an OTC setting. In this reviewer's evaluation of the medical literature on advance provision, there were no cases of overdose or excessive use. If a large dose of levonorgestrel were ingested, the margin of safety appears to be high. Likewise, the cost would be a deterrent, and the label clearly states that the product is not for routine contraception. Moreover, there are no reports of any person overdosing with this product in the Agency's AERS database or in the medical literature.*

7.3.2 Repeated Dosing of Levonorgestrel for Postcoital Contraception.

The best safety data for exposure to higher and/or repeated doses of levonorgestrel comes from clinical trials in South America and Eastern Europe conducted between 1973-87 in which women used levonorgestrel as a regular postcoital contraceptive for at least 6 months. In these postcoital contraceptive trials, women used up to 20 levonorgestrel 0.75 mg tablets in a single menstrual cycle (total monthly doses far in excess of those to be expected with the OTC use of Plan B for emergency contraception) and/or up to 3 levonorgestrel 0.75 mg tablets in 24 hours with repeated dosing allowed. In these latter clinical trials, only one serious adverse event (an ectopic pregnancy) was reported[21].

Among reported studies of the use of levonorgestrel for regular postcoital contraception was a trial by Larranaga et al.[22] This study enrolled 298 women who took 1 mg of postcoital levonorgestrel as their regular method of contraception. The average duration of participation in the study was 8.6 months with total monthly levonorgestrel exposure ranging from 4-20 mg. No serious adverse events were reported. Common adverse events (and the percentage of women reporting each) included menstrual irregularities (76%), headache (18%), nervousness (4%), dysmenorrhea (3%), nausea (3%), dizziness (2%), and acne (2%).

Medical Officer's Comment

- *The above data on exposure and reported adverse events is very reassuring concerning the safety of chronic monthly exposure to doses of levonorgestrel that are far higher than the 1.5 mg dose of Plan B that is likely to be taken infrequently.*

7.3.3 Repeat Use of Emergency Contraception (Behavioral Issues)

Studies investigating how often women use emergency contraception have found that using it more than 4 times in one year is uncommon. An observational cohort study by Rowlands in the U.K. reviewed >15,000 medical records of women, age 14-29, who used emergency contraception without advance provision and were followed from 1994-97; he found that repeat emergency contraception use was uncommon. Only 3% used emergency contraception twice in the 4 years; 1% used emergency contraception 3 times in the 4 years; and 0.8% used emergency contraception >3 times in the 4 years. In addition, more than 70% of the women with no regular use of a birth control method prior to using emergency contraception used regular contraception within 1 year of first emergency contraception use.[23]

Studies in which emergency contraception was provided by "advance provision" are helpful to assess the likely use of emergency contraception when it is easily accessible as well as overall contraceptive practices. Advance provision is the term that is used to describe the setting in which women are provided with one or more doses of an emergency contraceptive product prior to its actual need. Several U.S. and international studies have indicated that advance provision of emergency contraceptive pills (ECPs) does not lead to women replacing their regular method of contraception with emergency contraception. A large 1-year study by Glasier and Baird (n = 1,071) compared the frequency of emergency contraception use in women who were provided with the product in advance of actual need (Advance Provision [AP] group) to that in women who were provided only with information but not proved with the product in advance (control or standard care group). In the AP group, 36% of subjects used ECPs once during the study and 11% used it more than once. In the standard care group, 14% of subjects used ECPs once and 13% used it more than once.[24] Another study (n = 411) reported no repeat use in either arm for up to one year.[25]

Medical Officer's Comments

- *Studies show that women of all ages with easier access to emergency contraception are more likely to use it when needed, potentially reducing unintended pregnancies and the number of induced abortions.*[26]
- *Guidelines from the World Health Organization, American College of Obstetricians and Gynecologists, and the American Society for Emergency Contraception clearly state that although frequent use of emergency contraception is not recommended, repeat use may be offered. In other words, there is no safety issue with the repeated use of emergency contraception.*

7.3.4 Use during Pregnancy:

The risks of inadvertent use of Plan B and/or progestin containing oral contraceptives (including those that contain levonorgestrel) during pregnancy were reviewed in Section 7.2.3.3. Based on clinical trial data from studies with Plan B, postmarketing safety data for ECPs containing levonorgestrel, and DRUDP's review of the contraceptive literature, there is no evidence that a woman's use of Plan B while she is pregnant will result in abortion. In addition, there is no evidence of risk to the fetus (i.e., likely development of a congenital abnormality) if an early pregnancy is exposed to Plan B (see Section 7.2.3.3 and Attachment B). Use in pregnant women in contraindicated because the product would not be effective, not because it has been shown to be unsafe.[27]

7.4 Contraindications

The labeled contraindications for prescription Plan B include (1) known or suspected pregnancy (not a safety issue, per se, but listed as a contraindication because the product will not interrupt an established pregnancy), (2) hypersensitivity to any component of the product, and (3) undiagnosed abnormal genital bleeding. These three conditions are listed in the class label for progestin-only contraceptive pills that are taken daily without interruption for routine contraception. The Plan B prescription label states, "It is not known whether these same conditions apply to the Plan B regimen consisting of the emergency use of two progestin pills." The terms 'undiagnosed abnormal genital bleeding' or 'unexplained vaginal bleeding' are not, in fact, a medically founded contraindication for using Plan B; the Applicant has proposed that this condition be removed from the OTC label. The DRUDP agrees with the Applicant's request.

Medical Officer's Comments

- ***This reviewer believes there are no medical contraindications to the use of Plan B except for a history of allergy to levonorgestrel.***
- *At the Advisory Committee meeting on December 16, 2003, the question of breast-feeding as a contraindication was raised. Progestin-only pills, taken continuously for contraception, are in fact labeled as safe for lactating women. It was the Committee's majority opinion that lactation is not a contraindication to taking Plan B. The DRUDP agrees with this opinion.*

7.5 Use of Emergency Contraception in Adolescents

7.5.1 Adolescent Safety Study

An open-label safety study (WCC-PED-001) in 60 adolescent girls aged 13-16 yr. who took the standard Plan B two-tablet dose 12 hours apart was conducted at the University of California at San Francisco (UCSF).[28] Participants recorded AEs on a diary card for 14 days and were followed for 3-5 weeks after dosing. The study population was 62% African-American, 20% Hispanic, and 15% other racial minorities. The mean age of the subjects was 15.5 yr.; the mean age of menarche was 12.3 yr., and the mean age at first intercourse was 14.2 yr. Thirteen percent (13%) had had a prior pregnancy and 13% had prior use of emergency contraception. Fifty-two (52) of the 60 enrolled subjects were evaluable; 98% reported taking both doses of study drug and 94% reported having no problems following the directions on the current prescription label, which is similar to the proposed OTC label.

No serious AEs were reported. The most common side effects in Week 1 (and the percentage of subjects reporting each of them) were: headache (50%), fatigue (40.4%), nausea (38.5%), dizziness (27%), lower abdominal pain (25%), breast tenderness (13.5%), and vomiting (11.5%). The Applicant speculated that the higher incidence of side effects reported in these young adolescents compared to that reported in adults in other studies may reflect lower levels of prior exposure to contraceptive steroids or other differences in the study population, including a higher tendency to report adverse events. A substantial number of the adolescent subjects also reported experiencing headaches, nausea, fatigue, and lower abdominal pain in the second week of the study, when PK data on levonorgestrel levels in young adolescents indicate that serum levels of drug product would be undetectable or extremely low (see Section 3.1). If the AEs reported during the second week of the study (Days 8-14) are used as the baseline incidence, the relative increases in reported AEs during Days 1-7 would be comparable to those observed in studies of adults (age ≥ 18 yr.). The sponsor concluded that this latter analysis shows that the safety (adverse event) profiles of Plan B in young adolescents and adults are comparable, and that the product can be safely used by adolescents (ages 13-16 yr.) in an OTC setting without medical oversight.

Medical Officer's Comments

- *Although the incidence of the above side effects is rather high, none were serious, severe, or debilitating. Only one of 52 evaluable adolescents failed to take the second Plan B dose, and 49/52 had no problems following the directions. This group of adolescents was at high risk of pregnancy as judged by their incidence of previous STIs (10.3%) and pregnancy (13%), prior use of emergency contraception (13%), and mean age of first intercourse (14.2 yr.). This is one of the target populations that can benefit most from ready access to emergency contraception, thereby potentially avoiding an unintended pregnancy and its emotional and physical sequelae.*
- *The majority of subjects had their next menses within 7 days of the expected time; 22% had a lighter menses, 22.5% had a heavier menses, 36% had an early menses, and 9% had a delayed menses. The mean duration of menses was not affected by treatment. These patterns of menstrual bleeding are similar to that observed in the 1998 WHO pivotal study and do not raise any safety concerns.*

7.5.2 Adolescent Use Data

In addition to the AUS, data from 3 other randomized controlled studies that enrolled adolescents was submitted by the Applicant with the original supplemental NDA (see Table 6). These studies involved advance provision of ECPs (varying from 1 to 3 packs) to a generally high-risk group of sexually active women age 14 to 24 yr. All subjects were provided with similar minimal information about the indication and correct dosing for ECPs. Subjects were then randomized to receive ECPs by either advance provision (AP) or standard access ([SA], i.e., needed a prescription and had to go to a pharmacy or clinic to obtain ECPs). Subjects were followed over a 6-12 month period (much longer than in the AUS).

Table 6 Enrollment Data by Age for Studies Enrolling Adolescents Receiving Emergency Contraception Pills either by Advance Provision or by Standard Access

Study Identifier	Enrolled (N)	Age Range (yr.)	N			Reviewer Comment
			≤16 yr.	≤17 yr.	≥18 yr.	
Study 9728 [1]	585	14-44	29	57	528	Actual Use Study conducted through family planning clinics or pharmacies
Gold [2]	301	15-20	115	187	114	Enrollment at an adolescent medicine clinic
Jackson [2]	370	14+	15	21	349	Postpartum mothers prior to hospital discharge
Raine [2]	2,090	15-24	254	476	1614	Women at family planning clinics not seeking EC at time of visit [4]
DIAL EC [3]	7,756	8-51	613 [5]	1,225	6,531	Toll-free phone in for a prescription to be filled at a pharmacy or clinic of choice
Totals	**11,102**		**1,026**	**1,966**	**9,136**	

[1] Final Study Report submitted with original supplemental NDA.
[2] Interim reports/data submitted with original supplemental NDA. Additional information obtained from study investigators during the review process. Studies each had an advance provision arm and a standard access arm.
[3] Prepublication manuscript provided by principal investigator during review process. See Medical Officer's Comments below for details of this study.
[4] Study had a third arm with pharmacy access for ECPs without requiring a prescription in the San Francisco area.
[5] Two hundred two (202) of the 613 subjects were age 13-15 yr. of age.

Medical Officer's Comments

- *The above studies greatly expand the number of adolescents for whom we have data concerning the use of emergency contraception and its impact on "risky behavior." There were over 1,000 adolescents age ≤16 yr., and almost 2,000 age ≤17 yr. When possible, this group of young adolescents (17 yr. and younger) was compared to the older adolescents age 18-20 yr.*
- *The statewide DIAL EC Project in North Carolina mimicked an OTC setting in many ways. Women did not have to go to a clinic or health care provider to get a prescription; they had to self-determine that they needed emergency contraception, make a phone call to the coordinating center, and then pick up the ECPs at a local pharmacy or Planned Parenthood Clinic (PPC). As in the OTC setting, they had to pay for the pills and more often chose to go to a local pharmacy than to a PPC. More than 9,700 prescriptions were issued to the 7,756 participants over a 29-month period.*

7.5.3 Adolescent Use and Behavior

At the December 2003 Joint Advisory Committee Meeting, some members of the Committee as well as other interested parties expressed concern over the OTC availability of emergency contraception and the effect that this might have on adolescent behavior (e.g., increasing sexual promiscuity). There is evidence to suggest that the OTC availability of emergency contraception will not increase sexual activity among young adolescents. A randomized controlled trial in the U.K. of a teacher led intervention in schools with 1,974 boys and 1,820 girls, all 14-15 yr. of age, demonstrated that education about emergency contraception did not increase sexual activity among this group of young adolescents. The intervention increased levels of knowledge about emergency contraception, but there were no differences observed in sexual activity or in frequency of emergency contraception use at a 6-month follow-up.[29] Although a large majority of the Advisory Committee members did not see this as an issue if Plan B is available OTC without age restriction, the following questions were posed:

1. Will adolescents use Plan B inappropriately or more frequently than older women?
2. Can adolescents follow the correct timing for the first and second doses of Plan B?
3. Will adolescents use Plan B as their regular form of contraception, or if regularly using effective contraception, will they switch to some other less effective method?
4. Will the OTC availability and presumed increased use of Plan B lead to an increase in sexually transmitted infections (STIs)?

These issues are addressed in Section 7.5.3.1 through Section 7.5.3.4.

7.5.3.1 Comparative Adolescent Use of Emergency Contraception

In the Gold study, the same percentage (18%) of the subjects aged 15-17 yr. as those 18-20 yr. used emergency contraception during the 6-month study period. In the Jackson study, 16% of the subjects • •19 yr. of age used emergency contraception compared to 9% of the subjects ≥ 20 yr. of age. In the Raine study, 38% of the 15-17 age group compared to 27% of the 18-24 yr. age group used emergency contraception during the 6-9 month study period. In the DIAL EC project, 82% of the 2,065 callers under age 19 yr. received 1 prescription compared to 84% of the 5,691 callers 19 yr. and older; 18% of the younger group were repeat callers compared to 16% of the older group.

Medical Officer's Comments

- *These data show that the use of emergency contraception in the younger adolescent group is similar to that in the older adolescent group. Because condom use is known to be higher in the younger adolescent group, and a condom accident is a common reason to use emergency contraception, it is not surprising that the Jackson and Raine studies each showed a higher*

percentage of emergency contraception use in the younger age group, although the differences were not large.

- *The DIAL EC data, which provides the largest single database on adolescent use of emergency contraception, shows virtually the same percentage of use for women 18 yr. and under (82%) compared to that in women over 18 yr. of age (84%).*

7.5.3.2 Correct Timing

This was carefully analyzed in four of the studies:

- In the Actual use Study, data on first dose was available for 42 adolescents under age 18: 100% took the first dose in 72 hours. Data on 46 subjects under age 18 showed that 100% took the second dose at 12 ±2 hours.
- In the DAIL EC Project, of the 2,056 adolescents under age 19, 95% called the coordinating center within 72 hours of unprotected intercourse, virtually the same as 94% for the 19 and older group.
- In the Gold study, mean time after intercourse for the first dose for the 15-17 yr. age group was 17.8 hours compared to 15.5 hours for the 18-20 yr. age group. The mean time for the second dose for the 15-17 yr. age was 11.4 hours compared to 11.5 hours for the 18-20 yr. age group. The timing of both doses was not noticeably different comparing the 2 age groups.
- In the Raine study, 82% of the adolescents under age 18 yr. took the first dose within 24 hours and 99% within 72 hours. This was comparable to the 18-24 age group. The worst compliance was with the SA (standard prescription access) group, which was unanticipated since this group had to go through a health care provider to get a prescription and then go to a pharmacy to purchase the ECPs. The AP (advance provision) adolescents already had the ECPs in their possession and therefore did not have health care provider intervention as a reminder for when to take the pills.

Medical Officer's Comment

- *The above findings clearly demonstrate that the younger adolescent group had no difficulty complying with the correct dosing regimen and compared favorably with the older adolescent group.*

7.5.3.3 Contraceptive Choices

Using a variety of measures of contraceptive method choice, the Jackson study found no evidence for less effective contraceptive use in women given advance provision ECPs compared to the standard access group. In the Gold study, the incidence of unprotected sex was 38% over 6 months in both the 15-17 yr. and 18-20 yr. age groups. In the Raine study, there were no differences in patterns of condom use or the percentage of women switching their regular contraception method from the time of enrollment to later follow-up by study group (advance provision, standard access, or pharmacy access without a prescription). Compared to the full sample, the young adolescents (age 15-17 yr.) were more likely to use emergency contraception; the pattern of use, however, was similar across the 3 study groups with few young adolescents using emergency contraception more than once. The proportions of young adolescents reporting unprotected sex and frequency of condom use was similar across the 3 study groups at follow-up, so advance provision or pharmacy access without a prescription did not significantly change contraceptive behavior in the young adolescent group.

Medical Officer's Comment

- *The above findings demonstrate that the younger adolescent group did not change to a less effective method of contraception, use condoms significantly less, or behave in an inappropriate way due to "easy access" to emergency contraception because of advance provision. This suggests that ready access to OTC Plan B also would have little impact on sexual behavior and contraceptive practices in younger adolescents.*

7.5.3.4 Adolescent Data on Sexually Transmitted infections (STIs)

Data for this area is limited. There were 14 reported cases of STIs in the 15-17 yr. age group of the Gold study. Six were in the advanced provision arm and 8 were in the standard access arm. In the Raine study, in the young adolescent group (under age 18 yr.), there were no significant differences in STIs across the 3 comparison arms.

Medical Officer's Comment

- *Across the Gold and Raine studies, a total of 663 young adolescents were followed for at least 6 months. There was no difference in the incidence of STIs across the 3 treatment arms (AP, SA, and pharmacy access).*

7.6 Overall Safety Conclusions for Levonorgestrel Emergency Contraception

From an extensive review of published randomized controlled clinical trials, large safety databases based on postmarketing data, and the overall medical literature, levonorgestrel emergency contraception pills (Plan B and the identical products worldwide) have a more than acceptable margin of safety with a low misuse and abuse potential. The individual woman can easily determine her need for emergency contraception and the treatment regimen is straightforward (two tablets 12 hours apart at any time during the menstrual cycle). Plan B is not recommended for routine contraception, but repeat use does not raise any safety concerns based on substantial safety data from clinical trials in which women used levonorgestrel for routine postcoital contraception. There is no absolute contraindication to the use of Plan B except for an established allergy to levonorgestrel, which has been rarely reported over the 35 years that levonorgestrel has been taken by millions of women using an implant contraceptive, combination hormonal oral contraceptives, or emergency contraceptives containing levonorgestrel. There are no demonstrated dangers to a fetus or a pregnancy if the drug is taken when a woman is already pregnant.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The approved prescription dosing regimen is two 0.75 mg tablets taken 12-hour apart with the first dose taken as soon as possible, and no later than 72 hours, after unprotected sex. The Sponsor is proposing the same dose and dosing regimen for the OTC product. There is data in the medical literature that indicates that a single dose of 1.5 mg of levonorgestrel is equally effective as the presently approved dosing regimen. There also is data from 3 randomized controlled trials with a total of 594 women taking emergency contraception pills between 72-120 hours (4 and 5 days) after unprotected intercourse; the combined pregnancy rate of 2.5% for women using the product 72-120 hours after unprotected intercourse in these trials demonstrates significant contraceptive effectiveness over the expected 8.0% pregnancy rate.[30]

Medical Officer's Comments

- *Timing of the second dose was one issue raised during the review of the Actual Use Study.*
  - *In the original NDA review for prescription Plan B, there were 37 pregnancies (10 with levonorgestrel alone; 27 with levonorgestrel + estrogen]); all of these subjects took their second dose within 11-12 hours of the first dose. In contrast, among 86 of 1955 evaluable*

subjects who took their second dose later than 12 hours (by at least 6 hours), there were no pregnancies. Only 7 of 1955 women did not take the second dose within 24 hours of the first dose, and none of these women became pregnant.

- *There have been two large, double-blind, randomized studies with 2712[31] and 1118[32] evaluable women that compared administering levonorgestrel as a single dose of 1.5 mg to the two dose 12-hour regimen of 0.75-mg levonorgestrel. In both studies, the contraceptive effectiveness was similar in subjects using the single dose regimen (20/1356 [1.5%] and 4/573 [0.7%] pregnancies) compared to that in subjects using the two-dose regimen (24/1356 [1.8%] and 7/545 [1.3%]).*
- *In summary, these data support the conclusion that, although the recommended time for the second dose is 12 hours, it can be taken sooner than 12 hours or later (by at least 6 hours). There are also limited data in the literature (N = 594 above) that suggest Plan B may be taken up to 5 days (120 hours) after unprotected intercourse with evidence of contraceptive effectiveness.*

9. USE IN SPECIAL POPULATIONS

9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity.

Gender. The product is intended for use only in women. No studies in men have been conducted.

Age. The product is intended only for use in reproductive-aged females at risk for pregnancy. It is not intended for use in geriatric (age 65 yr. or older) populations or in premenarchal pediatric populations. As with other hormonal products for prevention of pregnancy, the DRUDP believes that the safety and efficacy of Plan B in postmenarchal adolescents is comparable to that of older reproductive-aged women. Data obtained from various sources are presented elsewhere in this review to support this opinion.

Race. No formal studies have evaluated the effect of race. However, clinical trials have demonstrated a higher pregnancy rate in the Chinese population with levonorgestrel emergency contraception. The reason for this apparent increase in the pregnancy rate of Plan B in Chinese women is unknown. This finding is stated in the current prescription product label.

9.2 Pediatric Program (e.g., Pediatric Waivers, Deferrals, Written Requests)

Pediatric exclusivity has not been granted for this product. The indications and regimen for this product are the same for all menstruating, sexually active women, regardless of age.

9.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy or Lactation.

Hepatic or renal impairment. No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of levonorgestrel EC tablets. Since the dosing regimen consists of only 2 doses over a 12-hour period, no studies to assess the effects of renal or hepatic impairment were considered necessary.

Pregnancy. Use in pregnancy is not indicated because the product is not effective once a pregnancy is established. Based on a large base of data from other levonorgestrel containing products, there is no evidence that the ingestion of 1.5 mg of levonorgestrel is harmful to either the woman or the fetus in instances in which the product may be inadvertently used in the presence of an established pregnancy.

Lactation. Based primarily on data from women taking daily progestin-only pills for routine long-term contraception, no adverse events have been found on breastfeeding performance or on the health, growth, or development of the nursing infant. This issue also was discussed by the December

2003 Joint Advisory Committee, and the opinion of the Advisory Committee members was that lactation is not a contraindication to the use of Plan B.

Drug-Drug Interaction. Theoretically, the effectiveness of Plan B and other levonorgestrel containing products could be reduced by certain hepatic enzyme-inducing drugs such as anti-convulsants (e.g., phenytoin, carbamazepine, and barbiturates), and the anti-tuberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1 Benefit/Risk Assessment for OTC Plan B

Safety considerations. As stated throughout this review, there is no clear risk associated with the use of levonorgestrel for emergency contraception. Postmarketing and surveillance data since the approval of prescription Plan B in the U.S. in July 1999 shows extensive worldwide exposure to levonorgestrel-containing emergency contraception products with over 6 million estimated uses globally. There have been **no** reported deaths, heart attacks, strokes or thromboembolic events attributed to the use of emergency contraception use based on review of the medical literature or postmarketing surveillance databases. There has been only one reported case of phlebitis[33] that occurred in a 22-year old woman in France.

There were 3 cases of convulsion, 10 cases of hypersensitivity, and 8 cases of possible pregnancy/fetal effects. All these events are discussed in the ODS safety review and are not considered to be a significant safety concern. The possible risk of ectopic pregnancy has also been thoroughly reviewed and the best evidence, obtained from over 7,800 women in randomized controlled trials, shows that the incidence of ectopic pregnancy found in the general population is the same as that seen with the use of levonorgestrel emergency contraception in the U.S. and globally.

Reported overdose is rare (or non-existent) and frequent use of levonorgestrel for emergency contraception is not a safety issue. Repeat use, although not recommended, does not raise any safety issues. Inadvertent use in pregnancy has not been shown to pose a fetal or maternal risk.

Data obtained from studies that enrolled significant numbers of adolescents who used Plan B showed no significant differences among use in young adolescents under 18 or 19 yr. of age compared to that in women 18-19 yr. of age and older and does not raise any safety concerns.

Efficacy considerations. In clinical trials assessing the effectiveness of prescription Plan B (levonorgestrel 0.75 mg administered as 2 doses 12 hours apart within 72 hours of unprotected intercourse), the product was shown to reduce the likelihood of pregnancy by more than 75%. Clinical trial data clearly indicated that the product is most effective if taken within 24 hours of unprotected intercourse or a contraceptive accident. Other data indicated that a single dose of 1.5-mg levonorgestrel (identical to a woman taking both doses of Plan B at the same time) is equally effective. Limited data also suggest that delaying the second 0.75-mg dose of levonorgestrel for up to 18 hours after the first dose has little impact on effectiveness. Limited data suggest that levonorgestrel emergency contraception may be effective in preventing pregnancy when taken up to 120 hours after intercourse, although effectiveness is reduced. In summary, although the dosing regimen for Plan B is very simple, some deviation from the recommended dosing regimen appears to have little, if any, impact on effectiveness.

Only limited information about the likely effectiveness of Plan B as an OTC product is available. However, because of the simplicity of the recommended dosing regimen and data that strongly suggest that some deviation from the recommended regimen does not impact effectiveness, it is likely the effectiveness of Plan B in the OTC setting will not be adversely affected. Since the effectiveness is directly dependent on timely use of the product after unprotected intercourse, it is possible that the actual use effectiveness of OTC Plan B, compared to prescription Plan B, may be enhanced because

of the more timely access to the product. In the Applicant's Actual Use Study (Study 9727), 14 pregnancies were confirmed in 540 women for whom follow-up data were available. This pregnancy rate (1.9%) is similar to that observed in clinical trials submitted in support of the original NDA for Plan B for prescription use.

Overall Benefit/Risk Assessment. Use of Plan B in an OTC setting will pose little risk either to the woman who uses the product or to an unrecognized pregnancy. Contraceptive products containing levonorgestrel have been used for over 35 years and are considered to be among the safest of the hormonal-based contraceptive products. A large body of data obtained from randomized controlled trials indicates that Plan B (or identical products) is highly effective and prevents at least 75% of undesired pregnancies.

Emergency contraception affords women a second chance to avoid unwanted or unplanned pregnancies. Because emergency contraception is more effective in preventing pregnancy the earlier it is taken after unprotected sexual intercourse,[34] over the counter status should enhance benefit by providing more timely access to the product than through current standard prescription access.

The risk of an adverse pregnancy outcome including low birth weight babies and premature delivery is much higher with young adolescents (age 11-15 yr. in one study[35]; age 13-17 yr. in another[36]) compared to older adolescents. Over-the-counter access to emergency contraception in young adolescents to avoid an unplanned pregnancy would be of particular value given the greater risk of an adverse pregnancy outcome in this high-risk group.

A recent report [37] enforces the point that widespread OTC availability of Plan B would be particularly beneficial to the large group of young women relying on condoms (30% of sexually active teens in the latest NSFG) or on no method of contraception (20% of sexually active teens). As stated in the discussion (pg. 244): "We had originally hoped to refer women not using hormonal contraception for FP (family planning) services. Though some women asked that we send them information about contraception, very few expressed interest in help making an appointment in a FP clinic, and fewer still actually attended appointments that were made for them. Moreover, most women reported having spoken to a medical provider about FP within the preceding year. These findings suggest that poor knowledge of available services and inadequate availability of care may not be the primary deterrents to effective contraception in this population. When it became apparent that referring women to a FP clinic for hormonal contraception would likely be unsuccessful, we began asking women whether they would be interested in APEC (advance provision emergency contraception). A majority of women who were not using hormonal or surgical contraception stated they would be interested in having emergency contraception at home in case they felt they needed it."

Based on (1) the excellent safety record of levonorgestrel in contraceptive products for over 35 years and levonorgestrel-based emergency contraceptive products (i.e., Plan B), and (2) the high effectiveness of Plan B, the benefit /risk ratio for OTC Plan B is highly favorable for all women at risk of becoming pregnant.

10.2 Proposed Labeling

The Applicant, in response to their Label Comprehension Study, made labeling changes before the Actual Use Study was started. From a safety perspective the following labeling messages are recommended:

- Do not take Plan B if you are allergic to levonorgestrel or any ingredient in Plan B
- Contact your health care provider if you experience the following:
  - Severe stomach or pelvic pain, since this can be a warning sign of a tubal (ectopic) pregnancy
  - No menstrual period by one week after the time of the next expected period, because you may be pregnant

  - Any severe symptoms or symptoms that last more than 48 hours
- Emergency contraceptive pills do not protect against sexually transmitted infections; condoms should be used if you are at risk for sexually transmitted infections

The Division of Reproductive and Urologic Drug Products agrees with the Applicant that "unusual or abnormal vaginal bleeding" is not a contraindication and should be removed from the label.

From an efficacy perspective, it is important for the label to carry messages regarding appropriate timing of administration:

- **Emergency contraceptive pills should be taken as soon as possible after unprotected sex** since they are more effective the earlier they are started
- The second dose should be taken 12 hours after the first dose

10.3 Recommendations Regarding Approval

10.3.1 Approvability

This reviewer recommends approval of the supplemental NDA, sNDA 21-045 (Plan B), for the change from prescription status to over-the-counter (OTC) status for emergency contraception (EC) without any age or distribution restrictions. This recommendation is based on the reviewer's determination that the Applicant has provided sufficient information regarding the safe and proper use of Plan B, as required under 21 CFR 310.200, to exempt Plan B from prescription-dispensing requirements. This reviewer's recommendation is further supported by the findings of the joint Advisory Committee Meeting of December 16, 2003 (Reproductive Health Drugs Advisory Committee and Over-the-Counter Advisory Committee) that recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over-the-counter without any age or distribution restrictions and without any further studies before approval.[38]

10.3.2 Basis for Recommendation regarding Approvability (Benefit/Risk Assessment)

As stated in Section 10.1 and throughout the review, Plan B has a very positive Benefit/Risk ratio. There are virtually no risks associated with its use, serious AEs are rare, and the overall safety profile is excellent. There is no evidence that American women will abuse Plan B as an OTC product. OTC consumers will be able to self-determine the need for the product and will be able to understand and follow the instructions for proper use of Plan B. The clear benefit is the prevention of pregnancy (roughly a 75-90% reduction in the number of expected pregnancies), which is directly related to how soon the product is taken after unprotected intercourse or a contraceptive accident. The compelling benefit for having OTC status for Plan B is that it will promote easier and ready access to the product that should in turn enhance its contraceptive effectiveness and significantly reduce the number of unplanned pregnancies.

10.3.3 Recommendations on Phase 4 Studies and Risk Management Program

10.3.3.1 Phase 4 Studies

No Phase 4 studies are recommended.

10.3.3.2 Risk Management Program

No risk management program, beyond that of appropriate modification of labeling and the Applicant's proposed educational program is recommended. The Applicant's marketing plan and postmarketing CARE^{SM} (Convenient Access, Responsible Education) Program are designed to limit the availability of Plan B to pharmacies and clinics, and to educate health care providers and

consumers regarding the (a) responsible use of emergency contraception and routine contraception and (b) prevention of sexually transmitted infections.

Daniel Davis, MD, MPH
Medical Officer, DRUDP (HFD-580)

Scott E. Monroe, MD
Medical Team Leader, DRUDP (HFD-580)

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[2] He CH, et al. A multicenter clinical study on two types of levonorgestrel tablets administered for postcoital contraception. *International J of Gyn and Obstet* 1991;36:43-8.

[3] Personal correspondence, 2-2-04, with Helena von Hertzen, the Principal Investigator for the WHO study.

[4] NDA, SE011, Volume 1 in Section 14 "Financial Disclosure", page 140.

[5] ICEC meeting, 10-2-03; Not-2-late.com, the emergency contraception website.

[6] Current NDA submission, Volume 9, page 116.

[7] The ODS Postmarketing Safety Review dated October 31, 2003 is found in Attachment C.

[8] ACOG Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists; February 2001, No. 24: 1.

[9] ACOG Practice Bulletin. Prenatal Diagnosis of Fetal Chromosomal Abnormalities. May 2001; No. 27:1-11.

[10] Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstetrics Gynecology* 1990;76:552-57.

[11] Current NDA submission, Volume 9, page 119.

[12] Correction sent by FAX dated 2-13-04: U.S. pregnancies should be 36 and the total pregnancies should be 266; there were 13 U.K. ectopics and none in the U.S.; percentage ectopics is thus 21/266 = 7.9%. See Reviewer comments.

[13] Rajkhowa M, et al. Trends in the incidence of ectopic pregnancy in England and Wales from 1966 to 1996. *Br J Obstet Gyn* 2000;107:369-74.

[14] Ectopic pregnancies: USA data, 1990 to 1992. *Morb Mortal Wkly Report* 1995;44:46-48.

[15] von Hertzen H, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial. *Lancet* 2002;360:1803-10.

[16] Arowojolu AO, et al. Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians. *Contraception* 2002;66:269-73.

[17] Task Force on Post-ovulatory Methods of Fertility Regulation. Randomized controlled trial of levonorgestrel versus Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998;352:428-433.

[18] Wu S, et al. A randomized, double-blind, multicenter study on comparing levonorgestrel and mifepristone for emergency contraception [in Chinese]. *Zhonghua Fu Chan Ke Za Zhi* 1999;34:327-30. In *J of Fam Plan and Repro Health Care* 2003;29(4):249.

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[20] NDA submission, Volume 13/59, pages 047-048j.

[21] NDA submission, Vol 9, page 090; also, MO review of the original articles for several large South American levonorgestrel trials in the 1970s.

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[27] Raman-Wills L, et al. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. *Obstetrics & Gynecology* 1995;85:141-9.

[28] NDA submission, Volume 32, Study Report and Protocol, pages 99-125.

[29] Graham A, et al. Improving teenagers' knowledge of EC: cluster randomized controlled trial of a teacher led intervention. *British J Medicine* 18 May 2002;324:1179-84.

[30] The 3 studies are found in Ellertson C, et al. Extending the time limit for starting the Yuzpe regimen of emergency contraception to 120 hours. *Obstetrics & Gynecology* June 2003; 101(6):1168-71, Von Hertzen H, et al. *Op. cit. Lancet* 2002(Dec), and Rodrigues I, et al. Effectiveness of ECPs between 72 and 120 hours after unprotected sexual intercourse. *Am J of Obstet Gyn* 2001;184:531-37.

[31] Von Hertzen H, et al. *Op. cit. Lancet* 2002(Dec).

[32] Arowojolu AO, et al. *Op. cit. Contraception* 2002

[33] NDA Volume 9, pg 115.

[34] This conclusion was clearly demonstrated in the FDA review of the original efficacy data from the comparative WHO multicenter Study 92808 submitted in the Plan B application in 1999, and has been substantiated by several articles in the peer-reviewed medical literature since 1999.

[35] Satin, AJ, et al. Maternal youth and pregnancy outcomes: middle school versus high school age groups compared with women beyond the teen years. *Am J Obstet Gyn* 1994;171(1):184-87.

[36] Fraser, AM, et al. Association of young maternal age with adverse reproductive outcomes. *NEJM* 1995;332(17):1113-17.

[37] Golden, MR, et al. Failure of family-planning referral and high interest in advanced provision EC among women contacted for STD partner notification. *Contraception* March 2004;69;241-46.

[38] Objections raised by Dr. Stanford from Utah can easily be solved by changes in the OTC label. He stated that if the changes were made, he would vote for the OTC switch. DRUDP agrees with his proposed changes [stating the mechanisms of action and contraceptive effectiveness more clearly as part of the label]. This would make the AC vote 24 in favor and 3 opposed to the OTC switch.

Attachment A

Studies of Levonorgestrel Taken after Intercourse for Postcoital Contraception and Regimens Used

STUDY	REGIMEN
WHO/HRP-sponsored multicenter studies: single 0.75 mg dose of levonorgestrel	
WHO/HRP 1987 – Study 82906 International	One 0.75 mg tablet within 8 hours after the first coital act in the periovulatory period, then one tablet 24 hours later, then one tablet after each coital act, but no more than one tablet per 24 hours.
He, China 1991	One 0.75 mg tablet within 8 hours after the first coital act in the periovulatory period, then one tablet 24 hours later, then one tablet after each coital act, but no more than one tablet per 24 hours.
WHO/HRP 1993 – Study 87908 International	One 0.75 mg tablet within one hour after each coital act, but no more than one tablet within a 3-hour period.
Other studies of levonorgestrel, 0.75 mg	
Seregely, Hungary (multicenter 16 small studies)	One 0.75 mg tablet within one hour after each coitus, but no more than one tablet per 3-hour period. In cases of "clustered coitions", 1 tablet after the first act, another three hours later, and a third the following day.
Chernev Bulgaria	One 0.75 mg tablet within one hour after each coital act; no more than four tablets per month.
Szczurowicz, Poland	0.75 mg tablets; up to 4 per cycle.
Nirapathpongporn Thailand	One 0.75 mg tablet within one hour after each coital act, but no more than one tablet within any three hour period. In cases of multiple acts, one tablet within one hour after the first act, a second tablet 3 hours later, and a third tablet the next morning.
Czekanowski Poland	One 0.75 mg tablet within one hour after each coital act, but no more than one tablet within any 3-hour period. In cases of multiple acts, one tablet within one hour after the first act, a second tablet 3 hours later, and a third tablet the next morning.
Klawe Hungary	0.75 mg tablets; regimen not stated.
Orley Hungary	One 0.75 mg tablet within one hour after intercourse. In case of repeated intercourse, one more tablet three hours later.
Sas, Hungary	One 0.75 mg tablet within one hour after each coital act.
Other studies: using various dose levels of levonorgestrel	
Kesserü Peru	One tablet (0.15, 0.25, 0.30, 0.35, 0.40 mg) within one hour after each coital act.
Moggia Argentina	One 0.35 mg tablet within one hour after each coital act.
Echeverry Columbia	1.0 mg within 8 hours after intercourse, but no more than one tablet in an 8 hour period.
Hurtado Peru	Various doses; regimens not stated. (Original efficacy data from files of Schering A.G.)
Larrañaga, Peru	One 1.0 mg tablet immediately after intercourse.
Canzler East Germany	Group A: One 0.4-mg tablet within 12 hours after each coital act. Group B: Two 0.25 mg tablets immediately before and one 0.25 mg tablet 8 hours after each coital act.

ATTACHMENT B

Teratogenic Risk of Emergency Contraception and Hormonal Products for Prevention of Pregnancy: A Review of the Literature

A. Teratogenic Risk of Emergency Contraception (EC)

There is very limited information specifically on EC use during pregnancy since it is taken for the prevention of pregnancy, requires only two doses, and will not interrupt an existing pregnancy. A review of the literature on inadvertent use of oral contraceptives (OCs) during pregnancy provides the most information relevant to fetal exposure to sex hormones in early pregnancy. Much of the epidemiological literature dates to the 1970s and 1980s when use of higher-dose oral contraceptives than currently prescribed was the usual practice, and reports of congenital anomalies were being analyzed as to general risk factors and all maternal medications taken around the time of conception or during pregnancy. The doses of sex hormones in EC pills are about 2-5 times that of single OC pills containing the same hormones. However, a course of treatment for EC requires the taking of only 2 doses (e.g., 0.75 mg levonorgestrel x 2 for Plan B) and is not intended for chronic or repeat use. There are many reported cases of women inadvertently taking OCs, either combination hormonal pills containing both an estrogen and a progestin, or progestin-only contraceptive pills (POPs), for up to several months while pregnant. The comprehensive reviews listed here provide strong evidence that exposure to sex hormones [both combination hormonal products and levonorgestrel-alone pills] in early pregnancy does not have a teratogenic effect.

Review articles

The following are important review articles about teratogenic risk with sex hormone exposure around the time of conception and during the first trimester of pregnancy. These articles summarize the current state of science and primarily rely on clinical trials and prospective, cohort studies, which have less bias than case-control observational studies.

1. *Reproductive Toxicity Review*, last revised 2/01/01, from REPROTOX®, a reproductive toxicity database.

"A large number of reports [13 are referenced] have failed to find an association between OC/progestin exposure just before or during pregnancy and congenital heart defects or other nongenital abnormalities. There have been reviews that detail the much larger collection of reports from which this sample was taken [5 are referenced]."

2. Raman-Wilms L, et al: Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995;85(1):141-9.

Out of 168 articles initially identified, 14 studies (7 cohort and 7 case-control) involving 65,567 women, met the criteria for meta-analysis. The authors concluded, "There was no association between first trimester exposure to sex hormones generally (or to OCs specifically) and external genital malformations. Thus, women exposed to sex hormones after conception may be assured there is no increased risk of fetal sexual malformation."

3. McCann MF and Potter LS: Progestin-only oral contraception: A comprehensive review. *Contraception* 1994;50(6)(S1):S9-195.

"Conclusion: based on the findings of these studies, it is unlikely that fetal anomalies or developmental lags will occur because of accidental use of POPs [progestin-only pills] during pregnancy, nor is there any hypothesized biological mechanism for such an effect." (page S52)

4. Simpson JL and Phillips OP: Spermicides, hormonal contraception, and congenital malformations. *Adv Contracept* 1990;6:141-67.

This detailed review of the literature examined 18 major prospective studies evaluating the effects of progestin exposure during pregnancy, and determined that the doses received were not teratogenic.

5. Bracken MB: Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990;76:552-57.

Overall, the author analyzed data from 6,102 exposed and 83,167 unexposed women. He points out that it is improbable that a single source of bias would have influenced all the studies systematically. He concluded that the overall relative risk for all malformations from the 12 prospective cohort studies was the same for exposed and unexposed women. "This lack of association between OCs and birth defects in prospective studies agrees with the results of most of the better-designed case-control studies."

6. Population Council: Norplant Levonorgestrel implants: a summary of scientific data. *The Population Council* 1990, New York.

Clinical trials of NORPLANT® system found no evidence of teratogenicity of levonorgestrel administered by implants.

7. Wilson JC and Brent RL: Are female sex hormones teratogenic? *Am J Obstet Gynecol* 1981;141:567-80.

The four major teratogenic concerns associated with sex hormones are heart, limb, vertebral, and GI tract anomalies. The authors concluded that there is no association between oral contraceptives and birth defects based on several findings, including extensive surveillance data that did not show a corresponding rise in the incidence of the suspected birth defects as the use of OCs increased. They pointed out that because sex hormones act specifically on tissues with hormone receptors that are primarily on reproductive/genital tissues, the probability of receptor binding causing anomalies on non-genital tissue is low.

B. Animal Toxicology Review

Maier WE and Herman JR: Pharmacology and toxicology of ethinyl estradiol and norethindrone acetate in experimental animals. *Regulatory Toxicology and Pharmacology* 2001;34:53-61.

The authors concluded, "for over 30 years various combinations of synthetic estrogens and progestins have been used in OCs. Ethinyl estradiol (EE) and norethindrone (NA) alone or in combination, possess low acute and chronic toxicity. These agents are not teratogenic when given in combination. Overall, the animal data demonstrates that long-term exposure to EE and NA formulations pose very little health risk to humans."

Attachment C

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH		ODS POSTMARKETING SAFETY REVIEW	
TO: Daniel Shames, M.D., Director Division of Reproductive and Urologic Health Products (DRUDP). HFD-580		**FROM:** Sarah J. Singer, R.Ph., Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	**ODS PID#,** **DATE:** D030586 October 31, 2003
DESIRED COMPLETION DATE: October 31, 2003	**REQUESTOR:** Daniel Shames, M.D.		
DATE RECEIVED BY ODS: September 30, 2003			
DRUG: Plan B® (levonorgestrel)	**NDA #:** 21-045	**SPONSOR:** Women's Capital Corporation, Barr Laboratories	

EVENT: All events, with an emphasis on ectopic pregnancies

EXECUTIVE SUMMARY:

As background information for an upcoming advisory committee meeting on a proposed OTC switch for Plan B®, DRUDP requested AERS information and information from the United Kingdom on adverse events reported in association with the use of postcoital levonorgestrel. The division indicated they would be most concerned about deaths (if any) and ectopic pregnancies.

Neither AERS nor the U.K.'s database contained any reports of death in women using postcoital levonorgestrel.

AERS contained 28 unduplicated cases of ectopic pregnancy (none from the United States) in users of postcoital levonorgestrel. Four of the cases had been published.

Most of the other reported events were nonserious and already are described in the product labeling. However, there were ten cases of hypersensitivity reactions, seven of which were considered life-threatening. The current Plan B® labeling does not address hypersensitivity reactions.

REASON FOR REQUEST/REVIEW:

As background information for an upcoming advisory committee meeting on a proposed OTC switch for Plan B®, DRUDP submitted a consult request but did not state what information they wanted ODS to provide. Daniel Davis, M.D., the medical officer for Plan B®, was contacted and indicated that he would be most interested in cases involving death (if any) and/or ectopic pregnancies. Information on other events reported to the FDA could be presented in tabular format.

Dr. Davis also asked if ODS could obtain information from the United Kingdom on adverse reactions to Levonelle and Levonelle-2 (the U.K. equivalents of Plan B®). He later requested U.K. utilization data as well.

USAGE INFORMATION:
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The utilization databases usually used by ODS were deemed inadequate to determine the use of Plan B®, which is often dispensed by family planning clinics rather than outpatient pharmacies or office-based physicians. Accordingly, sales data were requested from the IMS HEALTH INC. National Sales Perspectives™ database, which captures sales to U.S. non-retail outlets such as clinics, as well as retail pharmacies. The data show that approximately 314,000 Plan B® kits were sold in the United States between the approval of the drug in July, 1999 and the end of August, 2003. There is no way of knowing what percentage of the sold kits have actually been distributed to patients.

At the request of HFD-580, ODS has also requested utilization data from the United Kingdom. If the U.K. is willing to provide it, we have asked that it be sent directly to DRUDP.

SEARCH DATE:	**DATABASE SEARCHED:**
October 9, 2003	Adverse Event Reporting System (AERS)

SEARCH CRITERIA:

A typical AERS search using the drug active ingredient (generic name), levonorgestrel, would capture all the Norplant® cases as well as those associated with Plan B®. Thousands of Norplant® cases have been received in association with class action lawsuits. Therefore, AERS was searched using only the trade name Plan B and various verbatim reported names such as foreign trade names (Levonelle, Levonelle-2, Postinor, Postinor-2). The search retrieved all AERS cases with any of those drug names listed as suspect products.

SEARCH RESULTS:

The search identified 130 cases, all of which were retrieved for hands-on analysis. After eliminating duplicate reports, a total of 116 unduplicated cases remained. There were no reports involving death.

Most of the reports involved nonserious expected (labeled) events and are tallied below. The other cases will be presented in the sections that follow.

Unintended pregnancy (no other event)[1]:	**21**
Delayed menstruation:	**3**
Menstrual dysfunction:	**2**
Vaginal bleeding:	**26**
Additional events:	
Cramps, pain, &/or backache:	**8**
Diarrhea:	**1**
Dizziness:	**1**
Headache:	**1**
Passing clots:	**3**
Nausea &/or vomiting:	**3**
Nausea and/or vomiting (no bleeding):	**8**
Additional events:	
Cramps or pain:	**3**
Dizziness:	**2**
Headache:	**1**
Mood swings:	**1**

[1] Three additional patients had unintended pregnancies resulting in spontaneous abortions, and a fourth had a missed abortion. See **POSSIBLE FETAL EFFECTS**.

ECTOPIC PREGNANCIES:

Number of cases, country of origin:

The AERS search identified 29 cases. During hands-on review, only one definite duplication was identified, so this analysis will be presented as covering 28 unduplicated cases[2].

None of the 28 cases occurred in the United States.

Twelve cases were reported from Gedeon Richter in Hungary without information on the actual country of origin. Levonelle-2 was listed as the drug in eight of the 12 cases, and Postinor-2 in the other four. Ten of the cases provided demographic information; among those ten cases, there does not appear to be duplication of a case reported from another country.

There were ten cases from the United Kingdom, one of which had been published:
Fabunmi L, Perks N. Caesarean section scar ectopic pregnancy following postcoital contraception. J Family Planning Repro Health Care **2002**;28:155-6.

Three cases came from Israel and had also been published:
Sheffer-Mimouni G, Pauzner D. Maslovitch S, Lessing JB, Gamzu R. Ectopic pregnancies following emergency levonorgestrel contraception. Contraception **2003**;67:267-9.

There was a single case from Sweden and a case from a Chinese study, as well as a literature case (see footnote 1) in which the country of origin could not be determined.

Characteristics of the cases:

The patients ranged in age from15 to 38 years (N=23).

The drug used for postcoital contraception was reported as Levonelle-2 in 18 cases, Postinor-2 in 8 cases, and "two-dose levonorgestrel" in 2 cases.

Most of the reports provided no information other than that an ectopic pregnancy had occurred. However, tubal pregnancies were specified in eight cases, and the published case from the United Kingdom presented a pregnancy occurring in the surgical scar from an earlier Caesarean section.

The event was considered life-threatening in 15 cases. Fifteen patients were stated to have been hospitalized, and surgery was performed in ten cases.

One patient was stated to have a history of three prior ectopic pregnancies, unassociated with postcoital contraception. Two patients (including the U.K. literature case mentioned above) had histories of prior Caesarean sections. One patient had undergone a D&C for a first-trimester termination of pregnancy 2 to 3 weeks before the unprotected intercourse for which she received levonorgestrel. Two patients were stated to have had histories of normal pregnancies.

Concomitant medications were only listed in three cases: mebeverine (an antispasmodic) and ranitidine in a patient with irritable bowel syndrome; topical erythromycin + zinc in a 15-year-old patient; and oral contraceptives, which had been discontinued two months before the unprotected intercourse, in the third patient. Six patients were specifically stated not to be taking any concomitant medications.

[2] Four of the 28 cases contained very little information (no demographic information) and therefore could be duplicates of more completely documented cases. One of the four is a literature report:
von Hertzen H et al for the WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet 2002;360:1803-10.
It mentions one patient in the two-dose levonorgestrel group who experienced an ectopic pregnancy requiring unspecified surgical treatment. The trial was conducted in China, Sweden, and the United Kingdom (among other countries). AERS contains reports of ectopic pregnancies from each of those countries, so this case may be a duplicate.

POSSIBLE FETAL EFFECTS:

A 14-year-old in the U.K. had been taking Microgynon (levonorgestrel/ethinyl estradiol) for contraception. For an unstated reason she was also given Levonelle-2 for postcoital contraception. Several conflicting reports were provided on the case, but the most recent followup indicates that conception had occurred 10 days before the use of Levonelle-2. She received x-rays for abdominal pain "at approximately 12/40 gestation (pregnancy was not diagnosed until 14/40)". At an unspecified time, major fetal anomalies were discovered: extensive abdominal wall defects, thoracic wall defects, amputation of left arm, loss of bony rib cage, and scoliosis. The reports do not provide the outcome of the pregnancy.

A 36-year-old woman in the U.S. reported that she had received Plan B® a year earlier, and had later determined that she had been pregnant at the time. She experienced 3 weeks of continuous spotting, so an ultrasound was performed. The fetus was detached from the uterine wall. A D&C was performed.

A 30-year-old woman received Levonelle-2 as postcoital contraception; erythromycin was started the same day and continued for a week (indication not stated). An unintended pregnancy occurred, and a baby with translocated Down syndrome was later born.

A 29-year-old woman who had received Levonelle-2 experienced an intrauterine death at 15 weeks' gestation. The fetus was found to have "possible Edward's syndrome (trisomy) on triple testing".

Three patients (none from the United States) had unintended pregnancies resulting in spontaneous abortions, and a fourth patient had a missed abortion.

CONVULSIONS:

The AERS search identified three unduplicated cases of convulsions. One occurred in the United States. The patient, of unstated age, reported that she had taken her first dose of Plan B® at 7 or 8 AM, and the second dose 12 hours later. The following morning a family member went to wake her and found her in bed "shaking with her eyes rolling back in her head". She was hospitalized and claimed that a physician had confirmed she had a grand mal seizure. However, an MRI and unstated blood tests had "appeared" normal. She had no history of seizures and was on no other medications.

The two other cases both involved Levonelle-2. One patient had no previous history of epilepsy. She experienced convulsions the day she took Levonelle-2, and was hospitalized. The report stated that she was also on Minulet (ethinyl estradiol/gestodene). The second patient had a long history of epilepsy, which was stated to have been well-controlled with carbamazepine. The reporter indicated that a drug interaction had been involved.

HYPERSENSITIVITY:

The AERS search identified ten unduplicated cases of hypersensitivity reactions, three of which occurred in the United States. Events ranged from minor rashes to urticaria, whole-body rashes and edematous reactions involving dyspnea. Seven of the cases were considered life-threatening. The time to onset was stated in 8 reports and ranged from four hours to two days after taking the drug. The current labeling for Plan B® does not mention hypersensitivity reactions.

MISCELLANEOUS (Single cases):

Thrombocytopenia:

Two days after taking Plan B®, the U.S. patient of unstated age noticed bruising and petechiae and had epistaxis. She was hospitalized with a platelet count of 1000. She was treated with immune globulin and prednisone and her platelet count rose to 9000 two days later. Two months later her platelet count was up to 146,000 and she was off prednisone. She had a history of a similar event occurring following a rubella vaccination several years earlier, but five months before using Plan B® her platelet count had been "in the mid-200,000 range".

Other events:

The other cases were:

- Numbness/tingling of the fingers, jaw tightening, shakiness, sore throat, nausea
- Breast soreness, tiredness, loss of appetite
- Urinary frequency/urgency/pain, breast tenderness, headache
- Abdominal bloating, cramping, extreme fatigue
- Ruptured corpus luteum cyst
- Headache, disorientation, dizziness

UNITED KINGDOM POST-MARKETING ADVERSE EVENT DATA:

The Medicines and Healthcare products Regulatory Agency (MHRA) sent printouts to ODS from the Adverse Drug Reactions Online Information Tracking (ADROIT) database of all events reported for Levonelle and Levonelle-2 since their approval in the United Kingdom. There were 45 total reports for Levonelle and 243 for Levonelle-2[3]. There were no deaths reported for either drug.

The printouts showed 5 reports of ectopic pregnancy with Levonelle and 16 with Levonelle-2.

Copies of the printouts have been provided to DRUDP.

SUMMARY:

A search of the Adverse Event Reporting System on October 9, 2003 identified 130 cases with Plan B® or a foreign equivalent as the suspect drug. Hands-on review of the cases eliminated 14 duplicates, leaving 116 unduplicated cases which were analyzed for this document.

There were no deaths.

The event of most concern to DRUDP was ectopic pregnancy. AERS contained 28 unduplicated cases (none from the United States) of ectopic pregnancy in users of postcoital levonorgestrel. Four of the cases had been published.

Most of the other reported events were nonserious and already are described in the product labeling. However, there were ten cases of hypersensitivity reactions, seven of which were considered life-threatening. The current Plan B® labeling does not address hypersensitivity reactions.

REVIEWER'S SIGNATURE / DATE:	DIVISION DIRECTOR SIGNATURE / DATE:
/S/ 10/31/03	/S/ 10/31/03
Sarah J. Singer, R.Ph.	Mark Avigan, M.D., Acting Director

[3] Presumably, any AERS reports from the United Kingdom are duplicates of cases in the ADROIT database.

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

/s/

Daniel Davis
3/25/04 02:53:25 PM
MEDICAL OFFICER

Scott Monroe
3/25/04 03:08:11 PM
MEDICAL OFFICER

Division Director Memo-Addendum

NDA #: 21-045
Drug Name: Plan B (Levonorgestrel 0.75 mg)
Sponsor: Women's Capital Corporation
Receipt Date: April 22, 2003
PDUFA Date: February 22, 2004
Type of Document: NDA supplement

Date: March 23, 2004

Introduction

Since my previous memo of January 9, 2004, upper management above the ODE level has expressed additional concerns regarding the possible Over-The-Counter (OTC) status of Plan B. This addendum is to summarize my interpretation of their concerns and also to summarize further analysis of existing data.

On January 15, 2004, Dr. Steven Galson, Acting Director of CDER convened a meeting and conveyed that he felt there was insufficient evidence, based on the actual use and label comprehension study, to demonstrate appropriate adolescent use to support approving Plan B for OTC marketing. He stated that the Plan B application would receive a non-approval action. He indicated that the actual use study did demonstrate that adolescents used the product correctly and did not exhibit changes in contraceptive behaviors. However, he felt the number of adolescent subjects was too small upon which to draw conclusions that could be extrapolated to the general population of adolescents. He outlined two key concerns, the first was adolescents timing of dose and the second being whether OTC access to Plan B would adversely affect contraceptive behaviors. Dr. Galson was unfamiliar with the data from the literature behavioral studies and suggested we summarize this data and present it to Commissioner McClellan. He also inquired whether any of the Plan B application reviews performed by the Divisions or ODEs had yet been finalized and placed into the DFS tracking system.

On February 18, 2004 a presentation of summary data was made to Commissioner McClellan (attachment 1) and attended by Janet Woodcock, John Jenkins, Steven Galson, Sandy Kweder and staff from the ODEs and divisions responsible for the review of the application. Included in the presentation were the Division's and ODE's recommendations for OTC marketing status without restriction. Dr. McClellan expressed concern about adolescent behavior, although he did not articulate the exact nature of his concern, what ages were included in his concern, what data was lacking or a path forward for the sponsor. Age restrictions on sales were briefly discussed, but the commissioner indicated that this type of program would probably require further public discussion.

The Divisions and ODE's subsequently met with Drs. Woodcock, Jenkins, Kweder and Galson on February 19, 2004. At this meeting, Dr. Woodcock expressed that she felt that the commissioner (and herself) was concerned with adolescents and stated that she felt we did not really know what behaviors adolescents would exhibit. As an example, she stated that we could not anticipate, or prevent extreme promiscuous behaviors such as the

medication taking on an "urban legend" status that would lead adolescents to form sex based cults centered around the use of Plan B. Dr. Galson indicated that he shared Dr. Woodcock's concerns.

In preparation for the Commissioner briefing, previous data has been reevaluated and new data, submitted by the sponsor and lead authors of various behavioral studies, was reviewed. This memo provides a summary of these new analyses. It also contains an exploration of Washington State epidemiologic data trends regarding STD's and pregnancy/abortion from 1997 to the most recent year for which data is available. Washington State data is examined because in 1997 programs were initiated which allowed consumers of all ages to obtain Plan B directly from a pharmacy without first going to a clinic. There are five states with similar programs, but Washington State has the oldest program and has more epidemiologic data available for review.

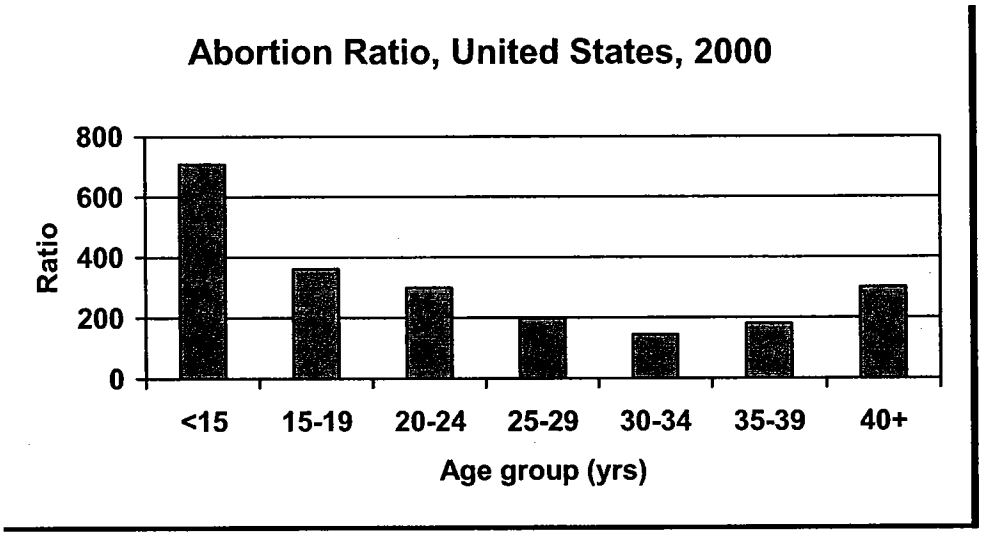
Background

Abortion Ratio

In considering the benefits of OTC access to plan B for various age groups, it is important to understand the abortion ratio for different age demographics. The abortion ratio is the number of abortions per 1,000 live births. In 2000, the abortion ratio was highest in adolescents as illustrated in Graph 1. This data was collected from 46 States, the District of Columbia, and New York City[1]. For adolescents less than 15 years of age, there are approximately 700 abortions for every 1000 live births. The next highest abortion ratio is in the 15-19 year old age group with almost 400 abortions for every 1000 liver births. This data is not surprising in that most of the pregnancies in the < 15 years of age group and many in the 15 to 19 year age group are unintended. Because many of these women are unmarried, are not prepared to care for children on their own, are attending school, do not have support systems in place to care for children, abortion becomes an important option in this younger age group. Granting OTC marketing to Plan B would improve access which should lead to increase use of Plan B resulting in decreased unwanted pregnancies and decreased abortions.

[1] MMWR, November 28, 2003

Graph 1. Abortion Ratio as a Function of Age. (Abortion Ratio is the number of abortions per 1000 live births).



Plan B is available as a full, unrestricted OTC drug in two countries, Norway and Sweden and it is instructive to examine abortion rates before and after approval of Plan B in these two countries. In Sweden, teenage abortion rates started increasing in 1999. The Swedish Government approved Plan B, initially behind the counter with subsequent full OTC approval, in 2001. In the first six months of 2003, teenage abortions were reduced by approximately five per cent.[2]

In Norway, Plan B was approved for OTC status in the second half of 2000. Abortion ratio's for 15-19 y/o decreased from 20.1/1000 in 2000 to 16.9/1000 in 2002. This is the lowest teenage abortion rate registered since the law of self-determination for women was implemented in 1979 and is far lower than that demonstrated in the United States for the same age group.[3]

Sexual Behaviors in Adolescents

In examining whether Plan B would affect contraceptive and sexual behaviors of adolescents, consideration must be given to the present sexual practices of adolescents. Presently 34% of high school students are sexually experienced at the 9th grade and 61% are sexually experienced by 12th grade.[4] At any given time, 33% of adolescent high school females are sexually active and only 51% report using a condom during their last sexual intercourse.[2] Condoms are the most used method of contraception for adolescents. Hormonal contraception is not frequently used by adolescent and some groups of adolescents can have low hormonal contraception continuation rates approaching 13%

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[2] Statistics-health and diseases: Abortions in Sweden 2003, National board of Health and Welfare, Centre for Epidemiology.

[3] Statistics Norway. Published 29 July 2003. Accessed 11 March 2004 at http://www.ssb.no/english/subjects/03/01/20/abort_en/main.html

[4] MMWR, September 27, 2002

use at 1 year and 2% use at 2 years.[5] This data demonstrates that the majority of adolescents are sexually experienced while in high school and are not adequately using contraception. Based on this information, it is not surprising that the pregnancy rate for females aged 15-19 y/o is 94 pregnancies/1000 females per year.

Sexually Transmitted Disease

Concern has also been voiced that access to Plan B may increase sexually transmitted disease (STD) rates in adolescents which would justify limiting the age of access to females that are less than 18 years old. However, when considering sexually transmitted diseases (STI's), the rate of chlamydia infections are very similar among women ages 15-19 (2619/100,000) and 20-24 (2570/100,000), which is substantially higher than the next highest group which is the 25-29 y/o (876/100,000).[6] Gonorrhea rates also demonstrate the same trend with rates of 676/100,000 for 15-19 y/o compared to 650/100,000 for 20-24 y/o and 251/100,000 for 25-29 y/o.[7] This data suggests that the current sexual behaviors of women in the 20 - 24 y/o age group place them at the same risk for STDs as the 15-19 y/o age group. The data also suggests that an arbitrary age limitation of less than 18 is not justified because the behaviors of each age group place them at essentially the same risk of STD's. Also, in evaluating if access to Plan B would adversely affect behaviors such that STD rates would increase it should be noted that STD rates in Washington State (discussed later) have been below national averages since 1996 even though greater access to Plan B for all ages through the pharmacy access program began in 1997.

Studies of Plan B Use in Adolescents

Other concerns are that there are insufficient numbers of adolescents that participated in the actual use study (AUS) limiting any conclusions for this demographic. OTC switches can be based on a variety of data including randomized trials or historic use of similar products. It is important to remember that "actual use" is just a title indicating that the study is used to analyze a product for OTC use. There are currently no study designs that can exactly mimic the OTC setting. Other studies that aren't titled "Actual use" can contribute data in the determination of OTC appropriateness. For plan B, there exist a large body of data supporting the actual use study including randomized clinical trials evaluating a variety of distribution mechanisms for emergency contraceptive pills (ECP) and a large study of women who accessed emergency contraception via telephone. These data give more adolescent information on timing of dose, self-selection, repeat use, diverse populations, clinic and non-clinic settings, behavioral changes over time and follow-up over several months.

Below is a table of behavioral studies similar to that reviewed with the Commissioner. This table demonstrates that there is data available on over 1900 adolescent's 17 years old and younger.

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[5] Zibners A, Comparison of contraception rates for hormonal contraception among adolescents. Jo Ped Adolescent Gyn, 1999, vol. 12; 90-94

[6] CDC, National Profile, STD Surveillance 2002, www.cdc.gov/std/stats/2002pdf/chlamydia.pdf

[7] CDC, National profile, STD Surveillance 2002, www.cdc.gov/std/stats/2002pdf/gonorrhea.pdf

Table 1. Studies Assessing Patient Behavior When Plan B Is Provided By Non-Prescription Mechanisms

Study	Age Range	Total N	Age		
			≤16 years	≤17 years	≥18 years
Actual Use	14-44	540	22	46	494
DIAL EC	8-51	7756	613	1225	6531
Gold	15-20	301	115	187	114
Raine	15-24	2090	254	476	1614
Jackson	14-?	370	15	21	349
Belzer	14-20	160	NA	NA	NA
Total		11,217	1,019	1,955	9,102

In reviewing these studies, adolescent use and contraceptive behavioral trends were similar to those in older age groups and had the same trends as those demonstrated in the AUS study. In prior discussions, upper level management was concerned that the extent that these studies can be used in decision making may be limited because these studies included healthcare provider intervention (counseling) that was not available in the actual use study and would not be available for an OTC drug. However, for the two behaviors of interest, timing of dose and contraceptive behaviors, the AUS provides data that health care provider intervention does not impact on timing of dose or contraceptive behaviors beyond what the label provides by itself (data presented below).

The Agency has received additional data from the Raines and Gold study. This review includes this data and provides additional analysis of the AUS as well as aspects of the Dial study. The Dial study is a study that was not included in the Advisory Committee Meeting briefing package but was discussed during the Commissioner briefing. This review will not be detailed, instead focusing only on the two concerns relayed to the Divisions and ODEs. Following this is a discussion of the epidemiologic trends in Washington State that demonstrate that improved access to Plan B did not correlate with adverse changes in STD, pregnancy or abortion rates.

Additional Analysis of Data

Actual Use study

This study has been reviewed in detail in previous reviews. Data from the actual use study indicate that the timing of 1st and 2nd dose in the AUS did not vary based on age. This study also includes subgroup analysis of "Previous users" and "First Time Users". Previous Users were subjects that had used the drug before and therefore would have had previous health care educational intervention and counseling regarding emergency contraception. First Time Users are those subjects that had never used the product and their use would demonstrate knowledge gained only from the labeling supplied with the product as subjects enrolled in this study did not receive any counseling. Table 2 provides data on the correct timing of dose based on Previous Use compared to First Time Use of ECP. Previous health care provider intervention (i.e. data from previous users) and age did not make a difference in timing of dose.

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These results suggest either the health care practitioner intervention had minimal impact on dosing or that the drug labeling included in the Plan B package had a similar effect to those who previously received information from health care providers. If intervention of the health provider is pivotal to the correct use of the product, it is not evident in the data from the actual use study.

Table 2. Timing of Dose as a Function of Age or History of Previous ECP Use

	Age (years)		Prior ECP Use	
	≤16 N=22	≥17 N=518	Previous Users N=213	First Time Users N=327
Timing for the first pill after sexual intercourse				
>72 hours	0	2 (0.4%)	2 (0.5%)	2 (0.6%)
Interval between the second and first pill				
At 12 hours	18 (82%)	369 (71%)	146 (69%)	241 (74%)

In Table 3, the data from the AUS demonstrate that the frequency of sexual intercourse during the study and contraception use were comparable between different age groups except that the 14-17 year old age group tended to use more effective contraception after receiving Plan B.

Table 3. Sexual and Contraceptive Behavior as a Function of Age during the AUS.

	% of subjects with sexual activity by age group			
Behavior	14-16 N=29	17-44 N=556	≤18 N=43	≥18 N=459
Sexual intercourse during study (4 weeks)	64%	64%	61%	64%
Change to more effective contraception	29%	11%	27%	10%
Change to less effective contraception	0%	9%	4%	9%
Change to condom use	0%	11%	0%	11%
Change to no condom use	0%	5%	4%	5%

Previous health care provider intervention also does not appear to impact upon contraceptive behaviors. If we compare behavioral changes with subjects that had prior experience with Plan B to novice users as seen in table 4, we see similar percentages of contraceptive behaviors between groups. This would again support that prior intervention of a health care provider did not influence subsequent contraceptive behaviors associated with the use of this product compared to no intervention of a health care provider.

Table 4. Sexual and Contraceptive Behavior as a Function Previous ECP Use.

	% of subjects with sexual activity by Prior EC Use	
Behavior	Previous user (n=234)	First time user (n=351)
Sexual intercourse during study (4 weeks)	65%	63%
Change to more effective contraception	9%	13%
Change to less effective contraception	10%	7%
Change to condom use	12%	9%
Change to no condom use	5%	5%

Within the 14-17 y/o subjects, contraceptive behavior was similar between those that had prior experience with Plan B compared to first time users. However the number of subjects in this cohort is limit and the results of this analysis should be considered in this context.

Table 5. Sexual and contraceptive Behaviors in 14-17 y/o subjects as a function of previous ECP use

	Prior EC Use (Adolescent Age 14-17 y/o)	
Behavior Change (% of Subjects)	Previous user (n=13)	First time user (n=33)
Sex acts during study (4 weeks)	38%	33%
Change to more effective contraception	15%	6%
Change to less effective contraception	8%	0%
Change to condom use	0%	3%
Change to no condom use	15%	0%

These analyses suggests that prior use of Plan B, which would have included health care provider intervention, does not significantly enhance the compliance with directions (timing of dose) or influence subsequent sexual and contraceptive behaviors compared to first time users. These analyses provide legitimacy to considering data from other studies where health care provider counseling occurred.

Dial EC Study

The DIAL EC Project, is a single-arm trial conducted in North Carolina. In this study females of all ages could call a toll-free number answered by a trained specialist and request that Plan B be called to a local pharmacy. Educational intervention from the trained specialist was limited to reading points from the emergency contraceptive label. In 29 months, the service issued 9,745 prescriptions to 7,774 callers. The study allowed females of all ages to enroll and there were 2,065 subjects age 18 or under and 5,691 subjects aged 19 or older. This study demonstrated that there were no differences between age groups for the reason to seek emergency contraception, requesting a prescription within appropriate time intervals or the percentage of females requesting a 2nd script (table 6). The data are useful as support to the actual use study because of the large number of adolescents enrolled and females self-select if they needed the medication. This data demonstrates that adolescents compared to older users used the

medication for the same reasons as older users, obtained the medication in a timely fashion and had the same amount of repeat use.

Table 6. Dial Study: Reasons for Use—Timely Use—Repeat Use

	18 or under (N=2065)	19 or above (N=5691)
Reason for Use		
No method Used	40%	42%
Broken condom	46%	42%
Missed OCP	4%	6%
Timely Prescription		
% with timely prescription	92%	92%
Repetitive use		
Repeat use	12%	11%

Gold Study

This was a randomized trial conducted in an adolescent medicine clinic in Pittsburgh. This study examined advanced provision (AP) vs. clinic access (requiring a standard clinic visit to obtain ECP) in a group of adolescent subjects aged 15-20. The AP group received one pack immediately with access to two additional courses as needed but not contingent upon experiencing an episode of unprotected intercourse. This study has 187 subjects 15-17 y/o and 144 subjects aged 18-20 y/o. Educational intervention was not provided by a physician. Distributing AP simulates OTC availability because the woman has emergency contraception in her home to use when she self-selects to use it. Also, subjects in the AP group were not going to use the product immediately so this would test consumer's ability to use the product without immediate instruction. It also gives important information regarding use of the product over a sustained period of time. The educational component was limited to a checklist that is similar to the consent form used for the pharmacy access program in Washington State and educational pamphlets on STDs, contraception and abstinence. The checklist enumerates the messages from the package insert/(labeling of OTC Plan B), and asks the woman to initial by each point. Over a six month period, no age based differences were seen regarding EC use, unprotected sex or condom use between the advanced (OTC-like) provision and clinic access (standard of care).

Table 7. Gold Study: Contraceptive Behaviors as a Function of Age

	15-17 y/o (N=187)	18-20 y/o (N=144)
Used ECP during study	18%	18%
Unprotected sex during study	39%	38%
Condom use on Study	88%	88%
Oral Contraceptive Pills (OCP) use on study	41%	58%
STD on study	9%	5%

There also was no difference, based on age, in timing of 1st or 2nd doses. The subjects in the Clinic Access group would be using Plan B almost immediately after obtaining the medication. The subjects in the AP group would not have had a health care provider

intervention since the time the course of AP Plan B was provided. This could be weeks or months between obtaining Plan B and use. The AP group would have been more likely to depend on the labeling for correct and appropriate use than the interaction with a healthcare provider (which was limited to a check list). Advanced provision to EC facilitated taking the drug sooner. The median time to first dose in those with advanced provision was 10 hours earlier on average for both age groups. This is important, as the drug is more effective the sooner it is taken.

Table 8. Gold Study: Timing of First and Second Dose of EC Stratified By Age

	15-17 y/o		18-20 y/o	
	Advanced Provision	Clinic Access	Advanced Provision	Clinic Access
First Dose (Hours after Sex)				
Median	14 h	24 h	9 h	14 h
Range	1-48 h	1-43 h	1-48 h	3-40 h
Second Dose (Hours after first dose)				
Median	12 h	12 h	12 h	12 h
Range	2-12 h	12-15 h	2-12 h	12-24 h

There were 12 (10%) pregnancies reported in the AP group and 19 (13%) pregnancies reported in the control group. Of the reported pregnancies, 18 (11%) were reported in the 15-17 y/o age group compared to 13 (13%) in the 18-20 y/o age group (table 9).

Table 9. Gold Study: Pregnancy during study

	Age 15-17		Age 18-20	
	AP	Control	AP	Control
Pregnancy During Study				
No	69	79	42	43
Yes	9 (12%)	9 (10%)	3 (7%)	10 (19%)

Finally, within the 15-17 year old group, there were no adverse sexual behaviors between the advance provision and the clinic access. Table 9 shows the percentage of 15 - 17 y/o subjects who engaged in unprotected sex, used condoms, used oral contraceptive use or acquiring an STD during the study. Although there appeared to be no difference in the percentage of subjects engaging in unprotected sex, those subjects with advanced provision were more likely to use ECP than those with clinic access.

Table 10. Gold Study: Sexual behaviors in 15-17 y/o based AP vs. Control

	15-17 y/o Advanced Provision	15-17 y/o Clinic Access
Used ECP on study	25%	15%
Unprotected Sex on study	36%	42%
Condom use on study	89%	86%
OCP use on study	39%	42%
STD on study	8%	9%

The Gold study demonstrates that advanced provision of ECP 1) does not increase promiscuous sexual behavior in 15 - 17 y/o adolescents compared to current methods of access, 2) is more likely to lead to use of the product earlier after unprotected sex, and 3) is more likely to lead to use of the product after unprotected sex compared to current methods of access.

Raine Study

This was a randomized clinical trial of high risk inner city females conducted in California. This study was originally a 3-arm trial arm with an advanced provision arm (AP), a pharmacy access arm (PA) at selected pharmacies and a clinic access only (CA) arm. The study was reduced to 2 arms - AP and PA six months into the study when pharmacy access was approved State-wide. Unlike the AUS, this study provided advanced provision of emergency contraception to females not actively seeking emergency contraception. In this study, women in the AP arm received three packages of EC to have ready access to a supply on hand at home. Education was a checklist of the label message points similar to that used in the Gold study.

This study had 476 females aged 15-17 y/o and 1,614 aged 18-24 y/o. At baseline, the adolescents had similar prior emergency contraceptive use and frequency of unprotected sex as the older group, but had fewer prior pregnancies, abortions and STDs. This would be expected because the younger subjects would have been sexually active for a shorter duration than the older group. At study end, the 15-17 y/o compared to the 18-20 y/o had no significant differences in emergency contraception use on study, emergency contraception use a second time, unprotected sex, or STDs as seen in table 10.

Table 10. Raines Study: Age Comparison of Contraceptive Behaviors During the Study

	15-17 y/o (N=476)	18-24 y/o (N=1614)
Used ECP on study	38%	27%
Used ECP two times	10%	6%
No method used some times	33%	27%
Experienced pregnancy	12%	6%
Contracted STD	14%	12%

The behavioral data comparing the adolescents in the advanced provision group (n=194) compared to the pharmacy access group (n=189) revealed no differences in frequency of sex/ month, number of sex partners or failure to use a contraceptive method as listed in the table 11. This suggests that ready access to a 3 month supply of emergency contraceptive in the house (advanced provision) did not alter the sexual or contraceptive behaviors of adolescents compared to pharmacy access.

Table 11. Raine Study: Sexual Behavior Trends from Baseline to Study End of Advanced Provision Compared to Pharmacy Access in Adolescents (15-17 y/o)

	Advanced Provision N=194	Pharmacy Access N=189
Sexual intercourse 1 or more times per week		
Baseline	39%	40%
Study end	44%	44%
2 or more partners		
Baseline	21%	24%
Study end	24%	22%
No contraception		
Baseline	8%	8%
Study end	10%	10%

This study enrolled a high risk population of subjects as evidenced by their high sexually transmitted disease rate, high pregnancy rate (15.6% of adolescents under the age of 18 at baseline) and failure to use a contraceptive method some of the time during the study. Sexual behavior in the 15 - 17 y/o subjects was not influenced by ready access to advanced provisions of ECP. The pregnancy rate was approximately double in the younger subjects compared to the older subjects despite a slightly higher percentage of younger subjects using ECP. This demonstrates the great need for this product in high risk youths and also demonstrates that adolescents are poor contraceptors. Without the availability of EC in this group, an even greater number of pregnancies would be expected. Sexually transmitted disease rates were similar regardless of age. Additionally, there were a large number of adolescents in this study and their contraceptive behaviors were similar to older age groups.

Washington State's Pregnancy, Abortion and STD Rates After Increased Access to ECP

At present, through collaborative agreements, five states allow consumers to obtain Plan B directly from a pharmacy without first obtaining a prescription from a health care provider. Washington State started their program in 1997 and therefore has the longest experience. It is instructional to examine abortion rates and STDs in this state compared to national trends. In 2002, the last year data is available, Washington State ranked 40th (ranked 39th in 1996) in gonorrhea rates at 49.6/100,000 compared to a national average of 125/100,000.[8] Also, Washington State ranked 35th (ranked 31st in 1996) for Chlamydia rates in 2002 at 253.4/100,000 compared to the national average of 296.5/100,000.[9] It should also be noted that the Chlamydia rates of Washington State approximated the national averages in 1994 and from 1995 to 2002 (last year data available), the State has had rates less than the national average. This again demonstrates that increased access to Plan B did not lead to increased rates of STD's compared to national averages.

[8] CDC. www.cdc.gov/std/stats/tables/table12.htm
[9] CDC. www.cdc.gov/std/stats/tables/table3.htm

Adolescent pregnancy rates and abortion rates in Washington State have consistently fallen since 1997 when pharmacy access to Plan B was initiated (see table below). It is also instructive to note that the abortion ratio (number of induced abortions per 1,000 live births) for women in all age groups has decreased in Washington State from 346 in 1997 to 322 in 2002, even while Washington State's general fertility rates mirrored United States fertility rates.[10, 11]

Table 12. Teenage Pregnancy Rates by Age in Washington State (per 1,000 women) Between 1997 - 2002

	Age 15-19		Age 15-17		Age 18-19	
Year	Pregnancy Rate	Abortion Rate	Pregnancy Rate	Abortion Rate	Pregnancy Rate	Abortion Rate
1997	74.5	29.6	45.7	20.2	122	45
1998	71.2	26.9	42.6	18.4	116.8	40.4
1999	66.5	25.5	38.0	16.1	109.6	39.6
2000	64.3	25.0	36.3	15.7	107.0	39.0
2001	59.6	23.8	32.9	15.1	100.3	37.1
2002	55.9	22.7	30.9	14.0	93.8	35.8

Table 13 demonstrates that number of legal abortions decreased for adolescents in Washington State from 1997-2000 (last year data was available from the CDC).[12] During this time frame, the total number of abortions for women of all age groups decreased. This would indicate that for a State where Plan B has minimal barriers to access, there was not an unforeseen consequence whereby Plan B was used inappropriately (used instead of regular contraception or increased promiscuity) and actually caused more pregnancies or abortions.

Table 13. The Number of Legal Abortions in Washington State by Year and Age Group

	Age				
Year	<15 y/o	15 y/o	16 y/o	17 y/o	≤19 y/o
2000	122	303	658	979	5231
1999	143	328	659	1016	5369
1998	137	350	689	1129	5312
1997	191	385	789	1195	5728

Overall, the data from Washington State would speak against the concerns that access to Plan B would increase promiscuity or that females may not be able to use the drug correctly. Since the State introduced reduced barriers to Plan B access, the data demonstrates decreased pregnancies and abortions for adolescent age groups, and STD rates below national averages. In fact, the State has decreased their National STD

[10] www.doh.wa.gov
[11] Center for health Statistics, Washington State Department of health, 10/2003
[12] MMWR Surveillance Summaries for 1997, 1998, 1999, 2000 at www.CDC.gov/mmwr

ranking over this time period for two common STD's. Also during the six plus years that Plan B has had pharmacy availability, there have no reports from Washington State that Plan B has led to an increase in promiscuity among teenagers. In regard to the possible abuse of Plan B, it must also be remembered that Plan B does not have any significant CNS effects and has a high rate of non-serious adverse events, such as nausea in over 23% of subjects and menstrual irregularities that would prohibit recreational use of this drug. Finally, as noted earlier, in Washington State, health care provider (pharmacist) input into women's decisions regarding Plan B use is minimal and consists of initialing a check list that highlights labeling concepts. This demonstrates that all ages of females seem able to use this drug with minimal health provider intervention.

Conclusions

As I described in my previous Divisional Memo, I feel Plan B adequately meets criteria for OTC marketing without restriction. The benefits of timely access include earlier dosing for greater efficacy to avoid unplanned pregnancy and possible abortion. The data indicates that benefits outweigh the risks. The data reviewed above is quite compelling to dispel any potential concerns regarding adolescent use or changes in sexually behaviors associated with plan B use. Additionally, there is no evidence supporting the possible exclusion of any demographic group from the benefits of this drug. The data demonstrate that adolescents are a subgroup that would derive great benefit from this product as they are poor contraceptors, do not plan ahead and tend to avoid health care providers. Any system that creates barriers to access, including restricted distribution or age restrictions, would defeat the purpose of this drug and lessen its public health potential. Additionally, placing age restrictions on this product may place a legal burden on pharmacies that they may not accept which would have the undesired effect of limiting access even more than is presently in place.

It should also be noted that emergency contraception is available in 33 countries without a prescription, five States in the United States with pharmacy access and there is an abundance of domestic literature where the drug has been available without a prescription and limited barriers to access to over 11,000 women including over 1900 adolescents. Washington State has had a pharmacy access program since 1997 allowing an evaluation of over six years of data. In terms of OTC switch applications, this drug has more information available to allow us to predict consumer behaviors than any drug the Division has approved for switch in recent memory. If this is not enough data upon which to base a decision, it is unclear what would constitute enough data or even if that is an obtainable goal.

A decision by the Agency to withhold OTC marketing of Plan B for reasons of theoretical abuse by a very small segment of the population despite the great benefit that could be derived from easier access could have ramifications for how we regulate other OTC drugs. To assure consistency of regulation, a natural progression of this line of regulatory reasoning would require that the Agency remove OTC marketing status for many drugs with known abuses including dextromethorphan because of reports of adolescent abuse, laxatives because of abuse by people suffering from bulimia, analgesics

because of abuse with subsequent health ramifications, or acetaminophen because of its use in suicides. This would be in spite of the great benefit derived from these drugs for the vast majority of users. Plan B falls into this category. The benefit to be derived from easier access outweighs the theoretical risk of a small percentage of users misusing the drug. Also, consideration must be given that the concerns of possible adolescent abuse have not been borne out by any studies or any worldwide safety or literature reports despite significant use.

At the Advisory Committee Meeting for Plan B, Dr. Galson asked the panel members, "If members of the committee feel that this drug should be restricted according to age, we'd like to know it". In response to this, three panel members specifically voiced favoring age restrictions, nine panel members specifically voiced not having age restrictions, and 14 members did not comment specifically regarding age restrictions although 13 of these members voted for full OTC approval. The fourteenth person in this group did not vote for approval because of concerns regarding informed consent and relaying effectiveness data, although he stated at the meeting and in a subsequent e-mail to the Agency that he thought with appropriate labeling he would change his vote to approval. One panel member felt that there should be post-marketing studies on consumers < 18 years of age. This is an overwhelming response by the committee that there should not be age restrictions.

A summary of the data reviewed demonstrates that:

- The Actual Use study demonstrated that users not receiving previous health care provider counseling had similar timing of dose and contraceptive behaviors compared to those users having had received prior health care provider counseling.
- The Dial study demonstrated that females 18 y/o and younger used ECP for the same reasons and had similar timing of medication and repeat use frequency as older females.
- The Gold study demonstrated that 15-17 y/o had the same sexual and contraceptive behaviors as older females, 15-17 y/o with advanced provision had the same sexual behaviors as 15-17 y/o obtaining the medication from a clinic and the advanced provision group started the medication 10 hours sooner on average.
- The Raines study demonstrated similar contraceptive behaviors between 15-17 y/o compared to 18-24 y/o and similar sexual behaviors in adolescents obtaining advanced provisions compared to adolescents using pharmacy access.
- The Washington State data demonstrated that since pharmacy access has been granted to Plan B in 1997:
    - Adolescents pregnancy rates have decreased
    - Adolescent abortion rates have decreased
    - The total number of adolescent abortions have decreased
    - STD rates have remained below national averages
    - The national ranking for Chlamydia has decreased from 31st to 35th
    - The national ranking for gonorrhea has decreased from 39th to 40th

There is compelling data evidencing that Plan B fulfills regulatory requirements for OTC marketing. An overwhelming majority of members comprising two advisory committees, with 12 out of 13 NDAC members and 12 out of 15 ACRHD members, voted for full OTC approval. There is a rich body of literature demonstrating appropriate and safe use of Plan B under decreased restrictions to access conditions. This memorandum reaffirms my previous recommendation that Plan B should be approval for OTC marketing without restriction.

_____

Curtis J. Rosebraugh, MD, MPH

cc: orig.

HFD-560 /frazier /cothran/solbeck/chen/leonard segal/ganley
HFD-580/griebel/beitz

What Information Do We Want from Studies for Plan B?

- Can consumers use the product safely and effectively in accordance with information on the label or other information tools?
  - Adolescent data
    - Timing and selection
    - Impact of learned intermediary

Benefits of OTC Availability of Plan B

- Improve timely access to product
- Avoid unplanned pregnancy
  - U.S. maternal mortality rate in 1999:
    - 13 deaths per 100,000 live births
  - 43% of women experience some morbidity during childbirth hospitalization
  - 25% morbidity during course of pregnancy
- Avoid abortion
  - For < 15 yo in US: 700 abortions/1000 live births
  - Teen abortion rates decreased in Sweden and Norway after OTC approvals in these countries

Adolescent Sexual and Contraceptive Behaviors

- High school students are sexually experienced
  - 34% at grade 9; 61% at grade 12
- 35% use no contraceptive with 1st intercourse
- Condoms = most common method
- Hormonal contraceptive use is age-related
  - Adolescents have low continuation rates
    - 13% at 1 years; 2% at 2 years

Outcomes Among Adolescents

- **Pregnancy**
  - 94 pregnancies/100 females aged 15-19
- **Fetal complications**
  - Pre-term birth
  - Low birth weight
  - Small for gestational age
- **STIs**
  - Chlamydia infection rates similar for ages 15-19 and 20-24

We are aware of concerns…

- Regarding proper use, repeat use, use of Plan B as routine contraception, potential increases in STIs, etc
- Caution should be used when concerns are voiced in:
  - Newspaper articles in the Daily Mail
  - Journal articles based on pharmacist or user surveys
  - UK National Health Service's report on Sexually Transmitted Infections in the UK; New episodes seen at GU Medicine Clinics, 1995-2000
    - predates the pharmacy access approval in UK
    - improved diagnostic testing
    - improved acceptability of clinic services
    - greater public and professional awareness

Data Required for OTC Switches

- Switches justified by a variety of data:
  - Randomized controlled trials (RCTs)
  - Historical use of similar products: NSAIDS, pepcid, loratadine
- "Actual Use Study" (AUS)
  - No more than a title indicating that study evaluates OTC use
  - Studies not titled AUS can evaluate OTC use
  - Guidance allows variable study designs
- For Plan B, large body of data exist in addition to AUS

Evidence Supporting OTC Switch of Plan B

- AUS supported by RCTs, and a large study of women who accessed EC via phone
- Data are available on:
  - Self-selection, timing
  - Repeat use, including access to multiple packs
  - Diverse populations
  - Clinic and non-clinic settings
  - Behavioral changes over time
  - Varying degrees of contact with HCPs
  - Longer follow-up

Global Dataset on Use: Enrollment by Age

Study	Age	Total N	≤ 16	≤ 17	≥ 18
Actual Use	14-44	540	22	46	494
DIAL EC	8-51	7756	613	1225	6531
Raine	15-24	2020	254	692*	1074*
Gold	15-20	301	115	187	114
Jackson	14-?	370	15	21	349
Belzer	14-20	160	NA	NA	NA
Totals		11,191	1,026	1,490	8,596
*Ranges are 17-19 and >19					

Key Messages:
Actual Use Study

- Adolescent "use" and "behavior" trends were similar to those in older age groups (and consistent with behavioral studies cited in NDA)
- Prior health care provider intervention does not appear to impact use or behaviors

Age-Based Demographics: Timing of 1st and 2nd Dose in AUS

	Age (years)			
	≤16 N=22	≤17 N=46	≥17 N=518	≥18 N=494
Timing of the first pill after sex act				
>72 hours	0	0	2	2
Interval between the first and second pill				
Exactly 12 hours	18 (82%)	36 (78%)	369 (71%)	352 (71%)

Prior EC Use History: Timing of 1st and 2nd Dose in AUS

	Prior EC Use	
	Previous Users N=213	First Time Users N=327
Total Correct Use	142 (67%)	224 (69%)
Timing for the first pill after sex act		
>72 hours	2	2
<72 hours	203 (95%)	296 (91%)
Interval between the first and second pill		
Exactly 12 hours	146 (69%)	241 (74%)

Behavior Changes in AUS: Age Demographics

Behavior Change	% of Subjects			
	14-16 N=29	17-44 N=556	≤ 17 N=43	≥ 18 N=459
Sex act before study (one month)	100%	100%	100%	100%
Sex acts during study (4 weeks)	64%	64%	61%	64%
Change to more effective contraception	29%	11%	27%	10%
Change to less effective contraception	0%	9%	4%	9%
Change to condom use	0%	11%	0%	11%
Change to no condom use	0%	5%	4%	5%

Behavior Changes in AUS:
No Impact of Prior EC Use (Learned Intermediary)

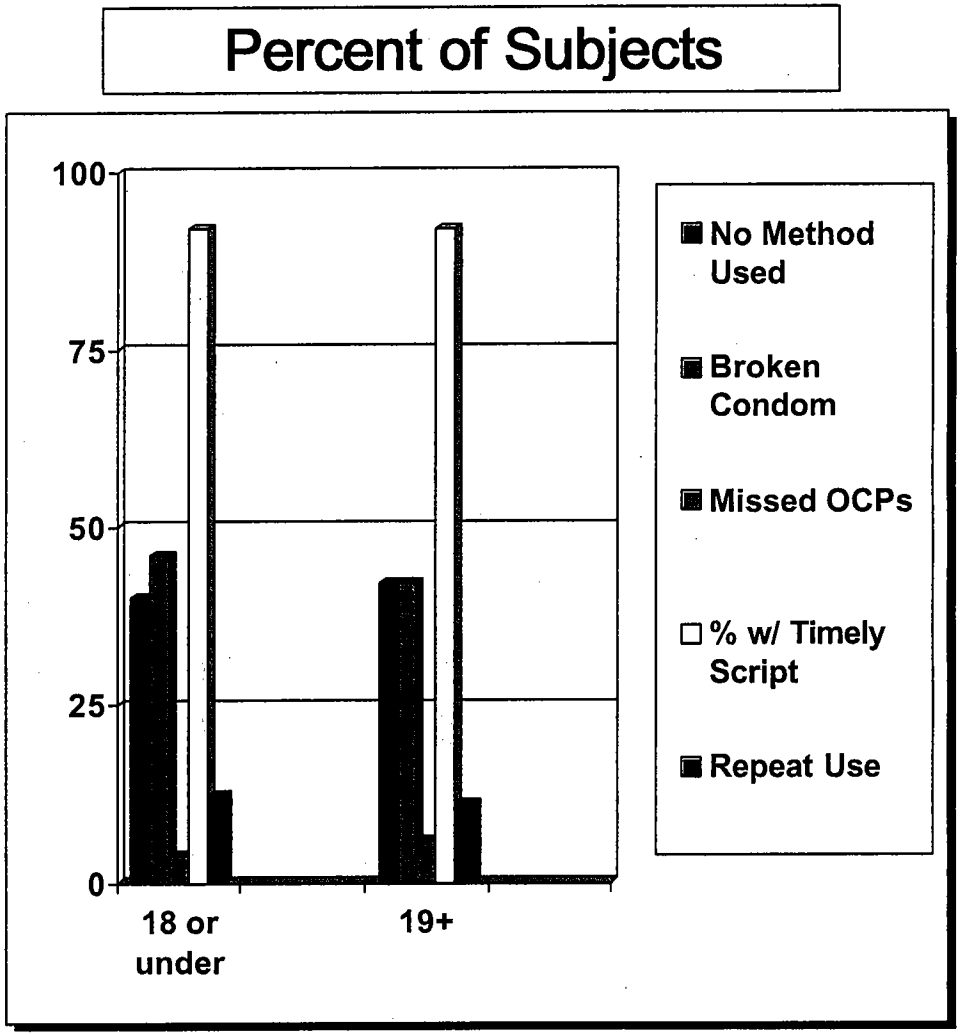
	Prior EC Use	
Behavior Change (% of Subjects)	Ever (n=234)	Never (n=351)
Sex act before study (one month)	100	100
Sex acts during study (4 weeks)	65	63
Change to more effective contraception	9	13
Change to less effective contraception	10	7
Change to condom use	12	9
Change to no condom use	5	5

Behavior Changes in AUS (adolescent):
No Impact of Prior EC Use (Learned Intermediary)

	Prior EC Use (Adolescent Age 14-17 y/o)	
Behavior Change (% of Subjects)	Ever (n=13)	Never (n=33)
Sex act before study (one month)	100	100
Sex acts during study (4 weeks)	38	33
Change to more effective contraception	15	6
Change to less effective contraception	8	0
Change to condom use	0	3
Change to no condom use	15	0

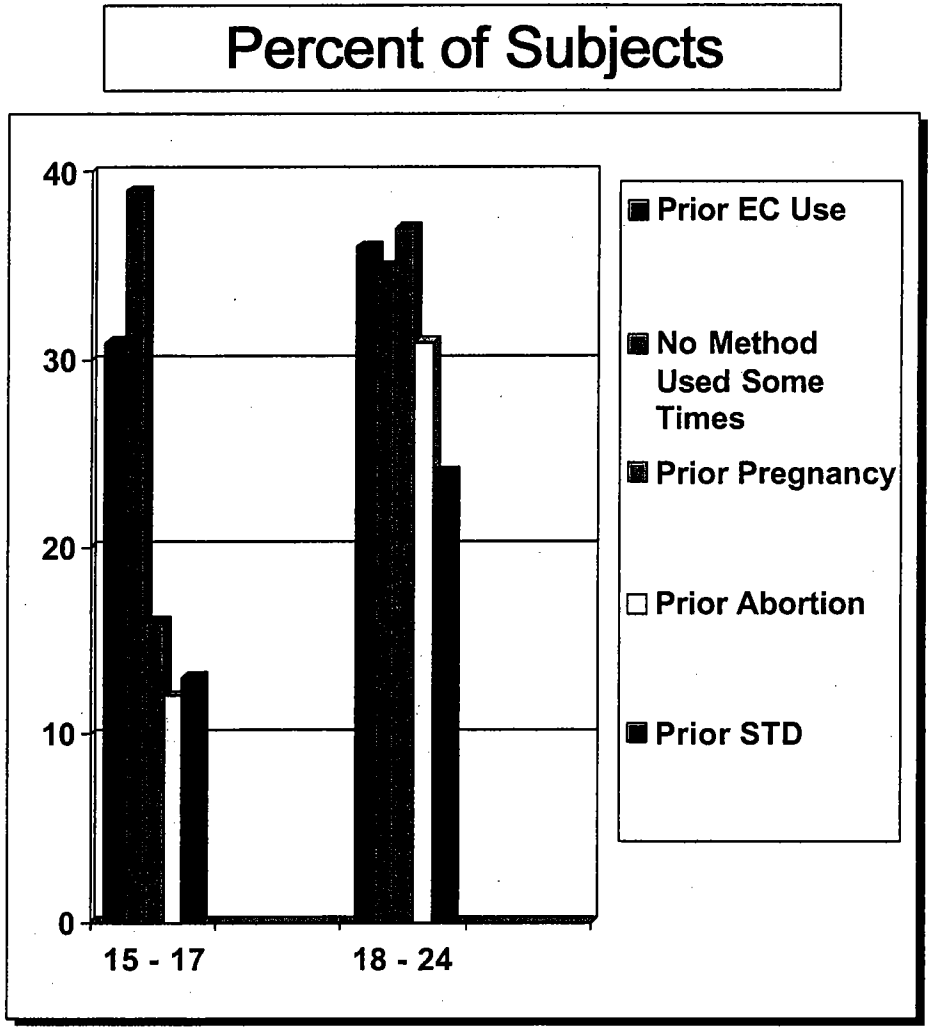
Dial EC Project: No Age Differences in Self-Selection, Timing, Repeat Use

- NC women called hotline to obtain EC
  - 2,065 aged 18 or under
  - 5,691 aged 19+
- No differences by age:
  - Reasons for seeking EC
  - Prescription ≤ 72 hr
  - % requesting 2nd script



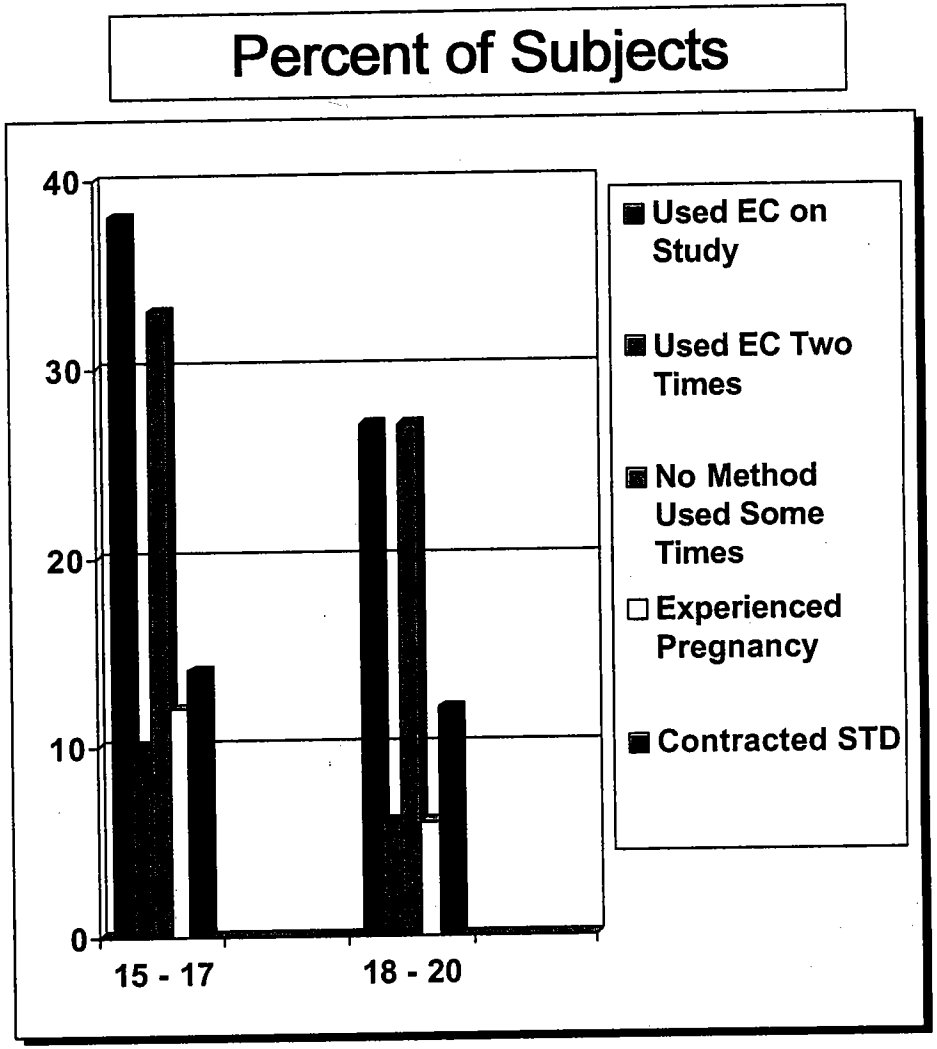
Raine Study: Baseline Data

- 3-arm study in 4 clinics; 13 pharmacies; 6 mos
  - EC info to all
  - 476 aged 15-17
  - 1,614 aged 18-24
- Adolescents had similar:
  - Prior EC use
  - Freq of unprotected sex
- Adolescents had fewer:
  - Prior pregnancies
  - Prior abortions
  - Prior STDs

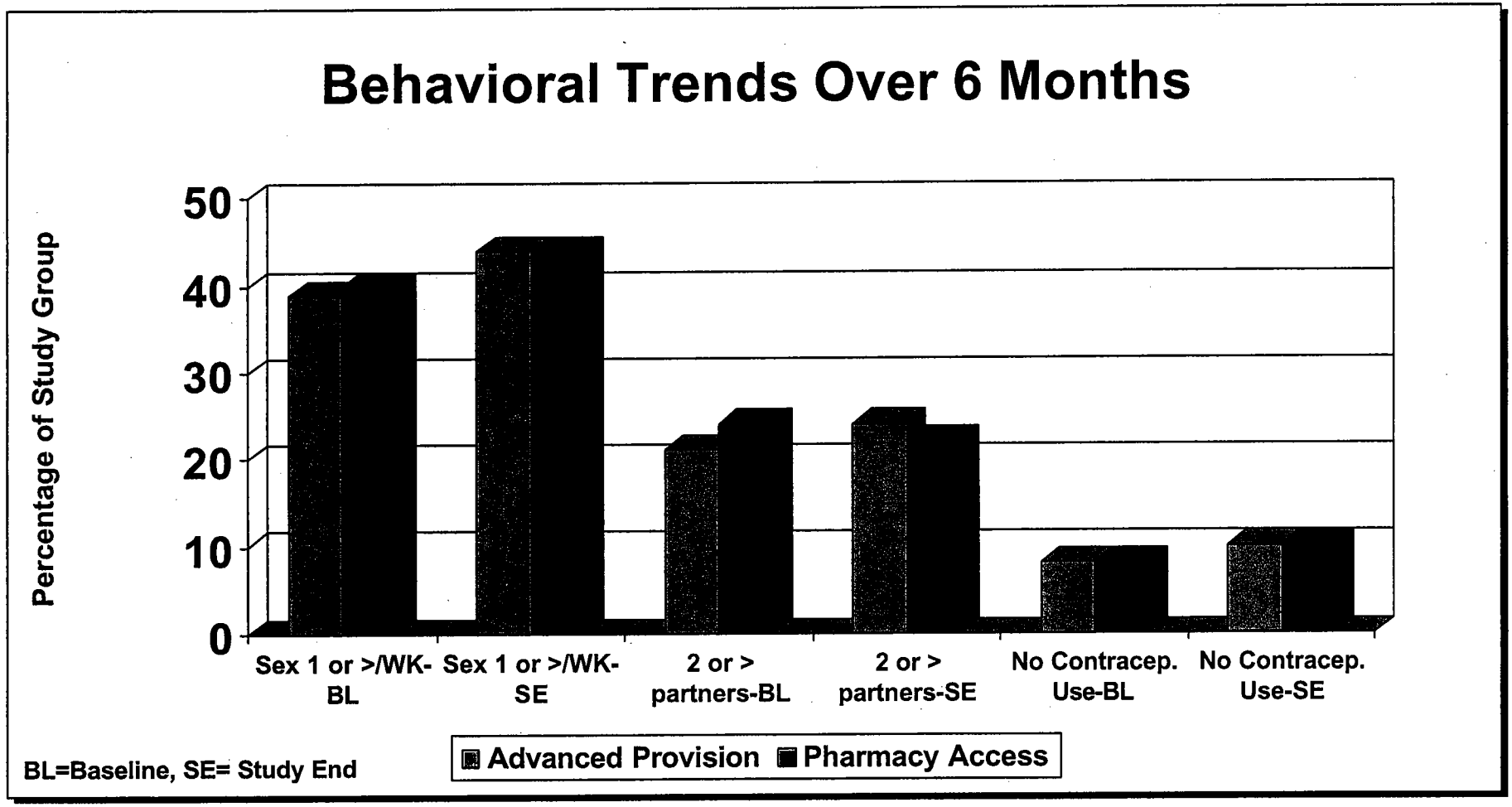


Raine Follow-Up: No Age Differences in EC Use, Sexual Behavior, Outcomes

- At 6 mo follow-up:
  - 455 aged 15-17
  - 1,485 aged 18-24
- Adolescents had no significant differences in:
  - EC use on study
  - Timing of first dose
    - 80% within 24 h
  - EC use a second time
  - Unprotected sex
  - Pregnancies
  - STDs

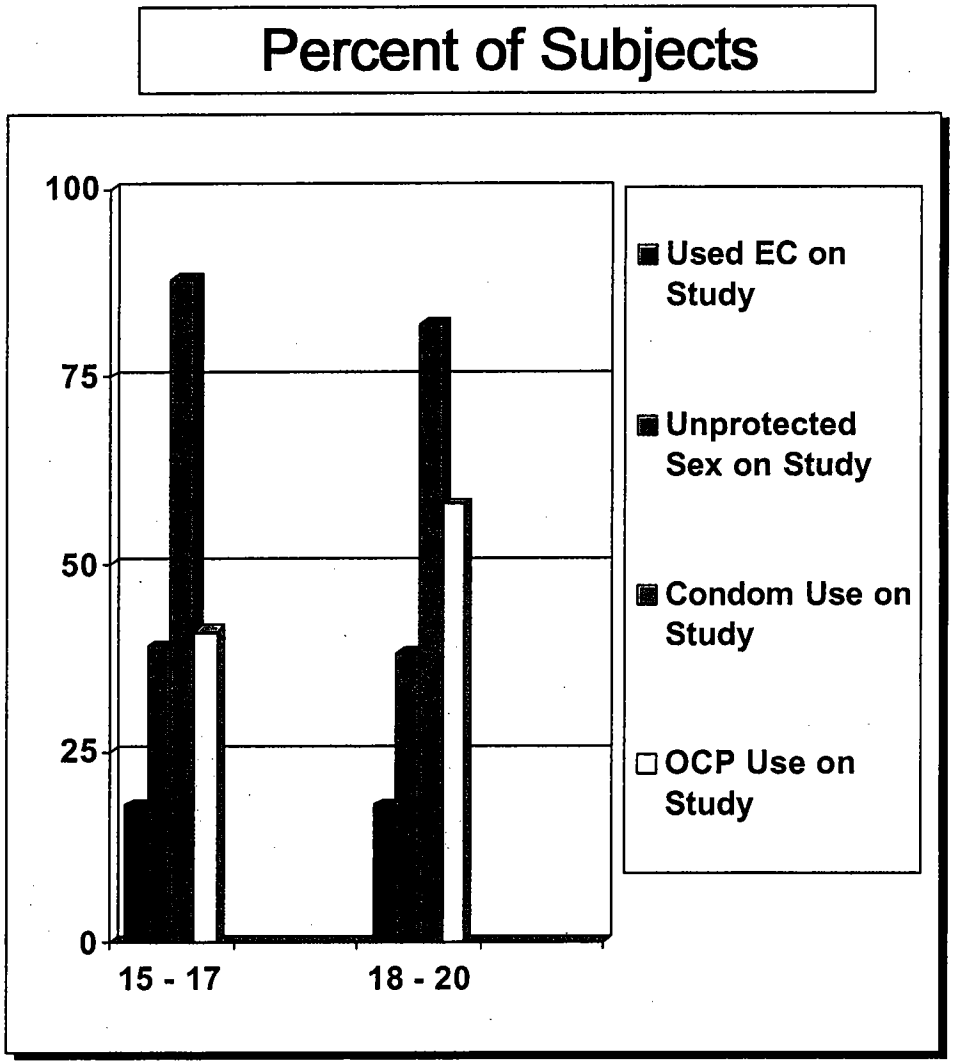


Raine Study: Behavioral Trends Ages 15-17



Gold Study: No Age Differences in EC Use, Timing, Sexual Behavior or Condom Use

- 2- arm study in Pittsburgh adolescent med clinic
  - EC info to all
  - 187 aged 15-17
  - 114 aged 18-20
- No significant differences in on study:
  - EC use
  - Timing of 1st or 2nd doses
  - Unprotected sex
  - Condom use
- OCP use higher in 18-20

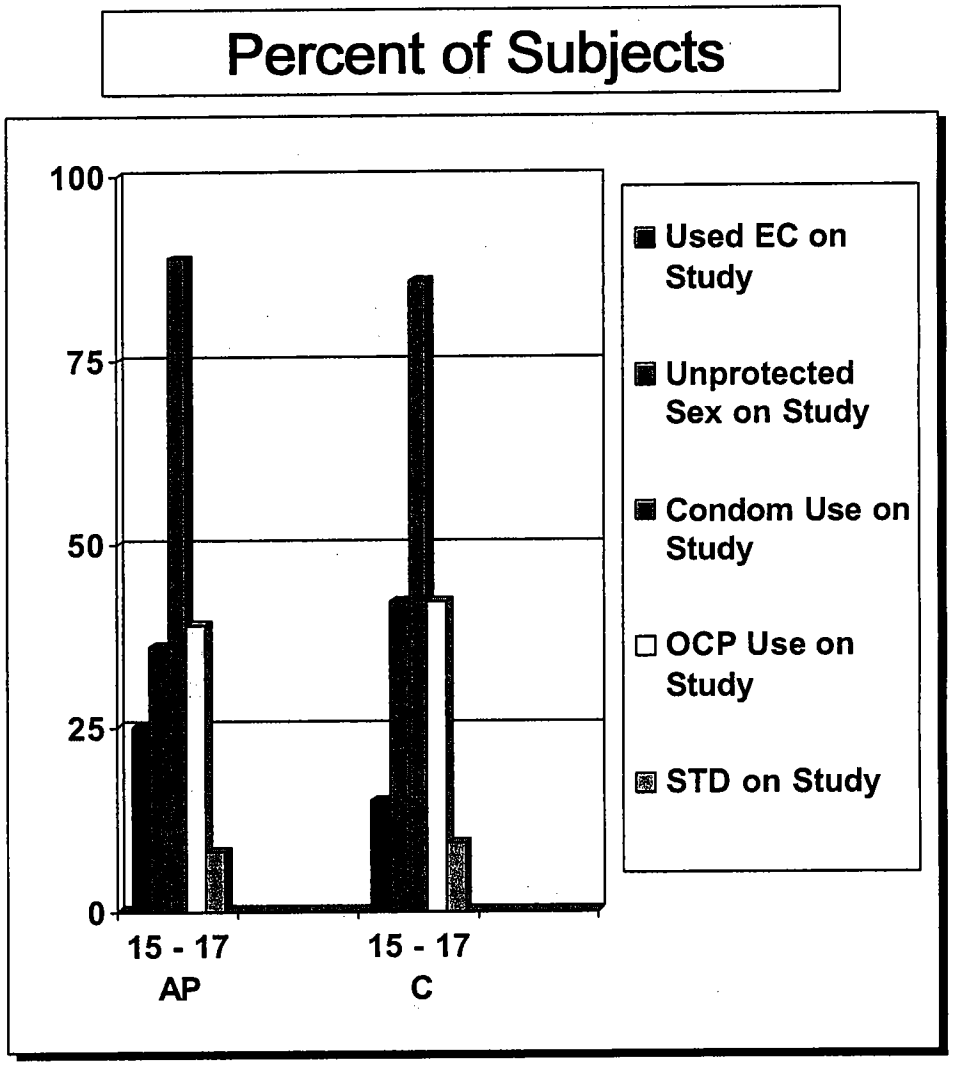


Gold Study:
Timing of First and Second Dose

	15-17		18-20	
	Advanced Provision	Control	Advanced Provision	Control
First Dose (Hours after Sex)				
Median	14 h	24 h	9 h	14 h
Range	1- 48 h	1- 43 h	1 – 48 h	3 – 40 h
Second Dose (Hours after First Dose)				
Median	12 h	12 h	12 h	12 h
Range	2 – 12 h	12 – 15 h	2 – 12 h	12 – 24 h

Gold Study: No Adverse Sexual Behaviors in 15-17 Advanced Provision vs. Control Group

- 2- arm study in Pittsburgh adolescent med clinic
  - EC info to all
- Regardless of whether EC was provided in advance, 15-17 had similar frequencies of:
  - Unprotected sex
  - Condom use
  - OCP use
  - STD on study



Plan B: Overall Risk-Benefit

- Plan B meets criteria for OTC switch
- Benefit of timely access (with improved efficacy) to
  - Avoid unplanned pregnancy
  - Avoid abortion
- Benefit outweighs the risks
  - Excellent safety record for levonorgestrel
    - No serious AEs
    - No harm to fetus if taken during pregnancy
  - Potential concerns regarding sexual behaviors unfounded
- Divisions and Offices do not believe there is a subgroup that should be excluded from these benefits

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/s/

Curtis Rosebraugh
3/30/04 10:37:55 AM
MEDICAL OFFICER
Plan B addendum with attachment

Jonca Bull
3/30/04 04:25:47 PM
MEDICAL OFFICER

Addendum to the *Plan B* Clinical OTC Review

Division of Over-The-Counter Drug Products, HFD-560 • CDER • FDA

NDA	**Supplemental NDA 21-045**
DRUG	**Plan B (0.75 mg levonorgestrel tablet)**
SUBMISSION	**Serial No. 119 (Letter date: February 6, 2004)**
SPONSOR	**Barr Research, Inc. and Women's Capital Corporation**
REVIEWER	**Jin Chen, MD, PhD, MPH Medical Officer**
DATE	**March 3, 2004**

BACKGROUND

The original sNDA for the Plan B OTC switch application was submitted on April 16, 2003 by the Women's Capital Corporation; the sponsorship was later transferred to the Barr Research, Inc. This reviewer conducted the clinical OTC review of *Plan B Actual Use Study, Plan B Label Comprehension Study and Behavior Study Literature,* submitted with the original sNDA. The review was completed and submitted to DFS on January 12, 2004. The recommendation from this reviewer was *Approvable* on the Plan B OTC switch application because more evidence is needed to assess the risky sexual behavior in target population, particularly teenage population.

On February 2, 2004, the Division of Reproductive and Urologic Drug Products (DRUDP/HFD-580) requested the sponsor to re-analyze the teenage data of the Plan B Actual Use (AU) Study, as quoted below:

> "Summary presentation of the Actual Use study data from the participants in the less than 18 years of age subset, including comparisons to the older subset within the study. Please submit accompanying tabular line listings for each patient < 18 years old screened for this study and include all data collected in the study for this group - from the screening date through end of follow-up. This table of line listings should be accompanied by an electronic version of the dataset in SAS transport file format."

The sponsor submitted the reanalysis summary in response to this request on February 9, 2004. The submission was forwarded to this reviewer by DRUDP/HFD-580 on February 26, 2004. This addendum is a brief review of the reanalyzed teenage data from the Plan B AU Study.

REVIEW

In this submission, the sponsor stratified data of the Plan B AU study into different age groups: ages 14-15, 16-17, 18-20 and >25 years. Approximately ***9% (n=46)*** of the 540 Plan B users were aged 14-17 years. As per the original sNDA submission, 22 users were aged 14-16.

Only correct timing/dosing data of Plan B 1st and 2nd pills were reanalyzed in this submission. There are no differences in timing to take both pills (following the dosing regimen of the proposed OTC label) between ages 14-17 and ages 18-44; the younger subjects tended to time both pills better than adults (Table 1). In addition, younger subjects without previous EC experience took both Plan B pills as correctly as those with previous EC experience.

Contraceptive behavior data among different age groups are not provided in this reanalysis submission. However, according to data (summarized from electronic submission of Subject Listings of the AU study) that Dr. Griebel (HFD-580) presented to the Commissioner on February 18, 2004, the subjects aged 14-16 and 14-17 years had no more adverse contraceptive behaviors than the subjects aged 18-44 years (Table 1).

Table 1. **Age Comparison of Plan B Actual Use Study**

Subject Age (years)	Plan B User		Correct Timing of Both Pills (%)†	Contraceptive Behavior Changes (%)‡			
	No.	%		▶ More Effective	▶ Less Effective	▶ Condom Use	▶ No Condom Use
14-16	22	4	77	29	0	0	0
14-17	**46**	**9**	75	27	4	0	4
18-44	494	91	72	10	9	11	5
Total	540	100	72	11	8	10	5

Data are extracted from the following 3 sources: the current submission (Serial no. 119, Attachment-2/p5633), the presentation of the briefing to the Commissioner (February 18, 2004 by Dr. Griebel/HFD-580; slides 8 and 12) and the original clinical OTC review (submitted to DFS on January 12, 2004; Table 21b of p38 for the total Correct Timing and Table 27b of p50 for the total Contraceptive Behavior Changes).

† The percentage calculation was not specified in the reanalysis submission; assuming that the numbers of users who provided sufficient timing information was used as a denominator.

‡ Percentage of subjects who had sexual acts during the study.

▶ "Change to..." from the baseline (a month before enrollment).

COMMENTS

1. Approximately 9% (n=46) of Plan B users in the AU study were aged 14-17 according to the re-analysis. This sample size and its proportion are still under-representative of the teenage population in the United States, a population who might use Plan B in an OTC setting.

2. Two unpublished studies (conducted by Dr. Beth Raymond[1], as per email communication with DRUDP/HFD-580) demonstrated that 16%-27% of women aged 14-17 and 37%-54% of women aged 14-19 years were seeking Plan B during the studies (Table 2). Subject recruitment in both studies was targeting to a general female population but not particularly to the teenage population.

Table 2. **Proportion of Teenagers Seeking EC in Two Unpublished Studies Targeting General Population of Women (*By Beth Raymond*[1])**

Subject Age (years)	DIAL EC* (n=7731)	RCT* (n=1250)
14-17	1225 (16%)	343 (27%)
14-19	2848 (37%)	673 (54%)

* An on-going randomized controlled trial (RCT); the data are extracted from a preliminary interim analysis and the target sample size is 1490 subjects aged 14-24 years in this trial.

3. The issues raised in the original sNDA AU study review, *4-week follow-up, provision of one course of Plan B, and re-enrollment process required for the repeat-users,* still significantly limit assessment of potential risky/unsafe sexual behavior associated with OTC accessibility of Plan B. This drug-behavior interaction may negatively impact on some important public health issues in the United States, such as sexually transmitted infections in teenage (particularly HIV/AIDS), and should be addressed with further studies.

CONCLUSION

The conclusion and "Approvable" recommendation made in my original OTC review of this sNDA will stay.

Jin Chen, MD, PhD, MPH
Primary medical reviewer/HFD-560

[1] Elisabeth Raymond, MD, MPH, a clinical investigator in Family Health International (Research Triangle Park, North Carolina) conducted "Plan B LC study" and "Plan B AU study" for the original sNDA 21-045 submission. Both studies were published in ***Obstet Gynecol*** (100: 342-349, 2002 for LC and 102:17–23, 2003 for AU).

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/s/

Jin Chen
3/3/04 04:31:20 PM
MEDICAL OFFICER
Addendum

OTC Drug Clinical Review
FOR NDA

Division of Over-The-Counter Drug Products • HFD-560
Center for Drug Evaluation and Research • Food and Drug Administration
Rockville • MD 20857

NDA	**sNDA 21-045**
DRUG NAME	**Plan B (Levonorgestrel)**
DOSAGE STRENGTH & FORM	**0.75 mg Tablet (2-tablet package)**
SPONSOR	**Barr Research, Inc. and Women's Capital Corporation**
PROPOSED INDICATION	**Emergency Contraception to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)**
ROUTE OF ADMINISTRATION	**Oral**
SUBMISSION DATE	**April 16, 2003**
REVIEW COMPLETE DATE	**January 12, 2004**

REVIEWER Jin Chen, *MD, PhD, MPH*

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This supplemental NDA for the OTC-switch of Plan B should be ***approvable*** for the following reasons:

1. The contraceptive behavior evaluation in the Plan B Actual Use Study is insufficient to assess whether OTC accessibility of Plan B may be associated with the risky (or unsafe) sexual behaviors over the long-term, particularly in the teenage population.

2. The behavior study literature does not provide strong evidence to address the inadequacy of the actual use study in assessment of risky sexual behaviors in the target OTC populations.

3. Some behavior studies in literature suggest that the advance provision of emergency contraception tends to prompt unsafe sexual behaviors in study populations.

B. Recommendation on Phase 4 Studies and Risk Management Steps

If Plan B becomes accessible OTC, the sponsor should monitor unsafe sexual behaviors and sexually transmitted infections (particularly HIV/AIDS) associated with OTC availability of Plan B. This may need to be incorporated into the Convenient Access Responsible Education (CARE) program that the sponsor proposed for post-marketing surveillance.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Plan B, 0.75 mg levonorgestrel tablet, is a progestin-only emergency contraceptive, in a 2-tablet package (2 oral doses). It was approved by the Agency on July 28, 1999 for marketing in the United States by prescription and indicated for use after unprotected sexual intercourse or contraception failure to prevent pregnancy. In this supplemental NDA (sNDA) submission, the sponsor proposed the OTC switch of Plan B with the same indication, dose strength, dosage form, and dosing regimen. Two pivotal clinical studies and 27 supportive clinical studies (mostly from literature) were submitted to support the OTC switch application. This review is focusing on *the Actual Use study, the Label Comprehension study and the Behavior Study Literature* submitted to the sNDA.

B. Efficacy

There were no new efficacy studies on Plan B submitted to this sNDA. Two efficacy-related evaluations were included in the *Actual Use Study*: one was to estimate self-selection and correct use (timing of doses) according to the indication and the dosing regimen in a proposed OTC label, and another was to estimate pregnancy rate (or emergency contraception failure) after Plan B use.

Self-selection: Approximately 95% of subjects who used Plan B correctly self-selected. However, subjects who presented to the study sites for reasons other than to request emergency contraception were excluded and thus the self-selection in that population can not be assessed.

Correct use (timing of doses): Overall correct use (timing of doses) of Plan B was 68%; 92% of users took the first pill within 72 hours and 72% of users took the second pill 12 hours later (the dosing instruction in the proposed OTC label). Approximately 87% of users who took the first pill within 72 hours timed the second dose between 6-18 hours.

Pregnancy rate: Ten (1.9%) of the 540 users had a confirmed pregnancy; 14 users (2.6%) had suspected pregnancy status at the 4-week contact but were lost to further follow-up. The overall pregnancy rate was from 1.9% (excluding missing data) to 4.5% (included missing data).

Comparisons among demographic subgroups: The overall *self-selection* and *correct use* were not comparable among different demographic subgroups. However, only 5% (n=29) of the 585 subjects were age 14-16 (22 used Plan B); only 0.3% (n=2) of the 585 subjects had an education $\leq 8^{th}$ grade and 13% (n=76) at $9^{th} - 11^{th}$ grade. The literacy test was not performed in the study.

C. Safety

The safety evaluation in this review includes adverse event reports and changes in contraceptive behavior from the Actual Use Study, and risk assessment of sexual and contraceptive behavior from eight literature reports. The medical officer in HFD-580 evaluates other safety data in a separate review.

Adverse event reports from the Actual Use Study: There were no serious adverse events (AEs) and no new safety signals reported in the actual use study. About 46% of users experienced adverse events; 85% of AEs were mild and 15% moderate. Most AEs resolved without medical intervention and 30% were treated with either prescription or OTC medication (*not specified in the report*). The most common AEs were abdominal pain, nausea, headache and asthenia.

Contraceptive behavior observation from the Actual Use Study: the following is the overall summary of changes in contraceptive behaviors observed during the 4-week follow-up, as compared to the month before study:

- Total sexual activity decreased from 100% (before study) to approximately 64% (during study).

- "At least one sex act without contraception" decreased from 60% (before study) to 20% (during study); use of withdrawal method decreased from 28% (before study) to 10% (during study); condom use increased from 79% (before study) to 90% (during study); and more subjects tended to switch to use more effective contraception methods during the study.

- Ten subjects re-enrolled and received Plan B twice (n=8) or 3 times (n=2); there were no significant differences in timing of doses and contraceptive behaviors between the multiple users and single users.

- Subjects with previous EC experience (40%) were more likely to have "at least one unprotected intercourse" and tended to use condoms less in the month prior to enrollment. For self-selection, more previous EC users had the reasons the "unprotected sex" or "used no contraception" to request and use Plan B. But during the study, those subjects apparently did not change condom use and effective contraception; the unprotect sex information was not available.

The following flaws in this study limits generalization of the behavior evaluation to an OTC setting, particularly in teenage population:

- The follow-up period was only 4 weeks;
- Only one course of Plan B at a time were offered to the subjects;
- Majority of subjects (94%) were recruited from clinics;
- Proportion of subjects age 14-16 yr was 5% (n=29);
- There was no literacy testing;
- Only 0.3% of subjects (n=2) had education $\leq$ 8th grade;

Contraceptive behavior observation from the eight literature reports: The sponsor submitted five published studies, three unpublished manuscripts and one abstract from literature that evaluated the sexual and contraceptive behaviors associated with advanced provision of emergency contraception (EC). Five studies were conducted in the USA and one each was from UK, India and Ghana.

Study Design: All subjects in the eight studies were recruited from family planning clinics or hospital-based clinics, age 15-45 years, and received education regarding emergency contraception. Most studies were of a randomized, controlled design. Subjects in the treatment group (Advance EC Provision) received one course (in six studies) or three courses (in two studies) of emergency

contraception pills in advance. Control groups had standard EC access (through prescription in clinics when needed). The followed up period was 2-12 months.

Adverse Changes in Behaviors: One US study suggests that subjects with advanced EC access was more likely to use less-effective contraception and tended to have less protected sex and to miss oral contraceptive pills. Another US study showed that the advance and pharmacy EC access decreased condom use. The study done in Ghana showed that advance EC provision tended to increase unprotected sex (but had significant flaws in study design). The UK study showed a decrease in condom use in both the advance EC and control groups compared to baseline.

No Changes in Behavior: The 5 other studies (three from US, one from UK and one from India) showed no increases in frequency of unprotected sex and (except the one from UK), no decrease in condom use in women receiving advance EC pills or no change in regular contraception methods. Subjects with advanced EC provision were more likely to use EC in all 8 studies.

Issues: Although results from most studies are in some degree complementary to the actual use study (such as longer follow-up period, relatively large sample size, diverse populations, more than one courses of EC in some studies, STD assessment in some studies), there are the following limitations with regard to extrapolation of results to an OTC setting.

- None of studies were conducted in a simulated OTC setting
- All subjects received EC education from clinical investigators;
- Six studies provided only one course of EC pills in advance;
- Two studies were of a non-randomized design.

D. Dosing and Labeling

The same dosage form/strength and dosing regimen as for prescription is proposed for OTC use of Plan B in US. There will be a 2-tablet package (0.75 mg levonorgestrel per tablet); the first tablet should be taken within 72 hours after unprotected intercourse and the second tablet 12 hours later. Understandability of the proposed OTC label in an OTC setting was tested with a Label Comprehension (LC) Study and a subsequent revised label was used in the actual use study. The following is the summary of the LC Study review.

This was a single-arm study conducted in family planning clinics (11% of the enrolled subjects) and shopping malls (89% of the enrolled subjects) in eight states of the US. A total of 656 women ages 12-50 years were enrolled. Eleven communication objectives corresponding to information in the proposed label were tested.

Indication and Warnings: About 93% of subjects could correctly understand the indication for Plan B. Most subjects (91-98%) could correctly understand the "Warnings" (pregnancy and allergy) and AIDS/STDs. About 67% subjects understood that Plan B is not for a regular contraceptive; and 75% of subjects were aware of the contraindication of unexplained vaginal bleeding.

Directions for Use: 97% of subjects could take the first pill before 72 hours or as soon as possible after intercourse. However, only 69% of subjects could take the second pill at 12 hours after the firs pill.

Side-effects: Over 80% of subjects could understand side effects of Plan B, including nausea, vomiting and some others, as well as possible severe abdominal pain (and seeking medical help immediately).

Issues identified from the label comprehension study and resolve/unresolved in the actual use study:

- Approximately 20% of subjects did not understand a potential serious adverse event (severe abdominal pain). The sponsor revised the label by bolding the phrase "a serious medical problem" and used in Actual Use study. Since no subjects reported severe abdominal pain or ectopic pregnancy in the AU study, this issue can not be assessed.

- Approximately 25% of subjects did not recognize that "unexplained vaginal bleeding" was a contraindication. About 1% (n=6) of users in the actual use study had "unexplained" vaginal bleeding.

- Less comprehension on "used as a back-up but not for regular contraception" was found in all subjects, particularly in subjects age 12-16 and those with low education/literacy. The sponsor bolded this phrase and the revised version was used in the actual use study. Although in the AU study, 95% of subjects correctly self-selected Plan B after unprotected sex or contraception failure and there were no decreases in using routine contraception methods, only one package of Plan B was offered to the subjects with short follow-up period. It is hard to predict if consumer can distinguish this in an OTC setting.

- The similar results were obtained on self-recognizing timing of the first and second tablets in the LC study and the AU study. Majority (> 90%) of subjects in both studies can understand when to take the first tablet, and approximately 70% of subjects recognized to time the second tablet at 12 hours after the first pill. In the AU study, 93% of users took the 2^{nd} pill between 6-18 hours after the first pill.

- Overall, lower comprehension rates on certain communication objectives in subjects ages 12-16 and subjects with lower literacy level or less than

high school education. The actual use study showed that overall *correct use (timing of doses), contraindicated use, AEs and adverse behavior changes* were not different between subjects aged 14-16 and age 17-44 years. However, the sample size of young subjects (age 14-16) in the AU study was too small (5%) for the conclusion.

- The LC study did not test the subjects whether "unprotected sex" was referred to prevent pregnancy but not STDs. Also, sexual transmitted diseases other than HIV/AIDS were not specified in questionnaires in the study. Although there were no adverse behavior changes observed in the AU study, the follow-up period was too short to assess long-term behavior changes and STDs in an OTC setting.

- Although overall comprehension on the proposed OTC label was comparable between clinics (11%, n=73) and malls (89%, n=583) in the LC study, the following subgroups of subjects from the clinics had significantly lower comprehension on the communication objectives such as "used as a back-up but not for regular contraception": *age 12-16, low income (≤ $15,000/yr), less education (< HS), and no prior EC experience*. The results suggest that certain OTC populations may potentially misuse Plan B in the OTC setting. No justification can be made from the actual use study since no subjects in the study were recruited from shopping malls.

E. Special Populations

Plan B is for sexually active female of reproductive age. The target populations were tested in the Plan B label comprehension, and partially evaluated in the Plan B actual use study and in behavior study literature.

Clinical Review

I. Introduction and Background

Plan B is a progestin-only emergency contraceptive, a 2-tablet package (2 oral doses). Each tablet contains 0.75 mg levonorgestrel. It was approved by the Agency on July 28, 1999 for marketing in the United States as a prescription, indicated for use after unprotected sexual intercourse or contraception failure to prevent pregnancy.

In this supplemental NDA (sNDA) submission, the sponsor proposed OTC marketing of Plan B in the US with the same indication, dose strength, dosage form, and dosing regimen. Two pivotal clinical studies, *the Actual Use study, the Label Comprehension study,* were submitted along with supportive clinical studies (mostly from literature) to support the Plan B OTC switch.

Plan B has been marketed in other countries as prescription, behind-the counter, or OTC, and pharmacy access in five states of US. See clinical review conducted by medical officer in HFD-580 for detailed global safety update of Plan B and other emergency contraception products. This review is only focusing on the actual use study, label comprehension study and the behavior study literature submitted to the sNDA.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There were no new studies submitted with this sNDA.

Statistics reviewer collocated to HFD-560 was consulted on issues related to the actual use study and label comprehension. See statistical memo (submitted to DFS) for details.

III. Human Pharmacokinetics and Pharmacodynamics

One pharmacokinetics study in pediatric subjects was submitted. Refer to PK/Biopharm review (in HFD-580) for details.

IV. Description of Clinical Data and Sources

The actual use study and the label comprehension study: both studies were co-sponsored by Women's Capital Corporation and the Family Health International. The final reports, summary tables, subject listings table and protocols for both studies were submitted in this sNDA.

Behavior study literature: A total of 8 literature reports were submitted by the sponsor in this sNDA. There were five published, two unpublished and one abstract. Five studies (including one abstract and 2 unpublished manuscripts) were conducted in US and one study each was from UK, India and Ghana. No raw data were submitted with these reports.

V. Clinical Review Methods

- Complete reviews of the actual use study and the behavior study literature were conducted by this reviewer.

- The label comprehension study review was an addendum. More detailed evaluation on this study was conduced by a social scientist in the Office of Drug Safety/HFD-410 through consulting request.

- Statistical reviewer collocated to HFD-560 were consulted for statistical issues in the actual use study, the label comprehension study and behavior studies.

- Division of Scientific Investigation (DSI) was consulted for auditing clinic site at Houston, Taxes, one of five clinic sites used for the actual use study.

VI. Integrated Review of Efficacy

There were no new efficacy studies submitted with this sNDA. The efficacy-related literature is reviewed by a medical officer in HFD-580; refer to their reviews for details.

Two aspects of Plan B efficacy-related evaluation were drawn from the *Plan B Actual Use Study*: one was to estimate self-selection and correct use or timing of doses (primary objectives) according to the proposed OTC label, and another was to estimate pregnancy rate (or emergency contraception failure) after Plan B use (a secondary objective). The following is the detailed review of this study (pages 11-60).

Study #9727: **Plan B OTC Actual Use Study**
(Volumes 27-30 of sNDA 21-045)

Title:	Phase 3 Non-Comparative Case Series Study of Plan B Levonorgestrel Emergency Contraceptive Pills Provided Using a Simulated Over-The-Counter Approach
Study date:	November 5, 2001 to April 11, 2002
Report date:	September 30, 2002, updated January 30, 2003
Sponsor:	Women's Capital Corporation (The sponsorship was transferred to the Barr Research in Nov, 03)
Investigators:	Family Health International (FHI), Research Triangle Park, NC
Study sites:	Five Family Planning Clinics sites (five states in US): Planned Parenthood League of Massachusetts, Boston, MA Planned Parenthood Centers of West Michigan, Grand Rapids, MI Planned Parenthood of Houston and SE Texas, Houston, TX Planned Parenthood of Central and Northern Arizona, Phoenix, AZ Planned Parenthood of Western Washington, Seattle, WA Five pharmacy stores Longs Drugs stores (in 5 cities of WA)
Study Design:	Open-label, one-arm, uncontrolled multi-center clinical trial
GCP Compliance:	Yes
Study Drug:	Plan B (0.75-mg Levonorgestrel tablet); Lot #: W110004

STUDY OBJECTIVES

Primary Objective:

To estimate the frequency of contraindicated and incorrect use of Plan B when dispensed under OTC-like conditions.

Secondary Objective:

To estimate repeat use, pregnancy, and adverse events when Plan B is dispensed under OTC-like conditions.

Additional Observation

To collect and compare uses of emergency and regular contraception at enrollment and follow-up.

METHODS

Study Procedure (Table 1)

1. Investigators used a written script to inform women presenting to the study sites about the study. Each woman who expressed an interest in study participation reviewed the Plan B label and then completed a Screening Form.

2. Eligible subjects who wished to purchase Plan B were asked to sign the Informed Consent Form, and then to complete a Background Questionnaire. Only subjects who presented for requesting emergency contraception purpose were recruited.

3. Each subject could purchase only one package of Plan B at a time. To purchase more, women had to repeat the enrollment process. Each woman received a Study Data Card (with stamped/addressed envelope) to complete after using Plan B and then to mail to the study site. Study staff did not provide instructions on how to use Plan B (other than the package label) unless the subject specifically asked a question; the questions and answers were recorded on a data form.

4. Subjects who purchased Plan B were contacted one week and four weeks later either by telephone or were seen in person at the study site, questioned about Plan B use, adverse events and pregnancy status. Information about prior and concomitant medications was collected but not interrupted (no restriction and no special instruction). Subjects with an uncertain pregnancy status or with adverse events (AEs) received weekly follow-up until the issue was resolved.

5. Subjects were told about monetary compensation for study participation after completing the Screening Form. They received $40 (for the clinic sites) or $45 (the pharmacy sites) compensation after both contacts.

Table 1. **Schedule of Study Procedures**

Procedure	Screening	Week 1 (5-8 days)	Week 4 (28 days or later	Weekly thereafter (if necessary)
Collect baseline and background data	X			
Determine eligibility	X			
Informed consent	X			
Provision of Plan B if eligible	X			
Provision of *Study Data Card*	X			
Collect information on use of product		X	X	
Collect information on adverse events		X	X	X
Collect information on pregnancy		X	X	X

Investigators

Family Health International (FHI) designed the study, distributed Plan B, and monitored the sites. They made at least 2 site visits during the study to monitor the progress of study, to confirm that the sites were following the protocol, and to review the data. Study staffs were trained separately at each site according to a standardized training curriculum.

Plan B Dispensing

Each subject enrolled in the study was initially allowed to purchase only one package of Plan B containing two 0.75-mg levonorgestrel tablets (a single bath with lot #W110004). The package design was the same as the approved Rx package but printed with the proposed OTC labeling (Appendix #1). No patient package insert was provided with the study product.

Subjects were allowed to continue their routine medication. Information was collected about medication used in the week before enrollment and concomitantly during the study. Subjects could repeat the enrollment process at a later time to qualify to purchase more Plan B.

Subject Screening and Enrollment

Admission criteria: A woman who met the following 5 criteria was eligible to receive Plan B:

1. Requested emergency contraception for personal use.
2. Had not previously participated in the Plan B Label Comprehension study.
3. Could read English, according to her own judgment.
4. Was willing to complete questionnaires and to be contacted or return to the study site in one week and four weeks for follow-up.
5. Wanted the study product after reading the text on the outside of the study package label.

The subjects were allowed to enroll repeatedly while the study sites were open. The same subject number was used for the "re-enrolled" subjects. Supportive documents included informed consent and contact information at the admission re-visits. The intervals between uses were recorded, but the data were not statistically analyzed due to low number of repeated users.

Minor subjects: Subjects aged 15 or younger were excluded from 2 sites (Phoenix and Houston) because parental consent for this age was required. The other clinical sites did not impose age restrictions. The sponsor stated that no specific measures were taken to recruit minors at the sites so that the population would be representative of that seeking emergency contraception.

Assessment of Self-Selection/De-Selection

Self-selection: Subjects were asked to review the drug package, to complete the Screening Form and to determine whether or not the product was appropriate for them. The validity of the self-selection decision was determined based on the reasons that the subject requested and used Plan B.

Self-deselection: Contraindicated uses were evaluated for assessment of self-deselection, as follows:

Determination of Pre-existing pregnancy: Pre-existing pregnancy was evaluated at screening time (last menstrual period and usual menstrual cycle length), at follow-up contact (menstrual profile, pregnancy test results since last menstrual period (LMP), other reasons to suspect pregnancy), and by estimated fertilization date (pregnancy at least 14 days after fertilization)

Unexplained vaginal bleeding: At the earliest follow-up contact, the medical monitor determined the onset of "any unusual" vaginal bleeding, and how it was unusual, before subject took the first pill.

Allergic to the product: Information on allergy to all medications, foods and Plan B was collected during both follow-up contacts to avoid influencing behavior.

The reasons to deselect Plan B in those subjects who did not request or who received Plan B but did not use it were not evaluated in the study.

Assessment of Correct/Incorrect use

The date and time of coitus and subsequent ingestion of each pill were collected. The following questions were asked to collect data about intentional and unintentional incorrect use:

> Did you use Plan B according to all the instructions on the box? If no, what instruction did you not follow?
> Did you know you were not following the instructions when you took the Plan B pills or did you realize that only after you took the pills?

Primary analyses of incorrect use: the subjects did not follow the dosing schedule: "Take the first tablet as soon as possible within 3 days (72 hours) after unprotected sex; Take the second tablet 12 hours after you take the first tablet".

Secondary analyses of incorrect use: First tablet up to 72 hours after intercourse and second tablet up to 16 hours after the first; First tablet up to 72 hours after intercourse and second tablet up to 6-18 hours (*the rationale for this timing was not provided in the report*) after the first; First tablet up to 120 hours after intercourse and second tablet up to 24 hours after the first.

Subjects with unclassifiable use patterns were excluded in the analyses.

Safety Assessment

Adverse events were defined as medical problems that started or worsened after Plan B use.

Adverse events were recorded in the Study Data Cards and were collected during the follow-up contacts (week 1, week 4 and thereafter for some subjects), and recorded in the "Adverse Events Notes page" by study staff, reviewed and then transferred to the Adverse Events data form by the clinician. The frequency, severity (mild, moderate or severe), and seriousness, and the relevance to the drug treatment were analyzed.

Site staffs did not investigate discrepancies of AE reports between the cards and the follow-up contacts unless the cards indicated the possibility of an unusual, serious, or severe event.

Adverse events were coded in COSTART terminology. The 95% confidence limits around frequencies within body system class were calculated by the exact binomial method.

Concomitant Medications: Medications used by enrolled subjects during the week before enrollment and during the follow-up period were coded according to the WHO Anatomical Therapeutic Chemical Classification system.

Efficacy Assessment

At the follow-up contacts, information about menstrual history, pregnancy test results since LMP, and any suspected pregnancy were collected and evaluated by medical monitors.

Criteria to determine pregnancy (any of the following):

a. Did not have menses following product use
b. Had a positive pregnancy test
c. Had any other evidence of pregnancy, such as ultrasound, abortion.
d. Had no evidence ruling out pregnancy as assessed by site staff.

Estimate Fertilization Date

Pregnancy occurring before Plan B use was determined by the estimated fertilization date (based on data collected from all pregnant subjects) or date of sexual intercourse. There was no diagnostic examination (ultrasound and/or blood/urine test) to confirm the fertilization date.

Criteria to exclude pregnancy

a. Had a menstrual period after Plan B use
b. Had a negative pregnancy test at least 2 weeks after the products
c. Other information (*not specified in the report*), confirmed by medical monitor individually

Undetermined pregnancy:

Subjects who did not meet the above inclusion and exclusion criteria to determine pregnancy were classified as "undermined pregnancy" and were followed up until pregnancy status was clarified.

Sexual and Contraceptive behaviors

Information about sexual behavior and contraception methods before (one month) and after (4 weeks) Plan B use were collected using multiple questions containing the following parameters:

Had sex: Subjects had sex with or without contraception during specific interval.

Had at least one sex act without contraception: included any subject who was classified as having had sex in the specified interval but indicated that she did not use any contraception at least once.

Used a "more effective" method: oral contraceptive pills, Depo-Provera, Lunelle, vasectomy, or intrauterine device at any time during the interval.

Used a "less effective" method: other than "more effective" methods, including those who did not indicate use of any method.

Used a specific contraceptive method: included any subject who indicated that she had used that method at any time in the specified interval.

Used no condoms: included any subject classified as having had sex in the specified interval who was not classified as ever having used condoms in that interval.

Subjects' reports of abstinence ("yes" answers to "have not had sex: in the past month, since receiving Plan B, or since One Week contact") were not included in these classifications because some subjects gave contradictory responses.

Data Collection

Data were collected by the investigators using the following forms at the study sites. Data recorded on all forms received at FHI were entered into the computer with Clintrial 4.3 software; the data entry system was validated by FHI data management staff.

Plan B Study Screening Form
Plan B Study Background Questionnaire

Plan B Study Disposition Form
Plan B Study One Week Contact Form
Plan B Study Four Week Contact form
Plan B Study Data Card
Plan B Study Data Card Transcription Form
Plan B Supplemental Contact Form

Study Data Card: Information about the LMP, the sex act prompting use of the product, timing of ingestion of each tablet, and pregnancy test were collected. Information was transcribed onto Study Data Card Transcription Form during site visits by FHI.

Site staffs were instructed not to investigate discrepancies between the information obtained at the follow-up contacts and on the cards.

Data Audit: There was computer hardware problem (p029, vol. 27) during the study, which may have compromised some data entries. It was/is unclear how much of the study data were affected by this problem. FHI conducted an audit analysis, showing the error rate was 0.011-0.036% of 95% CI. The sponsor stated that this was less than the pre-defined 0.05% (audited 61,336 data points from key data fields for the primary outcomes).

Data Analyses

Statistical analyses: Data were summarized in tabular forms with SAS (version 8.0). The mean, median, minimum-maximum, and standard deviation (SD) were calculated for continuous variables and frequency tables were used for categorical data. For proportions, exact binomial 97.5% confidence intervals were calculated.
[*See statistical review for certain statistical issues*].

Definition of analysis populations:

Screened Population: All subjects screened in the study and no one was excluded.

Enrolled Population: All subjects who enrolled in this study (i.e., received study product).

Per-Protocol Population: The Enrolled Population excluding subjects enrolled with violations of any of the study admission protocol criteria.

Incomplete Follow-up Population: All subjects who did not complete follow-up procedures (i.e., did not complete both scheduled contacts and all required supplemental contacts or did not mail in the Study Data Card).

Lost to Follow-up Population: All subjects who provided no follow-up data.

Missing Data: Analyses of contraindicated use, incorrect use, and pregnancy included only subjects with sufficient data to allow classification of the status of the outcome. The sponsor assumed that subjects with missing data had the same outcomes as subjects who provided data.

Data obtained at visits that were outside the "per protocol" time windows were included in the primary outcome analysis. In all analyses, the data from the Study Data Cards were used only if the corresponding data from the contact visits were missing (except where otherwise noted).

Deviations from the Study Protocol

1. Informed Consents: Two versions of the Informed Consent forms were used, one (amendment #1) at 4 clinical sites and pharmacy sites and another at the Boston site (using the final version, amendment #2), as listed in Table 2. The IRB at each site approved the consent form that the site actually used. (*Reviewer: the discrepancies were minor and may not affect either subject welfare or the integrity of the data*).

Table 2. **Differences between the informed consents used in different study sites**

Deviations	Boston Site	All others
Version of Consent Form used	Amendment #2 (final)	Amendment #1
Consult health care professionals	"Please let us know if you would like to speak with a pharmacist/clinician at any time during the research study."	"You may speak with a pharmacist/clinician at any time during the research study."
Ask additional contact	verbally inform each subject at the four-week contact (at all sites)	Grand Rapids, Seattle, and the pharmacies, but others, did not specifically state that subjects might have additional contacts after the one-month contact.
State special warning	No special warnings were used in the informed consent.	"Make sure that you understand the risks and side effects of the package insert instructions before you take the pill. If you have any questions, call [name] or the clinic/pharmacy".

2. Missing package: Study drug packages (dispensed or returned) were accounted for all sites except at the Houston site where 2 packages were missing.

3. Evaluable population: In the protocol, this was all screened subjects who met all eligibility criteria, who used the product, and who completed both follow-up contacts. In the actual analysis, the evaluable population included those subjects who received and used the study product and completed one or both follow-up contacts.

4. Repeat users: The number of repeat uses was low and thus no separate analysis was conducted in the report.

5. An analysis of "deliberate incorrect and contraindicated uses" was proposed in the protocol, but the final report focused on "unintentional incorrect and contraindicated use".

RESULTS

Subject

Enrollment: A total of 665 women were screened at least once in the 5 clinical sites and 5 pharmacy sites; 585 (***88%***) subjects met all eligibility criteria and 80 **(12%)** were ineligible. The distribution of screened subjects and their eligibility were summarized in Table 3. Of the 80 ineligible subjects, 38 women who indicated eligibility did not sign the informed consent and thus became ineligible; the other 42 failed to meet one or more criteria listed in Table 4.

Table 3. **Subjects Screened and Enrolled in Each Study Site**

	Clinical Site						Pharmacy Sites	Total
	Boston	Grand Rapid	Houston	Phoenix	Seattle	Total		
Screened Subjects	129	125	170	123	79	626	39	665
Eligible Subjects	111	117	138	111	72	549	36	585
	86.0%	93.6%	81.2%	90.2%	91.1%	87.7%	92.3%	88.0%
Ineligible Subjects	18	8	32	12	7	77	3	80
	14.0%	6.4%	18.8%	9.8%	8.9%	12.3%	7.7%	12.0%

Table 4. **Reasons that screened subjects did not receive Plan B**
No. (%)

	Clinical Sites N=626	Pharmacy Sites N=39	Total N=665
Ineligible subjects	77	3	80 (12%)
Did not sign the consent form (but eligible)	ND	ND	38 (48%)
Did not think they should receive Plan B	42	0	42 (50%)
Change mind	2	0	2
Indication	10	0	10
Instruction	1	0	1
Side effect	7	0	7
Want more info	17	0	17
Other options	1	0	1
No reason recorded	4	0	4

Data were extracted from text and Table 1.3 (vol. 28, p011). ND: no data available.

Subject Disposition: The disposition of subjects is summarized in Figure 1 and Table 5. Of the 585 eligible subjects, 576 (98%) were enrolled at first screening into the study (received the study product). Nine eligible subjects declined to participate in the study but 6 of them ultimately received prescription Plan B. Of the 80 ineligible subjects, 60 received prescription Plan B, 9 received the study product, 9 received no treatment and 2 received oral contraceptive pills.

Table 5. **Subjects Who Received Treatment**

Eligibility	Subjects Screened	Subjects Received Study Plan B	Subjects Received Rx Plan B	Subjects not Received Plan B
Eligible	585	576	6	3
Ineligible	80	9	60	11
Total	665	585	66	14

Demographics: The demographic characteristics of screened and enrolled populations are summarized in Tables 6 and 7. The mean age of the enrolled subjects was 22.1±5.0 (14-44) years old. Seventy-four percent of subjects were 17-25 years old and 5% were ages 14-16. Approximately 74% of the enrolled subjects had at least some college education and 0.3% had less than a 9th grade education.

The demographic characteristics between the screened and enrolled populations (Table 6), and between the incomplete follow-up/lost to follow-up populations and the screened population seemed to be comparable.

All subjects ages 14-16 were in middle school or high school. Nine percent of subjects age 17-44 had less than an 11^{th} grade education; 0.2% had less than an 8^{th} grade education and 8.6% had completed 9^{th}-11^{th} grade (Table 7).

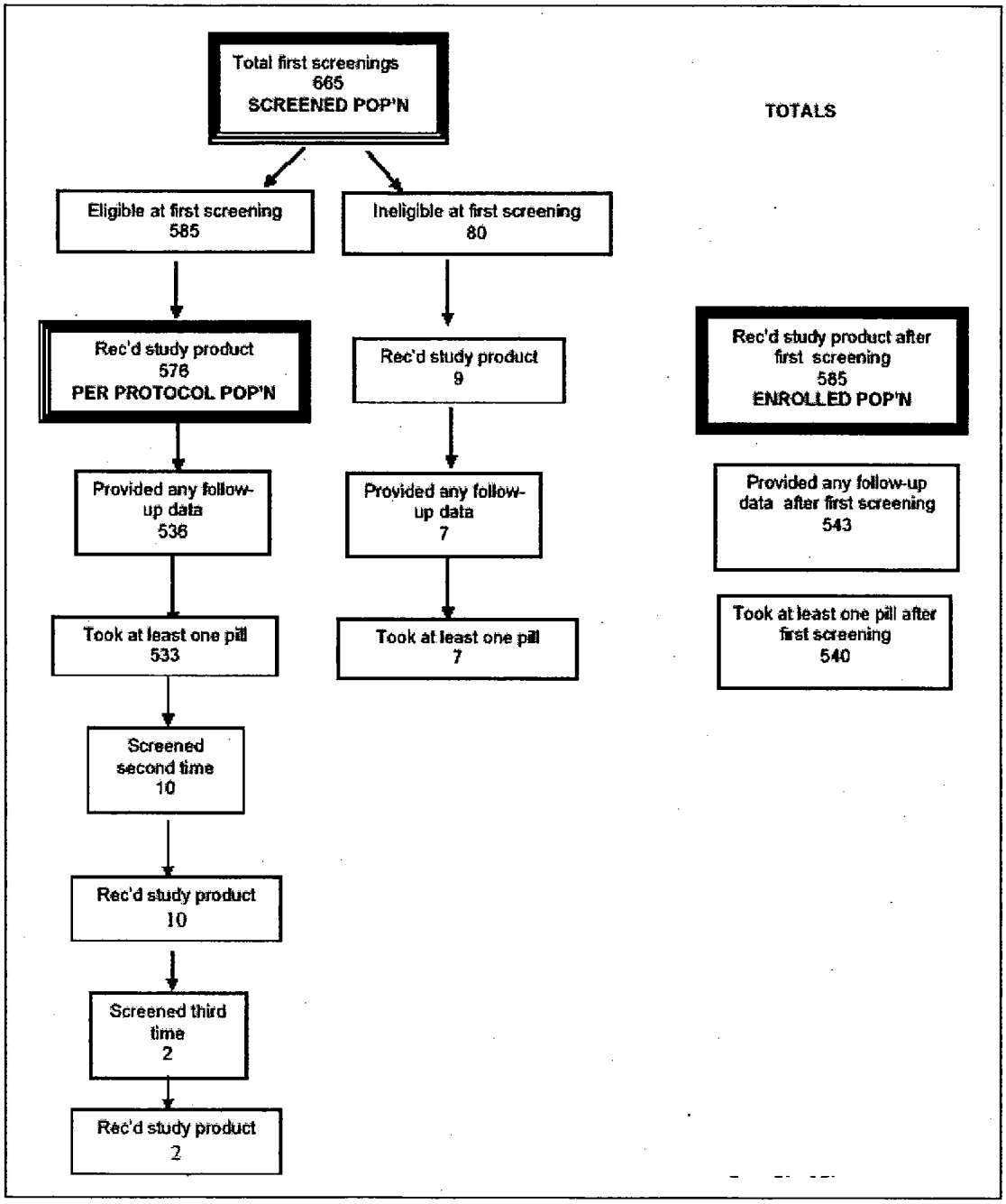


Figure 1. **Disposition of Subjects**
(Adapted from the sponsor's Figure 1 in page 070 of vol. 27)

Table 6. **Demographics of Screened and Enrolled Populations**
(Adapted from the sponsor's ***Table F*** in page 44 of vol. 27)

	Screened Population			Enrolled Population			
Age (years)	Total Clinics	Total Pharmacies	Total All Sites	Total Clinics	Total Pharmacies	Total All Sites	U.S. Women (14-44)
14-16	5.1	0.0	4.8	5.3	0	5.0	9.2
17-25	75.7	79.5	75.9	74.0	80.0	74.4	26.8
26-30	13.1	7.7	12.8	14.4	8.6	14.0	15.5
31-35	3.8	7.7	4.1	4.0	5.7	4.1	16.2
36-44	2.2	5.1	2.4	2.4	5.7	2.6	32.2
Missing	0	0	0	0	0	0	
Ethnic Hispanic							
Yes	15.0	17.9	15.2	13.8	20.0	14.2	13.9
No	84.5	79.5	84.2	85.8	77.1	85.3	86.1
Missing	0.5	2.6	0.6	0.4	2.9	0.5	
Race							
Asian	5.9	15.4	6.5	5.6	17.1	6.3	4.3
American Indian/ Alaskan Native	1.6	5.1	1.8	1.5	5.7	1.7	1.0
Black or African American	10.1	12.8	10.2	10.0	8.6	9.9	13.7
Native Hawaiian or other Pacific Islander	1.6	2.6	1.7	1.6	2.9	1.7	0.2
White	74.6	74.4	74.6	76.5	74.3	76.4	72.0
Missing	8.3	2.6	8.0	6.9	2.9	6.7	
Marital status							
Single	89.8	84.6	89.5	89.5	82.9	89.1	
Married	5.1	12.8	5.6	5.1	14.3	5.6	
Divorced	2.6	2.6	2.6	2.9	2.9	2.9	
Separated	2.2	0	2.1	2.4	0	2.2	
Missing	0.3	0	0.3	0.2	0	0.2	
Education							
8th grade or less	0.5	0	0.5	0.4	0	0.3	
9th to 11th grade	14.5	2.6	13.8	13.6	2.9	13.0	
High school/GED	13.6	20.5	14.0	12.5	22.9	13.2	
Vocational/ technical school	1.3	7.7	1.7	1.1	8.6	1.5	
Some college	48.2	48.7	48.3	49.8	45.7	49.6	
Finished college	16.1	12.8	15.9	16.4	14.3	16.2	
Graduate school	5.6	7.7	5.7	6.2	5.7	6.2	
Missing	0.2	0	0.2	0	0	0	
Household income							
$0 - 15,000	38.7	28.2	38.0	40.0	31.4	39.5	
$15,001 - 25,000	12.1	30.8	13.2	12.2	28.6	13.2	
$25,001 - 35,000	12.5	10.3	12.3	12.5	11.4	12.5	
$35,001 – 45,000	7.0	10.3	7.2	7.5	11.4	7.7	
≥ $45,001	10.7	10.3	10.7	10.7	8.6	10.6	
Missing	19.0	10.3	18.5	17.1	8.6	16.6	

Detail provided Tables 2.1.2.2a and U.S demographic data from the U.S. Census 2000.

Table 7. **Demographics of Enrolled Subjects by Age**
(% of enrolled subjects in parentheses)

Characteristics	Age (years)		Total
	14-16 N=29	17-44 N=556	N=585
Education			
≤ 8th Grade	1 (3.4)	1 (0.2)	2 (0.3)
9th-11th Grade	28 (96.6)	48 (8.6)	76 (13.0)
High school/Graduated	0	77 (13.8)	77 (13.2)
Vocational/Technical School	0	9 (1.6)	9 (1.5)
Some college	0	290 (52.2)	290 (49.6)
Finished college	0	95 (17.1)	95 (16.2)
Graduate School	0	36 (6.5)	36 (6.2)
Race*			
Asian	2 (6.9)	35 (6.3)	37 (6.3)
American Indian/Alaskan Native	2 (6.9)	8 (1.4)	10 (1.7)
Black	3 (10.3)	55 (9.9)	58 (9.9)
Native Hawaiian or pacific Islander	0	10 (1.8)	10 (1.7)
White	23 (79.3)	424 (79.3)	447 (76.4)
Missing	1 (3.4)	38 (6.8)	39 (6.7)
Prior EC Use			
Ever	8 (27.6)	226 (40.6)	234 (40)
Never	21 (72.4)	330 (59.4)	351 (60)

Data were extracted from Table 2.2c and g (p027 and p035 of vol. 28). * Some subject listed more than 1 race.

Compliance of Follow-up Contacts (Figure 2, Table 8)

Of the 585 enrolled subjects (576 eligible and 9 ineligible), 42 subjects (7.4%) did not provide follow-up data, constituting the Lost to Follow-up Population; 501 subjects (*85%*) completed both contacts, but only 262 subjects (45%) provided contact information within the per-protocol time windows (5-8 days for the first contact and ≥ 28 days for the second contact). Contacts were by phone (98%) and in person (2%).

Compliance with the follow-up schedule was less complete for subjects age ≤ 16 years and subjects with less than a high school education (Table 9). There were no significant differences in the follow-up compliance among those of different races, ethnicity and history of emergency contraceptive pill (ECP) use.

The compliance for the 1st contact was much better at the clinics than at the pharmacies.

A total 322 subjects (*55%* of enrolled population) completed follow-up contacts (2 contacts and required supplemental contacts) and mailed the Study Data Card.

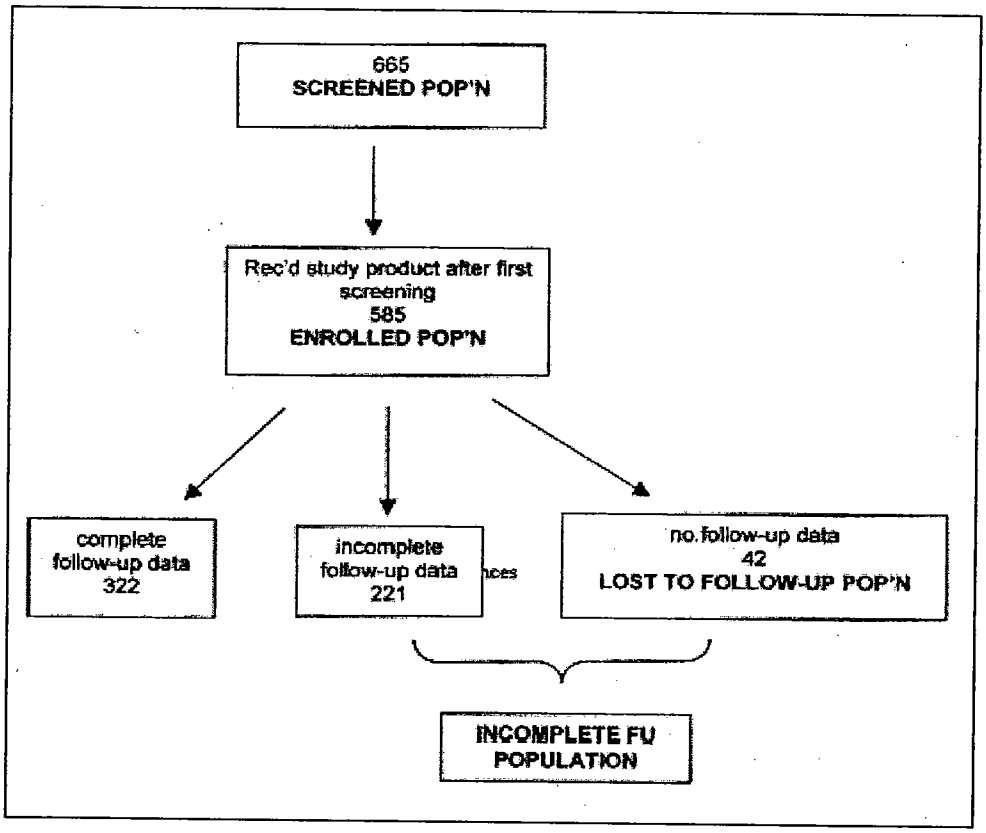


Figure 2. **Incomplete or Lost Follow-up Subjects**
The figure was adapted from the sponsor's Figure 2 in page 071 of vol. 27. "Complete follow-up" was referred to those subjects who completed ≥ 2 follow-up contacts as well as mailed in the study data cards.

Table 8. **Compliance of Follow-up Contacts**
(% of enrolled population)

Follow-up Contact	Clinical Sites N=550	Pharmacy Sites N=35	All sites N=585
0 Contact	7.1%	11.4%	**7.4%**
1 Contact	5.3%	0	5.0%
2 Contacts (Total)	85.5%	88.6%	85.6%
≥ 3 Contacts	2.2%	0	2.1%
≥ 2 Contacts (per protocol)†	46.5%	17.1%	**44.8%**
Timing of 1st Contact			
5-8 days	52.5%	17.1%	50.4%
Mean days (Min-Max)	11.0±7.9 (4-81)	21.3±21.6 (6-92)	11.6±9.5 (4-92)
Timing of any 2nd Contact			
≥ 28 days	80.7%	88.6%	81.2%
Mean Days (Min-Max)	32.5±8.0 (12-94)	38.5±14.2 (28-92)	32.9±8.6 (12-94)
Study Data Card Received	57.8%	51.4%	57.4%

Data are extracted from the sponsor's Table 1.4a (vol. 28, p012).
†The 1st contact at 5-8 days and the 2nd contact at ≥28 days

Table 9. **Follow-up Compliance in Subjects by Ages and Education Levels**
(% of enrolled population)

No. of Follow-up Contacts	Age (years)		Education Levels		Prior EC Use		Total N=585
	14-16 N=29	17-44 N=556	< HS N=78	≥ HS N=507	Ever N=234	Never N=351	
0	24.1	6.5	19.2	5.5	9	6.3	7.4
1	20.7	4.1	11.5	3.9	4.7	5.1	5.0
2	55.2	87.2	66.7	88.6	85.0	86.0	85.6
≥ 3	0	2.2	2.6	2.0	1.3	2.6	2.1

Data are extracted from Tables 1.4c and 1.4f (vol. 28, p012).

Disagreements between Follow-up Contact and the Study Data Card

Approximately **57%** of the enrolled subjects (336/585) returned the Study Data Card. Most of the returned cards (80%) contained at least one discrepancy compared to the follow-up contact. Approximately 50% of the returned cards included adverse event information that differed from the follow-up contact information; however, all AEs from the cards and the follow-up contacts were included in analysis (as seen in Safety section of this review). The overall discrepancy of data (excluding AEs) obtained from the Study Data Card was 41% (138/336) compared to the data from follow-up contacts (Table 10).

Table 10. **Discrepancies between data (excluding AEs) obtained from the Study Data Card and the Follow-up Contacts**
(% of 336 subjects who returned the Study Data Card)

Parameters	No Discrepancy	Discrepancy	Data from Card only	Data from Contact only
Onset date of menstrual period before Plan B use	61.9	33.6	1.5	3.0
Date of sex act that caused subject to want Plan B	80.1	13.1	6.3	0.6
Date and time 1st Plan B pill taken	76.5	19.0	0.9	3.6
Date and time 2nd Plan B pill taken	69.3	25.0	1.8	3.9
Had menstrual period after taking Plan B	69.3	18.8	0.3	11.6
Onset date of menstrual period after taking Plan B	73.8	19.3	1.5	5.4
Date and results of pregnancy test	81.3	3.6	3.6	11.6
All information combined	20.2	41.1	12.5	26.2

Data were extracted from Table 4.1a in page 094 of vol. 28.

Due to the low return rate of the Study Data Cards, there was greater available data from follow-up contacts for the final analyses. Considering that this may have introduced interview bias into the results, the Agency sent a request to the sponsor on Oct 1, 2003 to provide data analyses based on data from the Study Card only. As per the sponsor's response on Oct 17, 2003, the incorrect use analysis using data recorded on the Study Card was no higher than that from the follow-up contact data as stratified by age, educational levels and Ever/Never EC experience.

Reproductive History

Approximately 68% of the enrolled subjects had no history of pregnancy before the first screening, and 84% had no living children (Table 11).

Table 11. **Gravidity History of Enrolled Subjects**
(% of enrolled population)

	Clinical Sites N=550	Pharmacy Sites N=35	Total N=585
Previous Pregnancy			
0	68.4	65.7	68.2
1	18.4	11.4	17.9
≥ 2	12.4	22.9	13.0
Missing	0.9	0.0	0.9
Living Children			
0	84.7	71.4	83.9
1	8.5	14.3	8.9
≥ 2	5.5	14.3	6.0
Missing	1.3	0	1.2

Data are extracted from the sponsor's Table 2.6a in page 047 of vol. 28.

Emergency Contraceptive History

About 60% of subjects had no previous experience using an emergency contraception (EC) (Tables 12 and 13). The demographic characteristics of *Ever* and *Never* EC users were comparable.

Of those with previous EC experience, 2% of subjects used it within the past month and 8% within the last 1-3 months (Table 14).

Subjects with prior emergency contraceptive use were more likely to have had at least one act of sexual intercourse without contraception in the past month ($p<0.05$) and to have a positive pregnancy history ($p< 0.01$). There were no significant differences in condom use between ever EC users and never EC users (Table 15).

Table 12. **Demographics of subjects with and without Previous Emergency Contraceptive Use Experience**
(% of the enrolled population)

Characteristics	Ever EC Use N=234 (40%)	Never EC Use N=351 (60%)	Total N=585 (100%)
Age (years)			
14-16	3.4	6.0	5.0
17-25	75.2	73.8	74.4
26-30	13.7	14.2	14.0
31-35	5.6	3.1	4.1
≥ 36	2.1	2.8	2.6
Education			
Some College	52.6	47.6	49.6
Finished College	13.7	17.9	16.2
High school	12.0	14.0	13.2
9^{th}-11^{th} Grade	12.0	13.7	13.0
Graduate School	8.1	4.8	6.2
Technical School	1.3	1.7	1.5
≤ 8^{th} Grade	0.4	0.3	0.3
Missing	0	0	0
Race*			
White	71.8	79.5	76.4
Black	13.7	7.4	9.9
Asian	5.1	7.1	6.3
Others	3.4	3.4	3.4
Missing	7.3	6.3	6.7
Marital Status			
Single	86.3	90.9	89.1
Married	7.3	4.6	5.6
Others	6.4	4.2	5.1
Missing	0	0.3	0.2

Data are extracted from the sponsor's Table 2.2g (vol. 28, p035). Some subjects had more than 1 race.

Table 13. **History of Previous Emergency Contraceptive Use**
(% of enrolled population)

	Clinical Sites	Pharmacy Site	Total
Never Used	60.7	48.6	60.0
Ever Used (times)	39.3	51.4	40.0
1	25.3	31.4	25.6
2	10.4	11.4	10.4
3	2.2	5.7	2.4
≥ 4	0.9	2.9	1.0
Missing	0.5	0	0.5

Data are extracted from the sponsor's Table 2.6a (vol. 28, p047).

Table 14. **Time since the Last Emergency Contraceptive Use**
(% of enrolled population)

Months Since Last Use	Clinical Sites N=550	Pharmacy Site N=35	Total N=585
< 1	2.2	2.9	2.2
1-3	7.8	14.3	8.2
> 3	29.3	34.3	29.6
Total	39.3	51.4	40.0

Data were extracted from the sponsor's Table H (vol. 27, p046) and Table 2.6a (vol. 28, p047).

Table 15. **Reproductive and Contraceptive History of Previous Emergency Contraceptive Users**
(% of enrolled population with or without previous ECP use)

Characteristics	Ever ECP Use N=234 (40%)	Never ECP Use N=351 (60%)	Total N=585 (100%)
Pregnancy History†			
None	62.0	72.4	68.2
1	19.7	16.8	17.9
≥ 2	18.4	9.4	13.0
Missing Data	0	1.4	0.9
Living Children			
None	80.3	86.3	83.9
1	10.7	7.7	8.9
≥ 2	9.0	4.0	6.0
Missing Data	0	2.0	1.2
Contraceptive Method used in previous month			
Condoms	76.5	80.3	78.8
Withdrawal	29.9	26.8	28.0
Oral Contraceptive Pills	22.2	20.5	21.2
Spermicide	7.7	8.5	8.2
Emergency Contraception	5.6	0	2.2
Natural Family Planning	2.6	1.7	2.1
DepoProvera or Lunelle	2.6	1.1	1.7
Other	0.4	0	0.2
At least one sex act without Contraception during past month‡	65.8*	56.1	60.0

Data are extracted from the sponsor's Table 2.6g (vol. 28, p054).
† $p < 0.003$ by Kruskal-Wallis test and ‡ $p = 0.02$ by Chi-square test compared between Ever ECP and Never ECP.

History of Contraception

A total of 536 subjects (92% of the enrolled population) used a contraceptive method in the previous month (Table 16); and the most common method was the condom (79% of the enrolled population). The Lost to Follow-up population and the entire enrolled population were comparable in their histories of contraception, emergency contraception, pregnancy, and sex without contraception.

Table 16. **History of Contraceptive Methods in Previous Month**
(% of the enrolled population)

Contraceptive Method	Clinical Sites N=550	Pharmacy Sites N=35	Total N=585
Condoms	79.6	65.7	78.8
Withdrawal	29.1	11.4	28.0
Oral Contraceptive Pills	20.9	25.7	21.2
Spermicide	8.5	2.9	8.2
Emergency Contraception	2.2	2.9	2.2
Natural Family Planning	2.2	0	2.1
DepoProvera or Lunelle	1.3	8.6	1.7
Other	0.2	0	0.2
At least one sex act without contraception	60.2	57.1	60.0

Data were extracted from the sponsor's Table I (vol. 27, p046) and Table 2.6a (vol. 28, p048).

Reasons to request Plan B (Table 17): The major reasons for the 585 enrolled subjects to request Plan B during the recruitment visit were "condom broke/slipped" (37%), "unprotected sex" (33%), "prevent pregnancy" (17%), and "Oral Contraceptive Pills (OCP) problem" (4%). The sponsor stated that subjects with the reason "prevent pregnancy" did not intend to use Plan B before sexual intercourse.

Ninety-seven percent had a correct reason to request Plan B (after excluding those subjects who provided "unspecified" reasons). See Table 17.

Reasons to use Plan B (Table 18): Approximately 98% of 540 subjects who used Plan B after enrollment had single (91%) or multiple sex acts (7%). The main factors to prompt the subjects to take Plan B were "condom broke/slipped", "used no contraception", and "missed OCPs". Correct self-selection calculated by exclusion of the reasons "Other" and "Doesn't remember/missing data" was 95±2.7% (514 of 540 users).

Overall, the factors prompting subjects to seek and use Plan B were similar among those of different ages, races, ethnicity, educational levels, or ever/never EC use experience (Tables 17 and 18).

Table 17. **Reasons to Request Plan B at Screening/Enrollment by Subgroups**
(% of the enrolled population)

Reason to Request Plan B	Study Sites		Eligibility		Age (year)		Education		Prior EC Use		Total N=585
	Clinics N=550	Pharmacy N=35	Ineligible N=9	Eligible N=576	≤16 N=29	≥17 N=556	<HS N=78	≥HS N=507	Ever N=234	Never N=351	
Condom broke or slipped	37.1	42.9	44.4	37.3	31.0	37.8	34.6	37.9	32.5	40.7	37.4
Unprotected sex	33.3	31.4	11.1	33.5	27.6	33.5	23.1	34.7	37.6	30.2	33.2
Prevent pregnancy	17.1	14.3	11.1	17.0	27.6	16.4	28.2	15.2	18.8	15.7	16.9
OCP problem	3.8	5.7	11.1	3.8	3.4	4.0	5.1	3.7	3.8	4.0	3.9
Mistake/accident	2.4	0.0	11.1	2.1	6.9	2.0	3.8	2.0	2.1	2.3	2.2
Contraceptive failure (unspecified)	1.8	0.0	0.0	1.7	0.0	1.8	0.0	2.0	1.7	1.7	1.7
Withdrawal	1.5	0.0	11.1	1.2	0.0	1.4	2.6	1.2	0.0	2.3	1.4
Prevention, unspecified	1.3	0.0	0.0	1.2	3.4	1.1	2.6	1.0	0.9	1.4	1.2
Unspecified	1.3	0.0	0.0	1.2	0.0	1.3	0.0	1.4	1.7	0.9	1.2
Sex, unspecified	0.5	2.9	0.0	0.7	0.0	0.7	0.0	0.8	0.4	0.9	0.7
Backup to spermicide	0.2	0.0	0.0	0.2	0.0	0.2	0.0	0.2	0.4	0.0	0.2
Missed injection	0.0	2.9	0.0	0.2	0.0	0.2	0.0	0.2	0.0	0.3	0.2

Data were extracted from Tables 2.10a, b, c, f and g (p061-p069 of vol. 28). The information was collected during the screening/enrollment visits.

Table 18. **Reasons to Prompt Plan B Use after Enrollment by Subgroups**
(% of subjects who used the product)

Reason to use Plan B	Study Sites		Eligibility		Age (year)		Education		Prior EC Use		Total N=540
	Clinics N=510	Pharmacy N=30	Ineligible N=7	Eligible N=533	≤16 n=22	≥17 n=518	<HS n=64	≥HS n=476	Ever N=213	Never N=327	
Reason to Prompt Plan B Use (Total Responses)	100	100	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Single sex act	91.6	86.7	85.7	91.4	95.5	91.1	92.2	91.2	91.1	91.4	91.3
Multiple sex acts	6.9	10.0	0.0	7.1	4.5	7.1	4.7	7.4	8.5	6.1	7.0
Other reason	0.8	3.3	14.3	0.8	0.0	1.0	1.6	0.8	0.0	1.5	0.9
Missing data	0.8	0.0	0.0	0.8	0.0	0.8	1.6	0.6	0.5	0.9	0.7
Nature of Contraception Failure (Total Responses)	98.6	100	85.7	98.9	100.0	98.6	96.9	98.9	99.5	98.2	98.7
Condom broke/slipped	44.9	50.0	42.9	45.2	54.5	44.8	46.9	45.0	39.9	48.6	45.2
Used no contraception	39.8	36.7	28.6	39.8	27.3	40.2	28.1	41.2	44.6	36.4	39.6
Missed OCPs	7.1	3.3	0.0	6.9	9.1	6.8	10.9	6.3	7.0	6.7	6.9
Withdrawal	3.7	0.0	0.0	3.6	9.1	3.3	7.8	2.9	3.8	3.4	3.5
Other	2.5	10.0	14.3	2.8	0.0	3.1	3.1	2.9	4.2	2.1	3.0
Doesn't remember/missing	0.6	0.0	0.0	0.6	0.0	0.6	0.0	0.6	0.0	0.9	0.6

Data were extracted from Table 5.2a, b, c, f and g (p106- of vol. 28). The information was collected during the follow-up contacts.
OCPs: oral contraceptive pills.

Contraindicated Use: There are three contraindications listed in the Warnings section of the proposed OTC label, and subjects should have deselected this product if they had any of them. A total of 523 (97%) of 540 users provided sufficient data for evaluation of contraindications after the first screening. Seventeen subjects (3.1% of 540) had insufficient data for evaluation and were excluded from analysis. The results by age, educational level, and previous EC experience were summarized in Table 19.

Seven subjects with contraindications (1.3% of 523 users) unintentionally used Plan B. The contraindicated users were in the "eligible" group; six of them were at least age 17 and had at a high school education or greater. By including 3.1% subjects with missing data, the maximum percentage of contraindicated use would be 4.4%.

Pregnancy: One subject was already pregnant when she used Plan B.

Unexplained vaginal bleeding: Six subjects had unexplained vaginal bleeding before use: one after intercourse, one early menses, and 4 unexplained bleeding.
Allergy: No subjects were allergic to Plan B.

The sponsor stated that they did not have information on the 45 subjects (585-540) who purchased Plan B but did not use it because of contraindications.

Table 19. **Contraindicated Use of Study Product**
(% of subjects who used the product)

	Study Site		Age (Years)		Education		Prior ECP Use		Total
	Clinics	Pharmacies	≤ 16	≥ 17	≤ HS	≥ HS	Ever	Never	
Users, *No.*	510	30	22	518	64	476	213	327	540
Total Contraindicated Use†									
Intentional	0	0	0	0	0	0	0	0	0
Unintentional	1.4	0	4.5	1.2	1.6	1.3	1.4	1.2	**1.3**
Insufficient data	3.3	0	13.6	2.7	9.4	2.3	2.8	3.4	3.1
Pregnancy at time of Use									
Yes	0.2	0	0	0.2	0	0.2	0	0.3	0.2
No	97.1	100	86.4	97.7	93.8	97.7	98.1	96.6	**97.2**
Insufficient data	2.7	0	13.6	2.1	6.3	2.1	1.9	3.1	2.6
Unexplained vaginal Bleeding									
Yes	1.2	0	4.5	1.0	1.6	1.1	1.4	0.9	1.1
No	98.4	100	95.5	98.6	96.9	98.7	98.1	98.8	**98.5**
Insufficient data	0.4	0	0	0.4	1.6	0.2	0.5	0.3	0.4
Allergy to Plan B									
Yes	0	0	0	0	0	0	0	0	0
No	99.0	100	100	99.0	96.9	99.4	99.1	99.1	**99.1**
Insufficient data	5	0	0	1.0	3.1	0.6	0.9	0.9	0.9

Data were extracted from the sponsor's Tables 5.5c, f and g in page 122-127 of vol. 28.
HS: high school education; ECP: emergency contraception pill
† "Intentional" indicates that subjects correctly recognized contraindications before use and "Unintentional" indicates that subject incorrectly recognized contraindications before use.

Correct Use (Timing of Doses)

Of the 585 enrolled subjects 540 took 2 pills or 1 pill (only one subject). A total of 506 subjects (94% of 540 users) provided sufficient data for evaluation of correct use and the remainder were excluded from the analysis.

Two subjects took the first pill before sexual intercourse (103 hours and 12.5 hours respectively). As shown in Table 20, the first pill was taken at 34.8±21.1 hours (-103 to 175 hours) in relation to the timing of sexual intercourse and the second pill was taken 12.5±3.2 hours (0-36 hours) after the first pill.

There was similar timing of Plan B use among those of different ages, ethnicities, races, educational levels and with/without emergency contraceptive experience.

Correct Use Analysis as per Protocol (Tables 21a & 21b): The per-protocol analysis (per label dosing regimen) for correct use demonstrated that 92±10% (n=499) of users took the first pill < 72 hours after intercourse and 72±14% (n=387) took the 2nd pill at 12 hr after the first pill. Overall, 68±17% (n=366) of users took both pills according to the label dosing instruction.

Of the 26% incorrect uses, 1.3% (n=7) were intentional and 24.6% (n=133) were unintentional.

A re-analysis of the data based on the 506 subjects who used Plan B and provided sufficient follow-up data (Table 21b), demonstrated that the correct use rate was 72% (366 of 506).

Therefore, overall correct use rate would be 68-72% as per label dosing regimen.

Table 20. **Disposition of Plan B in the Enrolled Population**
(% of enrolled population)

	Age (years)		Education		Prior ECP Use		Total
	≤16	≥17	<HS	≥HS	Ever	Never	
Enrolled Subjects	29	556	78	507	234	351	585
Gave product away							
Yes	0	1.3	0	1.4	1.3	1.1	1.2
No	75.9	92.3	80.8	93.1	89.7	92.6	**91.5**
No data	24.1	6.5	19.2	5.5	9.0	6.3	7.4
Number of pills taken							
0	0	0.5	0	0.6	0.4	0.6	0.5
1	0	0.2	0	0.2	0	0.3	0.2
2	75.9	93.0	82.1	93.7	91.0	92.9	**92.1**
No data	24.1	6.3	17.9	5.5	8.5	6.3	7.2
The first pill taken†							
Subject (%)	65.5	88.1	71.8	89.3	88.5	86.0	**87.0**
Hours after sex act	40.2±19.2 (11.5-70)	34.6±21.2 (-103-175)	35.0±18.1 (5-70)	34.8±21.5 (-103-175)	34.1±18.7 (-12.5-88)	35.3±22.7 (-103-175)	34.8±21.1 (-103-175)
The second pill taken‡							
Subject (%)	72.4	90.3	78.2	91.1	88.9	89.7	**89.4**
Hours from the 1st pill	12.1±0.5 (11-14)	12.5±3.3 (0-36)	12.9±3.0 (11-24.5)	12.5±3.2 (0-36)	12.6±3.1 (0-36)	12.5±3.2 (0-36)	12.5±3.2 (0-36)

Data were extracted from the sponsor's Tables 5.1c, 5.1f and 5.1g in page 101-105 of vol. 28.
† including subjects who took at least one pill; subjects may take pills before sex.
‡ including subjects who took pills and the interval between pills was not negative.

Table 21a. **Incorrect Use of Plan B by Primary Definition**
(% of subjects who used the product, **including** those who provided insufficient data)

	Age (years)		Education		Prior ECP Use		Total N=540 *No. (%)*
	< 16 N=22	≥ 17 N=518	< HS N=64	≥ HS N=476	Ever N=213	Never N=327	
Total Correct Use, no. (%)	17 (77.3)	349 (67.4)	43 (67.2)	323 (67.9)	142 (66.7)	224 (68.5)	**366 (67.8)**
Total Incorrect Use, no. (%)	3 (13.6)	137 (26.4)	16 (25.0)	124 (26.1)	63 (29.6)	77 (23.5)	**140 (25.9)**
Intentional†	0	1.4	0	1.5	1.9	0.9	7 (1.3)
Unintentional‡	13.6	25.1	25.0	24.6	27.7	22.6	**133 (24.6)**
Missing data	9.1	6.2	7.8	6.1	3.8	8.0	34 (6.3)
Timing for the first pill after sex act							
> 72 hours	0	1.9	0	2.1	1.9	1.8	10 (1.9)
< 72 hours	86.4	92.7	87.5	93.1	95.3	90.5	**499 (92.4)**
Missing data	13.6	5.4	12.5	4.8	2.8	7.6	31 (5.7)
Interval between the second and first pill							
</> 12 hours	13.6	25.7	25.0	25.2	29.1	22.6	136 (25.2)
At 12 hours	81.8	71.2	70.3	71.8	68.5	73.7	**387 (71.7)**
Missing data	4.5	3.1	4.7	2.9	2.3	3.7	(3.1)

Data were extracted from the sponsor's Tables 5.8c, 5.8f and 5.8g in page 133-137 of vol. 28.
† "Intentional" was that subjects correctly recognized the instruction before use;
‡ "Unintentional" was that subject incorrectly recognized the instruction before use.

Table 21b. **Incorrect Use of Plan B by Primary Definition**
(% of subjects who used the product, **excluding** those who provided insufficient data from denominator)

	Age (years)		Education		Prior ECP Use		Total
	≤16	≥17	<HS	≥HS	Ever	Never	*No. (%)*
Valid Users*	**20**	**486**	**59**	**447**	**207**	**301**	**506**
Total Correct Use, no. (%)	17 (85.0)	349 (71.8)	43 (72.9)	323 (72.2)	142 (68.6)	224 (74.4)	**366 (72.3)**
Total Incorrect Use, no. (%)	3 (15.0)	137 (28.2)	16 (27.1)	124 (27.7)	63 (30.4)	77 (25.6)	**140 (27.7)**
Intentional†	0	1.4	0	1.6	1.9	1.0	7 (1.4)
Unintentional‡	15.0	26.7	27.1	26.2	28.5	24.6	**133 (26.3)**
Timing for the first pill after sex act							
> 72 hours	0	2.1	0	2.2	1.9	2.0	10 (2.0)
< 72 hours	95.0	98.8	94.9	99.1	98.1	98.3	**499 (98.6)**
Interval between the second and first pill							
</> 12 hours	15.0	27.4	27.1	26.8	30.0	24.6	136 (26.9)
At 12 hours	90.0	75.9	76.3	76.5	70.5	80.0	**387 (76.5)**

Data were reprocessed based on the sponsor's Tables 5.8c,f,g, 5.10a in page 133-140 of vol. 28.
* "Valid users" were subjects who used the product and provided sufficient data: Valid Users = (Total Users – Users with missing data).
† "Intentional" was that subjects correctly recognized the instruction before use;
‡ "Unintentional" was that subject incorrectly recognized the instruction before use.

Incorrect Use Analysis with Alternative Criteria: The sponsor re-analyzed the data using alternate criteria (different dosing regimens), as summarized in Tables 22a and 22b, which decreased the incorrect use from 27% to 2%. The sponsor did not provide any evidence in the submission to support if the alternate criteria/dosing regimens produced comparable efficacy to the labeled dosing regimen (both in Rx and the proposed OTC label). There was also no explanation as to why the number of subjects with insufficient data varied from 34-42 among the different analyses.

Table 22a. **Timing of two doses by Different Criteria**
(% of 540 enrolled subset population who used the product)

	Primary Criteria†	Alternate Criteria I‡	Alternate Criteria II*	Alternate Criteria III#
Dosing Regimen	1st pill <72 hrs 2nd pill =12 hrs	1st pill <72 hrs 2nd pill <16 hrs	1st pill <72 hrs 2nd pill 6-18 hrs	1st pill <120 hrs 2nd pill <24 hrs
Subjects with Insufficient Data *No. (%)*	34 (6.7)	40 (7.4)	39 (7.2)	42 (7.7)
Incorrect Use *No. (%)*	140 (25.9)	33 (6.1)	32 (5.9)	10 (1.9)
Correct Use *No. (%)*	366 (67.8)	467 (86.5)	469 (86.9)	488 (90.4)

† Data were extracted from Table 5.8a (vol. 28, p131); ‡ from Table 5.11a (vol. 28, p141); * from Table 5.14a (vol. 28, p151); # from Table 5.17a (vol. 28, p160a).

Table 22b. **Alternate timing interval of 2nd dose**
(% of 540 enrolled subset population who used the product)

	Primary Criteria†	Alternate Criteria I‡	Alternate Criteria II*	Alternate Criteria III#
2nd Dosing Interval	12 hrs	<16 hrs	6-18 hrs	<24 hrs
No. of Users	387	501	500	516
% of Users (n=540)	72	93	93	96
Insufficient data	34	17	17	17

† Data were extracted from Table 5.8a (vol. 28, p131); ‡ from Table 5.11a (vol. 28, p141); * from Table 5.14a (vol. 28, p151); # from Table 5.17a (vol. 28, p160a).

In a pivotal efficacy trial (WHO trial) submitted to the original Plan B NDA (*the trial # was not provided*), the time interval between the 1st pill and 2nd pill was variable (Table 22c) and "high effectiveness" was obtained, as the sponsor quoted in the report.

Table 22c. **Comparison of Dosing Interval of Second Pills between Current Study and Previous Clinical Trial (submitted to the original NDA)**

Time Interval between 1st pill and 2nd pill	Current AU Study N=540 No. (%)	WHO Trial* N=974 (%)
<12 hours	52 (9.6)	(9)
At 12 hours	387 (71.6)	(74)
12-16 hours	63 (11.7)	(13)
> 16 hours	21 (3.9)	(5)

* The sponsor reanalyzed the data submitted to the original NDA. No details were provided in the report; data were % only.

Consultation with Health Care Providers

At Admission: Of the 585 enrolled subjects, 92 (16%) consulted with a clinician or pharmacist at the initial study visit (right after enrollment). The most common questions that these subjects asked were related to safety and contraindications (5.8%) and instructions for use (3.1%) (Table 23a).

Table 23a. **Consultation with Clinician or Pharmacist at Admission**
(% of enrolled population)

	Clinical Sites N=550	Pharmacy Sites N=35	All Sites N=585
Consulted Subjects	14.9	28.6	15.7
Consulted Topics			
Safety	5.6	8.6	5.8
Instruction (use)	3.3	0	3.1
Take with food	2.2	2.9	2.2
Other contraception	1.8	0	1.7
Products	1.3	8.6	1.7
Efficacy	1.3	5.7	1.5

Data were extracted from the sponsor's Table 1.5 in page 020 of vol. 28.

During Plan B Use: Thirty-one (6%) subjects who used Plan B consulted a health care provider for the reasons listed in Table 23b. It is unknown if these 31 subjects were part of the 92 who consulted at the initial study visit.

Table 23b. **Consultation with Health Care Providers during Study**
(% of enrolled population who provided any follow-up data)

Consultation	Clinical Sites N=522	Pharmacy Sites N=31	Total N=553
Yes (total 31 users)	5.0	16.1	5.6
Reasons			
Contraindication question	0.2	0.0	0.2
Informed Physician	1.3	9.7	1.8
Medical problem or side effect	1.5	3.2	1.6
Nonspecific questions	0.2	0.0	0.2
Ongoing contraception	0.8	3.2	0.9
Pregnancy test (+)	0.2	6.5	0.5
Question about Plan B	0.6	0.0	0.5
Repeat ECP use	0.6	0.0	0.5
Routine appointment	0.2	6.5	0.5
Wanted pregnancy test	0.2	0.0	0.2

Data were extracted from Table 6.9 (vol. 28, p218)

Incorrect and contraindicated uses after consultation: Consultation with health care providers tended to increase contraindicated use and decrease incorrect use (Table 23c). It appears that the 85 subjects in Table 23c who consulted a healthcare provider had used Plan B and had provided enough information for this analysis. It is unclear that all subjects who consulted a healthcare provider actually used Plan B.

Table 23c. **Contraindicated and Incorrect Use of Plan B by Subjects Who Consulted/did not Consult Health Care Provider**

Plan B Use	Consultation with Health Care Provider		Total Users N=540 No. (%)	P-value
	Yes N=85 No. (%)	No N=455 No. (%)		
Contraindicated use	3 (3.5)	4 (0.9)	7 (1.3)	0.08
Incorrect Use				
Primary criteria	16 (18.8)	124 (27.3)	140 (25.9)	0.21
Alternate I	3 (3.5)	30 (6.6)	33 (6.1)	0.45
Alternate II	3 (3.5)	29 (6.4)	32 (5.9)	0.45
Alternate III	0 (0)	10 (2.2)	10 (1.9)	0.37

Data were extracted from Table 23 in the *Addendum to Final Study Report*, p27

Pregnancy and Menstrual Period

Menstrual Period Status after Plan B (Table 24a): Of the 540Plan B users, 513 (95%) had a menstrual period before the end of their study participation. The median time of onset of the menstrual period was 6 days (0-49 days) after product use (2nd pills).

Table 24a. **Menstrual pattern after first use of Plan B**

Menstrual Period Onset	Age (years)		Total N=540
	≤ 16 N=22	≥ 17 N=518	
% of Users			
Yes	81.8	95.6	95.0
No	18.2	4.1	4.6
Missing	0	0.4	0.4
Days after the first pill			
Mean ± SD (Range)	13.3±11.8 (1-40)	10.3±8.4 (0-49)	10.4±8.5 (0-49)
Median	8	7	7

Data were extracted from Table 6.8b (vol. 28, p217).

Pregnancy after Plan B (Tables 24b and 24c): Of the 540 users , 58 met the criteria for pregnancy review by the medical monitor from Family Health International. Ten were

confirmed to be pregnant and at least some may have been pregnant prior to using Plan B. All 10 pregnant subjects took the first pill within 72 hours after sex and the second pill at 12 or 13 hours after the first pill. Their characteristics are summarized in Table 24c.

The sponsor reported a 1.9% pregnancy rate for this study population (10 of 540). However, there were 14 "unclassifiable" pregnant subjects who did not complete the follow-up. The maximal possible pregnancy rate for the study subjects was 4.4% (10+14 of 540), so the true pregnancy rate was from 1.9% to 4.4%.

Table 24b. **Pregnancy in the enrolled subjects who use Plan B**

	Subject		
	Number	%	
Total Users	540	100	
Suspected Pregnancy	58	10.7	
Classifiable Pregnancy	10	**1.9**	**4.4%**
Unclassifiable Pregnancy	14	2.6	

Data were extracted from the text of the report (vol. 27, p059). Classifiable and unclassifiable pregnancy was determined by the medical monitor from FHI; unclassifiable pregnancy was due to insufficient data because of only one follow-up contact.

Table 24c. **Characteristics of the 10 Classifiable Pregnant Subjects**

Subject ID	Age (yr)	Marital Status	Education	Prior EC Use	Race	Ethnicity
4072	17	Single	= HS	Yes	African-American	Non- Hispanic
2123	18	Single	≥ HS	No	White	Non- Hispanic
1058	19	Single	≥ HS	No	White	Non- Hispanic
2042	19	Single	≥ HS	Yes	White	Non- Hispanic
2065	22	Single	≥ HS	No	White	Non- Hispanic
5058	23	Single	≥ HS	Yes	White	Non- Hispanic
3037	25	Single	≥ HS	Yes	White	Non- Hispanic
5098	26	Single	≥ HS	No	White	Non- Hispanic
3057	32	Single	≥ HS	No	White	Non- Hispanic
6021	36	Single	≥ HS	No	African-American	Non- Hispanic

Data were extracted from Listing 9 (vol. 29, p016-017)

Adverse Events (AEs)

There were no new safety signals for Plan B noted during this study. Of the 540 subjects who used the study product, 246 (46%) reported at least one adverse event. There was a total of 412 AEs.

AE reports ≥ 1.0 % of enrolled subjects who used Plan B were summarized in Table 25a from both data collection sources. AEs presented by body system are listed in Table 25b. The most common AEs occurred in the digestive and nervous systems and were abdominal pain, nausea, headache, and asthenia.

***Table 25a.* Common Adverse Event Reports**
(AEs ≥ 1.0 % of enrolled subjects who used the study product)

Adverse Events	Total AEs from both Sources† (%)	AEs from Follow-up Contact (%)‡
Abdominal pain	14.3	8.9
Nausea	12.4	9.4
Headache	11.3	4.3
Asthenia	8.0	3.7
Metrorrhagia	4.3	2.4
Dizziness	3.7	1.9
Breast Pain	2.8	1.9
Pharyngitis	2.6	ND
Menorrhagia	1.9	1.7
Emotional Liability	1.7	0.9
Somnolence	1.5	ND
Vaginal Hemorrhage	1.3	0.6
Diarrhea	1.3	0.9
Vomiting	1.1	0.6
Allergic reaction	1.1	ND
Total Subjects with AEs	**246/540 (45.6%)**	**150/540 (27.8%)**

† Total AEs were pooled from the Study Data Card and the follow-up contacts; the data were extracted from Table 6.1a (vol. 28, p170-172)

‡ Data were extracted from Table 6.2a (vol. 28, p185); ND: no data available in the Table.

Table 25b. **Adverse Event Reports by Body System**
(% of enrolled subjects who used the study product, n=540)

Body System	Total AEs from both Sources† (%) N=246	AEs from Follow-up Contact (%)‡
Body as a whole	37.6	16.9
Digestive System	16.5	11.5
Urogenital System	14.8	7.4
Nervous System	9.1	3.0
Respiratory System	5.4	ND
Skin and Appendages	0.6	0.4
Cardiovascular System	0.4	0.2
Special Senses	0.4	0.2
Hemic and Lymphatic System	0.2	ND

† Total AEs were pooled from the Study Data Card and the follow-up contacts, extracted from Table 6.3a (vol. 28, p192) and Table 6.5a (vol. 28, p203); the number of Plan B users who reported AEs from both sources was 246 (45.6% of 540 users). A subject may have more than one category of AEs.
‡ Data were extracted from Table 6.6b (vol. 28, p207); the number of subjects who reported AEs based on the follow-up contact only was 150 (27.8% of 540 users).
ND: data were not available in the report.

The pattern of Plan B -related AEs was similar across subgroups defined by ethnicity, race, and education (Table 25c). The users <16 years old tended to report fewer AEs than those ages 17 years and above; however, the sample size in the age <16 subgroup was quiet small (n=22).

The AE reports were comparable between correct and incorrect users. The contraindicated users tended to report more AEs; however, the sample size of contraindicated users were too small (n=7) for a meaningful comparison.

Of all 412 AEs, 52.7% (217) were determined to be Plan B related. Regarding severity, 85% of 412 AEs were mild and 15% moderate. There were no serious AE reports. Approximately 33% of AEs were treated with either prescription or OTC medication (*The medications were not specified in the report*). Ninety-eight percent of subjects stated that the AEs would not stop them from using the product in future.

***Table 25c.* Adverse Event Reports among demographic subgroups**
(% AEs of enrolled subjects who use the product in each subgroup)

Subjects	Total AEs from both sources (%)†	AEs from follow-up contacts (%)‡
Overall % in all users, n=540	45.6	27.8
Age (years)		
< 16, n=22	31.8	13.6
> 17, n=518	46.1	28.4
Ethnic Hispanic		
Yes, n=76	51.3	28.9
No, n=461	44.7	27.8
Race		
White, n=397	43.8	27.2
Non-White, n=100	51.0	28.0
Education Level		
< high school, n=64	37.5	20.3
≥ High school, n=476	46.6	28.8
Eligibility Status		
Eligible users, n=533	45.8	28.1
Ineligible users, n=7	28.6	0
Previous EC Use		
Ever, n=215	44.0	27.4
Never, n=325	46.6	28.0
Study sites		
Clinics, n=510	44.7	27.8
Pharmacies, n=30	60.0	26.7
Use Correctness#		
Correct users, n=393*	45.8	ND
Incorrect users, n=142	43.7	ND
Contraindicated users, n=7	57.1	ND

† Total AEs were pooled from the Study Data Card and the follow-up contacts; the data were extracted from Table 6.1b-g (vol. 28, p173-184); ‡ Data were extracted from Table 6.2b- (vol. 28, p186-191); ND: data were not available in the report.

* % AE subjects in the correct users: total numbers of users with AEs = 246/540, incorrect users with AEs = 62/140 and contraindicated users with AEs =4/7; the total correct users = 393 (540-140-7).

AEs in the contraindicated users were from Table 6.4b (vol. 28, p201) and Table 6.5b (vol. 28, p204); and AEs in the incorrect users were from Table 6.4c (vol. 28, p202) and Table 6.5c (vol. 28, p205).

Concomitant Medications and Allergic Reactions

No subjects reported allergies to Plan B. Medications taken before and after the first screening and allergic reactions are summarized in Table 26. Of the 543 subjects who provided any follow-up data, 36.6% took at least one other medication and 19% reported allergies to at least one medication other than Plan B.

Table 26. **Medications and allergy**
(% of enrolled population)

	Previous Week At the 1st Screening† N=585	After 1st Screening (Follow-up Contacts)‡ N=543
Medications Taken		
Subjects (%)	42.9	36.6
Total #	140	114
Medication Allergy	No data	19.0*

† Extracted from the sponsor's Table 3.1a-b (page 070-078 of vol.28);
‡ Extracted from the sponsor's Table 3.3a-b (page 087-092 of vol. 28);
* Extracted from the sponsor's Table 2.12 (page 067 of vol. 28).

Behavior Changes

Sexual activity: Sexual activity and contraceptive methods before and after Plan B use are summarized in Table 27a. The results presented were based on the 543 subjects who provided follow-up data after the first screening. After Plan B, subjects used condoms more and the withdrawal method less. Sexual activity decreased from 100% within the month before screening to 62% after screening. Unprotected sexual intercourse, or "At least one sex act without contraception", decreased from 60% before screening to 20% after screening. A comparison of he unprotected sexual intercourse information among the different demographic subgroups after enrollment was not available in the report.

Contraception methods: Table 27b shows changes in contraception methods between pre- and post-Plan B in different demographic subgroups, based on the 502 subjects who provided follow-up contact data at $\geq$ 28 days. A slight increase in condom use and decrease in withdrawal method were noted after screening.

Multiple Uses: Ten (1.7%) of the 585 enrolled women had multiple enrollments (8 for twice and 2 for 3 times). The 10 subjects, ages 17-25 years, were eligible at all screenings and received the study product at each screening. Second screenings occurred between 4-80 days (media 8 days). Multiple screenings occurred at all sites except the Seattle clinic and the pharmacies. Eight of 10 subjects used Plan B; 2 (enrolled twice) lost contact. Six

of a total of 18 uses (twice for 6 subjects and 3 times for 2 subjects) were incorrect because of the incorrect use of the 2nd pill.

As seen in Table 27c, compared to the "once" users, more multiple users had "at least one unprotected sex" (88% vs. 59%), and used the "withdrawal" method (50% vs. 27%), but more multiple users used "condoms" (88% vs. 79%) and did not have previous EC use experience (75% vs. 60%). However, the sample size of the subset of multiple users was too small to make an accurate assessment of contraceptive behaviors.

Table 27a. **Sexual activity and Contraception before and after Plan B Use**
(% of the screened subjects who provided any follow-up data)

Sex and Contraception	1 month before Study† N=543	1 month during study‡ N=543
Subjects who had Sex	100.0	61.9 (336)
At least one sex w/o contraception	59.7 (324)	19.6* (66)
Contraception Methods		
Condoms	79.0	89.6
Withdrawal	27.6	10.1
Oral contraceptives	21.9	20.5
Spermicide	8.7	10.7
Natural family planning	2.2	0.3
Emergency contraceptives	1.7	1.2
DepoProvera or Lunelle	1.5	1.2
Other	0.2	1.2

Data were extracted from Tables 7.1a and 7.1b (vol. 28, p219-220); a subject may have used more than one method. Data in the parentheses are the number of subjects.
† Data collected from the month before the first screening;
‡ Data collected from all follow-up contacts after the first screening.
* % of subjects who had sex acts.

***Table 27b.* Changes in Contraception Methods before and after First Screening by Demographics**
(% of enrolled subjects who provided any follow-up data at ≥ 28 days)

Demographics	Sexual Activity		Switching in Effective Methods			Switching in Condom use		
	one month before screening	between screening and end of follow-up	less ► more	more ► less	more effective before and after†	► use no condom	► use condom	used condom before and after†
Enrolled subjects, n=502	(502) 100	319 (63.5)	36 (11.3)	26 (8.2)	37 (11.6)	15 (4.7)	33 (10.3)	251 (78.7)
Age (years)								
≤ 16, n=22, no. (%)	22 (100)	14 (63.6)	4 (28.6)	0	1 (7.1)	0	0	14 (100)
≥17, n=480, no. (%)	480 (100)	305 (63.5)	32 (10.5)	26 (8.5)	36 (11.8)	15 (4.9)	33 (10.8)	237 (77.7)
Ethnic Hispanic								
Yes, n=70	70 (100)	45 (64.3)	5 (11.1)	3 (6.7)	7 (15.6)	1 (2.2)	8 (17.8)	33 (73.3)
No, n=429	429 (100)	273 (63.6)	31 (11.4)	23 (8.4)	30 (11.0)	14 (5.1)	25 (9.2)	217 (79.5)
Race								
White, n=373	373 (100)	226 (60.6)	26 (11.5)	16 (7.1)	26 (11.5)	10 (4.4)	25 (11.1)	179 (79.2)
Non-White, n=94	94 (100)	69 (73.4)	6 (8.7)	8 (11.6)	9 (13.0)	4 (5.8)	9 (5.8)	54 (78.3)
Education								
< High school, n=60	60 (100)	37 (61.7)	8 (21.6)	2 (5.4)	5 (13.5)	3 (8.1)	3 (8.1)	31 (83.8)
≥ High school, n=442	442 (100)	282 (63.8)	28 (9.9)	24 (8.5)	32 (11.3)	12 (4.3)	30 (10.6)	220 (78.0)
Prior ECP Use								
Ever, n=195	195 (100)	127 (65.1)	12 (9.4)	13 (10.2)	12 (9.4)	6 (4.7)	15 (11.8)	94 (74.0)
Never, n=307	307 (100)	192 (62.5)	24 (12.5)	13 (6.8)	25 (13.0)	9 (4.7)	18 (9.4)	157 (81.8)
Study site								
Clinics, n=471	471 (100)	301 (63.9)	34 (11.3)	23 (7.6)	35 (11.6)	12 (4.0)	31 (10.6)	237 (78.7)
Pharmacies, n=31	31 (100)	18 (58.1)	2 (11.1)	3 (16.7)	2 (11.1)	3 (16.7)	1 (5.6)	14 (77.8)

Data were extracted from the sponsor's Tables 7.2a-g (p221-227 of vol. 28), which covered from one month before first screening to the end of follow-up contacts. Any of the following was defined as "more effective methods": oral contraceptive pills, Depo-Provera, Lunelle, vasectomy, IUD; otherwise, as "less effective methods". † % of subjects who had sex during study (between screening and end of follow-up); "before" – one month before screening and "after" – end of follow-up contacts (≥ 28 days).

Table 27c. **Demographics and Contraceptive Behavior of subjects with multiple screening and using Plan B**

Characteristics	Screened		Used	
	Once N=655	Multiple N=10	Once N=532	Multiple N=8
Age (years)				
<16	31 (4.7)	1 (10.0)	22 (4.1)	0
17-25	497 (75.9)	8 (80.0)	398 (74.8)	7 (87.5)
26-30	84 (12.8)	1 (10.0)	77 (14.5)	1 (12.5)
Marital status				
single	585 (89.3)	10 (100)	472 (88.7)	8 (100)
married	37 (5.6)	0	31 (5.8)	0
Education				
8th grade or less	3 (0.5)	0	2 (0.4)	0
9th-11th grade	90 (13.7)	2 (20.0)	61 (11.5)	1 (12.5)
high school/GED	91 (13.9)	2 (20.0)	70 (13.2)	2 (25.0)
vocational/technical school	11 (1.7)	0	9 (1.7)	0
Some college	317 (48.4)	4 (40.0)	268 (50.4)	3 (37.5)
finished college	105 (16.0)	1 (10.0)	89 (16.7)	1 (12.5)
graduate school	37 (5.6)	1 (10.0)	33 (6.2)	1 (12.5)
missing	1 (0.2)	0	0	0
Previous EC use				
No	347 (53.0)	8 (80.0)	321 (60.3)	**6 (75.0)**
Yes	234 (35.7)	2 (20.0)	211 (39.7)	2 (25.0)
Once	151 (23.1)	1 (10.0)	137 (25.8)	1 (12.5)
Twice	60 (9.2)	1 (10.0)	55 (10.3)	1 (12.5)
Contraception methods in previous month				
OC pills	123 (18.8)	2 (20.0)	118 (22.2)	1 (12.5)
Condoms	458 (69.9)	**8 (80.0)**	420 (78.9)	**7 (87.5)**
Spermicide	49 (7.5)	0	47 (8.8)	0
DepoProvera or Lunelle	10 (1.5)	0	8 (1.5)	0
Withdrawal	160 (24.4)	5	145 (27.3)	**4 (50.0)**
Natural fam. planning	12 (1.8)	0	12 (2.3)	0
EC pills	13 (2.0)	0	9 (1.7)	0
Other	1 (0.2)	0	1 (0.2)	0
At least one unprotected sex	346 (52.8)	**8 (80.0)**	315 (59.2)	**7 (87.5)**

Data were extracted from the sponsor's tables 8.2, 8.3, 8.4, 8.5 (p229-234 of vol28); only corresponding screening data to multiple use were presented.

The numbers in parentheses are % of the screening subjects in "Screening" population, or % of the users in "Used" (subjects who used Plan B during study).

SUMMARY

1. **Study Design:**

This was a multi-center, open-label, single-arm, uncontrolled clinical trial conducted in 5 family planning clinic sites across 5 states in the United States and 5 pharmacy stores in Washington State to assess self-selection, self-administration (timing of doses), contraceptive behavior, safety and efficacy of Plan B when used in an OTC-like setting. Of 665 women screened, 585 (88%) were enrolled (age 14-44 years) and received one package of Plan B, and 540 (92%) used Plan B during the study.

2. **Data Collection:**

All data were collected by pre-designed questionnaires and study data cards (diary card). Screening and background data were obtained in person at study sites; follow-up contacts were conducted by phone (98% of contacts) or in person (2% of contacts); and the study data card was received by mail. The follow-up contact data were superior to the diary card for the actual data analyses (except AEs). Five hundred two (86%) of the 585 enrolled subjects completed 2 follow-up contacts (45% per-protocol which was the first contact at 5-8 days and the second contact at $\geq$ 28 days; 41% off-protocol).

Less compliance with follow-up was noted in subjects at age 14-16 and subjects with less than high school education. The compliance in subjects for other demographic characteristic (races, ethnicity and history of emergency contraception use) appeared to be comparable.

3. **Results**:

Self-selection:

Approximately 95% (n=514) of subjects who used Plan B could correctly self-select, and 1.3% (n=7) of subjects with contraindications used Plan B (already pregnancy and unexplained vaginal bleeding).

Data on subjects who did not use Plan B in the study were not reported, thus the self-selection in that subgroup is unknown.

Correct use (timing of doses):

Approximately 68±17% (n=366) of users (n=540) took both pills of Plan B according to dosing instruction in the proposed OTC label; 92% (n=499) took the first pill within 72 hours after intercourse and 72% took the 2nd pill at 12 hours later. Of those incorrect users, 95% was unintentional.

The alternate 2nd dosing analysis showed that 93% of users took the 2nd pill between 6-18 hours after the 1st pill; 87% of users took both pills according to the alternate 2nd dosing interval and the fist pill < 72 hours.

There were no significant differences in per-label dosing among subjects with different ages, educational levels, previous EC experience and ethnicities/races.

Pregnancy rate:

Ten of 540 subjects (1.9%) were pregnant. They were ages 17-36 years; nine had at least a high school education; eight were white and two African-American; all were non-Hispanic; and four had previous EC experience.

In addition, 2.6% of users (n=14) had suspected pregnant status at the 4-week contact but were lost to further follow-up. Therefore, the pregnancy rate in a conservative analysis was 4.5% (1.9%+2.6%).

Contraceptive behaviors:

The following are behavioral changes recorded during the 4-week follow-up period, as compared to the 1 month before enrollment in study (collected during enrollment):

Sexual Activity:	Decreased from 100% (before study) to approximately 64% (during study) (Table 27b);
Unprotected sex:	"At least one sex act without contraception" decreased from 60% (before study) to 20% (during study) (Table 27a);
Condom Use:	Increased from 79% (before) to 90% (after) and withdrawal decreased from 28% (before) to 10% (after) (Table 27a);
Routine Contraception:	No increase in switching to less-effective contraception methods (Table 27b);
Multiple Use:	Ten (1.7%) of the 585 enrolled subjects re-enrolled and received Plan B more than once (8 used twice and 2 used 3 times). There were no significant differences in contraceptive behaviors between the multiple users and the single users.

However, this AU study was not primarily designed for assessment of risky sexual behaviors in an OTC-like environment..

Adverse events:

There were no serious adverse events (AEs) and no new safety signals reported in the study. Overall, about 46% of users experienced some AEs. The most common AEs were abdominal pain, nausea, headache and asthenia; 85% of AEs were mild and 15% moderate. Most AEs resolved without any medical intervention and 30% were treated with either prescription or OTC medication.

Comparison between age 14-16 and 17-44:

- A total 29 subjects (5% of the 585 enrolled subjects) age 14-16 were recruited from clinic sites in the study and 22 of them used Plan B.

- Overall, *self-selection, correct use (timing of doses), contraindicated use, AEs and behavior changes* were not different between subjects age 14-16 and age 17-44 years (Table 28).

- The follow-up compliance rate was relatively lower in the subjects age 14-16 years than those in ages 17-44 years, with lost-to-contact 24% *vs.* 7% and 2 contacts 55% *vs.* 87%.

Comparison among educational levels:

- There were 0.3% (n=2) of subjects with $\leq 8^{th}$ grade education and 13% (n=76) of subjects with a $9^{th} - 11^{th}$ grade education.

- There were no significant differences between subjects with $\leq 11^{th}$ grade educations and those with $\geq$ high school educations in self-selection, and timing of doses, contraceptive behaviors and AEs (Table 29).

Comparison between Ever and Never previous EC use:

- There were no significant differences in *correct dosing, contraindicated use, AEs and contraceptive behaviors* between subjects with EC experience (40%) and those without EC experience (Table 30).

- The subjects with previous EC use experience were more likely to have "at least one act of unprotected sexual intercourse" and tended to use condoms less in the month prior to enrollment (Table 15).

- More subjects with prior EC experience requested and used Plan B in this study with the reasons "unprotected sex" or "used no contraception" (Table 30).

Comparison between clinic and pharmacy sites:

- About 6% of the enrolled subjects (n=35) or users (n=30) were recruited from pharmacy stores in Washington state.

- At the baseline, as compared to those from clinics (94%), more subjects from the pharmacies had previous experience using EC (51% vs. 39%) and taking OC pills (26% vs. 21%); fewer used condoms (66% vs. 80%) and the withdrawal method (11% vs. 29%).

- The pharmacy subjects had slightly less correct self-selection (91% vs. 96%).

- The pharmacy subjects tended to have adverse change in their contraceptive behaviors during the study, such as stopping condom use and switching to less effective contraception.

- Pharmacy subjects also had better compliance with timing the first pill (100% vs. 92%) and the 2nd pill (97% vs. 70%) with overall correct use of 96% (vs. 66% in clinics).

COMMENTS

1. The majority (94%) of subjects were recruited from family planning clinics. This may fully not represent the target OTC populations, although there are some difficulties to conduct an actual use study for the Plan B indication in public areas such as shopping malls.

2. The subjects were followed for only 4 weeks. This may provide only short-term assessment of contraceptive behaviors associated with OTC availability of Plan B.

3. Analysis of the timing of 2nd pill using alternate dosing interval, 6-18 hours after the 1st pill, show better compliance in the study population, 93% (6-18 hours) vs. 72% (12 hours). However, the sponsor did not provided data in the study report to support efficacy for this alternate dosing regimen.

4. Although no significant differences in actual use evaluation were noticed in subjects age 14-16, as compared to the subgroup age 17-44, only 5% (n=29) of subjects ages 14-16 were enrolled and all were from the clinics.

5. The small sample size of subjects with less than a completed high school limits meaningful conclusions for this population, 0.3% (n=2) with $\leq 8^{th}$ grade education and 13% (n=76) at 9^{th} -11^{th} grade education.

6. There was no literacy testing in this study, so the actual use of Plan B in different literacy populations can not be assessed.

7. The subjects were allowed to purchase only one package of Plan B (single course of treatment) at a time and had to re-enroll in order to purchase additional package. This does not simulate the OTC setting and limits assessment of contraceptive behaviors.

CONCLUSION

1. The study subjects can properly self-select Plan B and appropriately time both doses of Plan B in an OTC-like setting.

2. There were no serous adverse events and no new safety signals during the 4-week observation period.

3. The study had inadequate design to assess risky sexual and contraceptive behaviors that may be associated with the Plan B use in the OTC environment.

4. This study limits assessment of Plan B OTC use in subjects age <16 years and subjects with less education and different literacy levels.

5. The pregnancy rate was 1.9%-4.5% in the study population who used Plan B during the study.

Table 28. **Comparison in Plan B use between age 14-16 and age 17-44**
(% of the enrolled subjects; otherwise % of users †)

Parameters	Age (years)		Total
	14-16	17-44	*No. (%)*
Enrolled Subjects, *No (%)*	29 (49.6%)	556 (95.0%)	585
Subjects used Plan B, *No. (%)*	22 (75.9%)	518 (93.2%)	540 (92.3)*
Compliance of follow-up contacts			
Lost Follow-up	24.1	6.5	43 (7.4)
One Follow-up	20.7	4.1	29 (5.0)
Two Follow-up	55.2	87.2	501 (85.6)
> 3 Follow-up	0	2.2	12 (2.1)
Prior EC Use	27.6	40.6	234 (40.0)
Education 8th Grade and less	3.4	0.2	2 (0.3)
9th – 11th Grade	96.6	8.6	76 (13.0)
HS above	0	91.2	507 (86.7)
Reason to Request Plan B			
Condom broke or slipped	31.0	37.8	219 (37.4)
Unprotected sex	27.6	33.5	194 (33.2)
Prevent pregnancy	27.6	16.4	99 (16.9)
OCP problem	3.4	4.0	23 (3.9)
Mistake/accident	6.9	2.0	13 (2.2)
Contraceptive failure (unspecified)	0.0	1.8	10 (1.7)
Withdrawal	0.0	1.4	8 (1.4)
Prevention, unspecified	3.4	1.1	7 (1.2)
Reason to Use Plan B†			
Condom broke/slipped	54.5	44.8	244 (45.2)
Used no contraception	27.3	40.2	214 (39.6)
Missed OCPs	9.1	6.8	37 (6.9)
Withdrawal	9.1	3.3	19 (3.5)
Disposition of Plan B			
Took both pills	75.9	93.0	539 (92.1)
Time taken 1st pill (hours after sex)	40.2±19.2 [11.5~70]	34.6±21.2 [-103~175]	34.8±21.1 [-103~175]
Time taken 2nd pill (hours after 1st pill)	12.1±0.5 [11~14]	12.5±3.3 [0~36]	12.5±3.2 [0~36]
Contraindicated Use†	4.5	1.2	7 (1.3)
Pregnancy before Plan B	0	0.2	1 (0.2)
Unexplained vaginal bleeding	4.5	1.0	6 (1.1)
Allergy to Plan B	0	0	0
Correct/Incorrect use†			
Overall Correct Use	77.3	67.4	366 (67.8)
Overall Incorrect Use	13.6	26.4	140 (25.9)
Overall Incorrect use (+missing data)	22.7	32.6	174 (32.2)
Correct use of 1st pill (<72 hr)	86.4	92.7	499 (92.4)
Correct use of 2nd pill (12 hr)	81.8	71.2	387 (71.7)
Adverse Events†			
From all sources; Subjects with AEs	31.8	46.1	246 (45.6)
Behavior change (% of subjects with sex)			
Sex act before study (one month)	100.0	100.0	502 (100.0)
Sex acts during study (4 weeks)	63.6	63.5	319 (63.5)
Change to more effective contraception	28.6	10.5	36 (11.3)
Change to less effective contraception	0	8.5	26 (8.2)
Change to condom use	0	10.8	33 (10.3)
Change to no condom use	0	4.9	15 (4.7)

Table 29. **Comparison in Plan B use between Subjects < HS and ≥ HS Education**
(% of the enrolled subjects; otherwise % of users †)

Parameters	Education*		Total
	< HS	≥ HS	*No. (%)*
Enrolled Subjects, *No (%)*	78 (13.3%)	507 (86.7%)	585
Subjects used Plan B, *No. (%)*	64 (82.1%)	476 (88.1%)	540 (92.3)
Compliance of follow-up contacts			
Lost Follow-up	19.2	5.5	43 (7.4)
One Follow-up	11.5	3.9	29 (5.0)
Two Follow-up	66.7	88.6	501 (85.6)
> 3 Follow-up	2.6	2.0	12 (2.1)
Prior EC Use	12.4	87.6	234 (40.0)
Reason to Request Plan B			
Condom broke or slipped	34.6	37.9	234 (40.0)
Unprotected sex	23.1	34.7	2 (0.3)
Prevent pregnancy	28.2	15.2	76 (13.0)
OCP problem	5.1	3.7	507 (86.7)
Mistake/accident	3.8	2.0	
Contraceptive failure (unspecified)	0.0	2.0	219 (37.4)
Withdrawal	2.6	1.2	194 (33.2)
Prevention, unspecified	2.6	1.0	99 (16.9)
Reason to Use Plan B†			23 (3.9)
Condom broke/slipped	46.9	45.0	13 (2.2)
Used no contraception	28.1	41.2	10 (1.7)
Missed OCPs	10.9	6.3	8 (1.4)
Withdrawal	7.8	2.9	7 (1.2)
Disposition of Plan B			
Took both pills	82.1	93.7	539 (92.1)
Time taken 1st pill (hours after sex)	35.0±18.1 [5~70]	34.8±21.5 [-103~175]	34.8±21.1 [-103~175]
Time taken 2nd pill (hours after 1st pill)	12.9±3.0 [11~24.5]	12.5±3.2 [0~36]	12.5±3.2 [0~36]
Contraindicated Use†	1.6	1.3	7 (1.3)
Pregnancy before Plan B	0	0.2	1 (0.2)
Unexplained vaginal bleeding	1.6	1.1	6 (1.1)
Allergy to Plan B	0	0	0
Correct/Incorrect use†			
Overall Correct Use	67.2	67.9	366 (67.8)
Overall Incorrect Use	25.0	26.1	140 (25.9)
Overall Incorrect use (including subjects with missing data)	32.8	32.2	174 (32.2)
Correct use of 1st pill (<72 hr)	87.5	93.1	499 (92.4)
Correct use of 2nd pill (12 hr)	70.3	71.8	387 (71.7)
Adverse Events†			
From all sources; Subjects with AEs	37.5	46.6	246 (45.6)
Behavior change (% of subjects with sex)			
Sex act before study (one month)	100.0	100.0	502 (100.0)
Sex acts during study (4 weeks)	61.7	63.8	319 (63.5)
Change to more effective contraception	21.6	9.9	36 (11.3)
Change to less effective contraception	5.4	8.5	26 (8.2)
Change to condom use	8.1	10.6	33 (10.3)
Change to no condom use	8.1	4.3	15 (4.7)

* "< HS": includes 8th grade (0.3%, 2 of 585) and 9th-11th grade (13%, 76 of 585).

Table 30. **Comparison in Plan B use between Subjects with and without Prior EC Use**
(% of the enrolled subjects; otherwise % of users †)

Parameters	Prior EC Use		Total
	Ever	Never	*No. (%)*
Enrolled Subjects, *No (%)*	234 (40.0%)	351 (60.0%)	585
Subjects used Plan B, *No. (%)*	213 (91.0)	327 (93.2%)	540 (92.3)*
Compliance of follow-up contacts			
Lost Follow-up	9	6.3	43 (7.4)
One Follow-up	4.7	5.1	29 (5.0)
Two Follow-up	85.0	86.0	501 (85.6)
> 3 Follow-up	1.3	2.6	12 (2.1)
Reason to Request Plan B			
Condom broke or slipped	32.5	40.7	234 (40.0)
Unprotected sex	37.6	30.2	2 (0.3)
Prevent pregnancy	18.8	15.7	76 (13.0)
OCP problem	3.8	4.0	507 (86.7)
Mistake/accident	2.1	2.3	
Contraceptive failure (unspecified)	1.7	1.7	219 (37.4)
Withdrawal	0.0	2.3	194 (33.2)
Prevention, unspecified	0.9	1.4	99 (16.9)
Reason to Use Plan B†			23 (3.9)
Condom broke/slipped	39.9	48.6	13 (2.2)
Used no contraception	44.6	36.4	10 (1.7)
Missed OCPs	7.0	6.7	8 (1.4)
Withdrawal	3.8	3.4	7 (1.2)
Disposition of Plan B			
Took both pills	91.0	92.9	539 (92.1)
Time taken 1st pill (hours after sex)	34.1±18.7 [-12.5~88]	35.3±22.7 [-103~175]	34.8±21.1 [-103~175]
Time taken 2nd pill (hours after 1st pill)	12.6±3.1 [0~36]	12.5±3.2 [0~36]	12.5±3.2 [0~36]
Contraindicated Use†	1.4	1.2	7 (1.3)
Pregnancy before Plan B	0	0.3	1 (0.2)
Unexplained vaginal bleeding	1.4	0.9	6 (1.1)
Allergy to Plan B	0	0	0
Correct/Incorrect use†			
Overall Correct Use	66.7	68.5	366 (67.8)
Overall Incorrect Use	29.6	23.5	140 (25.9)
Overall Incorrect use (including subjects with missing data)	33.4	31.5	174 (32.2)
Correct use of 1st pill (<72 hr)	95.3	90.5	499 (92.4)
Correct use of 2nd pill (12 hr)	68.5	73.7	387 (71.7)
Adverse Events†			
From all sources; Subjects with AEs	44.0	46.6	246 (45.6)
Behavior change (% of subjects with sex)			
Sex act before study (one month)	100.0	100.0	502 (100.0)
Sex acts during study (4 weeks)	65.1	62.5	319 (63.5)
Change to more effective contraception	9.4	12.5	36 (11.3)
Change to less effective contraception	10.2	6.8	26 (8.2)
Change to condom use	11.8	9.4	33 (10.3)

* 539 took both pills and 1 took 1 pill.

Table 31. **Comparison in Plan B use between subjects from Clinics and Pharmacies**
(% of the enrolled subjects; otherwise % of users †)

Parameters	Study Site		Total
	Clinics	Pharmacies	*No. (%)*
Enrolled Subjects, *No (%)*	550 (94%)	35 (6%)	585
Subjects used Plan B, *No. (%)*	510 (94%)	30 (6%)	540 (92.3)*
Compliance of follow-up contacts			
Lost Follow-up	7.1	11.4	43 (7.4)
One Follow-up	5.3	0	29 (5.0)
Two Follow-up	85.5	88.6	501 (85.6)
> 3 Follow-up	2.2	0	12 (2.1)
Ages (years): 14-16	5.3	0	29 (5)
17-44	94.7	100	556 (95)
Prior EC Use	39.3	51.4	234 (40.0)
Education 8^{th} Grade and less	0.4	0	2 (0.3)
$9^{th} - 11^{th}$ Grade	13.6	2.9	76 (13.0)
HS above	86.0	97.2	507 (86.7)
Reason to Request Plan B			
Condom broke or slipped	37.1	42.9	219 (37.4)
Unprotected sex	33.3	31.4	194 (33.2)
Prevent pregnancy	17.1	14.3	99 (16.9)
OCP problem	3.8	5.7	23 (3.9)
Mistake/accident	2.4	0.0	13 (2.2)
Contraceptive failure (unspecified)	1.8	0.0	10 (1.7)
Withdrawal	1.5	0.0	8 (1.4)
Prevention, unspecified	1.3	0.0	7 (1.2)
Reason to Use Plan B†			
Condom broke/slipped	44.9	50.0	244 (45.2)
Used no contraception	39.8	36.7	214 (39.6)
Missed OC pills	7.1	3.3	37 (6.9)
Withdrawal	3.7	0.0	19 (3.5)
Disposition of Plan B			
Took both pills, *No. (%)*	509 (92.5)	30 (85.7)	539 (92.1)
Time taken 1^{st} pill (hours after sex)	35.2 ± 21.3 [-103~175]	29.3 ± 18.1[3~71]	34.8±21.1 [-103~175]
Time taken 2^{nd} pill (hours after 1^{st} pill)	12.6 ± 3.3 [11~12]	12.0 ± 0.2 [0~36]	12.5±3.2 [0~36]
Contraindicated Use†			7 (1.3)
Pregnancy before Plan B	0.2	0	1 (0.2)
Unexplained vaginal bleeding	1.2	0	6 (1.1)
Allergy to Plan B	0	0	0
Correct/Incorrect use† No. (%)			
Overall Correct Use	337 (66.1)	29 (96.7)	366 (67.8)
Overall Incorrect Use	139 (27.3)	1 (3.3)	140 (25.9)
Overall Incorrect use (+ missing data)	173	1	174 (32.2)
Correct use of 1^{st} pill (< 72 hr)	469 (92)	30 (100)	499 (92.4)
Correct use of 2^{nd} pill (12 hr)	358 (70.2)	29 (96.7)	387 (71.7)
Adverse Events†			
From all sources; Subjects with AEs	228 (44.7)	18 (60.0)	246 (45.6)
Behavior change (% of subjects with sex)			
Sex act before study (one month)	471 (100)	31 (100)	502 (100.0)
Sex acts during study (4 weeks)	301 (63.9)	18 (58.1)	319 (63.5)
Change to more effective contraception	34 (11.3)	2 (11.1)	36 (11.3)
Change to less effective contraception	23 (7.6)	3 (16.7)	26 (8.2)
Change to condom use	32 (10.6)	1 (5.6)	33 (10.3)
Change to no condom use	12 (4.0)	3 (16.7)	15 (4.7)

VII. Integrated Review of Safety

The global safety update of Plan B, including all clinical safety trials from literature, is reviewed by a medical officer in HFD-580; refer to that review for details.

Two parts of safety evaluation are covered in this review, one is the adverse event reports and behavior observation from the Plan B Actual Use Study which is included in the full study review under "VI. Integrated Review of Efficacy"; and the other is the sexual and contraceptive behaviors associated with emergency contraception from eight literature reports. The following are the detailed literature review of the eight studies (pages 62-110).

Sexual and Contraceptive Behavior studies on Emergency Contraception (EC)
A Literature Review

The sponsor submitted 8 literature reports regarding contraceptive behaviors related to the advance provision of emergency contraception. The literature includes five published study reprints, two unpublished study manuscripts and one abstract. Five of studies were conducted in the United States and one study each was from UK, India and Ghana. There were no raw data submitted with these literature reports. The overall summary of eight behavioral studies is presented below and in Table 1 followed by the individual reviews.

OVERALL STUDY DESIGN

1. ***Study Location***: Five studies were conducted in the USA and one each was conducted in the UK, Africa and India.

2. ***Subjects:*** All subjects in the eight studies were recruited from family planning clinics or hospital-based clinics. The purposes for visiting the clinics were EC consultation, post-abortion follow-up and postpartum evaluation but not for requesting EC. The age range was 15-45 years with most enrollees being around 20 years old.

3. ***Study Groups:*** Subjects were randomly (in most studies) assigned to the following 2 or 3 groups. All subjects received education regarding emergency contraception use (this is in contradistinction to the actual use study submitted by the sponsor where education was not given to the subjects enrolled in the study, thereby more closely mimicking an OTC environment).

   Advance EC Provision Group: Subjects received in advance one course of EC pills in six studies and three courses of EC pills in two studies (one in US and one on India);

   Control Group: Subjects received EC education only (including advice on where to get and how to use EC) except for one study where routine contraception counseling (not focusing on EC) was given in the control group.

   One study (in California) had Pharmacy EC Access as an additional control group, in which subjects received EC from pharmacy stores when needed.

4. ***Sample Size:*** Number of subjects ranged from 160 to 1020 in the five US studies and 210-1083 in three studies outside US.

5. ***Follow-up Period:*** Subjects were followed from 8 weeks up to 1 year after admission to the studies.

RESULTS

1. ***EC Use:*** All studies suggest that the advance EC provision increase EC use. This supported the hypothesis of the studies that easier access would translate into increased use.

2. ***Unprotected Sex:*** In these studies, unprotected sex was defined as lack of use of a contraceptive. All studies demonstrated that compared to baseline, the advance EC group and control group had decreased frequency of unprotected sex. However, in some studies, the decrease in unprotected sex was less in the advance EC provision group.

3. ***Condom Use:*** One US study (sponsored by Women's Capital Corporation) suggests that the advance, pharmacy and standard EC access groups plus EC education had an increase in more effective methods of contraception with a corresponding decrease in condom use. The other 6 studies either demonstrated no significant decrease in condom use with advance EC provision or in education alone (control groups) or demonstrated that "used condoms every time" increased in treatment and control groups when compared to baseline.

4. ***Consistent Use of Regular Contraception:*** Most of the studies demonstrate that women in both the treatment and control groups increase their use of a regular contraception compared to baseline. One US study suggest that women with advance EC access are more likely to use less-effective contraception, and another US study showed higher frequency of missing oral contraceptive pills in subjects provided with advance EC than those in the control group.

COMMENTS

The following concerns in the eight studies may limit the long-term assessment of risky or unsafe sexual behaviors in target populations if Plan B becomes OTC availability. The risky behaviors may impact on epidemics of STDs, particularly HIV/AIDS, in teenage population.

1. All 8 studies were conducted in the clinic settings, instead of simulated OTC setting.

2. Subjects were recruited exclusively from clinic sites and received EC education from clinical investigators during enrollment, which are not generalizable to the OTC population.

3. Three studies were conducted in foreign countries, which may not represent the US population.

4. Six studies provided only one course of EC pills in advance. In those studies, after the one course of EC pills were used, subjects in the advance EC group would have the same accessibility to EC as the control group.

5. There were limitations of design and/or methodology of the studies and conclusions should be considered in that context.

6. There were comparison analyses among different age subgroup in all 8 studies.

SUMMARY AND CONCLUSION

1. In all eight studies, subjects with the advanced EC provision were more likely to use EC pills.

2. One US study showed that subjects with advanced EC access was more likely to use less-effective contraception and tended to have less protected sex and miss oral contraceptive pills, as compared to control group. Another US study showed that the advance, pharmacy and standard EC access groups with EC education decreased condom use as compared to the baseline, but greater decease in the advance and pharmacy EC access groups. The study done in Ghana showed that advance EC provision tended to increase unprotected sex (but had significant flaws in study design). The UK study showed a decrease in condom use in both the advance EC and control groups compared to baseline.

3. The remaining 4 studies showed that subjects with the advanced EC provision apparently didn't have more frequent unprotected intercourses, didn't stop using condom use, and didn't switch to less effective contraception methods.

4. The behavior studies are complementary to the Plan B AU study in some degree:

   - Those studies had a longer follow-up period; subjects were followed for more than 6 months in 5 of the 8 studies.

   - The sample size was relatively large in some studies.

   - Subjects in the treatment group had advance EC provision in all eight studies; two studies provided three courses of EC pills in advance.

   - Study populations were heterogeneous across all 8 studies. This diversity is desirable reflecting some aspects of OTC populations.

Table 1. **Effects of Emergency Contraception under Advance Provision on Sexual and Contraceptive Behavior**

Author & Publication	Study Design	Study Location	Subjects	Follow-up Periods	*Advance EC access caused changes in*	
					Sexual Behavior	Contraceptive Behavior
Raine et al: *Obstet Gynecol* 2000 Literature #1	Non-randomized 2 groups: Advance EC (one EC course) & Control (EC education)	***USA,*** Family planning clinics	263 women age 16-24 (64% adolescents); 32% Latina & 29% AA; Excluded subjects presenting for EC	4 months	Decrease in unprotected sex in both groups vs. baseline; Tx group had less decrease in the unprotected sex	More likely to use less effective contraception Increased condom use in both groups vs. baseline; Tended to have less protected sex and miss OC pills vs. control; Increase in EC use;
Raine et al: UCSF Study *(NDA: vol 13, p134)* Unpublished Literature #2	Randomized 3 groups: Advance EC Provision (3 EC courses), Pharmacy EC Access; Standard EC Access	***USA,*** Family planning clinics	1020 women age 15-24 years (20±3 yrs); 20% Latina & 17% AA Excluded subjects presenting for EC	6 months	Decrease in unprotected sex in all 3 groups *vs.* baseline (SA>PA>AP); AP group had less decrease in unprotected sex ($p<0.05$ in PA & SA but not AP groups); No increase in incidence of STDs compared to Stnd EC Access	Increase in OC use in all 3 groups with an offset decrease in condom use in all 3 groups Decrease in condom use greatest in AP & PA groups
Jackson et al, *Obstet Gynecol* 2003 Literature #3	Randomized 2 groups by date of hospital admin: Advance EC (one EC course) & Control (***but no EC education***)	***USA,*** Inner-city hospital	370 Postpartum women age 26±6 yrs 72% Latina; 43% Married	6 months & 12 months	Increased consistent use contraception and more effective method in both groups. No increase in report of unprotected sex	No change in routine contraception and condom use; Increase in EC use.
Belzer et al: *J Adol Health* (Abstract), 2003 Literature #4	Randomized 2 groups: Advance EC (one EC course) & Control	***USA,*** Inner-city (unknown site)	160 adolescent mothers age 14-20 yrs; 83% Latina & 16% AA	6 months	No increase in unprotected sex (but limited data available)	No decrease in condom use and primary contraception between groups. No data provided on within group changes; (limited data available) Increase in EC use

Table 1 (Cont). **Effects of Emergency Contraception under Advance Provision on Sexual and Contraceptive Behavior**

Author & Publication	Study Design	Study Location	Subjects	Follow-up Periods	*Advance EC access caused changes in*	
					Sexual Behavior	Contraceptive Behavior
Gold: *Unpublished Manuscript* Literature #5	Randomized 2 groups: Advance EC (one EC course) & Control	***USA,*** an urban hospital-based adolescent clinic	301 adolescent women age 15-20 (17±2); 58% AA	8 months	No increase in unprotected intercourse No increase in STDs compared to control	No decrease in condom use; Other info not available
Glasier & Baird: *New Eng J Med* 1998 Literature #6	Randomized 2 groups by birth date: Advance EC (one EC course) & Control (EC education)	***UK,*** Family planning clinics	1083 women age 16-44 (23% age 16-20), 20%>30 y/o Post EC or Therapeutic abortion	1-year	Decrease in unprotected sex in both groups vs. baseline.	Increase in OC use in both groups with decrease in condom use similar changes between 2 groups. Increase EC use.
Lovvorn et al: *Contraception* 2000 Literature #7	Non-randomized 2 groups: Advance EC (one EC course) & Control (EC education)	***Ghana,*** Family planning clinics	211 women (spermicide users) age 18-45 yrs	8 weeks	Decrease in unprotected sex compared to baseline in both groups (Control>AEC) Significant limitations in study design.	Increase EC use; Other info not reported. Significant flaws in study design.
Ellertson et al: *Obetet Gynecol* 2001 Literature #8	Randomized 2 group: Advance EC (3 EC course) & Control	***India,*** family planning clinics	411 women (condom users); age 25±4 yrs (83% 20-29 yr); Barrier method users	12 months (38% 12-month; 90% 3-month); pts off study if switched to more reliable method (23%)	Similar proportion having unprotected sex vs. the control	Increase EC use.

Information in the table is extracted and summarized from the individual literature reviews as attached in the following pages.
The Advance EC (AEC) or the Advance EC Provision (AP) or Treatment (Tx) group : Subjects received EC pills in advance plus EC education at the enrollment.
The Control or Standard EC access (SA) group: Subjects received only EC education (except the Jackson's study, Literature #3) and were advised to request EC pills from the clinics (the same sites as the advance group) by prescription when needed.
The Pharmacy EC Access (PA) group: Subjects received EC pills from pharmacy without prescription.
OC: Oral Birth Control Pills; AA: Africa American; EC: Emergency Contraception; STDs: sexually transmitted diseases;

Literature #1 (vol. 13, page 068)

Emergency Contraception: Advance Provision in a Young, High-Risk Clinic Population

Author:	Tina Raine, Cynthia Harper, Kathleen Leon, and Philip Darney
Affiliate:	Department of Obstetrics, Gynecology, and Reproductive Sciences Center for Reproductive Health Research and Policy University of California, San Francisco, California.
Sponsor:	Compton Foundation, Menlo Park, California Fred Gellert Family Foundation, San Francisco, California.
Study Location:	***USA,*** Family Planning Clinics, San Francisco, California From June to November 1998
Publication:	***Obstet Gynecol*** 96:1–7, 2000
Design:	Single-center, ***non-randomized***, clinical trial; 4-month follow-up Single course of Advance EC Provision

METHODS

Subject

A total of 263 female subjects were recruited and enrolled from a family planning clinic of San Francisco General Hospital between June and November 1998.

Inclusion criteria:
Women age 16–24 years
Able to speak English or Spanish
Available for follow-up in 4 months.

Exclusion criteria:
Pregnancy
Using contraceptive implants
Using intrauterine devices
Presentation for emergency contraception
Contraindications to oral contraceptive (OC) pills.

The subjects were assigned on an ***alternating basis*** into the following 2 groups:

Treatment groups: 130 subjects received EC education and one course of EC pills (comprised 8 OC pills; each contained 0.15 mg of levonorgestrel and 30 ug of ethinyl estradiol).

Control group: 133 subjects received EC education alone.

Data Collection

Research assistants interviewed subjects at enrollment and at follow-up (at 4 months by telephone or clinic visit) using a questionnaire to obtain demographic information and to measure outcomes, including contraceptive methods and patterns of use.

Data Analysis

All analyses were conducted using the intent-to-treat population, with all study subjects analyzed according to their initial group assignment. Differences between Treatment and Control were analyzed with a Chi-square test for categorical variables and t tests for continuous variables. A multiple logistic regression analysis was used to determine the effect of advance provision of emergency contraception on use at follow-up.

RESULTS

Subject Demographics

Only age and race/ethnicity were reported in the article, as summarized in Table 1. The mean age was 19 years (64% adolescents). Most subjects were minorities. The demographic distribution between 2 groups was similar.

Table 1. **Demographics of Subjects**
(% of enrolled subjects)

Demographic	Treatment n=130	Control n=133	Total n=263
Mean age (years)	19.2	18.8	19.0
Race or ethnicity			
Hispanic	33.1	30.1	31.6
Black	26.2	31.6	28.9
White	16.9	12.8	14.8
Asian	14.6	16.5	15.6
Other (biracial)	9.2	9.0	9.1
Primary language Spanish	16.2	14.3	15.2

Data were extracted from the author's Table 1.

Baseline Characteristics

At enrollment the sexual activity, contraception, pregnancy history and reasons for clinic visit were comparable between treatment and control groups (Table 2), except that the history of unprotected sex was lower in the treatment group than in control group (15% vs. 24%). The most common contraception method used by the study population was condoms, and a higher proportion of subjects in the treatment arm reported at baseline that they used condoms for contraception than in the control arm (47% vs. 39%). At baseline a higher proportion of the subjects in the control arm reported that their use of either condoms or oral contraceptives was consistent (used condoms every time, never missed pills) than subjects in the treatment arm. Consistent condom use was reported in 24% of control subjects who used condoms compared to 12% on the treatment arm. Consistent use of oral contraceptives was reported in 42% of the control subjects who used oral contraceptives, compared to 25% on the treatment arm.

The table below demonstrates that the subjects in the treatment arm reported higher frequency of sexual acts, higher proportion of condom use as a method of contraception, lower rate of unprotected sex, higher proportion with a history of elective abortion, higher proportion with a history of pregnancy and more births. More subjects in the treatment arm presented to the clinic visit for an "infection check".

Table 2. **Baseline Traits of Subjects at enrollment**
(% of enrolled subjects)

Baseline Characteristics	Treatment n=130	Control n=133	Total n=263
Reason for clinic visit*			
Papanicoloau smear or check-up	16.2	19.5	17.9
Contraception	39.2	32.3	35.8
Follow-up abortion	7.7	6.8	7.2
Pregnancy test	37.7	44.4	41.4
Infection check	20.8	13.6	17.1
First visit to clinic	38.8	40.6	39.7
Pregnancy History			
Ever pregnant	56.2	47.4	51.7
Ever gave birth	20.8	16.5	18.6
Ever had an elective abortion	40.8	34.6	37.6
History of sexually transmitted disease	18.6	18.0	18.3
Sexual Acts in past 4 months			
None	3.8	5.3	4.6
Sporadic†	33.9	39.8	36.9
Once a week	25.4	27.8	26.6
More than once a week	36.9	27.1	31.9
New sexual partner	23.1	21.0	22.0
Current contraception‡			
Condoms	**46.9**	**39.1**	43.0
Oral contraceptive	27.7	24.8	26.2
Depot medroxyprogesterone acetate	10.0	11.3	10.6
Other	0.7	0.8	0.8
None (unprotected sex?)	**14.6**	**24.1**	19.4
Dual use (hormonal with condoms)	16.9	17.3	17.1

* Participant might have had more than one reason for clinic visit.
† Sporadic: once or twice in past 4 months or once to twice a month.
‡ Current contraception: most effective method reported if more than one used.

Changes in Sexual and Contraceptive Behavior (Table 5)

EC Use:

- Women in the treatment group were significantly more likely to use emergency contraceptives than those in control groups (20% *vs.* 7%, p=0.006). This difference between treatment arms remained statistically significant in multiple logistic regression analyses that evaluated the impact of contraceptive method, pattern of contraceptive use at enrollment and frequency of unprotected sex reported at enrollment.

- Overall EC use increased from enrollment to follow-up (4% *vs.* 14%) in both groups, with more increase in the treatment group.

Routine Contraception:

- Women in the treatment group were more likely to have switched to a less-effective contraception method than those in the control groups at the time of follow-up (28% *vs.* 17%, p=0.05). (Level of effectiveness was ordered from most effective to least effective for this analysis as follows: depot, oral contraceptive, barrier, none.) The proportion that didn't change method or continued to use no method at all was similar between arms at the time of follow-up.

- Women in the treatment group tended to be less likely to use more effective contraception than those in the control groups (20% *vs.* 29%, p=0.1).

- The proportion of women in the treatment group who reported consistent oral contraceptive (OC) use was less than in the control group at baseline (25% vs. 42%, p=0.08) Although the proportion reporting consistent oral contraceptive use remained lower on the treatment arm relative to the control arm at the time of follow-up (32% *vs.* 58%, p=0.03), the proportion of subjects who reported consistent use increased in both groups at the time of follow-up.

Unprotected Sex:

- Overall "never had unprotected sex" (had protected sex) increased at the follow-up as compared to that at the enrollment (33% *vs.* 56%). As compared to the baseline, increase in protected sex was 18% (from 32% to 50%) in the treatment group and 28% (from 34% to 62%) in the control group (no statistical tests were available).

Condom Use:

- Condom use increased in both groups at follow-up as compared to at enrollment (Treatment group: 12% *vs.* 47.4%, Control group: 24.3% vs 50%).

- There was no significant difference at the time of follow-up between treatment and control groups in the proportion of condom use.

- Since there was less condom use at baseline in the treatment group than in control group, the proportionate increase in condom use in the treatment group was greater than in control group (4x increase *vs.* 2x increase).

Table 5. **Contraceptive Behavior during the Study Period Compared to Baseline Between Treatment and Control Groups**
(% of enrolled subjects)

Contraceptive Behavior	Treatment % (*n*)	Control % (*n*)	Total % (*n*)	*P*
Initial (at Enrollment)				
Never had unprotected sex	32.3 (42)	33.8 (45)	33.1 (87)	0.92
Used condoms every time	**12.0 (10)**	**24.3 (18)**	17.8 (28)	0.08
OC users who never missed pills	**25.0 (11)**	**42.2 (19)**	33.7 (30)	0.08
Used emergency contraception	4.6 (6)	3.0 (4)	3.8 (10)	0.75
Follow-up				
Never had unprotected sex	50.4 (56)	61.8 (63)	55.9 (119)	0.42
Used condoms every time	47.4 (18)	50.0 (19)	48.7 (37)	0.71
OC users who never missed pills	**31.7 (13)**	**57.8 (26)**	45.4 (39)	0.03
Used emergency contraception	**19.8 (22)**	**6.9 (7)**	13.6 (29)	0.006
More effective method†	**19.8 (22)**	**29.4 (30)**	24.4 (52)	0.10
Less effective method‡	**27.9 (31)**	**16.7 (17)**	22.5 (48)	0.05
No method at enrollment and follow-up	7.2 (8)	6.9 (7)	7.0 (15)	0.92
Same method at enrollment and follow-up	45.0 (50)	47.1 (48)	46.0 (98)	0.77

Data are extracted from the author's Tables 2, 4 and 5.
† More effective methods: Depot medroxyprogesterone acetate and OC;
‡ Less effective methods: spermicides, diaphragms, and withdrawal.

COMMENTS

1. The subjects were not randomly assigned. This created an imbalance at baseline (unprotected sex, condom use, missed OC pills and EC use) and could have introduced bias into the study. This is a major flaw and limits conclusions.

2. Only a single course of EC was provided to the treatment group (advance provision), so the study observation may not truly reflect changes in sexual and contraceptive behaviors that may occur in the OTC setting.

3. Information on education, literacy level, and income of subjects were not provided. Given the non-randomized design there are no assurances of an even distribution of these demographics.

4. Sample size was small (n=130 in the Advance group and n=133 in the Control group).

5. Subjects were recruited from clinical sites and were high risk, which may not be generalizable to OTC population.

CONCLUSION

This study demonstrated the following: compared to their baseline, women age 16-24 with advance EC provision are:

- Less likely to have protected sex
- More likely to use condoms (also in both control)
- More likely to use EC pills
- More likely to miss OC pills
- More likely to switch to a less effective routine contraception method

When compared to the treatment group, the control group was more likely to have a greater absolute change in "Never had unprotected sex" and "Never missed pills". However, it should also be noted that at baseline, the treatment group appeared to potentially be a higher risk group compared to the control group, with a greater percentage of subjects who were presenting to the clinic for contraception and infection checks, who had been pregnant, given birth or an elective abortion, or who had a new sexual partner in the past 4 months. Because of these imbalances at baseline, between group comparisons should be made with caution.

Literature #2: **UCSF Study** #H9738-18501-02
(Vol. 32/p134; EDR dated 2003-09-08)

Provision of Emergency Contraception to Women enrolled in the study prior to December 31, 2001: Pharmacy Access and Advance Distribution Evaluation

Investigator: UCSF (by Tina Raine, et al)

Sponsor: Women's Capital Corporation

Study Location: ***USA,*** Family Planning clinics four clinical (San Francisco)
July 9, 2001 to December 31, 2001

Report Date: January 30, 2003 (prepared by Pinney Associates)

Published: Not

Study Design: Randomized 3-arm clinical trial
6-12-month follow-up
3 courses of advance EC.

Primary objectives:

To compare the rates of unintended pregnancy and sexually transmitted disease (STD) among three different distributions (***advance provision, pharmacy access and standard access***) for emergency contraception.

Secondary objectives:

To assess the effects of the three different emergency contraception distribution methods on ***sexual and contraceptive behaviors***, such as the frequency of unprotected sex, and use of condoms, oral contraceptives, and emergency contraception use.

METHODS

Subjects

Subjects were recruited from four family planning clinic sites (Table 1) in the San Francisco bay area (CA) with the following inclusion and exclusion criteria.

Inclusion Criteria

- Women age 15-24 at high risk for unintended pregnancies
- Speak either Spanish or English
- Be available in 6 months for a follow-up visit.

Exclusion Criteria

- Women were currently pregnant;
- Actively trying to get pregnant;
- Sterilized; using Depo-Provera, IUD, Norplant or Lunelle;
- Reported having had unprotected sexual intercourse in the past 3 days.
- Women who presented to the clinic specifically requesting emergency contraception (*the rationale was not specified*)

Table 1. **Enrolled subjects and follow-up compliance from 4 clinical sites**

Clinical Sites (San Francisco, CA)	Pharmacy Access (N = 343)	Advance Provision (N = 340)	Standard Access (N = 337)	Total (N = 1020)
City College	30 (96.8)	29 (90.6)	31 (96.9)	90 (94.7)
Planned Parenthood: Dale City	44 (97.8)	42 (95.5)	40 (88.9)	126 (94.0)
New Generations	136 (91.9)	141 (95.9)	128 (90.8)	405 (92.9)
Planned Parenthood: San Francisco	104 (87.4)	104 (88.9)	107 (89.9)	315 (88.7)

Data were adapted from the author's Table 4 (p6).

Subject Disposition

Of the 2012 screened women, 1,020 were enrolled (see below) and randomly assigned into 3 groups.

Total approached women:	2,012	(100%)
Total screened women:	1,804	(89.7%)
Ineligible women:	992	(49.3%)
Eligible women:	1,024	(56.7%)
Enrolled subjects:	1,020	(56.4%)

Pharmacy Access (PA): Subjects in this group obtained Plan B at the local pharmacy without a prescription through a collaborative agreement between clinics and pharmacies;

Advance Provision (AP): Subjects were given Plan B (3 complete packages) to take home and use as needed;

Standard Access (SA): Subjects returned to the clinic to obtain supplies.

All subjects received information and counseling on emergency contraception, and were reimbursed $10 (during the visit). They were also reimbursed $20 for completing the follow-up visit procedure.

Data Collection

Baseline data: urine tests (for pregnancy, Chlamydia and gonorrhea) and blood test (for HSV-2 antibody) and interview (for demographics, sexual history, knowledge of emergency contraception).

Follow-up visit: occurred 6 months or more (up to 1 year) after enrollment. Data were collected on sexual history, use of emergency contraception, urine test (for pregnancy, Chlamydia, and gonorrhea), and blood test (for HSV-2 antibody).

Data Analysis

One-way analysis of variance, contingency table analyses, and a Chi-square test were used for different variables. In cases of small numbers, when cells had fewer than 5 observations, the Fisher's exact test was conducted. All analyses were evaluated at the two-tailed probability level of $p<0.05$ and no adjustments were made for the number of analyses or pair-wise comparison.

RESULTS

Subject Demographics

Demographic characteristics of the enrolled subjects are summarized in Table 2. Overall they were comparable among the 3 study groups. Races (white, black, Latina, and Asian) were evenly distributed among 3 groups. The following were the major characteristics:

Mean age:	20±2.6 (15-24) years
Marital status:	86% single
Active sex (within 6 months):	100%
Unprotected intercourse (within 6 months):	50%
Currently using condoms:	67%
Currently using oral contraceptives:	41%
Previous emergency contraception:	35%
Education and literacy level:	unknown (not reported).

A third of participants reported having been pregnant previously, with 9% reporting ever given birth.

Follow-up Compliance

Approximately 92% of subjects (936 of 1,020) in each group completed follow-up assessment within one year (211±39 days) (Table 3).

Table 2. **Demographics of subjects**

Demographics	Pharmacy Access (N=314)	Advance Provision (N=316)	Standard Access (N=306)	Total (N=936)
Age (years)				
Mean ± SD	19.7 ± 2.6	19.7 ± 2.6	19.9 ± 2.6	19.7 ± 2.6
Race				
Latina	66 (21.0)	64 (20.3)	60 (19.6)	190 (20.3)
Black	53 (16.9)	54 (17.1)	52 (17.0)	159 (17.0)
White	79 (25.2)	100 (31.7)	83 (27.1)	262 (28.0)
Asian/Pacific Islander	57 (18.2)	62 (19.6)	69 (22.6)	188 (20.1)
Multiracial	48 (15.3)	29 (9.2)	35 (11.4)	122 (12.0)
Other	11 (3.5)	7 (2.2)	7 (2.3)	25 (2.7)
Marital Status				
Single	263 (83.8)	273 (86.4)	271 (88.6)	807 (86.2)
Cohabiting	42 (13.4)	31 (9.8)	28 (9.2)	101 (10.8)
Married	7 (2.2)	10 (3.2)	6 (2.0)	23 (2.5)
Married, but separated	2 (0.6)	-	-	2 (0.2)
Divorced	-	2 (0.6)	1 (0.3)	3 (0.3)
Widowed	-	-	-	-

Data were extracted from the author's Table 5 (p7) and presented as "No. (%)."

Table 3. **Subject Disposition at Follow-up**

Disposition	Pharmacy Access *No. (%)*	Advance Provision *No. (%)*	Standard Access *No. (%)*	Total *No. (%)*
Enrolled Subjects	343	340	337	1020
Lost to Follow-up	23 (6.7)	23 (6.8)	27 (8.0)	73 (7.2)
Refused Follow-up	6 (1.8)	1 (0.3)	4 (1.2)	11 (1.1)
Completed Follow-up*	**314 (91.6)**	**316 (92.9)**	**306 (90.8)**	**936 (91.8)**

* Mean follow-up days (post-baseline) was 211±39 days, median follow-up days: 195 days. There were no statistical differences in demographics of subjects between Lost-to-Follow-up and Completed-Follow-up.

Sexual and Contraceptive Behavior

Pregnancy:

The overall pregnancy rate (Table 4) in the 936 subjects who completed the follow-up interview was 8%. There were no differences in pregnancy rate among 3 groups including when analysis was controlled for baseline history of pregnancy ($p<0.89$, Chi-square test).

Sexually Transmitted Diseases (STDs):

Subjects were considered to have acquired an STD during the follow-up period if they were positive for herpes (new diagnosis), chlamydia, gonorrhea (self-reported *or* by laboratory tests), trichomonas, PID (self-reported). There were no differences in STD acquisition among 3 groups when controlling for baseline history of STDs ($p<0.427$, Chi-square test).

Table 4. **Pregnancy and STD during study**

Outcome		Pharmacy Access (N = 314)	Advance Provision (N = 316)	Standard Access (N = 306)	Total (N = 936)
Pregnancy	Previous	108 (34.4)	97 (30.7)	99 (32.5)	304 (32.5)
	Follow-up	24 (7.6)	26 (8.2)	25 (8.2)	75 (8.0)
STDs*	History	62 (19.8)	69 (21.8)	77 (25.4)	208 (22.3)
	Acquired during Study	58 (18.5)	47 (14.9)	51 (16.7)	156 (16.7)

Data were extracted from author's Tables 6, 7 & 8 (p8-9) and presented as "No. (%)."
* STDs at follow-up were newly acquired (not included baseline).

Emergency Contraception (Table 5):

Overall 29% (269 of 936) of subjects used emergency contraception during the study period.

1. Subjects were more likely to use emergency contraception in the Advance Provision group (39.2%) than in the Pharmacy Access group (26.5%) or in the Standard Access group (20.3%); they were also more likely to report convenience of emergency contraception compared to those in the Pharmacy Access group or the Standard Access group (96%, 87% and 87%, respectively).

2. There were no differences in the time to take the first pill among the 3 groups or in overall proper use of emergency contraception ($p>0.05$). Subjects in the Standard Access group tended to have higher correct use than other 2 groups, 97% (SA), 92% (AP) and 90% (PA), and were more likely (100%) to take the second pill than the Advance Provision group (93%) and the Pharmacy Access group (90%). It should be

noted that the time interval for use of the second pill was not defined in this study as it was in the actual use study (12 hours after first pill).

3. The proportion of repeat use was highest in the Advance Provision group. The baseline EC use was 35% for the entire study population.

Table 5. **Emergency Contraception Usage during Study**

EC Use	Pharmacy Access (N=314)	Advance Provision (N=316)	Standard Access (N=306)	All Subjects (N=936)
Total*	83 (26.5)	124 (39.2)	62 (20.3)	269 (28.8)
Never	230 (73.5)	192 (60.8)	244 (79.7)	666 (71.2)
One time	52 (16.6)	75 (23.7)	45 (14.7)	172 (18.4)
Two times	20 (6.4)	28 (8.9)	13 (4.3)	61 (6.5)
> 3 times	11 (3.5)	21 (6.7)	4 (1.3)	36 (3.8)

Data were extracted from the author's Table 10 (p13) and presented as "No. (%).
*Pair-wise comparisons: AP vs. PA ($p<0.001$), AP vs. SA ($p<0.001$), and PA vs. SA ($p<0.067$).

Sexual behavior (Table 6):

Overall 96.6% (903 of 936) were sexually active during the study period.

1. There were no statistically significant differences in the rates of unprotected sex among the 3 groups. Subjects in the Advance Provision group tended to have higher frequency of unprotected intercourse (47% in AP, 41% in PA and SA).

2. As compared to the baseline, the frequency of unprotected sex decreased in all three groups. This change was statistically significant in the SA and PA groups but not in the AP group (Decrease from 50% to 41% in PA, and from 53% to 41% in SA, $p< 0.01$ by McNemar's test; but from 49% to 47% in AP, p=NS).

Table 6. **Sexual and Contraceptive Behaviors**

Behavior	Pharmacy Access N=314	Advance Provision N=316	Standard Access N=306	Total N=936
Unprotected Intercourse				
At Baseline (past 6 month)				
Total	**156 (49.7)**	**153 (48.6)**	**162 (52.9)**	471 (50.4)
Every time	12 (3.8)	13 (4.1)	12 (3.9)	37 (4.0)
Most of the time	18 (5.7)	32 (10.2)	25 (8.2)	75 (8.0)
Some of the time	126 (40.1)	108 (34.3)	125 (40.9)	359 (38.4)
Never	158 (50.3)	162 (51.4)	144 (47.1)	464 (49.6)
At last sex	26 (8.3)	32 (10.1)	35 (11.4)	93 (9.9)
At Follow-up(≥ 6 month)				
Total	**127 (40.6)**	**147 (46.7)**	**124 (40.5)**	398 (42.6)
Every time	9 (2.9)	11 (3.5)	7 (2.3)	27 (2.9)
Most of the time	16 (5.1)	24 (7.6)	22 (7.2)	62 (6.6)
Some of the time	102 (32.6)	112 (35.6)	95 (31.1)	309 (33.1)
Never	186 (59.4)	168 (53.3)	182 (59.5)	536 (57.4)
At last sex	30 (9.6)	37 (11.8)	24 (7.9)	91 (9.7)
Condom Use				
At Baseline (past 6 month)				
Total	**257 (81.8)**	**254 (80.4)**	**248 (81.3)**	759 (81.2)
Every time	87 (27.7)	83 (26.3)	75 (24.6)	245 (26.2)
Most of the time	86 (27.4)	83 (26.3)	86 (28.2)	255 (27.3)
Some of the time	84 (26.8)	88 (27.9)	87 (28.5)	259 (27.7)
Never	57 (18.2)	62 (19.6)	57 (18.7)	176 (18.8)
Use at last sex	**190 (60.5)**	**184 (58.2)**	**174 (56.9)**	548 (58.6)
Currently using	219 (69.8)	214 (67.7)	192 (62.8)	625 (66.8)
At Follow-up(≥ 6 month)				
Total	**226 (72.7)**	**232 (74.4)**	**224 (73.4)**	682 (73.5)
Every time	84 (27.0)	68 (21.8)	78 (25.6)	230 (24.8)
Most of the time	77 (24.8)	82 (26.3)	75 (24.6)	234 (25.2)
Some of the time	65 (20.9)	82 (26.3)	71 (23.3)	218 (23.5)
Never	85 (27.3)	80 (25.6)	81 (26.6)	246 (26.5)
Use at last sex	**159 (50.6)**	**154 (48.9)**	**170 (55.7)**	483 (51.7)
Currently using	178 (56.7)	179 (56.7)	186 (60.8)	543 (58.0)
Oral Contraceptive Use				
At Baseline (past 6 month)				
Missing pill (per pack)	243 (63.6)	74 (58.3)	90 (68.7)	79 (63.7)
Use at last sex	117 (37.3)	125 (39.6)	115 (37.6)	357 (38.1)
Currently using	129 (41.1)	132 (41.8)	125 (40.9)	386 (41.2)
At Follow-up(≥ 6 month)				
Missing pill (per pack)	276 (68.0)	96 (65.7)	97 (70.3)	83 (68.0)
Use at last sex	159 (50.6)	150 (47.8)	141 (46.2)	450 (48.2)
Currently using	159 (50.6)	150 (47.5)	139 (45.4)	448 (47.9)

Data were extracted and summarized from author's Table 6 (p8) and Table 9 (p11), presented as "No. (%)

Contraception Methods (Table 6):

There were no statistically significant differences in condom and OC uses among the 3 groups during the study period.

1. Overall condom use decreased in all 3 groups as compared with the baseline; condom use "at last sex" significantly decreased in the Advance Provision and the Pharmacy Access groups ($P< 0.01$), but remained relatively stable in the Standard Access group ($p< 0.65$).

2. During the same period that condom use decreased, there were increases in "currently using" OC in all groups compared to the baseline. The "Use at last sex" increased in all groups (PA change=37% to 51%, AP change=40% to 48% and SA change=38% to 46%).

Age difference:

There were no significant differences in observed parameters (pregnancy, condom use, unprotected sex, routine OC use) between adolescents (15-17 years old) and adults (18-24 years old).

COMMENTS

1. The proportion of 15-17 year olds and the literacy level of subjects were not provided.

2. "Baseline" STDs were reported, but the exposure period over which an infection was acquired was not captured. However, STDs acquired during the study among the 3 groups were comparable and were lower than the "baseline" history.

3. Overall unprotected intercourse decreased in all three groups compared to baseline. This change was statistically significant in the SA and PA groups but not in the AP group (from 50% to 41% in PA, and from 53% to 41% in SA, $p< 0.01$ by McNemar's test; but from 49% to 47% in PA, p=NS).

SUMMARY

1. Advance Provision did not increase STDs as compared with the Pharmacy Access and the Standard Access to EC.

2. Subjects in the Advance Provision group were more likely to use EC pills as compared to the Standard and Pharmacy Accesses.

3. All three groups had less unprotected intercourse during the follow-up as compared to baseline. When compared to baseline, the PA and SA groups decreased more ($P<0.01$) than the advance EC provision group (p=NS).

4. All three EC accesses were associated with a decrease in condom use, with statistically significant decreased differences in "use at last use" among the Advance Provision and the Pharmacy Access groups. However, the decrease in condom use was offset with increased oral contraceptive use.

5. Although there was greater OC use at study end compared to baseline for "use at last sex" and "currently using" in all 3 groups, the proportion in all three groups who reported "missing OC pills" at study end compared to baseline increased.

CONCLUSION

1. Advance Provision of emergency contraception was not found to be associated with a difference in pregnancy rates or acquired STDs compared to Pharmacy Access or Standard Access.

2. Advance Provision decreased unprotected intercourse compared to baseline, but to less of an extent than in the Pharmacy Access or Standard Access groups.

3. All three groups had increased OC use and decreased condom use.

4. All three groups increased "missing oral contraceptive pills" compared to baseline at study end. The highest rate of unprotected sex was in the AP group (49% vs. 41% in the PA & SA groups).

Literature #3 (sNDA 21-045, Serial No. 105, p5162)

Advance Supply of Emergency Contraception: Effect on Use and Usual Contraception—A Randomized Trial

Author: Rebecca A. Jackson, Eleanor Bimla Schwarz, Lori Freedman, and Philip Darney

Affiliate: Center for Reproductive Health Research and Policy and Department of Obstetrics, Gynecology, and Reproductive Sciences, and Division of General Internal Medicine
Department of Medicine, UCSF, and San Francisco General Hospital, San Francisco, California.

Sponsor: Partially funded by an unrestricted grant from the Packard Foundation. The Packard Foundation is a nonprofit organization. They provided funds for supplies and oral contraceptive pills.

Study Location: ***USA,*** a public inner-city hospital in San Francisco
From September 1998 through March 1999

Publication: ***Obetet Gynecol*** 102: 8-16, 2003

Design: Randomized (by date of discharge) controlled clinical trial
1 year observation
Single course of advance EC provision

METHODS

Subject: A total of 370 ***postpartum women*** were enrolled from a public inner-city hospital (San Francisco, CA) from September 1998 through March 1999, with the following eligibility criteria:

Age: (*was not specified in the Method*)
Postpartum women (had a live birth)
Spoke English or Spanish
Available for follow-up in 1 year
Had not undergone a postpartum tubal ligation

Subjects were randomly assigned to the following 2 groups:

Advance Provision Group: 184 subjects received one course of EC pills and EC education. The one course EC contained 8 oral contraceptive pills containing 0.15 mg of levonorgestrel and 30 ug of ethinyl estradiol. The educational session was a 5-minute

intervention and included instructions for obtaining additional emergency contraception pills if needed.

Control group: 186 subjects received only routine contraceptive counseling, and this did not usually include EC education.

To prevent interference of the difference educations that provided to each group, the investigators enrolled all women on a given day to the same group.

Data Collection: A Kaiser Family Foundation Questionnaire (survey) was the data collection instrument. The questionnaire was administered in person at enrollment and by phone at 6 and 12 months. The primary outcome was self-reported use of emergency contraception. Secondary outcomes included change in use of other contraceptive methods and knowledge about emergency contraception. Contraceptive and sexual behaviors were assessed by asking about types of contraception used and consistency of use.

Data Analysis: The individual subject was used as the unit of analysis. Differences between groups and differences within each group over time were analyzed using the Fisher exact test, Student *t* test, or the McNemar test.

RESULTS

Subject Demographics

Of the 721 screened subjects, 370 were enrolled and randomized to the Advance EC group (184) and Control group (186). The demographics and baseline characteristics of the enrolled subjects are summarized in Table 1; there were no statistically significant differences between the two groups. Approximately 18% were teens; 72% were Latina; 43% married. About half had a high school education.

Follow-up Compliance

At 6 months after enrollment, follow-up was available for 78% and at 1 year, 69%. Overall, 85% were available for at least one follow-up session. There were no differences between groups in the proportion lost to follow-up; nor were there differences in baseline traits between those lost to follow-up and those who completed the study (Table 1).

Table 1. **Demographics and Baseline characteristics of enrolled subjects**
(% of enrolled subjects)

Characteristic	Advance EC ($n = 184$)	Control ($n = 186$)
Age (mean ±SD), *years*	26 ± 6	26 ± 6
Ethnicity		
Hispanic	69	74
Non-Hispanic black	11	11
Asian/Pacific islander	10	11
Non-Hispanic white	9	3
Education		
High school graduate	47	48
Employed	62	53
Income > $20,000	11	11
Private insurance	4	2
Married	42	45
Pregnancy history		
Multiparous	49	48
Prior elective abortion(s)	16	18
Index pregnancy unplanned	65	64
Prior unwanted pregnancy	39	38
Lost to Follow-up		
At 6 months	25	20
At 12 months	30	31
Both 6 and 12 months	17	12

Data were extracted from author's Table 1 and Figure 1.

Sexual and Contraceptive Behavior

Sexual and contraceptive behaviors of subjects during 6 month period before and after enrollment in both groups were summarized in Tables 2 and 3.

Unprotected sex:

- Half the women in both groups reported at least one episode of unprotected intercourse during the 1-year follow-up period with no significant differences between groups, although the proportion was somewhat lower on the EC arm.

EC use:

- Women in the Advance EC provision group were significantly more likely to use ECPs during the study (13% vs 2% at one year).

- Subjects in both groups became more knowledgeable about emergency contraception during study periods; the Advance group demonstrated the greatest increase in knowledge.

- Five subjects used multiple doses of EC over the one year period, and three of them were in the Advance EC group.

- Approximately 25% of the study subjects could state the correct timing for using EC pills, which was consistent with results (18% correct use) from another study (Endres et al: *Experience with self-administered emergency contraception in a low-income, inner-city family planning program. J Reprod Med 2000;45:827–30*).

Condom use:

Among exclusive condom users, there was an increase in the routine use ("use mostly or always") of condoms in both groups as compared to the baseline. The proportion of routine condom use was similar between groups at follow-up although the proportional increase from baseline was greatest in the control group.

Primary contraception:

As compared to baseline, there was a significant improvement in contraceptive use (more effective methods and consistency) in both groups during the 12-month follow-up, which was similar between groups.

COMMENTS

1. The study population, postpartum women from an inner-city hospital, is not completely generalizable to the spectrum of sexually active women expected in an OTC setting.

2. Only a single course of EC was provided to the Advance provision group, and few requested additional EC pills during the study.

3. There were not observed differences between the Advance EC group compared to the control group regarding unprotected intercourse rates at 6 month and 12 months..

4. Randomization procedure was by date of discharge was not ideal and the sample size was small (n=370). The majority of the study population was Latina postpartum women.

CONCLUSION

Advance EC access in the ***postpartum women*** during the 1-year observation:

1. Increased EC use

2. Did not adversely change routine contraception, including condom use. The advance EC group maintained similar contraception use as the control group. Routine contraception use increased in Advance EC and Control groups.

3. Did not increase the frequency of unprotected intercourse as compared to control subjects and over time.

Table 2. **Use and knowledge of Emergency Contraception**
(% of subjects who provided data)

Outcome	Baseline		At 6 months			At 12 months		
	Advance EC N=184	Control N=186	Advance EC N=138	Control N=149	RR (95% CI)	Advance EC N=128	Control N=128	RR (95% CI)
Use of EC in prior 6 months								
Use at least once	3	3	10	3	3.56 (1.19, 10.7)	13	2	5.21 (1.55, 17.5)
New users of EC			8	1	6.03 (1.36, 26.7)	10	2	4.17 (1.21, 14.4)
In those with any unprotected intercourse			22	3	7.74 (1.81, 33.2)	16	3	5.14 (1.14, 23.1)
General EC knowledge†								
Has heard of "EC" or "MAP"	34	38	90	47	1.91 (1.59, 2.29)	91	70	1.31 (1.16, 1.49)
Salient knowledge about EC	18	20	70	32	2.14 (1.66, 2.77)	71	52	1.38 (1.13, 1.69)

Data were extracted from author's Table 2.
† "Heard of EC" indicates familiarity with the name "emergency contraception" or "morning-after pill." "Salient knowledge" indicates the subject was able to correctly name or describe EC pills.

Table 3. **Changes in contraceptive behavior**
(% of subjects who provided data)

Outcome	Baseline		At 6 months			At 12 months		
	Advance EC N=184	Control N=186	Advance EC N=136	Control N=149	RR (95% CI)	Advance EC N=120	Control N=125	RR (95% CI)
Consistency of contraceptive use								
Routine use of contraception	35	37	85	83	1.02 (0.92, 1.12)	83	81	1.02 (0.91, 1.15)
Less consistent use compared with prior 6 mo			8	13	0.60 (0.30, 1.21)	18	25	0.74 (0.45, 1.20)
Any unprotected intercourse	?*	?*	**47**	**52**	0.91 (0.71, 1.17)	**47**	**54**	0.87 (0.67, 1.13)
Routine use of condoms in exclusive condom users‡	**43**	**28**	**76**	**75**	1.02 (0.79, 1.31)	**87**	**92**	0.94 (0.80, 1.12)
Effectiveness of contraceptive method §								
Very (< 5% failure)	56	57	71	70	1.01 (0.87, 1.18)	70	67	1.04 (0.88, 1.23)
Poor (> 10% failure)	44	43	29	30	0.97 (0.68, 1.38)	30	33	0.92 (0.63, 1.33)
Less effective method compared with prior 6 mo			18	22	0.79 (0.50, 1.27)	21	20	1.02 (0.62, 1.67)

§ Very effective methods: sterilization, intrauterine device, depot medroxyprogesterone acetate, levonorgestrel implants, and oral contraceptives. Poorly effective methods: barrier, withdrawal, rhythm, and none.

‡ Condom use mostly or always in those who use only condoms. Numbers in EC and control at baseline, respectively: n = 54, 53; at 6 months: n = 38, 40; at 12 months: n = 31, 36; *however, calculation of the percentages on this event in the Table was not specified in the report.*

* The frequency of unprotected intercourse at baseline was not reported.

Literature #4 (vol. 13, page 007; Abstract)

Advanced supply of emergency contraception for adolescent mothers increased utilization without reducing condom or primary contraction use

Author: Marvin Belzer, Elizabeth Yoshida, Talar Tejirian, Diane Tucker, Katie Chung, Kathleen Sanchez

Affiliate: Children's Hospital Los Angeles, Los Angeles, California

Sponsor: Unknown

Study Location: ***USA,*** a large urban city (LA, California)
(Unknown site)

Publication: ***J Adolescent Health*** 32 (2): 5086 (Abstract only), 2003

Design: Randomized, 2-arm, single center trial
6-month follow-up
Single course of advance EC provision

METHODS

Subject

Adolescent mothers were recruited and enrolled from a large urban city (location and sites were not specified), age 14–20 years and not desiring pregnancy. Exclusion criteria were not reported. The subjects were randomized into the following 2 groups:

Treatment groups: subjects received ***an advance supply*** of levonorgestrel-only EC;

Control group: subjects received education on emergency contraception alone.

Data Collection

Subjects were contacted by phone at 6 months to collect the following data with a questionnaire: hormonal contraception use, condom use, sexual activity, unprotected sex, EC use, reasons for not using EC and pregnancy.

Data Analysis

Chi-square tests were conducted to assess differences between groups. Odds ratio and 95% CI were calculated to determine the association between contraceptive use and group assignment at baseline and follow-up.

RESULTS

Subject Demographics and Follow-up compliance

A total of 160 ***adolescent mothers*** were enrolled (number of screened subjects was not provided); their compliance with follow-up contacts at 6th and 12th month after enrollment is summarized in Table 1.

Table 1. **Subject enrollment and follow-up compliance**

Subject	Treatment	Control	Total
Enrollment	82	78	160
6th month follow-up	57	54	110 (69%)*
12th month follow-up	42	46	88 (55%)*

* % of enrolled subjects.

Demographics:

Mean age:	14-20 years
Hispanic:	83%
African American:	16%
Education:	unknown

Changes in Contraceptive Behavior

There were limited data available in the abstract about sexual and contraceptive behavior at baseline and follow-up (6th and 12th month) from both groups. Table 2 was extracted from text of the abstract.

Unprotected sex: The author stated that there were no increases in unprotected sex in the treatment group; but no data were provided.

EC use: Subjects in the treatment group were more likely to use EC.

Condom use: The author stated that there were no changes in condom use at the 6th month between treatment and control groups, but no data were provided.

Primary contraception: The author stated that there were no changes in primary contraception at the 6th month between 2 groups, but no data were provided.

Table 2. **Sexual and contraceptive behavior**

	Treatment *One package EC* N=57	Control *Education only* N=54	Total N=111
Sexually active			
Baseline	ND	ND	59%
At 6th month	62%	57%	
Unprotected sex			
Baseline			7%
At 6th month	ND	ND	No change
EC Use*			
At 6th month	85%	19%	
At 12th month	79%	21%	
Pregnancies at 6th month	4 (7%)	10 (18%)	
Change in primary contraception	OR = 0.77 Between group comparison (95% CI: 0.47-1.25)		
Change in condom use	OR = 0.71 Between group comparison (95% CI: 0.32-1.57)		

ND: no data were reported in the abstract.
* % of subjects who had unprotected sex.

COMMENTS

1. There were limited data provided on primary parameters to evaluate changes of interest, particularly condom use and unprotected sex.

2. Subjects were adolescent mothers and may have limited generalizability to the OTC setting.

3. Only a single course of EC was provided to the advance provision group, which did not reflect access in an OTC setting.

4. Small study size may have led to lack of observed statistically significant differences.

CONCLUSION

Advance EC provision was reported not to decrease condom use and primary contraception during the 6-month follow-up.

Literature #5 (vol 13, page 023)

The Effects of Advance Provision of Emergency Contraception on Adolescent Women's Sexual and Contraceptive Behaviors

Author: Melanie A. Gold

Affiliate: University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh, Division of Adolescent Medicine

Sponsor: Laurel Foundation (unknown location) for financial support.
Woman's Capital Corporation provided Plan B.

Study Location: ***USA,*** an urban hospital-based adolescent clinic
Pittsburgh, PA from June 1997 to June 2002.

Publication: Unpublished Manuscript

Design: Single-center, randomized clinical trial
8 months follow-up
Single course of advance EC provision

METHODS

Subject

Sexually active female adolescents were recruited from the waiting room of an urban hospital-based adolescent clinic in a Children's Hospital in southwestern Pennsylvania between June 1997 and October 2001, with the following criteria:

Inclusion criteria:
Age 15–20 years
Available for monthly follow-up by phone.

Exclusion criteria:
Live in a foster-care or group home setting
Using long-acting contraception (such as IUD, Norplant, Depo-Provera)
OC users were not excluded.

Of 779 screened adolescent women, 301 (39%) were enrolled and randomly assigned to the following 2 groups:

Advance EC group: 150 subjects received EC education information and one course of EC pills, and were informed that they could obtain up to 2 additional EC courses during 6 months. The Yuzpe regimen (Jun 1997 – March 2000) and Plan B (after March 2000) were used.

Control group: 151 subjects received EC education information and were told how to request EC from the adolescent clinic (the same regimen as the Advance EC) if/when needed.

Data Collection

Self-reported sexual, contraceptive behavior, pregnancy, STDs and EC use for the past month and at last episode of intercourse were collected monthly by telephone interview for 6 months after enrollment. At least 5 attempts were made to reach each subject for monthly interview. EC knowledge was assessed at month 1 and 6 interviews only.

RESULTS

Subject Demographics

The following are major demographic characteristics. They were comparable between the 2 groups.

Mean age:	17.1 ± 1.7 years.
Race:	57% African-American (45% used public Medical Assistance for health care insurance coverage); 30% white.
Pregnancy history:	20%
STD history:	30%
Education:	59% high school (*not specified "in" or "completed"*) 28% college/trade school.
Contraception:	73% condom use; 69% aware of EC.

Compliance of follow-up

Approximately 85% of enrolled subjects at month 1 and 65% at month 6 were interviewed. The median length of follow-up was 252 ± 32 days from enrollment. The follow-up compliance between the 2 groups was comparable.

Changes in Sexual and Contraceptive Behaviors

Sexual and contraceptive behaviors of subjects from the Advance EC and control groups at the 1st and 6th month after enrollment are summarized in Table 1. In the original Table, the author did not indicate how the percentages were calculated. Therefore, this reviewer compiled the data from the original table using the number of subjects who completed interview as a denominator (Table 1). The trends of the results are similar to the original presentation. At study entry 20% of subjects had a history of pregnancy, 30% had a history of STD, and 69% reported awareness of EC. Twenty-five percent reported their last intercourse was unprotected, 73% reported condom use and 38% reported OC use.

Table 1. **Sexual and contraceptive Behaviors**
[No. (% of subjects who completed interview)]

Behavior	First Month Follow-up		Sixth Month Follow-up	
	Advance EC	Control	Advance EC	Control
Enrolled Subjects†	150	151	150	151
Completed Interview†	123 (82)	131 (87)	91 (61)	105 (70)
EC Use‡	(15)	(8)	(8)	(6)
STDs‡			12 (13)	12 (11)
In past month				
Unprotected intercourse	24 (20)	28 (21)	16 (18)	19 (18)
Used condom	73 (59)	85 (65)	70 (77)	65 (62)
Used OC pills	42 (34)	51 (39)	33 (36)	50 (48)
Used any hormonal contraception	42 (34)	51 (39)	40 (44)	56 (53)
At last intercourse				
Unprotected	21 (17)	25 (19)	10 (11)	19 (18)
Used condom	70 (57)	80 (61)	67 (74)	66 (63)
Used OC pills	35 (28)	41 (31)	34 (37)	46 (44)
Used any hormonal contraception	35 (28)	41 (31)	39 (43)	50 (48)

Data were extracted from the author's Table 2, or Figure A (†) or text (‡).
The denominators used for percentage calculation was not defined in original Table, nor indicated in the report. The percentages in this table were recalculated using number of subjects who completed interview as a denominator.

EC Use:

At the first month, Advance EC group used EC more than control group (15% vs. 8%, p=0.05); there was no difference between the 2 groups at the 6th month. In multivariate analysis the only independent variable that predicted EC use was past pregnancy.

During the entire study, 22 subjects (15%) in the Advance EC group returned to request extra course of EC (17 returned once, 4 twice, and one 3 times). The Advance EC group reported more rapid first dose administration compared to the control group- 11 hours *vs.* 22 hours (p<0.005).

Unprotected Sex:

At both the first and sixth month, there were not differences in unprotected intercourse recorded for "in past month" or "at last intercourse" between Advance EC and control

groups. The proportion for both arms at month 1 and 6 were slightly lower than the baseline rate of unprotected intercourse, 25% on the Advanced EC arm and 24% on the control arm.

Contraception:

There were no significant differences in condom use, OC pill use or injectable contraceptive methods between Advance EC and control groups at one month. The proportion of EC subjects who reported condom use, 59% decreased from the baseline 76%. At 6 months a higher proportion of EC subjects reported use of condoms, 77%, than the control, 62% (p=0.02). At 6 months the proportion of EC subjects reporting condom use had returned to the baseline level. Over the course of the study, there were 13 (9%) pregnancies reported by the advance therapy group compared to 18 (11%) pregnancies reported by the control group.

STDs

There were 12 subjects each in the Advance EC and control groups who reported a newly-diagnosed STD during the study. By using the number of subjects who completed the interview as a denominator, 10% of subjects in the Advance EC group acquired STDs, compared to 9%.

COMMENTS

1. Data process and analysis were not clearly presented.

2. Only one course of EC was provided. Although the subjects could obtain an additional 2 courses, few subjects returned for additional request.

3. Subjects were interviewed monthly; however, only data from months 1 and 6 were reported.

4. About 50% of eligible women declined to participate in the study due to "lack of interest".

5. Comparisons between months 1 and 6 should be made with caution due to high attrition rate in both groups at month 6.

CONCLUSION

Advance provision of EC did not increase the frequency of unprotected intercourse and did not decrease condom use during the 6-month follow-up in women ages 15-20 compared to a control group.

Literature #6 (vol 13, page 012)

The Effects of Self-Administering Emergency Contraception

Author: Anna Glasier and David Baird

Affiliate: Edinburgh Healthcare National Health Service Trust Family Planning and Well Woman Services
Department of Obstetrics and Gynaecology
University of Edinburgh, Scotland. United Kingdom.

Financial Support: Chief Scientist's Office
Scottish Home and Health Department.

Study Location: **UK,** Family planning clinic and hospital in Edinburgh
From Jan 1994 to Dec 1996

Publication: *New Eng J Med* 339 (1): 1-4, 1998

Design: Randomized clinical trial, randomized by birthdate
1-year follow-up
Single course of advanced EC provision

METHODS

Subject

A total of 1083 women, ages 16-44, were recruited from a family-planning clinic and a large hospital in Edinburgh (Scotland, UK) between January 1994 and December 1996; 60% (650) were returning for follow-up of prior EC consultations and 40% (433) were returning for follow-up after therapeutic abortion.

Subjects were randomly assigned into the following 2 groups (on the basis of their birthday (even-numbered birthdays were assigned to the treatment group):

Treatment group: 553 women received one package of EC pills (four pills, each contained 50 µg of ethinyl estradiol and 0.25 mg of levonorgestrel), written instructions and telephone numbers to call with questions.

Control group: 530 women received EC education and informed where to get and how to use emergency contraception.

Data Collection

A questionnaire was sent to subjects ***one year*** after enrollment to collect information about EC use, other contraception methods, and pregnancy. If EC was used subjects

were to mail in a notification card with time of administration relative to intercourse and date of last menstrual period. They were also instructed to go to the clinic within one week after the date of expected menstrual period. At that time they were given a replacement packet.

Data Analysis

Differences between the groups were tested by chi-square tests with Yates' correction for binary factors or Mann–Whitney tests for ordinal factors.

RESULTS

Subject Demographics

Only age and education of subjects were reported (Table 1). Twenty-three percent of subjects were age < 20 years old. Comparability of the UK educational levels to the US system is unknown; but the author stated in the report, approximately 50% of subjects had gone to a university or college and <20% had left school before age 16.

Table 1. **Demographics and follow-up compliance of subjects**
[No. (% of enrolled subjects)]

Variable	Treatment Group	Control Group
Enrolled Subjects	***553***	***530***
Recruited after EC use	323 (58)	327 (62)
Recruited after abortion	230 (42)	203 (38)
Lost to Follow-up	34 (6)	44 (8)
Subjects with results available for analysis	***549 (99)***	***522 (98)***
Age (years)		
<20	132 (24)	116 (22)
20–29	314 (57)	309 (58)
>30	107 (19)	105 (20)
Education		
Age full-time education ended		
< 16 yr	93 (17)	92 (17)
17–18 yr	127 (23)	106 (20)
19–22 yr	116 (21)	114 (22)
≥ 23 yr	54 (10)	61 (12)
Still in school full time	154 (28)	145 (27)
Educational status unknown	9 (2)	12 (2)

Data were extracted from the author's Table 1.

Follow-up Compliance

Approximately 98% of subjects had data available for analysis of pregnancy at the one-year follow-up. Ascertainment methods included contacting the family doctor and the Scottish Health Department. However, only 64% the subjects in both groups (350 of 549 in the treatment group and 336 of 522 in the control group) were used for the final analyses of sexual and contraceptive behaviors because they provided the responses to the detailed questionnaire.

Changes in Contraceptive Behavior:

Sexual and contraceptive behaviors of subjects from treatment and control groups at the enrollment and one-year follow-up are summarized in Table 2.

EC Use:

Women in the advance EC group were more likely to use emergency contraceptives than those in control groups; 47% used EC at least once in the treatment group vs. 27% in the control group at the one year follow-up. The difference in single use between groups (36% vs. 14%) was statistically significant ($P<0.01$).

The proportion of subjects in each arm who were recruited after prior use of EC was 58% in the treatment group and 62% in the control group. Comparison of multiple users was not statistically different between treatment and control groups.

Condom Use:

Condom uses similarly decreased in both arms. Condom use decreased from 74% at baseline to 31% at one year in the treatment group and from 70% at baseline to 28% at one year in the control group.

Contraception Methods

The proportion of oral contraception use increased similarly in both groups.

Unprotected Sex:

Data on unprotected sex were not provided in the report. The "None contraception" shown in Table 2, which may include unprotected sex, decreased in both groups at one year follow-up.

Table 2. **Contraceptive behavior of subjects at enrollment and one year later**
[No. (% of subjects who provided contraception data)]

Contraceptive Behavior	Treatment Group N=350*		Control group N=336*	
	At Enrollment	One Year Later	At Enrollment	One Year Later
Contraception Methods				
Oral contraception	45 (13)	169 (48)	46 (14)	171 (51)
Condom	***258 (74)***	***108 (31)***	***235 (70)***	***94 (28)***
Diaphragm	7 (2)	7 (2)	11 (3)	15 (4)
Combination	3 (1)	31 (9)	6 (2)	34 (10)
None	34 (10)	21 (6)	33 (10)	15 (4)
Other or no answer	3 (1)	12 (3)	5 (1)	6 (2)
EC Use†				
Did not use		199 (53)		239 (73)
Used once		***135 (36)***		***45 (14)***[#]
Used twice		27 (7)		33 (10)
Used 3 times		13 (3)		8 (2)
Used > 3 times		5 (1)		1 (<1)
Pregnancy‡				
Total Pregnancies		28 (5)		33 (6)
Unintended Pregnancies		18 (3)		25 (5)
Abortions		15 (3)		19 (4)

* The number of subjects who responded to the question regarding the method of contraception.
† Percentage was calculated based on the subjects who provided data, 379 in the Treatment group and 326 in Control group.
‡ Percentage was calculated based on the subjects who provided data, 549 in the Treatment group and 522 in the Control group.
[#] $P < 0.001$

COMMENTS

1. The study population may not represent an OTC setting in US. Subjects were recruited from UK clinics (60% of them previously used emergency contraception and 40% had an abortion). Half of the subjects went to college/university.

2. Only 64% of enrolled subjects provided data for analysis.

3. A single course of EC was provided to the subjects in the advance EC provision group but they could return for further Advance Provisions after use of the single course.

CONCLUSION

1. Women with advance EC access were more likely to use EC, and had lower frequency of "none" method of contraception compared to baseline at one year. The control group had a greater decrease in "none" method of contraception at one year compared to baseline than the advance EC group.

2. Although 135 (36%) of the treatment group used the advance supply of EC, only about half returned for subsequent provisions of advanced supplies.

3. Oral contraception use increased in both groups and condom use decreased in both groups compared to baseline.

Literature #7 (vol 13, page 067a)

Provision of Emergency Contraceptive Pills to Spermicide Users in Ghana

Author: Amy Lovvorn, Joana Nerquaye-Tetteh, Evam Kofi Glover, Alex Amankwah-Poku, Melissa Hays, and Elizabeth Raymond

Affiliate: Family Health International
Research Triangle Park, North Carolina, USA;
Planned Parenthood Association of Ghana, Accra, Ghana

Sponsor: Family Health International (FHI) with funds from the United States Agency for International Development (USAID).

Study Location: *Africa,* Planned Parenthood Association of Ghana
July 1998 - June 1999

Publication: ***Contraception*** 61: 287–293, 2000

Design: Nonrandomized clinical trial
8 weeks follow-up
Single course of advance EC provision, with opportunity to return for additional courses

METHODS

Subject

A total of 210 women ***spermicide users*** were recruited and enrolled from 4 Planned Parenthood clinics (Accra, Nkawkaw, Kumasi, Takoradi) in Ghana, with the following eligibility criteria:

- Age 18-45 years
- No current pregnancy.
- Spermicides as the primary contraception method and EC as a backup method during the 8-week study period
- Expected to have at least 6 coital acts per month
- No history of thromboembolic disease

Subjects were counseled on the use of spermicide and given at least 40 spermicide tablets, and then non-randomly assigned into the following 2 groups (2 clinic sites each group):

Control (On Demand Provision) Group: 100 subjects recruited from clinics in Kumasi and Takoradi received EC education and advised to return to the clinic within 3 days after unprotected intercourse to obtain EC.

Advance Provision Group: 110 subjects recruited from clinics in Accra and Nkawkaw were given one packet of EC and advised to return to the clinic for re-supply immediately if she used, lost, or gave away the ECPs. Subjects were also asked to refill the ECPs at each of 2 visits.

The EC pills were LoFemenal oral contraceptive pills (each pill contains 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel).

Data Collection

Subjects returned to the clinics for follow-up visits at 4 and 8 weeks after enrollment to collect the following information: the reason for EC use or EC request, the dates and times of unprotected sex, the disposition of ECPs dispensed, side effects of ECPs, coital activity, and contraceptive use.

Data Analysis

All data were presented separately by clinics without any statistical analysis.

RESULTS

Subject Demographics and Follow-up Compliance

Of 210 enrolled subjects, 95% (200) provided any follow-up information for analyses. The duration of follow-up was 8.2-8.6 weeks per subject.

The demographics of the enrolled subjects were summarized in Table 1. Differences in the following characteristics of subjects were found among the 4 clinics: age, education, marriage and condom use (unknown statistical significance).

Table 1. **Demographics of enrolled subjects**
No. (% of enrolled subjects)

Characteristics	Advance clinics		Control clinics	
	Accra	Nkawkaw	Kumasi	Takoradi
Enrolled subjects	**60**	**50**	**51**	**49**
Age (years)				
18–24	20 (33)	6 (12)	13 (25)	14 (29)
25–34	26 (43)	21 (42)	14 (27)	18 (37)
≥ 35	14 (23)	23 (46)	24 (47)	16 (33)
Education				
None	3 (5)	6 (12)	11 (22)	3 (6)
Primary	14 (23)	9 (18)	21 (41)	1 (2)
Middle school	26 (43)	22 (44)	11 (22)	24 (49)
Higher	17 (28)	13 (26)	8 (16)	21 (43)
Marital status				
Single	8 (13)	5 (10)	6 (12)	21 (43)
Married	52 (87)	45 (90)	45 (88)	28 (57)
Contraception in Past month				
Spermicide	51 (85)	37 (74)	47 (92)	21 (43)
Oral contraceptive pills	4 (7)	10 (20)	0	1 (2)
Condom	14 (23)	2 (4)	2 (4)	11 (22)
Pregnancy History				
Pregnancies (mean)	3.6	3.9	4.5	3.2
Living children (mean)	2.3	3.2	2.9	2.0
Miscarriages/abortions (mean)	1.3	0.7	1.4	1.1

Data were extracted from the author's Table 2.

Changes in Contraceptive Behavior

Sexual and contraceptive behaviors of subjects before (one month) and after (approximately 8 weeks) enrollment were summarized in Table 2.

Table 2. **Sexual and contraceptive behavior**

Behavioral Variables	Advance Clinics		Control Clinics	
	Accra	Nkawkaw	Kumasi	Takoradi
Analyzed subjects	**53**	**50**	**48**	**49**
Mean Number of sex acts†				
Month before enrollment	7.1	11.4	9.4	10.9
During study	18.1	24.3	18.4	24.6
Mean Unprotected sex acts‡				
Month before enrollment	1.3	0.1	1.2	2.9
During study	1.2	0.1	0.2	0.1
EC Use during study (8 weeks)				
Total subjects	48 (91)	6 (12)	14 (29)	6 (12)
0 use	5 (9)	44 (88)	34 (71)	43 (88)
1 use	26 (49)	5 (10)	10 (21)	6 (12)
2 uses	16 (30)	0	3 (6)	0
3 uses	6 (11)	1 (2)	1 (2)	0

Data were extracted from the author's Table 3 but re-processed/re-calculated.
† mean sex acts per subjects; ‡ % of unprotected sex over total sex acts.
* % of EC use over unprotected sex.

Unprotected sex: The mean number of sex acts per participant per month increased at all clinic sites, but the proportion of acts that were unprotected declined. This study was not randomized and there were imbalances between study sites in many factors. Comparisons between Advanced Clinics and Controlled Clinics are not valid.

EC use: Subjects in Advance Clinics group seemed more likely to use EC although this conclusion is powered by the Accra site. Repeat use was 8% in 3 clinical sites (41% in Accra site).

Condom use: Changes on condom use was not assessed during the study.

Primary contraception: Change in primary contraception (spermicide) before and after enrollment, and the differences in primary contraception between Advance and Control were not reported.

COMMENTS

1. Study has significant flaws; the assignment was not randomized and there was great variability in demographics between the 4 clinic sites.

2. Study subjects did not have access to other forms of contraception.

3. The study was conducted outside US, and is not readily generalizable to US population, particularly an OTC setting.

4. A single course of EC was provided to the advance provision group. Subjects were asked to receive refills of advanced EC. There was 41% of participants that had repeat use at one advanced provision clinic and 2% at the other. This compared to 8% at one "on demand" clinic and 0 % at the other "on demand" clinic.

5. There were 2 follow-up visits (weeks 4 and 8) during the study. However, comparisons in sexual and contraceptive behaviors of subjects between 2 visits were not reported.

CONCLUSION

1. Subjects with advance EC access were more likely to use EC.

2. Behavioral changes between groups cannot be assessed due to significant deficiency in study design.

Literature #8 (vol 13, page 011a)

Emergency Contraception: Randomized Comparison of Advance Provision and Information Only

Author: Charlotte Ellertson, Shubba Ambardekar, Allison Hedley, Kurus Coyaji, James Trussell, and Kelly Blanchard

Affiliate: Population Council, Mexico City, Mexico (CE)
K.E.M. Hospital, Pune, India (SA, KC)
Office of Population Research, Princeton University (AH, JT),
Population Council, Johannesburg, South Africa (KB)

Sponsor: The David and Lucile Packard Foundation (Los Altos, California) funded this study

Study Location: ***India,*** family planning clinics
From April 1997 to June 2000

Publication: ***Obstet Gynecol*** 98:570-575, 2001

Design: Randomized clinical trial
1-year follow-up (38% 12-month and 90% 3-month)
Three courses of advance EC provision

METHODS

Subject

A total of 411 ***condom users*** visiting an urban family planning clinic in Pune (India) between April 1997 and June 2000 were recruited and randomly assigned into the following 2 groups:

Control group: 198 women received EC education to obtain emergency contraception if needed.

Advance EC group: 213 women received EC education plus ***three courses*** of EC pills (Yuzpe regimen). Each course consisted of 8 tablets (30 mg ethinyl estradiol and 30 mg norgestrel per tablet) of combined oral contraceptive.

Data Collection

Subjects returned quarterly to the clinic for follow-up for up to 1 year to collect information about frequency of unprotected intercourse, EC use, pregnancies, and sexually transmitted infections.

RESULTS

Subject Demographics (Table 1)

The mean age was 25 years, and approximately 5% of subjects were < 20 years old. Comparability of the educational levels in India to the US was unknown; apparently, 84% of subjects completed ≥ 9 years education.

Table 1. **Demographics and Follow-up Compliance of Enrolled Subjects**

Characteristics	Control (n=198)	Advance EC (n=213)
Age (years), No. (%)		
< 20	10 (5)	9 (4)
20–29	166 (84)	172 (81)
> 30	22 (11)	32 (15)
Mean ±SD	24.9 (3.7)	25.1 (3.8)
Years of schooling, No. (%)		
0–8	29 (15)	36 (17)
9–12	96 (48)	103 (48)
13–16	60 (30)	61 (29)
> 16	13 (7)	13 (6)
Mean ± SD	11.7 ± 3.5	11.4 ± 3.4
Follow-up Compliance†, No. (%)		
Lost to Follow-up	45 (33)	34 (16)
3 months	172 (87)	194 (91)
12 months	66 (33)	99 (46)

Data were adapted form the author's Table 1, otherwise from Table 2 and Figure 1 (†).

Follow-up Compliance

Approximately 87% (n=172 in control group) and 91% (n=194 in advance EC group) of subjects completed at least 3 months in study and available for analysis. Women who switched to non-barrier contraceptives left the study.

Sexual and Contraceptive Behavior (Table 2)

Unprotected sex: Women with advance EC provision did not have statistically greater frequency of unprotected sex and a similar proportion of women on the two study arms reported unprotected sex during the study, 8% in the advanced provision vs. 6% in the control group.

EC use: Women with advance EC provision were more likely to use EC pills (79% vs 44%) after unprotected intercourse. Eleven (5%) EC users were in the Advanced Provision group and four (2%) in the control group.

Condom use: The study subjects used condom as a primary contraception method and 23% in both arms went off study because they changed to a more effective contraceptive method. Ninety-eight percent of women in the advanced supply arm stated that availability of EC did not "tempt them to take changes with their condoms".

STDs: One subject reported an STD. Details of the STD (nature and study group) were not provided in the report. STDs were self reported and no clinical laboratory screening was performed.

Table 2. **Unprotected sex and Emergency contraceptive Use**
(Excluded 24 subjects who left the study)

Unprotected Intercourse	Control	Advance EC	*P* value
Mean number of unprotected sex acts per month among all women followed	0.016	0.012	0.62
Median number of unprotected sex acts per month among women with at least one unprotected sex	0.250	0.292	0.97
Number of women, *no.* (%)	9/157 **(5.7)**	14/185 **(7.6)**	0.53
EC use, *no.* (%)	4/9 (44.4)	11/14 (78.6)	0.18

Data were adapted from the author's Table 3.

COMMENTS

1. It is not clear if the rate of unprotected sex changed from baseline since baseline information (at the enrollment) was not provided.

2. The study was conducted in India, which is unlikely to be representative of US population.

CONCLUSION

Advance EC provision did not appear to increase the frequency of unprotected sex as compared to control in the population who used condom as a primary contraception method. The proportion of participants who did have unprotected sex who used EC was higher in the Advanced EC group.

VIII. Dosing, Regimen, and Administration Issues

Plan B is a 2-tablet package, as currently marketed for prescription. Each tablet contains 0.75 mg Levonorgestrel (an active ingredient). The first tablet should be taken within 72 hours after unprotected sex and failure to regular contraception methods, and the second tablet should be taken 12 hours after the first tablet.

The proposed OTC label was tested in an OTC setting with the Label Comprehension study and a subsequent revision was then used in the actual use study. The following is a review of ***Label Comprehension Study*** from the medical perspective (pages 112-131).

The more detailed and intensive review is conducted by Dr. Karen Lechter, a social scientist in the Office of Drug Safety/HFD-410, CDER/FDA.

Study #9728: **Plan B OTC Label Comprehension Study**

Report location: Volume 31

Study date: June 18, 2001 to July 18, 2001

Sponsors: Women's Capital Corporation
Family Health International (FHI)
(The sponsorship was transferred to the Barr Research in Nov, 03)

Investigators: Family Health International (FHI), Research Triangle Park, NC
(study design and monitoring; data collection, management and analyses)

Study sites: Eight malls in US:
Aurora, CO; Northridge, CA; Phoenix, AZ; Matteson, IL; Springfield, VA; San Antonio, TX; Deptford, NJ; and Pembroke Pines, FL

Four Family Planning Clinics sites in US
Boca Raton, FL; Chicago, IL; Los Angeles, CA; and San Antonio, TX

Study Drug: Plan B package containing no tablets

Study Objective: To test if consumers can understand the proposed OTC Plan B label.

Subject Recruitment:

A total of 663 women were screened from 8 shopping malls and 4 family planning clinics across the US (8 States); 656 were enrolled. The clinical sites were selected for enrollment of subjects that were minors so that parental consent was not necessary.

Communication objectives:

The following 11 communication objectives were tested and the corresponding questionnaire follows each objective:

1. ***Plan B is indicated for prevention of pregnancy after unprotected sex.***

Comprehension: correct or acceptable answers to at least 2 of the 4 questions.

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q7: Without looking at the label, tell me what *Plan B®* is used for.	emergency contraception; (***Acceptable:*** contraception)	after sex (purpose unspecified); STI/HIV; emergency (sex not mentioned); other; don't know/refused
Q14: A woman's partner used a condom during sex with her but the condom broke. The next morning, she used *Plan B®* to prevent pregnancy. Was this a correct use of *Plan B®*?	correct	Incorrect; refused
Q16: A woman with asthma had unprotected sex. The next day, she took *Plan B* to prevent pregnancy. Was this a correct use of *Plan B®*?	correct	Incorrect; refused
Q19: A woman had unprotected sex 2 days ago and then used *Plan B®* to prevent pregnancy. Was this a correct use of *Plan B®*?	correct	Incorrect; refused

2. ***Plan B is intended as a back up method and should not be used for regular contraception.***

Comprehension: Correct answer to at least 3 (Q8 was not listed under this objective, but it appears it should be here) of the following 5 questions.

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q8: Is *Plan B®* the same as ordinary birth control pills or is it different from ordinary birth control pills?	Different	Same; Refused
Q9: According to the label, should *Plan B®* be used as regular birth control?	No	Yes; Refused
Q21: A woman is planning to have sex tonight. She usually uses condoms to prevent pregnancy. This time she plans to use *Plan B®* instead because her husband complains about using condoms. Is this a correct use of *Plan B®*?	Incorrect	Correct; Refused
Q22: A woman used *Plan B* every day instead of her usual birth control pills. Was this a correct use of *Plan B®*?	Incorrect	Correct; Refused
Q25: A woman and her husband don't like using condoms and the woman doesn't want to take birth control pills. They decide to use *Plan B®* as their main contraceptive method. Is this a correct use of *Plan B®*?	Incorrect	Correct; Refused

3. ***Plan B does not prevent sexually transmitted diseases or HIV/AIDS.***

Comprehension: correct answer to the following 2 questions

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q13: A woman used *Plan B®* to be sure she doesn't get any sexually transmitted diseases. Was this a correct use of *Plan B®*?	Incorrect	Correct; refused
Q27: According to the label, does *Plan B* protect against HIV (the virus that causes AIDS) and other sexually transmitted diseases?	No	Yes; refused

4. ***The first pill should be taken as soon as possible after intercourse.***

Comprehension: correct or acceptable answer to at least 2 of the 4 questions

Question	Comprehension Responses/Answers		
	Correct	Acceptable	Incorrect
Q10: After unprotected sex, when is the best time to take the first tablet?	as soon as possible ***and*** within 72 hours or 3 days	within 72 hours ***or*** 3 days; as soon as possible	72 hours or 3 days; other; don't know/refused
Q29: How many days does the label say is the longest after sex a woman should wait before taking the first *Plan B®* tablet?	3 days or 72 hours		any other answer; refused
Q19: A woman had unprotected sex 2 days ago and then used *Plan B®* to prevent pregnancy. Was this a correct use of *Plan B®*?	Correct		Incorrect; refused
Q20: A woman had unprotected sex a week ago and then used *Plan B* to prevent pregnancy. Was this a correct use of *Plan B®*?	Incorrect		Correct; refused

5. ***The first pill should be taken within 72 hours after intercourse.***

Comprehension: correct or acceptable answer to either of the following questions.

Question	Comprehension Responses/Answers		
	Correct	Acceptable	Incorrect
Q10: After unprotected sex, when is the best time to take the first tablet?	as soon as possible ***and*** within 72 hours or 3 days	within 72 hours ***or*** 3 days; as soon as possible	72 hours or 3 days; other; don't know or refused
Q26: Will *Plan B*® be more effective if a woman takes it 1 day after unprotected sex or if she takes it 2 days after unprotected sex?	1 day		both the same; 2 days; refused

6. ***The second pill should be taken 12 hours after the first.***

Comprehension: correct or acceptable answer to the following question 30 (Q23 was not listed under this objective by the sponsor).

Question	Comprehension Responses/Answers		
	Correct	Acceptable	Incorrect
Q23: A woman took both *Plan B*® tablets at the same time. Was this a correct use of *Plan B*®?	Incorrect		Correct; Refused
Q30: When should a woman take the 2nd *Plan B*® tablet?	12 hours after the first tablet	other but mentioned 12 hours; the next morning	other; don't know/refused

7. ***Plan B should not be used by women who are already pregnant (because it will not be effective).***

Comprehension: correct answer to either of questions 11 and 17

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q11: Suppose I told you a woman who is 2 months pregnant used *Plan B®*. Would you say she used *Plan B®* correctly or incorrectly?	Incorrectly	Correctly; refused
Q12: Why? (following Q11)	because she was already pregnant, it won't work, it's too late	other reason; don't know or refused
Q17: A woman has missed her period. She did a home pregnancy test and it was positive. She then used *Plan B®* because she didn't want to be pregnant. Was this a correct use of *Plan B®*?	Incorrect	Correct; Refused

8. ***Plan B should not be used by women with unexplained vaginal bleeding***

Comprehension: correct answer to the following question

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q15: A woman had unusual vaginal bleeding during the past week. She had unprotected sex and then she took *Plan B®* to prevent pregnancy. Was this a correct use of *Plan B®*?	Incorrect	Correct; Refused

9. ***Plan B should not be used by women with allergy to any ingredient in the product.***

Comprehension: correct answer to the following question

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q18: A woman knows she is allergic to an ingredient in *Plan B®*. She used *Plan B®* because she noticed that her partner's condom broke during sex with her. Was this a correct use of *Plan B®*?	Incorrect	Correct; Refused

10. ***Side effects of Plan B® include nausea and vomiting.***

Comprehension: correct answer to questions 32 and 34, or name nausea and vomiting to question 37, or yes to questions 32-36.

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q32: Can nausea be a side effect of *Plan B®*?	Yes	No; Refused
Q33: Can trouble breathing be a side effect of *Plan B®*?	No	Yes; Refused
Q34: Can vomiting be a side effect of *Plan B®*?	Yes	No; Refused
Q35: Can fever be a side effect of *Plan B* ?	No	Yes; Refused
Q36: Are there any other possible side effects that I haven't mentioned?	Yes	No; Refused
Q37: Please name one of these other possible side effects.	named a condition listed on package	did not name condition listed on package; refused

11. ***If severe abdominal pain develops, the user should seek medical care immediately.***

Comprehension: correct answer to the following question

Question	Comprehension Responses/Answers	
	Correct	Incorrect
Q31: According to the label, if a woman gets severe stomach pain after using Plan B, what should she do?	See/call a doctor (time not mentioned); see/call a doctor immediately	See/call a doctor but not immediately; stop using it; call number on box; other; don't know/refused

12. ***Outcome after taking Plan B***

Comprehension: correct or acceptable answer to the following question

Question	Comprehension Responses/Answers		
	Correct	Acceptable	Incorrect
Q28: After a woman takes *Plan B®*, when should she expect her next period? Should she expect it immediately, at about the normal time, 1 week late, or never?	at about the normal time	1 week late	immediately; never; refused

RESULTS

Subject Demographics

Age and Race: The median age of 656 subjects was 21 years (12-50 years) and approximately 11% of them (76 of 656) were ages 12-16 (Table 2). Half of the participants were Caucasians and about 23% were Hispanic.

Table 2. **Demographics of 656 Eligible Subjects**

Demographic Characteristics	Number	%
Age (years)		
12-16	76	11.6
17-25	355	54.1
26-50	225	34.3
Race		
White	324	49.4
Black	155	23.6
Asian or Pacific Islander	30	4.6
American Indian or Alaska native	6	0.9
Other	115	17.5
Refused/missing	26	4.0
Ethnicity		
Hispanic	154	23.5
non Hispanic	500	76.2
Refused/missing	2	0.3
Income		
0-$15,000	57	8.7
$15,001-$25,000	63	9.6
$25,001-$35,000	101	15.4
$35,001-$45,000	111	16.9
$45,001 or more	159	24.2
did not know	139	21.2
refused/missing	26	4.0
Marital status		
single	487	74.2
married	143	21.8
divorced	17	2.6
widowed	8	1.2
refused/missing	1	0.2

Data were adapted from the sponsor's Table 2 (pa16, vol 31)

Education and Literacy: Approximately 27% of subjects (178 of 656) had educational levels less than high school (Table 3). About 30% of subjects (139 of 395) ≥ 18 years of age who had not completed college were at a literacy level of ≤ 8th grade.

Sexual activity and Contraception: About 79% (474 of 599 who responded) of subjects were sexually experienced; 71% of subjects (314 of 440 who responded) had a history of unprotected intercourse with concern about an unwanted pregnancy at some time in the past; 89% (410 of 460) of subjects used a condom.

Previous EC experience: Six percent (32 of 473 who responded) had previously used emergency contraceptive pills.

Table 3. **Education and Literacy**

Education (highest level completed)	No of subjects	% of 656
6th grade or less	4	0.6
7th or 8th grade	26	4.0
9th-11th grade	148	22.6
high school or GED	199	30.3
vocational/technical school	18	2.7
less than 4 years college	117	17.8
college	105	16.0
graduate school	37	5.6
refused/missing	2	0.3
Literacy level Subjects age ≥ 18 not completed college n=395	No of subjects	% of 395
3rd grade or less	1	0.3
4th-6th grade	17	4.3
7th-8th grade	121	30.6
high school	254	64.3
missing	2	0.5

*Assessed using Rapid Estimate of Adult Literacy in Medicine (Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. Fam Med 1993;25:391-5.)

Comprehension of Communication Objectives

Comprehension rates for each communication objective are summarized in Table 4, which corresponds to the following parameters evaluating marketability of OTC drug:

Indication: Ninety-three percent of subjects understood that *Plan B®* is indicated for prevention of pregnancy after unprotected sex (objective 1).

Warnings:

1. Pregnancy: 98% of subjects understood that Plan B should not be used by pregnant women; (objective #7)
2. Unexplained vaginal bleeding: 75% of subjects understood that Plan B should not be used by women with unexplained vaginal bleeding; (objective #8)
3. Allergy: 91% of subjects understood that Plan B should not be used by women with allergy to any ingredient in the product. (objective #9)

Regular contraception: Sixty-seven percent of subjects understood that Plan B is intended as a back up method and should not be used for regular contraception (objective #2).

HIV and other STDs: Ninety-four percent of subjects understood that Plan B does not protect against HIV or any other sexually transmitted disease (objective #3).

Direction for Use: Ninety-seven percent of subjects understood that the first pill should be taken within 72 hours or as soon as possible after intercourse (objective #4/5). Sixty-nine percent of subjects understood that the second pill should be taken 12 hours after the first (objective #6).

Adverse Events: Eight-nine percent of subjects understood that side effects of Plan B include nausea and vomiting (objective #10). Two irrelevant side-effects, "fever" and "trouble breathing," were included in the questionnaires; 80% and 83% of subjects, respectively, responded that "fever" and "trouble breathing" were not side effects of Plan B. However, if subjects responded that both relevant and irrelevant AEs were side-effects of Plan B, the responses were considered as correct. Therefore, the true comprehension on "nausea" and "vomiting" would be less than 89%.

Management of serious complication: Eight-one percent of subjects understood that if severe abdominal pain develops, the user should seek medical care immediately (objective #11).

Table 4. **Comprehension of each communication objectives**
(% of enrolled subjects)

	Communication Objectives		Response	95% Confidence Interval
1	*Plan B®* is indicated for prevention of pregnancy after unprotected sex	Correct	90	0.87 - 0.92
		Acceptable (1A) †	93	0.91 - 0.95
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.		67	0.64 - 0.71
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.		94	0.92 - 0.96
4	The first pill should be taken within 72 hours after intercourse.		85	0.82 - 0.88
5	The first pill should be taken as soon as possible after intercourse.		82	0.79 - 0.85
4/5	The first pill should be taken within 72 hours or ASAP after intercourse		97	0.96 - 0.98
6	The second pill should be taken 12 hours after the first.	Correct	69	0.65 - 0.72
		Acceptable (6A) ‡	85	0.83 - 0.88
7	*Plan B®* should not be used by women who are already pregnant		98	0.97 - 0.99
8	*Plan B®* should not be used by women with unexplained vaginal bleeding		75	0.72 - 0.79
9	*Plan B®* should not be used by women with allergy to any ingredient in the product		91	0.88 - 0.93
10	Side effects of *Plan B®* include nausea and vomiting.		89	0.87 - 0.91
11	If severe abdominal pain develops, the user should seek medical care immediately.		81	0.78 - 0.84

Data were extracted from the sponsor's Table 8 (p30, vol 31).
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.

Comprehension rates among subjects with different Demographics

Ages: Significantly fewer subjects ages 12-16 understood objectives #1A, #2, #4 and #6 compared with those ages ≥ 17 years (Table 5a). The comprehension rate on "not for regular contraception" in subjects age 12-16 was 20% in the clinics and 61% in mall (Table 5b).

Education and Literacy (Tables 6a & b): Lower comprehension rates on correct self-selection (related to objectives 1A, 2, 3 and 4) of Plan B were found in subjects who did not complete high school, as compared to those who completed high school. Subjects at age 18 or older with ≤ 8^{th} grade literacy scored significantly lower on objectives related to self-selection/deselection and correct use. Only 46% of the low literacy group understood that Plan B was not intended for routine contraception. Compared between clinic and mall sites, subjects with less than a high school education from clinic sites had less understanding of that "Plan should be used for emergency contraction but not for regular use" (Table 6c); subjects with less than 8^{th} grade literacy from the mall sites had less understanding that Plan B does not prevent STDs or HIV/AIDS (Table 6d).

Study Sites (Table 7a): Approximately 89% of subjects (583 of 656) were recruited from family planning clinics and the rest, 11% (73 of 656) from shopping malls in the original sNDA submission. However, in the sponsor's response (October 30, 2003) to the Agency' request on comparing the demographics of subjects between both locations, the proportion of the subjects recruited from both location was transposed; the sponsor claimed that 89% subjects were from the malls and 11% from the clinics. According to the re-submission, some differences were noted in comprehension on some communication objectives between clinic and mall sites, as described above.

Table 5a. **Comprehension rate of communication objectives in different age groups**
(% of enrolled subjects)

Communication Objectives		Age (years)			Total
		12-16 n=76	17-25 n=355	26-50 n=255	N=656
1A†	*Plan B®* is indicated for prevention of pregnancy after unprotected sex.	**86#**	93	95	93
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.	**57**	67	71	67
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.	93#	96	92	94
4	The first pill should be taken within 72 hours after intercourse.	**77**	86	87	85
5	The first pill should be taken as soon as possible after intercourse.	84	83	81	82
4/5	The first pill should be taken within 72 hours or ASAP after intercourse.	94	97	98	97
6A‡	The second pill should be taken 12 hours after the first. ‡	**77***	90	82	86
7	*Plan B®* should not be used by women who are already pregnant.	97	99	97	98
8	*Plan B®* should not be used by women with unexplained vaginal bleeding.	72	77	74	75
9	*Plan B®* should not be used by women with allergy to any ingredient in the product.	90	91	91	91
10	Side effects of *Plan B®* include nausea and vomiting.	90*	93	84	89
11	If severe abdominal pain develops, the user should seek medical care immediately	81	84	77	81

Data were extracted from the sponsor's Table 9 (p30).
* $P < 0.01$ and # $P < 0.05$
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.

***Table 5b.* Comprehension rate of communication objectives in subjects age 12-16 years between clinics and malls**
(% of enrolled subjects)

Communication Objectives		Age 12-16		Total N=76
		Clinics n=5	Mall n=71	
1A†	*Plan B®* is indicated for prevention of pregnancy after unprotected sex.	**60**	**89**	**86**
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.	**20**	**69**	**57**
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.	**80**	**96**	**93**
4	The first pill should be taken within 72 hours after intercourse.	80	87	77
5	The first pill should be taken as soon as possible after intercourse.	**60**	**84**	**84**
4/5	The first pill should be taken within 72 hours or ASAP after intercourse.	100	97	94
6A‡	The second pill should be taken 12 hours after the first. ‡	80	90	77
7	*Plan B®* should not be used by women who are already pregnant.	80	99	97
8	*Plan B®* should not be used by women with unexplained vaginal bleeding.	80	76	72
9	*Plan B®* should not be used by women with allergy to any ingredient in the product.	100	92	90
10	Side effects of *Plan B®* include nausea and vomiting.	100	92	90
11	If severe abdominal pain develops, the user should seek medical care immediately	80	85	81

Data were extracted from the sponsor's re-submission (Tables 9.1 and 9.2) dated on October 30, 2003. No statistical analyses were provided on the comparisons between clinic and mall sites.
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.

Table 6a. **Comprehension rates on communication objective at different education levels**
(% of enrolled subjects)

	Communication Objectives	Education		Total
		<HS n=178	≥HS n=476	n=654
1A†	*Plan B*® is indicated for prevention of pregnancy after unprotected sex.	**86***	96	93
2	*Plan B*® is intended as a back up method and should not be used for regular contraception.	**55***	72	67
3	*Plan B*® does not prevent sexually transmitted diseases or HIV/AIDS.	**90#**	96	94
4	The first pill should be taken within 72 hours after intercourse.	**77***	89	85
5	The first pill should be taken as soon as possible after intercourse.	85	81	82
4/5	The first pill should be taken within 72 hours or ASAP after intercourse	97	97	97
6A‡	The second pill should be taken 12 hours after the first.	84	86	86
7	*Plan B*® should not be used by women who are already pregnant.	97	98	98
8	*Plan B*® should not be used by women with unexplained vaginal bleeding.	75	75	75
9	*Plan B*® should not be used by women with allergy to any ingredient in the product.	88	92	91
10	Side effects of *Plan B*® include nausea and vomiting. (P=0.0075)	88	90	89
11	If severe abdominal pain develops, the user should seek medical care immediately.	84	80	81

Data were extracted from the sponsor's Table 15 (p37).
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.
* $P < 0.01$ and # $p < 0.05$
< HS: did not complete a high school education; ≥ HS: completed a high school education

Table 6b. **Comprehension rates on communication objective at different literacy levels**
(% of enrolled subjects)

Communication Objectives		Literacy Level		Total
		$< 8^{th}$ n=139	HS n=254	n=393
1A†	*Plan B®* is indicated for prevention of pregnancy after unprotected sex.	84*	96	92
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.	46*	78	67
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.	84*	99	93
4	The first pill should be taken within 72 hours after intercourse.	71*	90	83
5	The first pill should be taken as soon as possible after intercourse.	84	83	83
4/5	The first pill should be taken within 72 hours or ASAP after intercourse	95	98	97
6A‡	The second pill should be taken 12 hours after the first.	82*	92	89
7	*Plan B®* should not be used by women who are already pregnant.	95*	99	98
8	*Plan B®* should not be used by women with unexplained vaginal bleeding.	69*	81	77
9	*Plan B®* should not be used by women with allergy to any ingredient in the product.	82*	95	90
10	Side effects of *Plan B®* include nausea and vomiting. (P=0.0075)	84*	96	92
11	If severe abdominal pain develops, the user should seek medical care immediately.	81	83	82

Data were extracted from the sponsor's Table 16 (p38).
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.
* $P < 0.01$
$< 8^{th}$: 8^{th} grade or less assessed with REALM test; HS: completed a high school education

***Table 6c.* Comprehension rate of communication objectives**
In subjects with less than a high school education between clinics and malls
(% of enrolled subjects)

Communication Objectives		Less than a HS education		Total N=73
		Clinics n=22	Mall n=156	
1A†	*Plan B®* is indicated for prevention of pregnancy after unprotected sex.	**77**	**87**	**86**
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.	**36**	**58**	**55**
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.	91	90	90
4	The first pill should be taken within 72 hours after intercourse.	77	77	77
5	The first pill should be taken as soon as possible after intercourse.	**77**	**87**	**85**
4/5	The first pill should be taken within 72 hours or ASAP after intercourse.	95	97	97
6A‡	The second pill should be taken 12 hours after the first. ‡	91	83	84
7	*Plan B®* should not be used by women who are already pregnant.	96	98	97
8	*Plan B®* should not be used by women with unexplained vaginal bleeding.	86	74	75
9	*Plan B®* should not be used by women with allergy to any ingredient in the product.	86	89	88
10	Side effects of *Plan B®* include nausea and vomiting.	96	87	88
11	If severe abdominal pain develops, the user should seek medical care immediately	86	84	84

Data were extracted from the sponsor's re-submission (Tables 15.1 and 15.2) dated on October 30, 2003. No statistical analyses were provided on the comparisons between clinic and mall sites.
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.

***Table 6d.* Comprehension rate of communication objectives in subjects with less than 8th literacy level between clinics and malls**
(% of enrolled subjects)

Communication Objectives		≤8th grade literacy		Total N=139
		Clinics n=16	Mall n=123	
1A†	*Plan B®* is indicated for prevention of pregnancy after unprotected sex.	88	84	84
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.	**44**	**46**	**46**
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.	**100**	**82**	**84**
4	The first pill should be taken within 72 hours after intercourse.	69	72	71
5	The first pill should be taken as soon as possible after intercourse.	94	83	84
4/5	The first pill should be taken within 72 hours or ASAP after intercourse.	100	94	95
6A‡	The second pill should be taken 12 hours after the first. ‡	81	82	82
7	*Plan B®* should not be used by women who are already pregnant.	100	95	95
8	*Plan B®* should not be used by women with unexplained vaginal bleeding.	75	68	69
9	*Plan B®* should not be used by women with allergy to any ingredient in the product.	75	83	82
10	Side effects of *Plan B®* include nausea and vomiting.	100	83	84
11	If severe abdominal pain develops, the user should seek medical care immediately	75	82	81

Data were extracted from the sponsor's re-submission (Tables 16.1 and 16.2) dated on October 30, 2003. No statistical analyses were provided on the comparisons between clinic and mall sites.
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.

Table 7a. **Comprehension rates in subjects recruited from Shopping Mall and Clinics**
(% of enrolled subjects)

Communication Objectives		Study Site		Total
		Mall# n=583	Clinic n=73	n=656
1A†	*Plan B®* is indicated for prevention of pregnancy after unprotected sex.	93	93	93
2	*Plan B®* is intended as a back up method and should not be used for regular contraception.	68	61	67
3	*Plan B®* does not prevent sexually transmitted diseases or HIV/AIDS.	94	97	94
4	The first pill should be taken within 72 hours after intercourse.	85	87	85
5	The first pill should be taken as soon as possible after intercourse.	83	79	82
4/5	The first pill should be taken within 72 hours or ASAP after intercourse	97	98	97
6A‡	The second pill should be taken 12 hours after the first.	85	90	86
7	*Plan B®* should not be used by women who are already pregnant.	98	98	98
8	*Plan B®* should not be used by women with unexplained vaginal bleeding.	75	76	75
9	*Plan B®* should not be used by women with allergy to any ingredient in the product.	91	93	91
10	Side effects of *Plan B®* include nausea and vomiting.	**88***	98	89
11	If severe abdominal pain develops, the user should seek medical care immediately.	81	83	81

Data were extracted from the sponsor's Table 13 (p35).
* $P < 0.01$ (by Chi-square test).
† using acceptable definition for Q7; ‡ using acceptable definition for Q30.
# The proportion of subjects from clinics and malls is updated from the sponsor's re-submission dated on October 30, 2003. In the original submission (April 2003), 583 subjects were recruited from clinic sites and 73 from shopping malls; the sponsor claimed this was transposed.

SUMMARY

1. ***Subjects:*** A total of 656 subjects (663 were screened) ages 12-50 were enrolled in the study; approximately 12% of subjects were age 12-16; 30% of subjects at age ≥ 18 who did not complete college were at a literacy level ≤ 8th grade. About 79% of subjects were sexually experienced and 6% had previous EC use experience.

2. ***Comprehension of Indication:*** Ninety-three percent of subjects could correctly understand that Plan B is to be used "after unprotected sex".

3. ***Comprehension of Warnings:*** Most subjects (91-98%) could understand the warnings (pregnancy and allergy) and that Plan B does not protect against the AIDS/STDs. However, only 67% of subjects could understand that Plan B is not for use as a regular contraceptive; and 75% of subjects were aware of the contraindication "unexplained vaginal bleeding".

4. ***Comprehension of Directions for Use:*** Ninety-seven percent of subjects understood to take the first pill before 72 hours or as soon as possible after intercourse. However, only 69% of subjects understood the need to take the second pill at 12 hours after the first pill.

5. ***Adverse Events:*** Over 80% of subjects could understand side effects of Plan B.

6. ***Ages:*** Lower comprehension rates were seen on the communication objectives #1A, #2, #4 and #6 in subjects ages 12-16 and on #1A, #2, #3 and #4 in subjects with lower literacy and less than a high school education.

7. ***Education levels:*** Lower comprehension rates on the communication objectives #1A, #2, #3 and #4 were noted in subjects with lower literacy and less than high school education.

8. ***Shopping Malls and Clinics:*** Overall comprehension rates on the communication objectives were comparable between the 2 types of locations, except for the lower comprehension of the possible adverse events demonstrated by participants from the malls. However, among demographic cohorts, there were trends of lower comprehension on some elements in the proposed OTC label in the clinic sites compared to the malls, particularly among subjects ages 12-16, those with less education, and those with low literacy.

9. ***STDs or HIV/AIDS:*** Ninety-four percent of subjects understood that Plan B does not prevent STDs or HIV/AIDS. However, the comprehension was less among the younger (12-16 years old) and lower literacy participants.

COMMENTS

1. Approximately 20% of subjects did not understand the potential seriousness of severe abdominal pain that may occur after using Plan B. This issue (related to ectopic pregnancy) will be addressed in the global safety update review by HFD-580.

2. Approximately 25% of subjects did not recognize that "unexplained vaginal bleeding" was a contraindication. The language may be too vague. The sponsor stated that there is no evidence to support this contraindication claim and proposed to remove it from the label. This issue will be addressed in the global safety update review by HFD-580.

3. Sexually transmitted diseases other than HIV/AIDS were not mentioned in the questionnaires.

4. The proportion of subjects from the clinics and the malls in the study was reported differently in the original submission and resubmission. In the original submission the sponsor reported that 89% of subjects were recruited from the clinics and 11% were from the malls. However, upon resubmission of this data, the sponsor rectified this error and stated that 89% of subjects were from the malls.

CONCLUSION

1. Overall, the majority of subjects could understand the proposed OTC label with regard to the indication for Plan B, and could recognize common and severe adverse events.

2. Subjects ages 12-16 and those with less education or low literacy were less apt to comprehend the indication and the directions for use.

3. A package insert is recommended to improve comprehension of concepts of "emergency" and "routine" contraception in populations with lower literacy and those ages 12-16.

4. The proposed changes on the OTC label from the sponsor: bolding the phrase "a serious medical problem" and removing "Unexplained (or unusual) vaginal bleeding".

5. The majority of study subjects were recruited from a mall setting (according to resubmission). This would probably more closely represent the general population than those subjects recruited in the actual use study and would help to evaluate the generalizability of the study results.

IX. Use in Special Populations

Plan B is for sexually active women of reproductive age. Adolescent women will likely be one of major target populations.

The target populations were partially tested in the Plan B actual use study, in which the study population was recruited from family planning clinics (94%) and pharmacy store (6%). No subjects were recruited from OTC-like public areas such as shopping malls. Only 5% (n=29) of the enrolled subjects were ages 14-16 years.

In the Plan B label comprehension study, 89% of enrolled subjects were recruited from shopping mall and 11% from family planning clinics. Approximately 12% (n=76) of enrolled subjects were ages 12-16 years.

The behavior study literature partially covered the target populations, including adolescent subjects in most studies.

X. Conclusions and Recommendations

1. The majority of subjects in the actual use study can correctly self-select and use Plan B based on their understanding of the proposed OTC label.

2. There were no serious adverse events and new safety signals reported in the Plan B Actual Use Study.

3. There were no adverse changes in contraceptive behaviors observed in the actual use study, However, the study was not adequately designed for risk assessment of contraceptive behaviors associated with Plan B in an OTC-like setting.

4. The behavior studies from literature can not fully address the inadequacy of the Plan B actual use study for the behavior assessment due to significant limitations in studies.

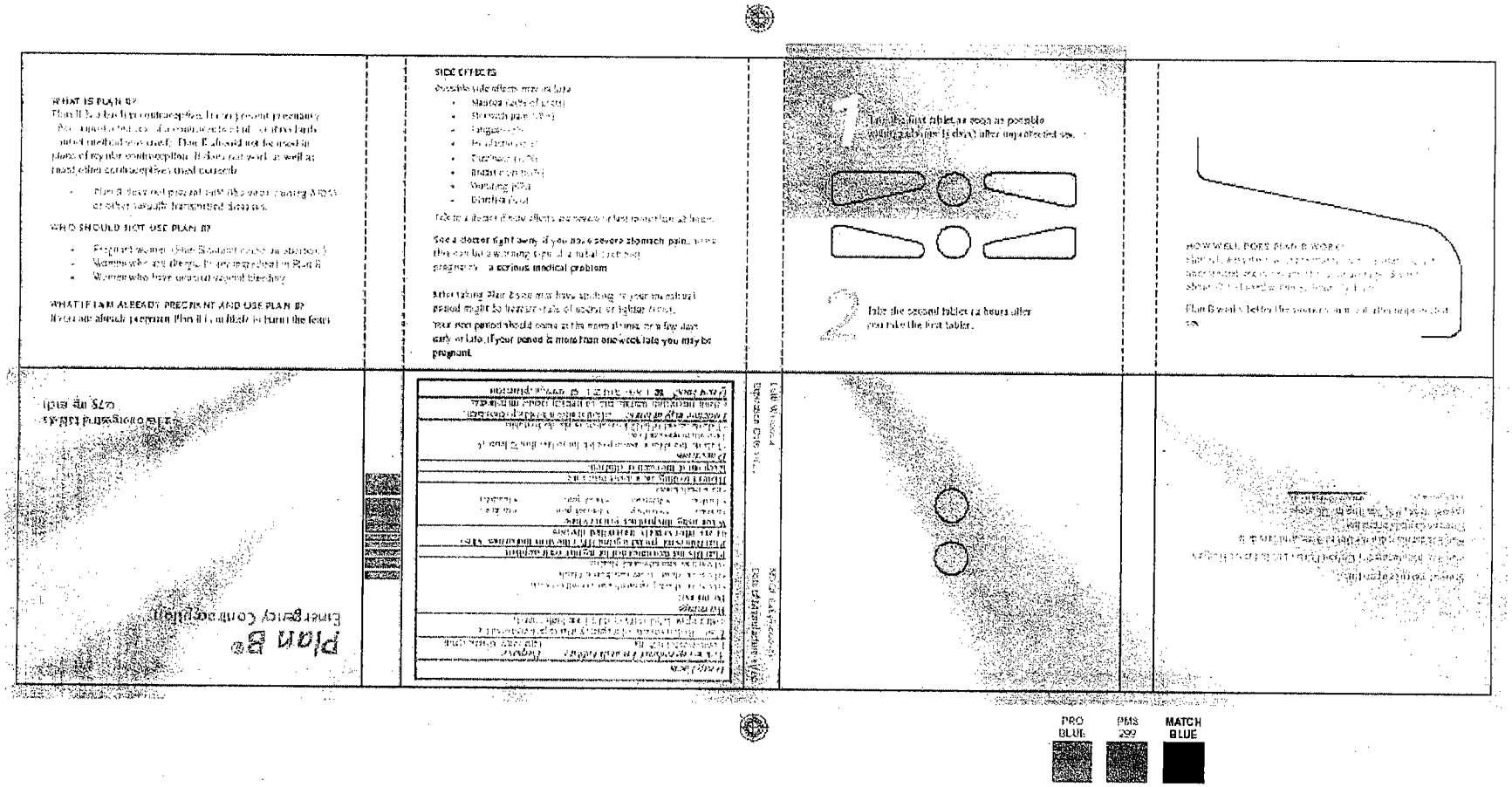
5. This sNDA is recommended for ***approvable*** because the data submitted in this sNDA do not provide enough evidence to *rule out* or *rule in* the possibility that OTC accessibility of Plan B may result in the risky/unsafe sexual behaviors in the OTC target populations.

{signature}
Jin Chen, MD, PhD, MPH
Medical Officer, HFD-560

Dr. Andrea Leonard-Segal, Medical Team Leader, advises me to sign this review alone due to disagreement with the recommendation. See her secondary review for details.

XI. Appendices

Appendix #1. The proposed OTC label used in the Actual Used Study



Appendix #2. The Proposed OTC label used for the Label Comprehension Study

Carton Text for Plan B® (no condom)

Panel 1 (front panel)

Plan B®
Emergency Contraception

2 levonorgestrel tablets
0.75 mg each

Left Spine

Lot No. Expiration Date x/xx

Panel 2 (inside far left)

WHAT IS PLAN B?
Plan B is a backup contraceptive. It can prevent pregnancy after unprotected sex (if a contraceptive fails or if no birth control method was used). Plan B should not be used in place of regular contraception. It does not work as well as most other contraceptives used correctly.

- Plan B does not prevent HIV (the virus causing AIDS) or other sexually transmitted diseases.

WHO SHOULD NOT USE PLAN B?
- Pregnant women (Plan B cannot cause an abortion.)
- Women who are allergic to any ingredient in Plan B.
- Women who have unusual vaginal bleeding.

Panel 3 (inside near left)

WHAT IF I AM ALREADY PREGNANT AND USE PLAN B?
If you are already pregnant Plan B is unlikely to harm the fetus.

SIDE EFFECTS
Possible side effects may include:
- Nausea (23% of users)
- Stomach pain (18%)
- Fatigue (17%)
- Headache (17%)
- Dizziness (10%)
- Breast pain (10%)
- Vomiting (6%)
- Diarrhea (6%)

Talk to a doctor if side effects are severe or last more than 48 hours.

Panel 4 (inside near right – blisters)

1 Take the first tablet as soon as possible within 72 hours (3 days) after unprotected sex.

2 Take the second tablet 12 hours after you take the first tablet.

Panel 5 (inside far right)

After taking Plan B, you may have spotting or your menstrual period might be heavier or lighter.

Your next period should come at the normal time, or a few days early or late. If your period is more than one week late, you may be pregnant.

See a doctor right away if you have severe stomach pain, since this can be a warning sign of a tubal (ectopic) pregnancy – a serious medical problem.

Panel 6 (outside far left)

HOW WELL DOES PLAN B WORK?
Plan B lowers the risk of pregnancy by 89% after one act of unprotected sex (from about 8%, on average, down to about 1%)

Plan B works better the sooner you use it after unprotected sex.

Do not take more than 2 tablets in 24 hours.

Panel 7 (outside near left)

Store at room temperature.

Plan B is manufactured by Gedeon Richter, Ltd. Budapest Hungary.

Plan B is distributed in the United States and Canada by:
Women's Capital Corporation
1990 M Street, NW, Washington, DC 20036
800-330-1271 www.go2planb.com

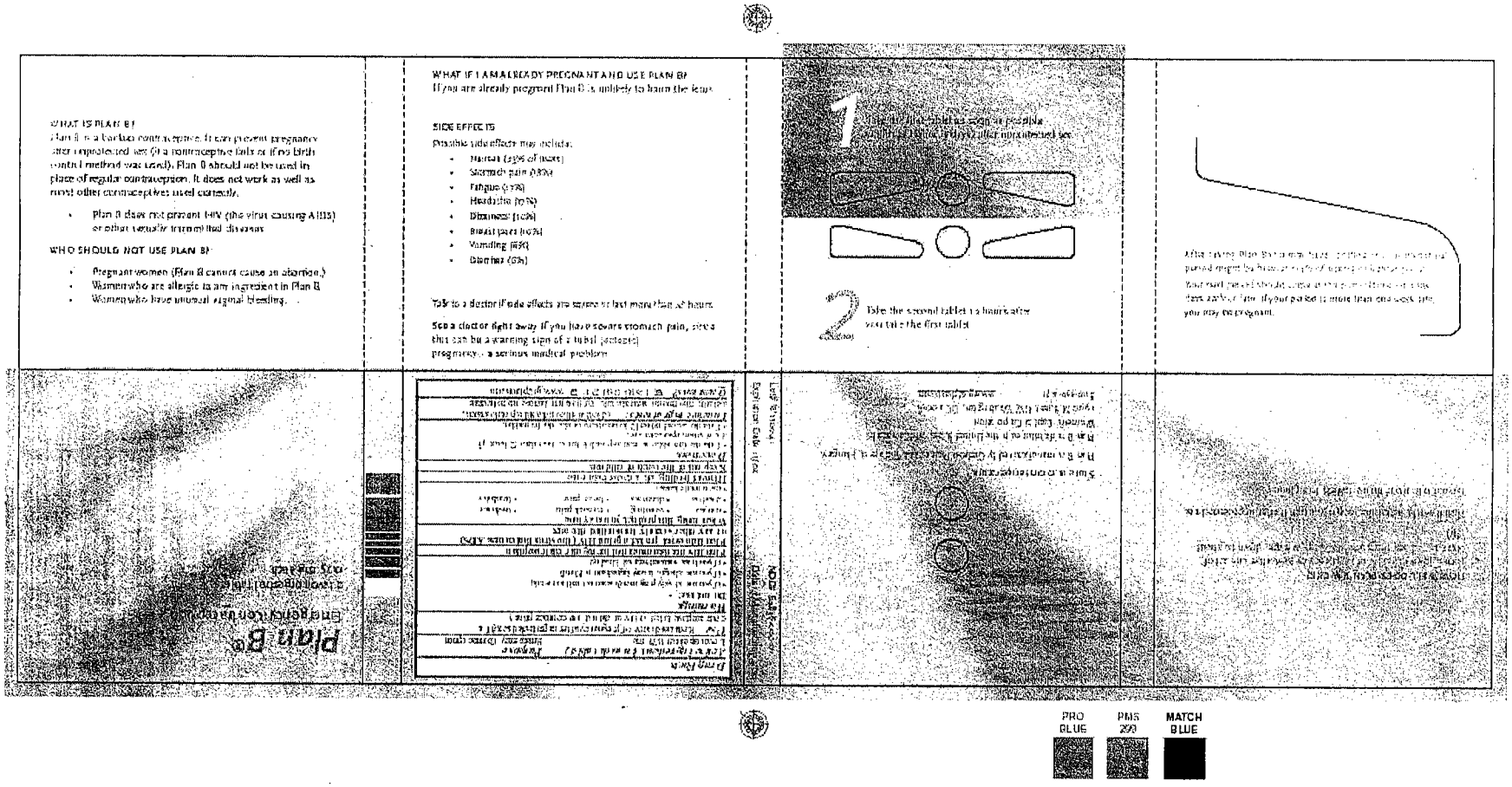
Right Spine

[Bar Code]

Panel 8 (back panel)

Drug Facts
Active ingredients (in each tablet) — *Purpose* Levonorgestrel 0.75 mg — Emergency Contraception
Use Reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use contraception)
Warnings Do not use: • if you are already pregnant (because it will not work) • if you are allergic to any ingredient in Plan B • if you have unusual vaginal bleeding
Plan B is not recommended for regular contraception.
Plan B does not protect against HIV (the virus that causes AIDS) or any other sexually transmitted diseases.
When using this product, you may have • nausea • vomiting • stomach pain • tiredness • diarrhea • dizziness • breast pain • headache • menstrual changes
If breastfeeding, ask a doctor before use
Keep out of the reach of children.
Directions • Take the first tablet as soon as possible but no later than 72 hours (3 days) after unprotected sex. • Take the second tablet 12 hours after you take the first tablet.
Inactive ingredients: colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, lactose monohydrate
Questions? ☎1-800-330-1271 🖳 www.go2planb.com

The proposed OTC label used for the Label Comprehension Study



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/s/

Jin Chen
1/12/04 08:37:23 AM
MEDICAL OFFICER

Dr. Andrea Leonard-Segal, medical team leader/HFD-560, has advised me to sign this review alone due to disagreement with the recommendation.

Office Director Memorandum
Office of Drug Evaluation V
Office of New Drugs
Center for Drug Evaluation and Research

Subject : NDA 21-045, Plan B (levonorgestrel) proposing Rx to OTC switch
Applicant: Barr Laboratories/Women's Capital Corporation
Date: January 21, 2004

Purpose: This memorandum provides for concurrence with the reviews of Dr. Rosebraugh and Dr. Leonard Segal and non concurrence with the recommended regulatory action by Dr. Chen. This is not a summary but serves to articulate my regulatory review concerns.

Regulatory History and Background
Over the Counter (OTC) availability of contraception is a well established and long standing regulatory category of products. Monographs promulgated pursuant to the provisions of 21CFR 330.5 provide for a category of "Contraceptive Products". The Advisory Panel Report (published 45 FR 82014, December 12, 1980) on OTC Contraceptives and Other Vaginal Drug Products (the Panel) placed nonoxynol 9 in category I (safe and effective).

The panel noted strong consumer interest in labeling communicating product effectiveness and clearly supported contraceptives as an appropriate category of product for widespread availability. There were no concerns cited in the report as to use by teenagers.

In addition, the current edition of the Code of Federal Regulations, 21 CFR 310.545(28), lists OTC vaginal contraceptive drug products approved as of October 22, 1998. These include dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate), Laureth 10S, methoxypolyoxyethyleneglycol 550 laurate, phenylmercuric acetate, phenylmercuric nitrate, and approved as of November 5, 2002, octoxynol 9. These additional regulatory examples are cited as evidence of a consistent and unquestioned record of regulatory precedent of contraception as an appropriate and established OTC product category.

Emergency Contraception Regulatory History
Based on extensive medical literature, on February 25, 1997, FDA announced in a Federal Register (FR) notice that certain combined oral contraceptives are safe and effective for emergency contraception and requested the submission of NDAs for this use. Of relevance to the concerns of this memo, this FR notice by the agency did address any need for data specific to use in teenagers. The agency has subsequently approved New Drug Applications (NDAs) for Preven and for Plan B in 1998 and 1999, respectively.

A citizen's petition requesting Rx to OTC switch of emergency contraception products was submitted to the Agency by the Center for Reproductive Law and Policy on February 14, 2001. The agency has not issued a final response to this petition.

NDA 21-045 for Plan B, is the first NDA submitted for an oral contraceptive product for the indication of emergency contraception for OTC marketing.

Overview of Submission

NDA 21-045, Plan B, Rx to OTC switch NDA application

Emergency contraception is defined as a method of pregnancy prevention to be started within 72 hours after a contraceptive failure or unprotected intercourse. Plan B (levonorgestrel) was approved in 1999 for this indication as an Rx product. For the purposes of this submission for the switch to OTC marketing, there are no outstanding efficacy concerns given that the proposed dose is the same as that approved for the prescription product. The labeling comprehension and actual use studies submitted have been extensively reviewed by FDA reviewers in the OTC and Reproductive Drugs divisions as well as in a public advisory committee in December 2003.

Regarding safety, the NDA database, ODS review, medical literature, as well as data from foreign marketing evidence a high level of safety for use of this product and that the product has an acceptable risk to benefit for its proposed OTC use.

Discussion

Concern has been raised by Dr. Chen of the following:

1. That the contraceptive behavior evaluation in the Plan B Actual Use Study is insufficient to assess whether OTC accessibility of Plan B may be associated with the risky (or unsafe) sexual behaviors over the long-term, particularly in the teenage population.

2. The behavior study literature does not provide strong evidence to address the inadequacy of the actual use study in assessment of risky sexual behaviors in the target OTC populations.

3. Some behavior studies in literature suggest that the advance provision of emergency contraception tends to prompt unsafe sexual behaviors in study populations.

The issues cited spuriously raise the review standard for approval of this product and indeed any contraceptive product. The issues are speculative and unbalanced in their proposition for the following reasons. The totality of data submitted has demonstrated an acceptable level of benefit to risk. There is no basis on which to assume that young women of child bearing potential would suddenly become promiscuous because of this product. Indeed, the data submitted evidenced a decrease in sexual activity short term. Conversely, there is also no basis on which to assume that minimizing available

contraceptive options will lead to a decrease in sexual activity by young women of child bearing potential.

The reviewer does not define what the risky sexual behaviors of concern are. Does the reviewer take into account that high risk sexual behavior could include sexual intercourse without recourse for pregnancy prevention? In this instance, the lack of emergency contraception as an option could conceivably be viewed as increasing the risk of high risk sexual activity.

The reviewer, particularly given the focus on teenagers, also does not take into account the following: the societal benefit based on the reduction of abortions and unwanted pregnancies as well as the societal cost of the higher morbidity associated with pregnancy at a young age to both the mother and the fetus, or more broadly, the costs to society due to parents who are not prepared for the responsibilities of child rearing.

I am unable to identify evidence in the medical literature to support the assertion that the availability of contraception directly increases high risk sexual behavior. It is however well documented that high risk sexual behavior is largely rooted in a history of child abuse, partner violence and abuse, and societal complexities of poverty and circumstances of inadequate parental involvement. Plan B nor any contraceptive can address these issues but clearly, from a public health perspective, do have a place in minimizing unplanned pregnancies and abortions resulting from these tragic circumstances. Indeed the agency's regulatory mandate is not to regulate behavior or morality but to serve the public by ensuring that safe and effective products are made available for prescriber and patient choice.

With regard to sexually transmitted infections (STIs), again, the logic is flawed and speculative. The reviewer fails to address relevant issues ranging from condom failure to drug resistance. Furthermore, from a public health perspective, there is far graver consequence to a lack of pregnancy prevention options, as evidenced by HIV fetal transmission during pregnancy, than the hypothetical concern proposed by the reviewer.

The reviewer has in effect proposed a new and unusual regulatory standard for contraceptive drug products. Based on this standard, should the agency undertake a call for data requesting that all contraceptive products, OTC and Rx, must demonstrate that use of their product does not increase high risk sexual behavior by teenagers or STIs? How the agency would credibly work with sponsors to develop a Phase 4 study to address these issues in light of privacy concerns, for the individual and legally, defies conceptualization.

As to the findings of the actual use study, it is noted that the actual use data submitted is consistent with prior Agency findings of acceptability for OTC switch determination. Specific to Agency concerns on teenagers, the findings of the study did provide a sufficient representation of subjects in the lower age groups of women of childbearing potential who are sexually active. It is noted that incorrect use was lower among subjects 16 years and younger (13.6%) than in those 17 years and older (26.4%). There was also a

higher percentage of subjects in this age group who changed to a more effective contraception (28.6% vs. 10.5%). Although a difference was found in taking of the protocol specified timing for the second dose (75.9% vs. 93%) there was no evidence that the difference in timing of the second dose adversely impacted efficacy and the reduction of the risk of pregnancy in the study population for this subgroup.

In conclusion, the sponsor has adequately demonstrated that women of reproductive potential across relevant age subgroups can use the product appropriately. The data submitted by the sponsor meets statutory requirements for safe and effective use in an OTC setting. Given that conditions of safe and effective use for this product optimally require ease of availability, there is a compelling rationale that OTC availability is imperative to better ensure proper use of the product.

I am in agreement with the overwhelmingly favorable assessment and the majority votes to agency questions by the Joint Advisory Committee (Reproductive Drug Products and the Non-Prescription Drug Products, December 2003) that adequate data has been submitted to approve Plan B for OTC marketing with product labeling modifications added to address concerns raised at this advisory committee meeting and in the Agency reviews.

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/s/

Jonca Bull
1/21/04 01:07:44 PM
MEDICAL OFFICER

Division Director Memo

NDA #: 21-045
Drug Name: Plan B (Levonorgestrel 0.75 mg) Sponsor: Women's Capital Corporation
Receipt Date: April 22, 2003
PDUFA Date: February 22, 2004
Type of Document: NDA supplement
Date: January 9, 2004

Introduction

This is the first review cycle for a new supplemental NDA for the use of Plan B as an emergency contraceptive available as a non-prescription drug product. For this application, the sponsor has submitted:

1. A label comprehension study.
2. An actual use study.
3. A literature review. Eight articles in this review assessed contraceptive behavior following advance provision of emergency contraception.
4. Safety data that included safety data from the original NDA and a review of post-marketing safety including safety reports from both domestic and foreign marketing, randomized clinical trials and published literature.
5. A new pharmacokinetic study (PK-002) in healthy female adolescents aged 13-16 years old.

Plan B was approved for prescription use on July 28, 1999 for the indication as an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Prescription directions for use indicate that to obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse and the second tablet should be taken 12 hours later. It has been demonstrated that the sooner the first pill is taken, the greater the effectiveness of the product is in preventing pregnancy. The sponsor has indicated that this has contributed to their desire to make this product available as a non-prescription product so that women will have easier access and therefore have a greater opportunity to prevent an unplanned pregnancy. Women's Capital Corporation, the applicant for the original prescription NDA, submitted an application for Plan B's switch from prescription to non-prescription status in April 2003. Barr laboratories, Inc. is now representing this NDA submission.

As the efficacy of Plan B when used as per directions has already been established, and the sponsor is not seeking new indications or a different dosage regimen, this will not be reviewed in this memo except in how OTC use may effect efficacy of the drug.

The regulatory requirements for non-prescription marketing are outlined in the Durham-Humphrey Amendment (enacted in 1951) to the Federal Food, Drug, and Cosmetic Act.

This amendment formally differentiates between prescription and non-prescription drugs and is articulated in the Code of Federal Regulations 21 CFR 310.200(b) which states:

"Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are 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 he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling".

The three key elements of the above that distinguish that a drug should be exempted from prescription-dispensing requirements are:

1. "The drugs toxicity or other potentiality for harmful effects" (acceptable safety profile, low misuse and abuse potential, reasonable therapeutic index of safety).
2. "The method of its use" (the product safe and effective when used under non-prescription conditions)
3. "The collateral measures necessary to its use" (the condition that it is used for is adequately self-recognized and self-treated by consumers with minimal health provider intervention).

The data and the studies that the sponsor has performed and submitted in this NDA are consistent with other submission that have been evaluated in the past where the switch did not involve a change in indication or dosage regimen of the product.

Conclusions/Recommendation

1. Based on my conclusions this application should be approved.
2. The sponsor has submitted adequate information to support the approval of Plan B for use as an emergency contraceptive as a non-prescription product. The label comprehension study, actual use study and review of the literature support that consumers: 1) can recognized the condition that the product should be used for and can adequately self-treat with minimal health provider intervention and 2) the product is safe and effective when used under non-prescription conditions. The safety data reviewed by HFD-580 demonstrates that Plan B has acceptable safety, a low misuse and abuse potential and reasonable therapeutic index of safety.
3. The sponsor needs to perform an adequate pharmacokinetic study in 13-16 year olds as a Phase IV commitment.
4. The sponsor needs to clearly address Plan B's mechanism of action and efficacy rates in the package insert.
5. There is also a pending Citizen Petition requesting that Plan B be considered for non-prescription status. The petition does not raise any new issues or data not already addressed in the reviews of Plan B. Should the Agency follow the OTC Division's recommendation of approval, the response to this petition, at least in regards to addressing Plan B, will be that we agree and the issue will become moot.

6. I disagree with Dr. Jin Chen's recommendation/conclusions for an "Approvable" action. I will discuss this in detail in the safety section.

Background

Drs. Chen, Lechter, Davis, Kim and Leonard-Segal have reviewed the history of the development program and have also reviewed the submitted data and this will not be restated in this memo. The history and summaries of the primary reviews were also presented at a joint session of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs on December 16, 2003. This committee meeting was held to discuss the possible non-prescription status of Plan B. My summary will review the pertinent points from the primary reviews and summarize the Committee Member votes.

Label Comprehension Study

The label comprehension study included 656 enrolled women, the majority of which enrolled from shopping malls. This study tested 11 communication objectives that were felt to be important for the safe and effective use of the product. Subjects that had not completed college received the Rapid Estimate of Adult Literacy (REALM) test so that the results of low literate subjects could be evaluated. This study was reviewed in depth by Dr. Karen Lechter, a social scientist from the Division of Surveillance, Research, and Communication Support (HFD-410) with a medical addendum review performed by Dr. Jin Chen, a medical officer from the Division of Over-The-Counter Drug Products (HFD-560).

By way of prioritizing the importance of this study in the review of this application, it is important to consider that in applications that include both a label comprehension and actual use study, the actual use of the product as determined in the Actual Use study is the basis to decide whether a concept of use is adequately conveyed. As expressed in Dr. Leonard-Segal's secondary review, the purpose of the label comprehension study in this application was to enable the sponsor to test if their label adequately relayed information that would allow proper use of the product in the Actual Use study and if not, to allow the sponsor to make changes in the label prior to initiating the Actual Use study. When label concepts demonstrate poor results, it can be either because the label language is difficult to comprehend, or because the question evaluating the concept is poorly constructed. Communication objective's for this label comprehension study that did not score in the highest ranges included:

1. Plan B is intended as a back up method and should not be used for regular contraception (67% correct).
2. The first pill should be taken as soon as possible after intercourse (85% correct).
3. The second pill should be taken 12 hours after the first pill (82% correct).
4. Plan B should not be used by women with unexplained vaginal bleeding (75% correct).

5. If severe abdominal pain develops, the user should seek medical care immediately (81% correct).

Regarding demographics differences in scoring, ages 12-16 y/o demonstrated slightly lower comprehension rates on the above compared to older age groups and, as is common in label comprehension studies, the low literacy population did not perform as well on many of the communication objectives.

Regarding the communication objectives above, the sponsor has proposed, and the agency agrees with, deleting #4 above as vaginal bleeding is not a contraindication to taking the medication. Concept #5 above is to alert women (and provide possible symptoms) that with any pregnancy, an ecoptic (tubal) placement is possible. However, data reviewed by Dr. Dan Davis (contained in the briefing document) and presented at the Advisory Committee meeting[1] indicates that ectopic pregnancy does not occur at greater frequency with this drug compared to spontaneous population rates, and therefore this medication does not warrant an ectopic pregnancy (severe abdominal pain) warning. Also, since ectopic pregnancy occurs several weeks after implantation, it would occur several weeks after use of this medication. Consumers would therefore not associate severe abdominal pain in conjunction with medication use due to the time delay and the warning as written will just be confusing. The sponsor should be congratulated that they are trying to educate women regarding ectopic pregnancy and this concept should be clarified and communicated as part of the package insert and removed from the drug facts.

In regard to #1, #2 and #3 above, the actual use study (to be discussed next) demonstrated that:

1) Routine contraception use and effective contraception use was not affected during the study.
2) Over ninety percent of subjects in the actual use study demonstrated dosing within 72 hours.
3) Over ninety percent of subjects took the 2nd pill between 6-18 hours after the 1st pill.
4) There were not any important differences across age demographics.

Therefore, concepts in the label comprehension study were either scored at a high level, or those concepts not scoring at the higher level had high levels of appropriate use during the Actual Use study.

Actual Use Study

This was a four-week, open-label, single-arm, multi-center study to evaluate self-selection and self-administration of Plan B in an OTC-like setting. This study was conducted in five family planning clinics across five states and five pharmacy stores in the State of Washington. A total of 585 subjects ages 14-44 years old were enrolled from family planning clinics (94%) and pharmacy stores (6%) in the United States. A total of

[1] NDA 21-045-proposing over-the-counter (OTC) use of Plan B (levonorgestrel)-December 16, 2003

540 enrollees took Plan B. Subjects were not given any educational intervention other than what they could obtain from the package containing the medication.

The results of the study are outlined in detail in Dr. Jin Chen's review. The results suggest that the study population:

1) correctly self-selected and use Plan B in an OTC setting.
2) demonstrated most of the incorrect use due to not taking the 2nd pill at 12 hours after the first pill (correct rate was 67.8%), however 93% took the 2nd pill between 6-18 hours after the 1st pill and studies have demonstrate that this time interval for the 2nd dose does not decrease drug effectiveness. Ninety-two percent of subjects took the 1st pill less than 72 hours after intercourse.
3) decreased "At least one sex act without contraception" from 60% (before study) to 20% (during study)
4) increased condom use from 79% (before study) to 90% (during study)
5) decreased withdrawal contraception from 28% (before study) to 10% (during study)
6) had more women switch from a "less effective" contraception method to a "more effective" contraception method compared to the converse during the four-week study
7) did not generate new safety signals
8) had similar self selection and contraceptive use across demographics
9) had similar self-selection and contraceptive use whether or not experienced with prior emergency contraception use before study

Pregnancies were confirmed in 10 participants who took Plan B with the pregnancy status of another 14 subjects unknown at the end of the study. This would equate to a pregnancy rate of 1.9%-4.5% as compared to a known baseline pregnancy rate of 8% with a single act of intercourse if a contraceptive method were not used. All confirmed pregnancies occurred in subjects 17 years old or older. There were no new safety signals that had not been demonstrated with the prescription use of this medication.

Limitations of the study are outlined in Dr. Leonard-Segal's review and for the most part are addressed by existing literature as summarized in the review of the behavioral studies. The results of the Actual Use study demonstrate that over 90% of study participants self-selected properly. Subjects did not substitute plan B for their regular method of contraception. The results were comparable across demographics and whether the user had experience with prior emergency contraception use or not before the study. These results suggest that the correct self-selection rate among OTC consumers would be high.

In regard to fulfilling the criteria for non-prescription status outlined in the Durham-Humphrey Amendment, the Actual Use study demonstrated that Plan B had a very low abuse/misuse profile, the product is safe and effective when used under non-prescription conditions and the condition that it is used for is adequately self-recognized and self-treated by consumers with minimal health provider intervention.

Relevant Advisory Committee questions and votes:

1. Does the Actual Use Study (AUS) demonstrate that consumers used the product as recommended in the proposed labeling?

Yes-27 No-1

2. Are the AUS data generalizable to the overall population of potential non-Rx users of Plan B?

Yes-27 No-1

Behavorial Studies Review

The sponsor submitted five published and three unpublished studies of varying quality that assess the effects of advance provision of emergency contraception on sexual and contraceptive behaviors. The overall summary of eight behavioral studies is presented below.

STUDY DESIGN

1. ***Study Location***: Five studies were conducted in the USA and one each was conducted in the UK, Africa and India.

2. ***Subjects:*** All subjects in the eight studies were recruited from family planning clinics (the purposes for visiting the clinics were EC consultation, post-abortion follow-up and postpartum evaluation). The age range was 15-45 years with most enrollees being around 20 years old.

3. ***Study Groups:*** Subjects were randomly (in most studies) assigned to the following 2 or 3 groups. All subjects received education regarding emergency contraception use (this is in contradistinction to the actual use study submitted by the sponsor where education was not given to the subjects enrolled in the study, thereby more closely mimicking an OTC environment).

   Advance EC Group: Subjects received in advance one course of EC pills in six studies and three courses of EC pills in two studies (one in US and one on India);

   Control Group: Subjects received EC education only (including advice on where to get and how to use EC) except for one study where EC education was not given in the control group;

   Pharmacy EC Access Group: Subjects received EC when needed from pharmacy in one US study (in California).

4. ***Sample Size:*** Number of subjects ranged from 160 to 1020 in the five United States studies and 210-1083 in three studies outside the United States.

5. ***Follow-up Period:*** Subjects were followed from 8 weeks up to 1 year after admission to the studies.

RESULTS

1. ***EC Use:*** All studies suggest that the advance EC provision increase EC use. This supported the hypothesis of the studies that easier access would translate into increased use. In those studies where it was measured, advance EC provision lead to a shorter time interval between intercourse and use of the medication.

2. ***Unprotected Sex:*** In these studies, unprotected sex was defined as lack of use of a contraceptive. All studies demonstrated that compared to baseline, the advance EC group and control group had decreased frequency of unprotected sex. In some studies, the decrease in unprotected sex was greater in the control group.

3. ***Condom Use:*** One US study (sponsored by Women's Capital Corporation) suggests that the advance, pharmacy and standard EC access groups plus EC education had an increase in more effective methods of contraception with a corresponding decrease in condom use. The other 6 studies either demonstrated no significant decrease in condom use with advance EC provision or in education alone (control groups) or demonstrated that "used condoms every time" increased in treatment and control groups when compared to baseline.

4. ***Consistent Use of Regular Contraception:*** Most of the studies demonstrate that women in both the treatment and control groups increase their use of a regular contraception compared to baseline. One US study suggest that women with advance EC access are more likely to use less-effective contraception (although they had less unprotected sex compared to baseline and increased "condom use every time" from 12% at baseline to 47% at study completion).

5. ***STD Acquisition:*** Two studies[2] measured STD acquisition and demonstrated that the acquisition of STD rates were equivalent between the control group and the advance provision groups. These studies were conducted over 6 months for one and 8 months for the other. In one of the studies, subjects received three courses in advance.

These studies were not conducted in a simulated OTC setting. However, several of the studies would have recruited a similar subject population as that used in the actual use study. Also subjects received advanced provisions to have at home for use as necessary which may simulate how consumers would use the products in an OTC environment. The main difference in design would be that subjects in the literature review would have received education compared to the subjects in the actual use study and would have received an advanced provision of EC.

The populations recruited for each study represented a different subset of general population and was heterogeneous among all these studies. This diversity is desirable

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[2] UCSF Study #H9738-18501-02, Provision of Emergency Contraception to Women (manuscript). Sponsored by Women's Capital Corporation.
Gold et. al. "The effects of advance provision of emergency contraception on adolescent women's sexual and contraceptive behaviors (in publication)".

reflecting many subgroups and capturing the many aspects of an OTC population. The similarity of results is also reassuring in that the different subsets tend to exhibit the same behavioral trends.

Conclusions that can be made from the review of these studies include:

1. The advance access of emergency contraception did not increase the likelihood of unprotected sex in women populations who visited family planning clinics. The study duration's ranged from 4-12 months in follow-up. The results provide supportive evidence to resolve whether consistent use of routine contraception persist greater than the one month of observation in the actual use study data submitted by the sponsors.

2. The studies did not simulate an OTC setting although some of the studies have recruited similar subject populations as those enrolled in the actual use study and having an advanced provision would simulate the access that consumers would enjoy if the product were available OTC.

3. Most of the studies demonstrate that women in both the treatment and control groups increase their use of a routine contraception (less unprotected sex) compared to baseline as demonstrated in the sponsor's actual use study.

4. Most of the studies either demonstrated no significant decrease in condom use with advance EC provision and control groups or demonstrated that "used condoms every time" increased in treatment and control groups when compared to baseline

These studies support the Actual Use study's demonstration of low misuse/abuse of emergency contraceptives and fulfill the Durham-Humphrey Amendment requirement that there are limited "other potentiality for harmful effects" (i.e. harmful changes in contraception behavior with ready access). These studies also demonstrate that women with advanced provisions took the first pill sooner than those women that had to obtain the pill from a clinic or by prescription.

Relevant Advisory Committee questions and votes:

3. Based on the AUS and literature review, is there evidence that non-Rx availability of Plan B leads to substitution of emergency contraception for the regular use of other methods of contraception?
   Yes-0 No-28

Safety Review

Levonorgestrel has been available as an oral contraceptive agent for over 20 years and has a well recognized safety profile. Plan B, levonorgestrel used as an emergency contraceptive agent, had over 2.4 million uses since it's approval with over 6 million uses worldwide. Levonorgestrel for emergency contraception is available in 101 countries and is available without a prescription (mainly behind the counter) in 33 of the 101 countries. There have been no reported deaths using this product as an emergency

contraceptive. The search of the Adverse Event Reporting System (AERS) and United Kingdom (UK) databases identified 116 unduplicated cases, most of which involved non-serious expected events. There were 28 cases of ectopic pregnancy, 10 cases of convulsions, 10 cases of hypersensitivity and 8 cases of pregnancy/fetal effects. As per Dr. Davis's review, it is currently felt that Plan B is not associated with ectopic pregnancy or fetal effects therefore these reports would represent the spontaneous cases expected in a population. None of the cases of hypersensitivity reaction required hospitalization. Studies have used 8 levonorgestrel 0.75 mg tablets in a single menstrual cycle and up to four 0.75 mg tablets in a single day. Foreign studies have found that using emergency contraception more than four times a year is uncommon and one study found that less than one percent of emergency contraception use occurred more than three times a year[3]. Plan B will not disrupt an established pregnancy (as defined by HHS regulations) and the only contraindication to Plan B use is hypersensitivity to the product.

To summarize, Plan B has an exceptional safety profile and fulfills the safety aspect of the Durham-Humphrey Amendment for non-prescription status.

I do not agree with Dr. Jin Chen's conclusions for an "approvable" action, which he states is because of insufficient data assessing "risky (or unsafe) sexual behaviors" associated with Plan B, for the following reasons:

1. Plan B is to be used as an emergency contraception agent. Studies have demonstrated that when users have ready access, they seldom use emergency contraception more than three times per year.

2. The agency has never required OTC contraceptives for regular use (emphasizing that they will be used regularly as opposed to emergency contraception which the majority of the population will use less than three times a year) to demonstrate whether they have an effect on sexually transmitted disease rates or "risky (or unsafe) sexual behaviors". This would be placing a new regulatory burden on Plan B, an agent that would be associated with less "sexual exposure" than regular contraceptives. We would therefore be placing greater requirements on an agent that has less risk than existing products that do not have that regulatory requirement.

3. Two studies from the literature review (referenced earlier) demonstrated no difference in sexually transmitted disease rates between groups that had access to Plan B as it presently exists and advanced provisions (either one or three provisions depending on the study). These studies had durations of six and eight months, which is more than adequate to assess if sexual transmitted disease rates would be affected. These studies included subjects 15-24 years old and 15-20 years old.

4. The overwhelming preponderance of evidence including data from the sponsor's actual use study and the review of the literature demonstrate that emergency

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[3] Rowlands S, Lawrenson R. Repeated use of hormonal emergency contraception by younger women in the UK. Br J Fam Plan 2000;26:138-43.

contraception had no adverse effect on users contraceptive methods. This included no adverse effects in adolescent age groups in those studies where demographic data was provided. Given this information, it is unlikely that Plan B would increase promiscuity and "high-risk sex" of users.

5. Plan B if approved for OTC use, like all OTC contraceptives, will carry labeling detailing the product's lack of protection regarding the transmission of sexually transmitted diseases. The package insert may actually serve as an education to consumers ignorant of risks and therefore serve an important public health initiative.

Relevant Advisory Committee questions and vote:

4. Do the data demonstrate that Plan B is safe for use in the non-prescription setting?
   Yes-28 No-0

Biopharmaceutical Study

Please refer to Dr. Myong-Jin Kim's (Office of Clinical Pharmacology and biopharmaceutics Review/Division of Pharmaceutical Evaluation II) detailed review. As part of the supplemental submission, the sponsor conducted study PK-002, a biopharmaceutical study evaluating a single dose of levonorgestrel (LNG) 0.75 mg in 22 females aged 12 to 16. The sponsor also resubmitted Study PK-001, a PK study conducted in 16 healthy females aged 18 to 45 years old, for comparison PK data.

The literature indicates that intra-individual variability (23-80%) and inter-individual variability (2- to 4-fold) is marked following LNG oral administration. The source of this variability is unknown. The effective dose range and therapeutic range of emergency contraception has not been established. The widely used emergency contraception regimen with estradiol and LNG was empirically established[4]. The literature indicates that LNG is completely absorbed after oral administration and is not subject to first pass metabolism. A food effect has not been studied. An effect of race has not been studied other than higher pregnancy rates have been noted in Chinese population studies with both Plan B and the Yuzpe regimen. Drug-drug interactions have not been studied.

The results of the cross-study comparisons demonstrated that the systemic exposure to LNG was lower in adolescent females than adult females:

1. Cmax mean ratio of adolescents/adults=0.53 (90% CI of 0.41, 0.68).
2. $AUC_{0-\infty}$ mean ratio of 0.77 (90% CI of 0.61, 0.98).

Summary table of PK data from NDA 21-045[5]

	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng*hr/mL)
Healthy adult female	14.1 ± 7.7	1.6 ± 0.7	24.4 ± 5.3	123.1 ± 50.1

[4] Yuzpee AA et al 1974, Yuzpee AA et al 1977.
[5] Taken from Dr. Kim's Biopharmaceutics Review

subjects (n=16) Study PK-001				
Healthy adolescent female subjects (n=22) Study PK-002	7.5 ± 3.8	1.5 ± 0.7	22.2 ± 6.8	94.5 ± 45.4

It is interesting to note, as presented in Dr. Kim's review, that He et al conducted a randomized single dose crossover relative bioavailability study of two marketed formulations of 0.75 mg LNG (Hungarian and Chinese formulations) in 10 healthy Chinese adult females. Blood samples were obtained up to 24 hours post-dose and the plasma samples were analyzed for LNG by radioimmunoassay. Both formulations were tested in a published clinical trial and shown to have a similar method failure rate of 1.1 % per treated cycle. Compare to a Postinor tablet (Hungarian formulation, similar to Plan B formulation), a Chinese pill showed lower relative bioavailability (about 28% lower for AUC_{0-24} and $AUC_{0-\infty}$ and 100 % lower for C_{max}). The investigators concluded that despite the fact that in the clinical trial no significant differences were observed between the two LNG formulations in terms of contraceptive efficacy, there was a marked difference between them in their pharmacokinetics (He C et al 1990, Contraception 41:557-67).

NDA 21-045[6]

	Hungarian Formulation LNG 0.75 mg tablet (Postinor)	Chinese Formulation LNG 0.75 mg tablet
*Cmax (ng/mL)	11.2 ± 3.4 (8.1 – 18.4)	5.9 ± 1.7 (3.4 – 8.2)
*AUC_{0-24} (ng*hr/mL)	92.2 ± 34.3 (54.0 – 152)	64.4 ± 21.9 (33.1 – 99.1)
$AUC_{0-\infty}$ (ng*hr/mL)	124.0 ± 42.8 (66.8 – 176.6)	92.3 ± 28.8 (42.7 – 121.8)

* denotes statistically significant difference between Postinor and the Chinese pill.

The following table compares the two studies.

NDA 21-045[7]

Study Design Comparison		
Study	**PK-001**	**PK-002**
Subjects	Healthy adult females (n=16)	Healthy adolescent females (n=22)
Study Design	A prospective, single-period, single-center, open-label, single dose study	A prospective, single-period, single-center, open-label, single dose PK study
Age (yrs)	28 ± 9 (19 – 44)	15 ± 1 (13 – 16)
Weight (kg)	65.3 ± 9.9 (51 – 79.5)	59.5 ± 9.4 (41.8 – 77.3)
Race	9 White (56%), 6 Black (38%), 1 Asian/Pacific Islander (6%)	12 Black (54%), 5 Multiracial (23%), 4 Latina (18%), 1 Asian (5%)
Fasting	Overnight 8 hr fasting pre-dose, 4 hr fasting post-dose	4 hr fasting pre-dose, 3 hr fasting post-dose
Dosing time	8 AM	Between 4 PM and 7 PM
Blood draw	72 hrs post-dose, 19 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, **6**, 8, 10, 12, **15**, **18**, 24, **30**, **36**, 48, 72 hr)	72 hrs post-dose, 14 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, 72 hr)

[6] Taken from Dr. Kim's biopharmaceutics Review
[7] Taken from Dr. Kim's biopharmaceutics review

It is noted that the studies had differences in ethnic distribution, average weight of subjects, collection times (AM vs. PM), duration of fasting and dosing times.

Also noted in the table below is that the Caucasian population (56%) of Study PK-001 had greater Cmax and AUC values than other ethnic groups (there were no Caucasian subjects in study PK-002).

NDA 21-045: Comparison of PK-001 and PK-002 ethnic demographics[8]

	PK-001 (Adult females)			PK-002 (Adolescent females)				Adult females	Adult females	Adult females
	Caucasian (U.S.) (n=9)	Black (U.S) (n=6)	Asian (U.S.) (n=1)	Black (U.S.) (n=12)	Multiracial (U.S.) (n=5)	Latina (U.S.) (n=4)	Asian (U.S.) (n=1)	Landgren et al 1989 (Sweden) (n=10)	He et al 1990 (China) (n=10)	Shi et al 1988 (China) (n=6)
C_{max} (ng/mL)	15.9	12.2	9.4	7.0	9.0	7.6	5.5	16.0	11.2	9.0
T_{max} (hr)	1.8	1.4	1.3	1.4	2.4	1.6	1.3	------	1.9	2-4
$AUC_{0-\infty}$ (ng*hr/mL)	131.5	120.7	62.5	84.0	114.4	80.2	61.1	------	124	116
$T_{1/2}$ (hr)	24.6	24.5	22.9	23.2	17.9	25.9	18	14.5	13.3	8.9
Assay	GC/MS/MS							Radioimmunoassay		

Landgren et al 1989 Contraception 39:275-89
He C et al 1990 Contraception 41:557-67
Shi et al 1988 Contraception 37:359-69

Since the effects of food, ethnic background, timing of sampling and body weight regarding the biopharmaceutical properties of LNG are not known, and previous studies have demonstrated intra-individual variability (23-80%) and inter-individual variability (2- to 4-fold), I think it is very difficult to make cross study PK comparisons and draw useful and reasonable conclusions, particularly when there are a great number of baseline differences as exist in this comparison. As such, I think it is justified that the sponsor should complete another study that is designed as a single study to answer whether there are possible exposure differences based on age categories. What data there is from this NDA package and the literature (and it is very little data) does not indicate that there are efficacy differences of Plan B based on age. It is also somewhat reassuring that the two different formulations of LNG discussed in the He et al study above gave different exposures (very similar to the cross-study comparisons of the sponsor's two different PK studies), but had similar efficacy profiles. As such I feel that the sponsor could complete this study as a Phase IV commitment.

Conclusions

As discussed above, Plan B fulfills the Durham-Humphrey Amendment for exemption from prescription dispensing requirements. Plan B has an acceptable safety profile, low misuse and abuse potential and a reasonable therapeutic index of safety. The condition it is used for can be self-recognized, the benefits outweigh the risks and when used under non-prescription conditions the product is safe and effective.

[8] Taken from Dr. Kim's biopharmaceutics review

Further thoughts regarding the benefit of Plan B include that 1997 rates for teen pregnancy rates were 79.8 per 1000.[9] During 1997, the teen abortion rates were 27.5 per 1000. Plan B has the potential to decrease unwanted pregnancies by 70%.[10] It follows that if Plan B decreased the number of unwanted pregnancies, the number of abortions should also decrease. The potential benefit of this for teen physical and mental health far outweigh the minor risks associated with Plan B use.

When examining pregnancy in females of all ages ranges, there are nearly three million unintended pregnancies each year in the united States with about half ending in abortion.[11] If Plan B were able to decrease these abortion rates by a significant percentage, the impact to women's health would be enormous and clearly illustrates the benefit of OTC approval of this product.

Relevant Advisory Committee questions and votes:

5. Are the plans for introduction of Plan B into the non-Rx setting with respect to consumer access and safe use? If no, what other options would you recommend?
   Yes-22 No-5 Abstain-1

6. Do you recommend Plan B be switched from prescription to non-prescription status?
   Yes-23 No-4 (one Member left before the vote)

Curtis J. Rosebraugh, MD, MPH

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HFD-560 /frazier /cothran/solbeck/chen/leonard segal/ganley
HFD-580/griebel/beitz

[9] www.advocatesforyouth.org. accessed 1/15/04
[10] Trussell J et. al. Fam Plann Perspect. 1992b;24;269-273.
[11] FDA Advisory Committee Briefing Document, 16 December 2003.

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/s/

Curtis Rosebraugh
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MEDICAL OFFICER

Division Director Memo-Addendum-Table Correction

NDA #: 21-045
Drug Name: Plan B (Levonorgestrel 0.75 mg)
Sponsor: Women's Capital Corporation
Receipt Date: April 22, 2003
PDUFA Date: February 22, 2004
Type of Document: NDA supplement
Date: April 13, 2004

Correction

There is an error in Table 2, page 6, from the Division Director memo-Addendum. This is how the table appears in the review:

Table 2. Timing of Dose as a Function of Age or History of Previous ECP Use

	Age (years)		Prior ECP Use	
	≤16 N=22	≥17 N=518	Previous Users N=213	First Time Users N=327
Timing for the first pill after sexual intercourse				
>72 hours	0	2 (0.4%)	2 (0.5%)	2 (0.6%)
Interval between the second and first pill				
At 12 hours	18 (82%)	369 (71%)	146 (69%)	241 (74%)

This is the corrected table and how it should appear (changes highlighted):

Table 2. Timing of Dose as a Function of Age or History of Previous ECP Use

	Age (years)		Prior ECP Use	
	≤16 N=22	≥17 N=518	Previous Users N=213	First Time Users N=327
Timing for the first pill after sexual intercourse				
>72 hours	0	2 (0.4%)	4 (2%)	6 (2%)
Interval between the second and first pill				
At 12 hours	18 (82%)	369 (71%)	146 (69%)	241 (74%)

Curtis J. Rosebraugh, MD, MPH

cc: orig.

HFD-560 /frazier /cothran/solbeck/chen/leonard segal/ganley
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Curtis Rosebraugh
4/13/04 10:23:17 AM
MEDICAL OFFICER

OTC Medical Team Leader Review

NDA 21-045
Drug Name: Plan B®
Sponsor: Barr Research, Inc.
Pharmacologic Category: Synthetic Progestin
Proposed Indication: Emergency Contraception
Dosage Form/Route of Administration: Tablet / Oral
Submission Date: April 16, 2003
Review Date: January 6, 2004
Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

Recommendation:

- The results of the Label Comprehension Study, Actual Use Study and Behavioral Studies support the approval of Plan B for OTC availability as an emergency contraceptive drug. This body of clinical data does not suggest the need for Phase IV studies.
- On the package label, it is reasonable to include information on the Plan B mechanism of action. It is also reasonable to provide information on effectiveness as it relates to the timing of the first dose following unprotected sexual intercourse. Alternatively, information on these two topics could be included in a package insert.
- A final decision on approval and the need for Phase IV studies must take into account the safety data and pharmacokinetics data reviewed by HFD-580, the studies reviewed by HFD-560, and the compliance of the proposed label with the Drug Facts labeling regulations.

Discussion:
The Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act draws a distinction between prescription and non-prescription drugs. This distinction is stated in the Code of Federal Regulations 21 CFR 310.200(b):

"Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are 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 he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling."

Thus, a non-prescription drug should have an acceptable safety profile based upon prior marketing experience, low abuse and misuse potential, and a reasonable therapeutic index of safety. Also, consumers should be able self-diagnose the condition for which the drug is indicated, and should be able to self-administer the drug properly and safely based upon the proposed product label.

To support their NDA to switch Plan B from a prescription to a non-prescription medication, the sponsor submitted:

- A labeling comprehension study
- An actual use study
- Eight articles (one funded by the sponsor) from the medical literature that assessed contraceptive behavior following advance provision of emergency contraception
- Comprehensive post-marketing safety data
- A pharmacokinetics (PK) study

Dr. Jin Chen, a medical officer from the Division of OTC Drug Products (DOTCDP), and Dr. Karen Lechter, a social scientist from the Division of Surveillance, Research, and Communication Support (HFD-410), reviewed the Label Comprehension Study. In addition, Dr. Chen reviewed the Actual Use Study and the eight studies (five published, two unpublished, one abstract) that assessed the influence of advance provision of emergency contraception on contraceptive behavior. The safety data and PK data were reviewed by Dr. Daniel Davis in HFD-580 and a co-located pharmacokinetics reviewer, respectively, and will not be discussed in this HFD-560 Medical Team Leader review. Interdisciplinary scientists in HFD-560 are reviewing the proposed OTC label for compliance with the Drug Facts Label regulations.

In his review, Dr. Chen expresses concerns about the possibility that consumer sexual behavior might become "risky" and increase the spread of sexually transmitted infections (STI) if emergency contraception were available OTC. This concern is simply speculative. There is nothing in the Actual Use Study data or the data from the Behavioral Studies that suggests that women would become more promiscuous, use less adequate pregnancy prevention methods or wantonly give up condom use if they had OTC access to Plan B; a large number, approximately 4,500, of women participated in these studies. The Agency did not request that the sponsor provide data on STIs as part of the NDA for this prescription to OTC switch. As with Plan B, other contraceptives for women have not been shown to protect against contracting STIs (oral contraceptives, intrauterine devices, patches, OTC spermicides, etc.), and are labeled as such, but they do prevent unwanted pregnancies. The present state of our knowledge is that only latex condoms can decrease the transmission of STIs, albeit not perfectly[1]. Thus, a woman using a contraceptive can only be certain of reducing her risk of acquiring an STI if her partner wears a latex condom or if she chooses to abstain from having sex.

When considering "risky" behavior, it is true that one risk not addressed by any of the studies, was the relative risk of preventing an unwanted pregnancy by using Plan B, versus the health risks, both physical and psychological, associated with carrying that pregnancy to term or associated with terminating the pregnancy. Since maternal death is a well-recognized complication of pregnancy, one could reason that it is riskier behavior to be pregnant, than not to be pregnant.

As a composite, the studies considered in this review form a body of evidence that demonstrates that, after reading the package label, women and teenage girls make a

[1] Fact Sheet for Public Health Personnel: Male Latex Condoms and Sexually Transmitted Diseases. Centers for Disease Control and Prevention, January 24, 2003.

correct decision about when it is appropriate for them to use Plan B. Compliance with timing of Plan B dosing is good. Results were good across the demographics. Providing emergency contraceptives in advance of need does not result in medication abuse or misuse and does not lure women away from regular contraception methods. No new safety signals emerged. If Dr. Davis' review (HFD 580) confirms that the product has a history of widespread safe use over years in the prescription arena, then this product meets the criteria set forth in the Durham-Humphrey Act for a non-prescription drug.

Label Comprehension Study

The function of the label comprehension study in this application was to enable the sponsor to craft a label that communicated well as the instrument for the Actual Use Study. Label comprehension studies can demonstrate poor results either because the label language is difficult to comprehend, or because the questionnaire is poorly constructed. Although consumers may demonstrate different levels of comprehension for different communication objectives, ultimately, proper actual use of the product is the goal. Thus, the label comprehension study, unlike the actual use study, is not pivotal. The label comprehension study in NDA 21-045 suffered from methodology problems with regard to the questionnaire and the scoring methodology. (For details see Dr. Lechter's review.) As is common in label comprehension studies, the low literacy population did not perform as well on many of the communication objectives as the normal literacy population. The differences were most apparent for the question as to whether Plan B should be used as regular birth control. The sponsor made minor modifications in the label before testing it in Actual Use (See reviews by Dr. Lechter and Dr. Chen).

Actual Use Study

Dr. Chen provided a comprehensive look at the methodology and results of this study in his review. My review will concentrate on the salient aspects of the study.

Recognizing the recruitment difficulties that the sponsor would encounter gathering a patient population interested in using Plan B from a public environment like a shopping mall, the Agency agreed that the sponsor could recruit from pharmacies and family planning clinics. Participants learned about Plan B only by reading the product label; investigators did not provide other education about that product or other forms of contraception. Participants made a self-selection decision after reading the product label.

Ninety-four percent of the enrolled population (585 females) came from clinics and 6% from pharmacies. The population was diverse in age (in that teenagers were among the participants), race, geography, and education level.

The results demonstrated that 540 enrollees took Plan B and 95% of them did so for correct reasons. Another 3% did not provide specific reasons why they self-selected. The remaining nine who erred in self-selection did so because of unexplained vaginal bleeding (6), pregnancy (1) or took Plan B before having unprotected sexual intercourse (2).

Ninety-two percent timed the first pill correctly, and 93% took the second pill between 6 – 18 hours following the first pill. Seventy-two percent took the second pill exactly 12 hours following the first.

Those who took Plan B gravitated towards more effective methods of contraception after enrollment than they had used during the month prior to enrollment. Ten subjects of the 585 who enrolled requested Plan B more than once during the 3-month enrollment period.

Pregnancies were confirmed in 10 participants who took Plan B and the pregnancy status of another 14 subjects was unknown at the end of the study. The actual use study did not reveal new safety signals for Plan B.

The aforementioned study results were not significantly different among the demographic subgroups. The limitations of the actual use study were:

- 1 month follow-up
- The relatively small number of teenagers enrolled under the age of 17 years
- The need to re-enroll to purchase another box of Plan B
- Use of education level in lieu of literacy testing
- Enrollment of participants who, in a sense, "pre" self-selected because they came to the clinic seeking emergency contraception

My assessment is that this actual use study strongly supports a conclusion that women used Plan B for the right reasons and were able to demonstrate good compliance with the timing of the pills. We do not have data that shows that the compliance with timing demonstrated by women in this study is better or worse than with use of Plan B when prescribed by a physician. The data supports a move toward more effective contraception by study participants. The data did not suggest women would abuse Plan B or increase the type of behavior that led to their interest in using Plan B in this study. Although women were somewhat inconvenienced by the need to re-enroll to purchase another box of Plan B, they still could have taken advantage of this opportunity to obtain more; few did. Data from efficacy studies support that efficacy decreases as time between intercourse and the first pill elapses. It is reasonable to think that with OTC access, a woman could purchase and thus take Plan B in closer proximity to the sexual act compared to if she needed to see a health care provider before obtaining the medication. The actual use study supports the safety of Plan B.

Eight Advance Provision Behavioral Studies

Refer to Dr. Chen's review for details about the individual studies. When viewed as a composite, the 8 advance provision studies enrolled females from 15 – 45 years of age with sample sizes ranging from 160 – 1083 participants. Since these studies enrolled teenagers, they complemented the actual use study. Five of the studies took place domestically and 3 were foreign studies. Six studies randomized the participants; two did not. Participants were either in an advance provision group or could obtain emergency contraception by prescription as a member of the control group. Participants from both

groups received education about emergency contraception from the clinics where they enrolled, unlike participants in the Actual Use Study. The Advance Provision Studies provided follow-up data over a longer period of time (8 weeks to 1 year) than the 1-month Actual Use Study, and provided information about how consumers who received up to 3 courses of emergency contraceptive in advance of need used the product. The majority of the participants in these studies used the Yuzpe regimen of emergency contraception, but some used Plan B.

It is important to remember that women who need emergency contraception for pregnancy prevention have already experienced risk, either unintentionally because a condom broke, inadvertently because they forgot to take their routine birth control pills, or because no contraception was used. In his review, Dr. Chen expresses concern that if Plan B were sold OTC that it would result in risky sexual behavior among women. This concern is not supported by the data. Five of the behavior studies demonstrated a decrease in unprotected sex in the advance provision and comparison groups. Three of the studies demonstrated no increase in unprotected sex. One study, Raine et al, demonstrated that condom use increased. Two studies, Jackson et al, and Beltzer demonstrated no decrease in routine contraception and condom use. The UCSF Study and the Glasier and Baird Study (from Scotland) demonstrated that oral contraceptive use increased in the advance provision and comparator groups and condom use decreased in the advance provision and comparator groups. Thus women in these studies went from less effective to more effective methods of contraception. This implies, that women were concerned about having an unwanted pregnancy. Clearly, those who chose to use more effective forms of contraception (not to continue to use emergency contraception) did not need to continue to use condoms for pregnancy prevention and those in marriages or monogamous relationships (with a low risk for contracting STIs) did not need to continue condom use to protect against contracting STIs. The study by Gold did not demonstrate a decrease in condom use. The study by Lovvorn, conducted in Ghana, enrolled women who used spermicides and did not have access to other forms of contraception; this study did not assess condom use. The Ellertson study, in India, enrolled women who used condoms as a primary method of contraception and 98% of women in the advance provision arm indicated that they would not change their use of condoms. Twenty-three percent of participants in each arm of the Ellertson study began to use a more effective form of birth control, however.

The important messages from the behavioral studies, were:

- Participants did not appear to supplant emergency contraception for their routine contraception. When viewed en mass, the data indicated that advance provision of EC did not result in a switch to less effective contraception, that in many cases women began to use a more effective form of pregnancy control than in the past.
- The studies that demonstrated a decrease in condom use also demonstrated an increase in use of more effective pregnancy prevention methods (oral contraceptives).
- The incidence of unprotected sexual intercourse did not increase.
- Women who received the advance provision of emergency contraception were more likely to use it.

Plan B Label

The label used in the Actual Use Study was associated with good results. This indicates that the label was informative to women and teenagers who participated in the study. At the Advisory Committee Meeting some members promoted the inclusion of a description of the Plan B mechanism of action on the label. Comments were made about the potential value of including label information on the relative effectiveness of taking the first pill within 24, 48 and 72 hours of unprotected sexual intercourse. Neither of these ideas is unreasonable and they should be explored. This information could be provided in a package insert if it is too copious to fit on the package label itself.

_____

Andrea Leonard-Segal, M.D., M.S.
Medical Team Leader
HFD-560

Concurrence:

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/s/

Andrea Segal
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MEDICAL OFFICER

Curtis Rosebraugh
1/20/04 08:53:22 AM
MEDICAL OFFICER
I concur with this review

Addendum to OTC Medical Team Leader Review

sNDA 21-045
Drug Name: Plan B®
Sponsor: Barr Research, Inc.
Pharmacologic Category: Synthetic Progestin
Proposed Indication: Emergency Contraception
Dosage Form/Route of Administration: Tablet / Oral
Submission Date: February 6, 2004 (Serial No. 119)
Review Date: March 5, 2004
Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

Discussion/Recommendation:
At the request of the Agency, the sponsor submitted a reanalysis of data on teenage use of Plan B from the Actual Use Study. The actual use data is predictive that teenagers 14 – 17 years of age would use OTC Plan B no less properly than those 18-44 years of age. This reanalysis lends further support to my view that the application to switch Plan B from prescription to over-the-counter marketing should be approved.

My recommendation remains unchanged and is in disagreement with the recommendation of Dr. Jin Chen (the HFD-560 primary reviewer) in his March 3, 2004 addendum to his Plan B primary review.

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Andrea Segal
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