

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-045/S011

ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS



**SECTION 11: PATENT INFORMATION ON ANY PATENT
WHICH CLAIMS THE DRUG**

In conformity with the provisions of the last paragraph of subsection §505(b)(1) of the Act (21 U.S.C. §355(b)(1)), the applicant states that as of the time of submission of this application, there is no patent which claims the drug that is the subject of this application, or which claims a method of using such drug, with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner were to engage in the manufacture, use, or sale of the drug. If, after the filing of this application, and before its approval, a patent is issued which claims the drug, or a method of using such drug, the applicant will amend the application to include the information required by the first sentence of subsection §505(b)(1) of the Act (21 U.S.C. §355(b)(1)).

EXCLUSIVITY SUMMARY

NDA # 21-045

SUPPL # SE6-011

HFD # 580

Trade Name Plan B

Generic Name levonorgestrel

Applicant Name Duramed Research Pharmaceuticals

Approval Date, If Known August 24, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-668 Nordette 21

NDA# 18-782 Nordette 28

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation 1 Study #9727 Plan B OTC Actual Use Study
Investigation 2 Study #9728 Plan B OTC Label Comprehension

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation 1 Study #9727 Plan B OTC Actual Use Study
Investigation 2 Study #9728 Plan B OTC Label Comprehension

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 45,796 YES ! NO
! Explain:

Investigation #2
IND # 45,796 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Jennifer Mercier
Title: Chief, Project Management Staff
Date: 8-23-06

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Jennifer L. Mercier
8/24/2006 09:24:06 AM

WOMEN'S
CAPITAL
CORPORATION



Plan B[®]

(levonorgestrel) tablets, 0.75 mg

Supplemental New Drug Application

Request for Switch to OTC

Debarment Certification

June 2003

Supplement to NDA 21-045

DEBARMENT CERTIFICATION

In accordance with the provisions of Section 306(k) of the Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §336, the applicant certifies that no services of any person debarred under Sections 306(a) or (b) of the Act were or will be used in connection with the application for a switch of Plan B[®] (levonorgestrel) tablets, 0.75 mg, from prescription status to OTC status.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-045 Supplement Type (e.g. SE5): SE6 Supplement Number: 011

Stamp Date: April 22, 2003 Original submission

Action Date: May 6, 2004

HFD 580 Trade and generic names/dosage form: Plan B[®] (levonorgestrel) Tablets

Applicant: Duramed Research

Therapeutic Class: 3S

Indication(s) previously approved:
Emergency Contraception

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Emergency contraception

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other:

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min <u> </u>	kg <u> </u>	mo. <u> </u>	yr. <u> </u>	Tanner Stage <u> </u>
Max <u> </u>	kg <u> </u>	mo. <u> </u>	yr. <u> </u>	Tanner Stage <u> </u>

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study

- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff

NDA 21-045/S-011

Page 3

HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA21-860
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Jennifer L. Mercier
8/24/2006 09:19:52 AM

MEMORANDUM

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

DATE: August 23, 2006

TO: NDA 21-045/S-011 File

FROM: Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products

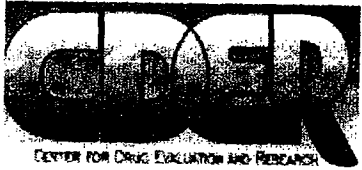
SUBJECT: NDA 21-045/S-011, Plan B (levonorgestrel) Tablets
Labeling for Physician Package Insert for prescription product

The applicant resubmitted labeling for their OTC and prescription products on August 23, 2006. The physician package insert for the prescription product is identical to that submitted on August 17, 2006. Therefore, further review of the physician package insert for the prescription product submitted on August 23, 2006 is not warranted. The reviews conducted by Drs. Davis (dated August 22, 2006) and Beitz (dated August 22, 2006) are not affected by the August 23, 2006 submission.

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/s/

Jennifer L. Mercier
8/23/2006 12:14:40 PM
CSO



ONP Drug Labeling Review

Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Date: August 23, 2006

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Duramed Pharmaceuticals, Inc.

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: August 23, 2006

Reviewer: Arlene Solbeck

Project Manager: Leah Christl

Background

- Following a July 31, 2006 letter issued by Acting FDA Commissioner von Eschenbach to Duramed Research, Inc., FDA held a meeting with the sponsor on August 8, 2006 to discuss moving forward with Plan B as an over-the-counter (OTC) drug for women 18 years of age and older. Plan B will remain R_x for under age 18.
- On 8/08/06 and 8/09/06, FDA received copies via email from the sponsor of the last version of the Plan B labeling that was reviewed by FDA (inner carton, outer carton, consumer information leaflet, and picture of the "booklet") that were submitted to the NDA on 1/14/05, 1/18/05, and 1/19/05.

- FDA made recommendations to the above referenced versions of the labeling and relayed those recommendations to the sponsor on August 10, 2006.
- Duramed responded to FDA's recommendations on August 17, 2006. Duramed submitted outer carton labeling, inner carton labeling, and the consumer information leaflet for review. Duramed submitted an amended response to address the requirement for child resistant packaging on August 18, 2006.
- FDA conveyed to the sponsor on August 22, 2006 via phone that on page 12 of the consumer information leaflet under directions for use, the second sentence did not end with a period and that Duramed should add a period after the words "healthcare professional".
- Duramed is responding to FDA's recommendations in the submission of August 23, 2006. Duramed submitted outer carton labeling, inner carton labeling, and the consumer information leaflet. The outer carton labeling and inner carton labeling are identical to those submitted August 17, 2006 and the recommendations in the August 18, 2006 review have not changed. The consumer information leaflet submitted August 23, 2006 was amended to include the recommendation conveyed August 22, 2006.
- FDA is responding to the August 23, 2006 submission in this label review. The subject of this review is only the consumer information leaflet.

I. Reviewer's Comments

Consumer Information Leaflet

FDA's August 22, 2006 phone call to Duramed conveyed:

On page 12 under directions for use, the second sentence does not end with a period and Duramed should add a period after the words "healthcare professional".

Sponsor's Response: Sponsor made the change and it is acceptable.

II. Reviewer's Recommendations

The consumer information leaflet submitted August 23, 2006 is acceptable.

The outer carton labeling and inner carton labeling are identical to those submitted August 17, 2006 and the recommendations in the August 18, 2006 review have not changed.

Arlene Solbeck 8/23/06

Arlene Solbeck, MS
IDS/Biologist
Division of Nonprescription
Regulation Development

Helen Cothran 8/23/06

Helen Cothran, BS
IDS/Team Leader
Division of Nonprescription
Regulation Development

NDA 21-405

HFD-580: Davis/Monroe/Mercier/Shames

HFD-560: Division File

HFD-560: Ganley/Segal/Solbeck/Cothran/Feibus/Christl

DOCID: PlanBLabel8_23_06.doc

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from this document

Reason:

_____ b(2) 'low'

 X b(4) CCI

_____ b(4) TS

_____ b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

22 pages proposed labeling



MEMORANDUM

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

DATE: August 22, 2006

TO: Charley Ganley, MD, Director
Office of Nonprescription Products

THROUGH: Ralph Lillie, RPh, MPH, Deputy Director (Acting for)
Gerald Dal Pan, MD, MHS, Director
Office of Surveillance and Epidemiology (OSE)

FROM: OSE Plan B CARE Program Review Team

DRUG: Plan B (levonorgestrel) tablets, 0.75mg

NDA #: 21-045/S011

SPONSOR: Duramed Research Inc.

SUBJECT: Review of CARE Program, dated August 17 and 18, 2006

PID #: 2006-60

Introduction/Background

The Office of Surveillance and Epidemiology (OSE) has reviewed the Convenient Access, Responsible Education (CARE) Program for marketing of Plan B for over-the-counter (OTC) status in women 18 years and older and prescription marketing for females 17 years and younger. The CARE Program includes an education component, labeling and packaging that meet both OTC and prescription requirements, a distribution plan, and a monitoring plan.

Plan B was originally approved on July 28, 1999 as a prescription product and was approved as emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The dose is two 0.75mg tablets, the first of which should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later. On April 22, 2003, the sponsor submitted an application for the OTC switch of Plan B. The review team recommended approval for OTC use in women of all ages. On May 6, 2004 the supplemental application received a not approvable because the supplement application lacked data in younger adolescents. The

Program” which allows anonymous shoppers aged 15 to 18 to visit locations that sell Plan B. The underage shoppers will report back to the company if they were able to purchase the product without a prescription. The sponsor states that repeat violators will be reported to the State Board of Pharmacy.

OSE believes having such a measure of monitoring the compliance of the age restriction is overly punitive and may have a negative impact on the availability of this product OTC. This proposal shifts the burden from the Sponsor to the pharmacist. For other products with restricted distribution plans, these types of findings are generally reported to the Agency, rather than professional licensing boards. A lack of pharmacy compliance may be reflective of an inadequate education plan and this information could be used as an opportunity to improve and/or revise the CARE Program.

- The size of the strength appears small in comparison to the established name. If the Sponsor intends to introduce future dosage strengths, we recommend an increasing the font size of the product strength in every location on the carton and container to minimize confusion and selection errors.

Conclusion

The OSE has reviewed the submitted CARE Program for Plan B and has found it to be generally acceptable with modifications as outlined above.

OSE Plan B CARE Program Review Team:

Mary Dempsey, Project Management Officer, OSE-IO Risk Management Team

Claudia B. Karwoski, PharmD, Scientific Coordinator, OSE-IO Risk Management Team

Carol Holquist, R.Ph., Director, Division of Medication Error and Technical Support

Mark Avigan, M.D., C.M., Director, Division of Drug Risk Evaluation

Toni Piazza-Hepp, Pharm.D., Deputy Director, Division of Surveillance, Research, and Communication Support

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/s/

Mary Dempsey
8/22/2006 12:31:07 PM
DRUG SAFETY OFFICE REVIEWER

Ralph Lillie
8/22/2006 12:40:34 PM
CSO



ONP Drug Labeling Review

Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Dates: August 17, 2006 and August 18, 2006

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Duramed Pharmaceuticals, Inc.

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: August 18, 2006

Reviewer: Arlene Solbeck

Project Manager: Leah Christl

Background

- Following a July 31, 2006 letter issued by Acting FDA Commissioner von Eschenbach to Duramed Research, Inc., FDA held a meeting with the sponsor on August 8, 2006 to discuss moving forward with Plan B as an over-the-counter (OTC) drug for women 18 years of age and older. Plan B will remain Rx for under age 18.
- On 8/08/06 and 8/09/06, FDA received copies via email from the sponsor of the last version of the Plan B labeling that was reviewed by FDA (inner carton, outer carton, consumer information leaflet, and picture of the "booklet") that were submitted to the NDA on 1/14/05, 1/18/05, and 1/19/05.

- FDA made recommendations to the above referenced versions of the labeling and relayed those recommendations to the sponsor on August 10, 2006.
- Duramed is responding to FDA's recommendations in the submission of August 17, 2006. Duramed submitted outer carton labeling, inner carton labeling, and the consumer information leaflet for review. Duramed submitted an amended response to address the requirement for child resistant packaging on August 18, 2006. FDA is responding to both submissions in this label review.

I. Reviewer's Comments

Principal Display Panel (PDP) on the Outer Carton

FDA's August 10, 2006 Information Request Letter to Duramed stated:

1. Revise the statement from "Rx only for women age 15 and younger" to read "Rx only for age 17 and younger".

Sponsor's Response: Sponsor made this change and it is acceptable.

Drug Facts

FDA's August 10, 2006 Information Request Letter to Duramed stated:

2. Revise the first bulleted statement under *Directions* in Drug Facts from "[bullet] adults 16 years of age and over:" to "[bullet] women 18 years of age and over:" Make this change wherever Drug Facts is found in the labeling (i.e., outer carton, inner carton).

Sponsor's Response: Sponsor made this change to inner and outer carton labeling and it is acceptable.

3. Revise the third bulleted statement under *Directions* in Drug Facts from "[bullet] prescription only for age 15 and under. If age 15 or under, see a healthcare professional." to "[bullet] prescription only for age 17 and under. If age 17 or under, see a healthcare professional." Make this change wherever Drug Facts is found in the labeling (i.e., outer carton, inner carton).

Sponsor's Response: Sponsor made this change to inner and outer carton labeling and it is acceptable.

4. Revise the fourth bulleted statement under *Other information* in Drug Facts about condom use to be consistent with the language currently proposed for condom labels. Change to read as follows: "when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of pregnancy and the risk of catching or

spreading HIV, the virus that causes AIDS. See condom labeling for additional STD information." Make this change wherever Drug Facts is found in the labeling (i.e., outer carton, inner carton).

Sponsor's Response: Sponsor made this change to inner and outer carton labeling and it is acceptable.

Consumer Information Leaflet

FDA's August 10, 2006 Information Request Letter to Duramed stated:

5. On page 12 under directions for use, revise the first bulleted statement from "[bullet] Adults 16 years of age and over:" to "[bullet] Women 18 years of age and over:"

Sponsor's Response: Sponsor made this change and it is acceptable.

6. On page 12 under directions for use, revise the second bulleted statement from "[bullet] Prescription only for age 15 and under. If age 15 or under, see a healthcare professional." to "[bullet] Prescription only for age 17 and under. If age 17 or under, see a healthcare professional."

Sponsor's Response: Sponsor made the change but did not end the second sentence with a period. Sponsor should add the period after the words "healthcare professional".

7. On page 16, revise the last sentence on the page about condom use from "If your partner uses a latex condom **correctly each and every time you have sex with him, this will help reduce the chance that you will catch an STD.**" to "If your partner uses a latex condom **correctly each and every time you have sex with him, this will help reduce, but not eliminate, the chance that you will catch an STD.**"

Sponsor's Response: Sponsor made the change and it is acceptable.

8. In addition, Duramed revised page 7, last word in the first paragraph. "Doctor" was changed to "healthcare professional". This is acceptable.

General Packaging Comments

FDA's August 10, 2006 Information Request Letter to Duramed stated:

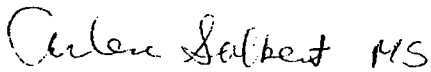
9. In the Federal Register of August 2, 2001 (66 FR 40111), the Consumer Product Safety Commission (CPSC) published a final rule requiring child-resistant (CR) packaging for OTC sale of drugs containing active ingredients previously available only in prescription drugs. This rule became effective on January 29, 2002, and applies to products for which the NDA or ANDA for the OTC switch is submitted to the FDA on or after that date. Therefore, your product needs CR packaging to conform to the regulation, which may be found at 16 CFR 1700.14 (a)(30).

Sponsor's Response: The current Duramed marketed Rx Plan B product complies with CR packaging as per 16 CFR 1700.15, and therefore the planned Rx and OTC Plan B product maintains compliance.

FDA's Response: We agree that sponsor is compliant with OTC CR packaging.

II. Reviewer's Recommendations

The inner and outer carton labeling and the consumer information leaflet are acceptable with one exception: on pg. 12, add a period to the end of the second sentence of the second bulleted statement. The period follows the words "healthcare professional". This can be done at the time of next printing.



Arlene Solbeck, MS
IDS/Biologist
Division of Nonprescription
Regulation Development



Helen Cothran, BS
IDS/Team Leader
Division of Nonprescription
Regulation Development

NDA 21-405

HFD-580: Davis/Monroe/Mercier/Shames

HFD-560: Division File

HFD-560: Ganley/Segal/Solbeck/Cothran/Feibus/Christl

DOCID: PlanBLabel8_18_06.doc



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045\S-011

INFORMATION REQUEST LETTER

Duramed Research, Inc.
Attention: Joseph Carrado, M.Sc., R.Ph
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

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

We also refer to your submissions dated January 14, 18, and 19, 2005.

Additionally, we refer to the meeting between representatives of your firm and the FDA on August 8, 2006.

We request that you submit revised labeling that incorporates the following revisions and recommendations. We request a prompt written response in order to continue our evaluation of your NDA.

Principal Display Panel (PDP) on the Outer Carton

1. Revise the statement from "Rx only for women age 15 and younger" to read "Rx only for age 17 and younger".

Drug Facts

2. Revise the first bulleted statement under the heading *Directions* from "[bullet] adults 16 years of age and over:" to read "[bullet] women 18 years of age and over:" Make this change wherever *Drug Facts* is found in the labeling (outer carton and inner carton).
3. Revise the third bulleted statement under the heading *Directions* from "[bullet] prescription only for age 15 and under. If age 15 or under, see a healthcare professional." to read "[bullet] prescription only for age 17 and under. If age 17 or under, see a healthcare professional." Make this change wherever *Drug Facts* is found in the labeling (outer carton and inner carton).

4. Revise the fourth bulleted statement under the heading *Other information* about condom use to be consistent with the language currently proposed for condom labels. The statement should read as follows: "when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of pregnancy and the risk of catching or spreading HIV, the virus that causes AIDS. See condom labeling for additional STD information." Make this change wherever *Drug Facts* is found in the labeling (outer carton and inner carton).

Consumer Information Leaflet

5. On page 12 under directions for use, revise the first bulleted statement from "[bullet] Adults 16 years of age and over:" to read "[bullet] Women 18 years of age and over:"
6. On page 12 under directions for use, revise the second bulleted statement from "[bullet] Prescription only for age 15 and under. If age 15 or under, see a healthcare professional." to read "[bullet] Prescription only for age 17 and under. If age 17 or under, see a healthcare professional."
7. On page 16, revise the last sentence on the page about condom use from "If your partner uses a latex condom **correctly each and every time you have sex with him, this will help reduce the chance that you will catch an STD.**" to read "If your partner uses a latex condom **correctly each and every time you have sex with him, this will help reduce, but not eliminate, the chance that you will catch an STD.**"

General Packaging Comments

8. The way you plan to package the product in the inner carton via a "booklet" is acceptable.
9. In the Federal Register of August 2, 2001 (66 FR 40111), the Consumer Product Safety Commission (CPSC) published a final rule requiring child-resistant (CR) packaging for OTC sale of drugs containing active ingredients previously available only in prescription drugs. This rule became effective on January 29, 2002 and applies to products for which the NDA or ANDA for the OTC switch is submitted to the FDA on or after that date. Therefore, your product needs CR packaging to conform to the regulation, which may be found at 16 CFR 1700.14 (a) (30).

Enclosed, please also find the suggested changes to the physician insert for the prescription only labeling for Plan B (levonorgestrel) Tablets.

We remind you to submit a revised CARE Program incorporating the changes and clarifications as discussed at our August 8, 2006 meeting.

If you have any questions, call me at 301-796-0869.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
8/10/2006 11:18:24 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Vice President, Clinical Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel) Tablets, 0.75 mg.

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2006. The purpose of the meeting was to discuss the status of your sNDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Acting Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 8, 2006

TIME: 10:30 A.M. – 12:00 P.M.

LOCATION: Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Conf. Room 1315
Silver Spring, MD 20903

APPLICATION: NDA-21-045

DRUG NAME: Plan B (levonorgestrel), Tablets 0.75 mg

TYPE OF MEETING: Status

MEETING CHAIR: Daniel Shames, M.D., F.A.C.S.

MEETING RECORDER: Nenita Crisostomo, R.N.

FDA ATTENDEES:

Daniel Shames, M.D., F.A.C.S.—Acting Deputy Director, Office of Drug Evaluation III
(ODE III)

Maria Walsh, R.N., M.S.—Project Management Officer, ODE III

Scott Monroe, M.D.—Acting Director, Division of Reproductive and Urologic Products (DRUP)

Jennifer Mercier—Chief, Project Management Staff, DRUP

Margaret Kober, R.Ph., M.P.A.—Chief, Project Management Staff, DRUP

Nenita Crisostomo, R.N.—Regulatory Health Project Manager, DRUP

Charles Ganley, M.D.—Director, Office of Non Prescription Products

Andrea Leonard Segal, M.D., M.S.—Director, Division of Non Prescription Clinical Evaluation

Leah Christl, Ph.D.—Supervisory Consumer Safety Officer, Division of Non Prescription
Clinical Evaluation

Gerald Dal Pan, M.D., M.H.S.—Director, Office of Surveillance and Epidemiology (OSE)

Claudia Karwoski, Pharm.D.—Scientific Coordinator for Risk Management, OSE

Jane Axelrad, J.D.—Associate Director for Policy, Center for Drug Evaluation and Research
(CDER)

Deborah M. Autor, Esq.—Acting Director, Office of Compliance

Mary Purucker, M.D., Ph.D.—Acting Associate Director, Medical and Scientific Affairs

Lee Lemley—Regulatory Health Project Manager, Executive Operations Staff Office of
Executive Programs

Suzanne Barone, Ph.D.—Consumer Safety Officer, Division of Compliance Risk Management
and Surveillance

Heidi Gertner, J.D.—Associate Counsel, Office of the Commissioner

EXTERNAL CONSTITUENT ATTENDEES:

Bruce Downey—Chairman and Chief Executive Office, Barr Pharmaceuticals, Inc.

Fred Wilkinson—President and COO, Duramed Pharmaceuticals, Inc.

EXTERNAL CONSTITUENT ATTENDEES (continued):

Christine Mundkur—Senior Vice President, Quality and Regulatory Counsel,
Barr Laboratories, Inc.

Joseph A. Carrado, M.Sc.,R.Ph.—Vice President, Clinical Regulatory Affairs, Duramed
Pharmaceuticals, Inc.

Amy Niemann—Vice President, Proprietary Marketing, Duramed Pharmaceuticals, Inc.

BACKGROUND:

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 submitted a major amendment containing additional data in support of the supplement. On July 31, 2006, Acting Commissioner Andrew von Eschenbach, M.D., sent the sponsor a letter indicating FDA was now ready to proceed with further evaluation of the sponsor's application and requested this meeting.

MEETING OBJECTIVES:

The objective of this meeting is to discuss the status of the current application and plans to move forward, including labeling and enforcement issues.

DISCUSSION POINTS:

A. Status Summary: The Agency initiated the discussion with a brief background summary of the history of the application and the letter from Acting Commissioner von Eschenbach dated July 31, 2006.

B. Discussion:

1. The Age Issue: The Acting Commissioner has decided that Plan B should be OTC for women over 18 years old and prescription-only for 17 years old and younger, to enhance the effectiveness of the enforcement of the age restriction. The company indicated it would have to consider whether to accept this change in the age restriction.

2. Packaging: The Agency stated that the company's proposal of one package for both the Rx and OTC versions of Plan B was acceptable.

3. Convenient Access Responsible Education (CARE) Program: The document has been reviewed by the Agency with the following recommendations to revise the wording of the program to include:

- a. Age Restriction: where an age restriction is mentioned in the CARE Program it should state that the drug is by prescription only for women age 17 years and younger, and OTC for those age 18 and older.
- b. Product Distribution: The description of the distribution program should be strengthened to note that the single package configuration will ensure that the drug will only be sold in retail outlets with pharmacies that are authorized to dispense prescription products. This will further serve to enhance enforcement of the age restriction for OTC use to those 18 years and older.

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/s/

Julie Beitz
8/23/2006 01:30:45 PM
Signing for Dan Shames, MD



July 31, 2006

NDA 21-045/S-001

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave, 11th floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

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

In our August 26, 2005, letter to you we stated that the Agency was unable to reach a decision on the approvability of your application at that time because of unresolved difficult and novel issues raised by your sNDA. On the same day, the Agency issued an Advanced Notice of Proposed Rulemaking (ANPRM) seeking input from the public on certain issues regarding Rx to OTC switches, which related to the regulatory issues raised by your application. The comment period on the ANPRM closed on November 1, 2005, and the Agency received approximately 47,000 comments. FDA then hired a contractor to summarize and categorize the comments, and we received the contractor's final reports on May 19, 2006. FDA has reviewed the comments and, while they have provided the agency with valuable insights regarding how the Agency might enforce an age-based restriction like the one proposed by your amended sNDA, we concur with the overwhelming majority of the comments (from individuals both for and against the approval of your sNDA) that it is not necessary to engage in rulemaking to resolve the novel regulatory issues raised by your application.

We are now proceeding with further evaluation of your sNDA. We would like to meet with you as soon as practicable, and preferably within seven days, to discuss the status of your sNDA, including any necessary amendments. For example, your sNDA seeks approval for OTC use for women ages 16 and older. As we informed you in our August 26, 2005 letter, the Center for Drug Evaluation and Research concluded the available scientific data are insufficient to support the safe use of Plan B[®] as an OTC product for everyone in that age group. Moreover, because of enforcement considerations, we believe that the appropriate age for OTC access is 18. Should you desire to proceed with your sNDA, you would need to amend it to seek approval for OTC status for women ages 18 and older. In addition, you would need to amend your sNDA with respect to packaging.

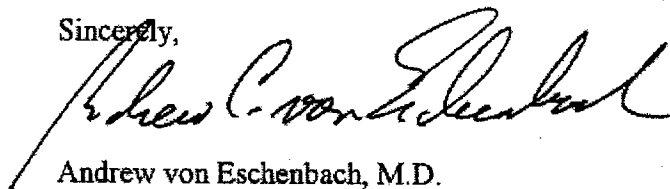
Joseph A. Carrado, M.Sc., R.Ph

July 31, 2006

Page 2

We would also like to discuss the details of the CARESM Program that you submitted with your sNDA. That program regards your proposed marketing, education, distribution, and monitoring for the OTC version of Plan B[®]. Specifically, we would like to learn more about your proposal to restrict distribution of Plan B[®] to certain pharmacies, i.e., the OTC version of Plan B[®] would not be available at gas stations, convenience stores, etc., but only to those pharmacies agreeing to (1) keep the OTC version of the drug behind the pharmacy counter and (2) dispense the drug only upon the production of a valid photo identification card establishing the age of the consumer. In particular, we would like to learn more about your plan to routinely monitor these pharmacies to make sure they comply with the restricted distribution plan. In addition, we are very interested in learning how you plan on enforcing the restrictions if a pharmacy fails to comply with them, e.g., whether the restrictions will be incorporated into the terms of a formal contract and, if so, what the terms of that contract (particularly those terms related to a breach) look like. If after our discussions we conclude that the CARESM Program isn't sufficiently rigorous to prevent the OTC version of Plan B[®] from being used by young girls who can't safely use the product without the supervision of a practitioner licensed by law to administer the drug, Plan B[®] will remain Rx-only for women of all ages.

Sincerely,



Andrew von Eschenbach, M.D.

Acting Commissioner of Food and Drugs

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/s/

Margaret Kober

8/4/2006 09:30:26 AM

This letter was signed and mailed in hard copy
with Dr. von Eschenbach's original signature. My electronic
signature is for archival process purposes only. Note
that the supplement number on the letter should
read 011 rather than 001.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

Duramed Research, Inc.
Attention: Joseph Carrado, M.Sc., R.Ph
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your supplemental new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B (levonorgestrel) Tablets, 0.75 mg

We also refer to the November 29, 2005 teleconference between representatives of your firm and the Office of Drug Evaluation III in which the status of your supplemental application was discussed. Per your request, we are providing the following clarification:

- The August 26, 2005 letter from Dr. Lester Crawford is an advice letter and not a regulatory action letter.
- NDA 21-045/S-011 is open and pending a regulatory action by FDA.

We have also included two printouts from our internal tracking system to demonstrate that the August 26, 2005 letter is coded "GC" (general correspondence) and that your July 21, 2004 complete response to our May 6, 2004 not approvable letter is coded "OP" (open). When a regulatory action is taken, your July 21, 2004 complete response will be coded "AP," "AE," or "NA" to indicate approval, approvable, or not approvable, respectively.



Plan B.pdf

If you have any questions, call Karen Kirchberg, N.P., Regulatory Health Project Manager, at (301) 796-0933.

Sincerely,

{See appended electronic signature page}

Florence Houn, MD, MPH
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Florence Houn
12/6/2005 03:03:07 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

August 26, 2005

NDA 21-045/S-011

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave, 11th floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

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

We acknowledge receipt of your submissions dated April 16, July 25 (3), and 31, August 8 (2), September 4, 8, 9, and 15, October 6, 10, 15 (2), 17, 21, 24, 29, 30, and 31, December 3, and 9, 2003, January 9, and 30, February 6, 10, 13, 20, and 24, March 11 and 26, May 6 and 11, June 30, July 21, 2004, and January 6, 12, 13, 14, 18, 19 and 21, 2005.

Your submission of July 21, 2004 constituted a complete response to our May 6, 2004 Not Approvable action letter.

The resubmitted supplemental new drug application provides for a switch from Rx only status to Over the Counter (OTC) status for women ages sixteen years and older. Plan B would remain Rx only for women under sixteen years of age. In addition, you have proposed that both the Rx and OTC version of Plan B be marketed in a single package.

The Center for Drug Evaluation and Research (CDER) has completed its review of this application, as amended, and has concluded that the available scientific data are sufficient to support the safe use of Plan B as an OTC product, but only for women who are 17 years of age and older. However, the Agency is unable at this time to reach a decision on the approvability of the application because of unresolved issues that relate to your NDA discussed below.

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

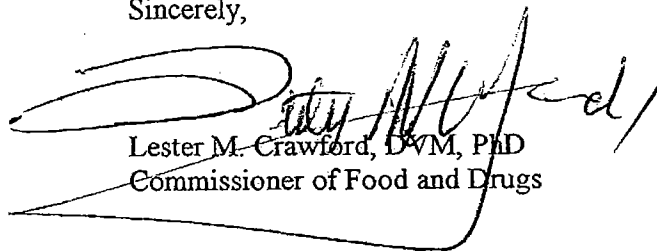
As you may be aware, questions have arisen over the years about whether there are any conditions under which an active ingredient may be simultaneously marketed in both a prescription drug product and an OTC drug product. Notwithstanding our having allowed the practice in those rare instances where there is a meaningful difference in the indication, strength, dosage form or route of administration of the two products, we recognize that FDA's interpretation of section 503(b) of the Act has not been explicitly set forth in any of the regulations that discuss the process by which FDA classifies (or re-classifies) drugs as OTC or prescription. See 21 CFR 310.200 and 310.201.

In this case, we have decided that the appropriate course is to ask for public comments on whether we should initiate a rulemaking to codify our interpretation of section 503(b) regarding when an active ingredient can be simultaneously marketed in both a prescription drug product and an OTC drug product. To this end, we have decided to publish an advance notice of proposed rulemaking in the Federal Register. In addition, the notice will seek public comments on questions related to the marketing of Rx and OTC versions of the same active ingredient in a single package.

At this time, the drug product may not be legally marketed OTC. In the future, you will be notified in writing regarding changes in the status of your application.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference to discuss what steps need to be taken before the application may be approved.

Sincerely,



Lester M. Crawford, DVM, PhD
Commissioner of Food and Drugs

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/s/

Bronwyn Collier

8/26/2005 04:54:54 PM

This letter was signed and mailed in hard copy
with Dr. Lester Crawford's original signature. This letter
was scanned and is being checked into DFS
for archival purposes. My signature is for process
purposes only.



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE V

facsimile transmittal sheet

DATE: January 19, 2005

To: Joseph A. Carrado, M.Sc., R.Ph.	From: Tia Frazier R.N., M.S.
Company: Duramed Research, Inc.	Division of Over-the-Counter Drug Products
Fax number: 610-747-2979	Fax number: (301)-827-2315
Phone number: (610) 747-2910	Phone number: 301-827-2271

Subject: Requested revisions to OTC Labeling

Comments: These comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are subject to change as we finalize our review of your application. Additional labeling advice may be forthcoming.

Total no. of pages including cover: 2

Document to be mailed: Yes No

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

Labeling Comments

APPLICATION: NDA 21-045/S-011

DRUG NAME: Plan B® (0.75mg levonorgestrel emergency contraceptive)
Tablets

RE-SUBMISSION DATE: July 22, 2004

We request that you make the following revisions to the OTC labeling (outer carton Principal Display Panel, outer carton *Drug Facts*, inner carton labeling, and consumer information leaflet) submitted to the Divisions of Over-the-Counter Drug Products and Reproductive and Urologic Drug Products by electronic mail on January 18, 2005:

1. Provide a more complete description of how the 2 imprinted seals on the outer carton are tamper-evident. If the tamper-evident statement is revised, make sure the tamper-evident statements on the inner carton and in the consumer information leaflet are consistent with the outer carton.
2. On page 7 of the Consumer Information Leaflet, between the section "What if I am already pregnant and use Plan B®?" and the section "Can I use Plan B® for regular birth control?", add the following section to read:

"What should I do if my menstrual period is delayed beyond one week and I have severe lower stomach pain?"

If you have severe lower stomach pain about 3-5 weeks after taking Plan B®, you may have a pregnancy outside the uterus (a tubal pregnancy). See a healthcare professional right away because a tubal pregnancy requires immediate medical treatment."

3. In the section "Can I use Plan B® for regular birth control?" of the Consumer Information Leaflet (page 8), add the following sentence at the end of the section:

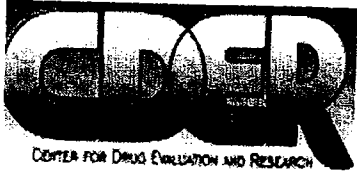
"You should not have unprotected sex following treatment because Plan B® will not protect you from getting pregnant."

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/s/

Tia Frazier
1/19/05 12:25:16 PM
CSO

Helen Cothran
1/19/05 01:00:43 PM
INTERDISCIPLINARY



OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Date: January 19, 2005

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Duramed Research, Inc. (formally Barr Research Inc.)

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: January 21, 2005

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Tia Frazier

Background

Plan B Timeline:

- July 28, 1999: FDA approved Plan B® for prescription use under NDA 21-045.
- April 16, 2003: sponsor submitted an NDA to switch Plan B® from prescription status to OTC.
- October 15, 2003: sponsor submitted revised carton and package insert labeling.
- December 16, 2003: Plan B® was reviewed jointly by the Advisory Committee on Reproductive and Urologic Drugs and the Nonprescription Drugs Advisory Committee. The committees recommended approval.
- May 6, 2004: sponsor received a not approvable letter for Plan B®.
- July 21, 2004: sponsor submitted amendment providing support for the marketing of Plan B® as a nonprescription product for women 16 years and older and as a prescription-only product for women 15 years and younger. Sponsor submitted outer carton labeling including Drug Facts, inner carton labeling including a “time reminder” strategy for remembering when to take the second pill, a consumer brochure, and a package insert.
- December 22, 2004: FDA sent letter to sponsor requesting labeling revisions
- January 12, 2005: Sponsor submitted revised labeling for Plan B’s outer carton, inner carton and consumer information leaflet
- January 14, 2005: FDA requested revised labeling via fax
- January 18, 2005: Sponsor submitted revised labeling
- January 19, 2005: FDA requested revised labeling
- January 19, 2005: Sponsor submitted revised labeling via e-mail

This is a review of the sponsor’s revised labeling sent to FDA via e-mail on January 19, 2005. The sponsor submitted revised labeling for the consumer information leaflet and a description of the tamper-evident labeling as requested.

Reviewer’s Comments

In a fax to the sponsor dated January 19, 2005, FDA requested the following labeling revisions:

1. Provide a more complete description of how the 2 imprinted seals on the outer carton are tamper-evident. If the tamper-evident statement is revised, make sure the tamper-evident statements on the inner carton and in the consumer information leaflet are consistent with the outer carton.

Sponsor’s Response: The sponsor responded as follows: “Tamper evident seals for the Plan B carton will be made from a pressure sensitive adhesive material, will have 4 perforated, diagonal lines, and will be one (1) inch in diameter. If someone attempts to

remove the seal or if the carton is opened, one or up to all of the 4 diagonal perforation lines will rip, indicating the carton has been compromised. Also, the tamper evident seal will be placed on an unvarnished area of the carton to ensure that proper adhesion is obtained and that the seal remains securely in place." This is acceptable. The sponsor, therefore, did not revise the tamper-evident statement. This is acceptable.

2. On page 7 of the Consumer Information Leaflet, between the section "**What if I am already pregnant and use Plan B®?**" and the section "**Can I use Plan B® for regular birth control?**", add the following section to read:

"What should I do if my menstrual period is delayed beyond one week and I have severe lower stomach pain?"

If you have severe lower stomach pain about 3-5 weeks after taking Plan B®, you may have a pregnancy outside the uterus (a tubal pregnancy). See a healthcare professional right away because a tubal pregnancy requires immediate medical treatment."

Sponsor's Response: The sponsor added this section as requested. This is acceptable.

3. In the section "**Can I use Plan B® for regular birth control?**" of the Consumer Information Leaflet (page 8), add the following sentence at the end of the section:

"You should not have unprotected sex following treatment because Plan B® will not protect you from getting pregnant."

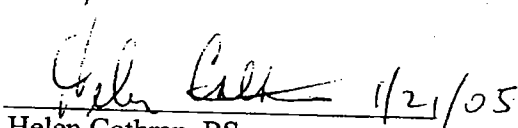
Sponsor's Response: The sponsor added sentence as requested. This is acceptable.

Reviewer's Recommendations

No further revisions to the Plan B® labeling are requested from the sponsor at this time.

 1/21/05

Arlene Solbeck, MS
IDS - HFD 560

 1/21/05

Helen Cothran, BS
IDS Team Leader - HFD 560

NDA 21-405

HFD-580: Griebel/Davis/Monroe/Kirchberg/Shames

HFD-560: Division File

HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/Chen/Frazier/Christl

DOCID: PlanBLabel1_21_05.doc

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Reason:

_____ b(2) 'low'

~~_____~~ b(4) CCI

_____ b(4) TS

_____ b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

21 pages LABGINS FROM

1/19/05 LABGINS REVIEW



OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Date: January 18, 2005

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Duramed Research, Inc. (formally Barr Research Inc.)

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: January 19, 2005

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Tia Frazier

Background

Plan B Timeline:

- July 28, 1999: FDA approved Plan B® for prescription use under NDA 21-045.
- April 16, 2003: sponsor submitted an NDA to switch Plan B® from prescription status to OTC.
- October 15, 2003: sponsor submitted revised carton and package insert labeling.
- December 16, 2003: Plan B® was reviewed jointly by the Advisory Committee on Reproductive and Urologic Drugs and the Nonprescription Drugs Advisory Committee. The committees recommended approval.
- May 6, 2004: sponsor received a not approvable letter for Plan B®.
- July 21, 2004: sponsor submitted amendment providing support for the marketing of Plan B® as a nonprescription product for women 16 years and older and as a prescription-only product for women 15 years and younger. Sponsor submitted outer carton labeling including Drug Facts, inner carton labeling including a “time reminder” strategy for remembering when to take the second pill, a consumer brochure, and a package insert.
- December 22, 2004: FDA sent letter to sponsor requesting labeling revisions
- January 12, 2005: Sponsor submitted revised labeling for Plan B’s outer carton, inner carton and consumer information leaflet.
- January 14, 2005: FDA requested revised labeling via fax

This current submission is the sponsor’s response to FDA’s fax of January 14, 2005. The sponsor submitted revised labeling for Plan B’s outer carton, inner carton, consumer information leaflet, and a carton showing a mock-up of the tamper evident feature.

Reviewer’s Comments

In FDA’s fax of January 14, 2005, the following revised labeling was requested:

- A. Outer Carton Labeling (Principal Display Panel (PDP) and Drug Facts)
 1. On the PDP, the phrases in purple/grey type which read “Reduces the chance of pregnancy after unprotected sex (i.e., if a regular birth control method fails or after sex without birth control)”, “Not Intended to Replace Regular Birth Control”, and “Plan B® Should Be Used Only in Emergencies” seem light and hard to read. Darken the print.

Sponsor’s Response: Sponsor darkened the print and is now acceptable.

2. On the PDP, the directions for taking the tablets also seem too light. Darken the print and bold the phrase “The sooner you take the first tablet, the more effective Plan B® will be.” to make it stand out.

Sponsor's Response: Sponsor darkened the print and bolded the directions. This is acceptable.

3. In Drug Facts under the subheading "**Do not use**" add the following bullet as the first bullet in this section to read "[bullet] if you are already pregnant (because it will not work)".

Sponsor's Response: Sponsor added the omitted bullet. This is acceptable.

4. In Drug Facts, remove the colon after the subheading "**When using this product** you may have".

Sponsor's Response: Sponsor removed the colon. This is acceptable.

5. In Drug Facts under the heading "**Directions**", remove the indent from the fourth bullet so that it is left justified and lines up with the first bullet.

Sponsor's Response: Sponsor realigned the bullet correctly. This is acceptable.

6. Revise the overdose warning to read "**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away."

Sponsor's Response: Sponsor revised the overdose warning. This is acceptable.

7. In Drug Facts, under the heading "**Other information**" regarding the tamper-evident feature:
 - a. Revise the fifth bulleted statement which describes the tamper-evident feature to read: "this package is sealed with 2 imprinted seals. **Do not use if these imprinted seals have been removed, torn, or broken.**"
 - b. Provide a package for review which demonstrates the tamper-evident feature.

Sponsor's Response: The sponsor sent a package with a tamper-evident feature somewhat but not exactly what would be on the actual package. What the sponsor sent was not a tamper-evident package. The seals could be easily removed and replaced. The sponsor was contacted and said that their actual imprinted seals could not be removed and replaced without tearing the box and the seals. FDA also reminded the sponsor that their blister package (inner carton) was tamper-evident but they only had to describe one tamper-evident feature in their labeling. However, the sponsor could describe both tamper-evident features, if they desired. The sponsor agreed to decide which tamper-evident feature they wanted to describe on the labeling and if it is the imprinted seals, to send in a more complete description of how the seals are tamper-evident. If the tamper-evident statement is revised, the sponsor needs to make it consistent with statements on the inner carton labeling and in the consumer information leaflet.

B. Inner Carton Labeling

8. Revise the Drug Facts labeling in the inner carton labeling to be consistent with the changes requested above for the outer carton labeling.

Sponsor's Response: Sponsor made changes to the Drug Facts in the inner carton labeling. The sponsor still has to revise Drug Facts on both inner and outer cartons to include the updated tamper-evident package features (see #7 above).

9. The directions statements for taking the tablets, the Time Reminder directions, and the statements which read "Not Intended to Replace Regular Birth Control" and "Plan B® Should Be Used Only In Emergencies" should be darkened to enhance readability.

Sponsor's Response: Sponsor darkened the print and it is acceptable.

C. Consumer Information Leaflet

10. The subject headings (e.g., What is Plan B®?) do not stand out. Darken the print or increase the print size.

Sponsor's Response: Sponsor increased the print size. The headings stand out. This is acceptable.

11. Under the heading "How effective is Plan B®" (page 4), revise the second sentence from "One out of every 8 women who would have gotten pregnant will still become pregnant." to "Seven out of every 8 women who would have gotten pregnant will not become pregnant."

Sponsor's Response: Sponsor revised the sentence and it is acceptable.

12. Revise the overdose warning (page 8) to be consistent with Drug Facts (see #6 above).

Sponsor's Response: Sponsor revised the overdose statement. This is acceptable.

13. Revise the last sentence on page 8 to include asking a healthcare professional. The sentence should read: "If you have questions or need more information about this product, call our toll-free number, 1-800-330-1271, visit our Web site at www.go2planb.com, or ask a healthcare professional.

Sponsor's response: The sponsor revised the sentence to include asking a healthcare professional. This is acceptable.

14. Revise the tamper-evident statement on page 9 to be consistent with Drug Facts (see #7.a. above).

Sponsor's Response: The sponsor should revise the tamper-evident feature in the leaflet (page 13) to be consistent with carton labeling if it is revised again (see #7 above).

15. On page 10, paragraph 3, remove the words "we know" from the second and third sentences. The sentences should read "It works well for this purpose. There are many other products that work very well for routine birth control."

Sponsor's Response: The sponsor removed the words "we know" from the second and third sentences and this is acceptable.

16. Move the statement on page 11 which reads "Please see enclosed important Product Information for Plan B®." to the front of the leaflet. It is unclear what the statement is referring to when it is at the end of the leaflet.

Sponsor's Response: The sponsor moved the statement to page 1 of the leaflet. This is acceptable.

In addition, we would like the sponsor to make the following changes to the Consumer Information Leaflet:

1. On page 7, between the section "**What if I am already pregnant and use PlanB?**" and the section "**Can I use Plan B for regular birth control?**", add the following section to read:

"What should I do if my menstrual period is delayed beyond one week and I have severe lower stomach pain?"

If you have severe lower stomach pain about 3-5 weeks after taking Plan B®, you may have a pregnancy outside the uterus (a tubal pregnancy). See a healthcare professional right away because a tubal pregnancy requires immediate medical treatment."

2. On page 8, in the section "**Can I use Plan B for regular birth control?**", add the following sentence at the end of the section:

"You should not have unprotected sex following treatment because Plan B® will not protect you from getting pregnant."

Reviewers Recommendations

The following comments may be conveyed to the sponsor:

1. Provide a more complete description of how the 2 imprinted seals on the outer carton are tamper-evident. If the tamper-evident statement is revised, make sure the tamper-evident statements on the inner carton and in the consumer information leaflet are consistent with the outer carton.

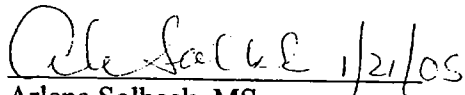
2. On page 7 of the Consumer Information Leaflet, between the section “What if I am already pregnant and use Plan B®?” and the section “Can I use Plan B® for regular birth control?”, add the following section to read:

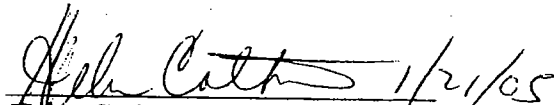
“What should I do if my menstrual period is delayed beyond one week and I have severe lower stomach pain?”

If you have severe lower stomach pain about 3-5 weeks after taking Plan B®, you may have a pregnancy outside the uterus (a tubal pregnancy). See a healthcare professional right away because a tubal pregnancy requires immediate medical treatment.”

3. In the section “Can I use Plan B® for regular birth control?” of the Consumer Information Leaflet (page 8), add the following sentence at the end of the section:

“You should not have unprotected sex following treatment because Plan B® will not protect you from getting pregnant.”


Arlene Solbeck, MS
IDS - HFD 560


Helen Cothran, BS
IDS Team Leader - HFD 560

NDA 21-405

HFD-580: Griebel/Davis/Monroe/Kirchberg/Shames

HFD-560: Division File

HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/Chen/Frazier/Christl

DOCID: PlanBLabel1_19_05.doc

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Reason:

_____ b(2) 'low'

 X b(4) CCI

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_____ b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

23 pages proposed LAACLINE

8/18/2006

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/s/

Arlene Solbeck
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INTERDISCIPLINARY

Helen Cothran
1/21/05 02:58:39 PM
INTERDISCIPLINARY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045\S-011

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your supplemental new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel) Tablets

We also refer to the acknowledgement letter for your complete response submission dated July 21, 2004. The action date for the supplement was noted in that correspondence as January 20, 2005. This letter is to inform you that the correct date is January 21, 2005.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Health Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
1/14/05 04:04:39 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2005

To: Joseph A. Carrado, M.Sc., R.Ph.	From: Tia Frazier R.N., M.S.
Company: Duramed Research, Inc.	Division of Over-the-Counter Drug Products
Fax number: 610-747-2979	Fax number: (302)-827-2315
Phone number: (610) 747-2910	Phone number: 301-827-2271
Subject: Requested revisions to OTC Labeling	

Comments: These comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are subject to change as we finalize our review of your application. Additional labeling advice may be forthcoming.

Total no. of pages including cover: 4

Document to be mailed: YES NO

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Labeling Comments

APPLICATION: NDA 21-045/S-011

DRUG NAME: Plan B® (0.75mg levonorgestrel emergency contraceptive)
Tablets

RE-SUBMISSION DATE: July 22, 2004

We request that you make the following revisions to the OTC labeling (outer carton Principal Display Panel, outer carton *Drug Facts*, inner carton labeling, and consumer information leaflet):

Outer Carton Labeling (Principal Display Panel (PDP) and *Drug Facts*)

1. On the PDP, the phrases in purple/grey type which read “Reduces the chance of pregnancy after unprotected sex (i.e., if a regular birth control method fails or after sex without birth control)”, “Not Intended to Replace Regular Birth Control”, and “Plan B® Should Be Used Only in Emergencies” seem light and hard to read. Darken the print.
2. On the PDP, the directions for taking the tablets also seem too light. Darken the print and bold the phrase “The sooner you take the first tablet, the more effective Plan B® will be.” to make it stand out.
3. In *Drug Facts* under the subheading “Do not use” add the following bullet as the first bullet in this section to read “[bullet] if you are already pregnant (because it will not work)”.
4. In *Drug Facts*, remove the colon after the subheading “When using this product you may have”.
5. In *Drug Facts* under the heading “Directions”, remove the indent from the fourth bullet so that it is left justified and lines up with the first bullet.
6. In *Drug Facts*, under the heading “Warnings”, revise the overdose warning to read “**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.”

7. In *Drug Facts*, under the heading “Other information” regarding the tamper-evident feature:
 - (a) Revise the fifth bulleted statement which describes the tamper-evident feature to read: “this package is sealed with 2 imprinted seals. **Do not use if these imprinted seals have been removed, torn, or broken.**”
 - (b) Provide a package for review which demonstrates the tamper-evident feature.

Inner Carton Labeling

8. Revise the *Drug Facts* labeling in the inner carton labeling to be consistent with the changes requested above for the outer carton labeling.
9. The directions statements for taking the tablets, the Time Reminder directions, and the statements which read “Not Intended to Replace Regular Birth Control” and “Plan B® Should Be Used Only In Emergencies” should be darkened to enhance readability.

Consumer Information Leaflet

10. The subject headings (e.g., What is Plan B®?) do not stand out. Darken the print or increase the print size.
11. Under the heading “How effective is Plan B®” (page 4), revise the second sentence from “One out of every 8 women who would have gotten pregnant will still become pregnant.” to “Seven out of every 8 women who would have gotten pregnant will not become pregnant.”
12. Revise the overdose warning (page 8) to be consistent with *Drug Facts* (see #6 above).
13. Revise the last sentence on page 8 to include asking a healthcare professional. The sentence should read: “If you have questions or need more information about this product, call our toll-free number, 1-800-330-1271, visit our Web site at www.go2planb.com, or ask a healthcare professional.
14. Revise the tamper-evident statement on page 9 to be consistent with *Drug Facts* (see #7.a. above).
15. On page 10, paragraph 3, remove the words “we know” from the second and third sentences. The sentences should read “It works well for this purpose. There are many other products that work very well for routine birth control.”

16. Move the statement on page 11 which reads "Please see enclosed important Product Information for Plan B®." to the front of the leaflet. It is unclear what the statement is referring to when it is at the end of the leaflet.

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/s/

Tia Frazier
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CSO



OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Date: January 12, 2005 (CDER stamp date January 13, 2005)

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Duramed Research, Inc. (formally Barr Research Inc.)

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: January 14, 2005

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Tia Frazier

Background

Plan B Timeline:

- July 28, 1999: FDA approved Plan B® for prescription use under NDA 21-045.
- April 16, 2003: sponsor submitted an NDA to switch Plan B® from prescription status to OTC.
- October 15, 2003: sponsor submitted revised carton and package insert labeling.
- December 16, 2003: Plan B® was reviewed jointly by the Advisory Committee on Reproductive and Urologic Drugs and the Nonprescription Drugs Advisory Committee. The committees recommended approval.
- May 6, 2004: sponsor received a not approvable letter for Plan B®.
- July 21, 2004: sponsor submitted amendment providing support for the marketing of Plan B® as a nonprescription product for women 16 years and older and as a prescription-only product for women 15 years and younger. Sponsor submitted outer carton labeling including Drug Facts, inner carton labeling including a “time reminder” strategy for remembering when to take the second pill, a consumer brochure, and a package insert.
- December 22, 2004: FDA sent letter to sponsor requesting labeling revisions

This current submission is the sponsor’s response to FDA’s letter dated December 22, 2004. The sponsor submitted revised labeling for Plan B’s outer carton, inner carton and consumer information leaflet.

Reviewer’s Comments and Recommendations

The comments below may be conveyed to the sponsor.

A. Outer Carton Labeling (Principal Display Panel (PDP) and Drug Facts)

1. On the PDP, the phrases in purple/grey type which read “Reduces the chance of pregnancy after unprotected sex (i.e., if a regular birth control method fails or after sex without birth control)”, “Not Intended to Replace Regular Birth Control”, and “Plan B® Should Be Used Only in Emergencies” seem light and hard to read. Darken the print.
2. On the PDP, the directions for taking the tablets also seem too light. Darken the print and bold the phrase “The sooner you take the first tablet, the more effective Plan B® will be.” to make it stand out.
3. In Drug Facts under the subheading “**Do not use**” add the following bullet as the first bullet in this section to read “[bullet] if you are already pregnant (because it will not work)”.
4. In Drug Facts, remove the colon after the subheading “**When using this product** you may have”.

5. In Drug Facts under the heading “*Directions*”, remove the indent from the fourth bullet so that it is left justified and lines up with the first bullet.
6. Revise the overdose warning to read “**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.”
7. In Drug Facts, under the heading “*Other information*” regarding the tamper-evident feature:
 - a. Revise the fifth bulleted statement which describes the tamper-evident feature to read: “this package is sealed with 2 imprinted seals. **Do not use if these imprinted seals have been removed, torn, or broken.**”
 - b. Provide a package for review which demonstrates the tamper-evident feature.

B. Inner Carton Labeling

8. Revise the Drug Facts labeling in the inner carton labeling to be consistent with the changes requested above for the outer carton labeling.
9. The directions statements for taking the tablets, the Time Reminder directions, and the statements which read “Not Intended to Replace Regular Birth Control” and “Plan B® Should Be Used Only In Emergencies” should be darkened to enhance readability.

C. Consumer Information Leaflet

10. The subject headings (e.g., What is Plan B®?) do not stand out. Darken the print or increase the print size.
11. Under the heading “How effective is Plan B®” (page 4), revise the second sentence from “One out of every 8 women who would have gotten pregnant will still become pregnant.” to “Seven out of every 8 women who would have gotten pregnant will not become pregnant.”
12. Revise the overdose warning (page 8) to be consistent with Drug Facts (see #6 above).
13. Revise the last sentence on page 8 to include asking a healthcare professional. The sentence should read: “If you have questions or need more information about this product, call our toll-free number, 1-800-330-1271, visit our Web site at www.go2planb.com, or ask a healthcare professional.
14. Revise the tamper-evident statement on page 9 to be consistent with Drug Facts (see #7.a. above).
15. On page 10, paragraph 3, remove the words “we know” from the second and third sentences. The sentences should read “It works well for this purpose. There are many other products that work very well for routine birth control.”
16. Move the statement on page 11 which reads “Please see enclosed important Product Information for Plan B®.” to the front of the leaflet. It is unclear what the statement is referring to when it is at the end of the leaflet.

Arlene Solbeck 1/14/05

Arlene Solbeck, MS
IDS - HFD 560

Helen Cothran 1/14/05

Helen Cothran, BS
IDS Team Leader - HFD 560

NDA 21-405

HFD-580: Griebel/Davis/Monroe/Kirchberg/Shames

HFD-560: Division File

HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/Chen/Frazier/Christl

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Reason:

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_____ b(4) CCI

_____ b(4) TS

_____ b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

15 PAGES FROM

OTC LABELING REVIEW

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/s/

Arlene Solbeck
1/18/05 02:32:20 PM
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Helen Cothran
1/18/05 02:42:12 PM
INTERDISCIPLINARY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045\S-011

INFORMATION REQUEST LETTER

Barr Research, Inc. [U.S. Agent for Duramed Pharmaceuticals, Inc.]
Attention: Joseph Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your April 16, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B (0.75 mg levonorgestrel) tablets.

We also refer to your submission dated July 21, 2004.

We request that you submit revised labeling that incorporates the following requested revision and recommendation. We request a prompt written response in order to continue our evaluation of your NDA.

Principal Display Panel (PDP) on the Carton

Add the phrase "Rx only for women age 15 and younger" to the Principal Display Panel instead of the phrase "Prescription only for women age 15 and younger".

This request revises advice that we provided on December 22, 2004. These comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

If you have any questions, call Tia Frazier, Project Manager, at 301-827-2271.

Sincerely,

{See appended electronic signature page}

Leah Cutter, Ph.D.
Acting Chief, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Leah Cutter

1/7/05 03:19:25 PM

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM: **Karen Kirchberg, N.P., Project Manager**
Division of Reproductive and Urologic Drug Products

DATE
January 5, 2005

IND NO.

NDA NO.
21-045

TYPE OF DOCUMENT
SE 6

DATE OF DOCUMENT
July 22, 2004

NAME OF DRUG
**Plan B (levonorgestrel)
Tablets**

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Emergency Contraception

DESIRED COMPLETION DATE
January 10, 2005

NAME OF FIRM: **Duramed Pharmaceuticals, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

III. BIOPHARMACEUTICS

- | | |
|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|

IV. DRUG EXPERIENCE

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We would like an AERS safety update for the Plan B product. Please include bleeding requiring hospitalization, ectopic pregnancies, birth defects, and any other serious adverse events.

Please contact Karen Kirchberg (7-4254) or Dr. Dan Davis (7-4240) if you have any questions.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 DFS MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Karen Kirchberg
1/5/05 09:27:58 AM

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: **Information from IMS HEALTH, INC. is copyrighted and cannot be used outside the FDA without prior clearance from IMS HEALTH.** 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 _____ 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. In 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: October 9, 2003	DATABASE SEARCHED: Adverse Event Reporting System (AERS)		

SEARCH CRITERIA:

ical 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 cases².

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 from 15 to 38 years (N=23).

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:

van Herten 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 34-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-2³. 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:

/S/ 10/31/03

Sarah J. Singer, R.Ph.

DIVISION DIRECTOR SIGNATURE / DATE:

/S/ 10/31/03

Mark Avigan, M.D., Acting Director

³ Presumably, any AERS reports from the United Kingdom are duplicates of cases in the ADROIT database.

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this page is the manifestation of the electronic signature.**

/s/

Sarah Singer
10/31/03 11:54:17 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
10/31/03 05:00:17 PM
DRUG SAFETY OFFICE REVIEWER

NDA 21-045 Plan B®

The Division of Reproductive and Urological Drug Products requests the following additional information and/or updates to assist us in our review of your Complete Response to the Agency's Not Approvable letter of May 6, 2004 concerning the switch of Plan B from prescription status to OTC status.

1. An update on all on-going studies with Plan B either sponsored by Barr or being conducted with support from Barr
2. An update on other on-going studies with Plan B or recently completed but unpublished studies with Plan B about which Barr has information
3. An update on USA pharmacy availability of emergency contraception products
4. Updated global data on the number of countries with true OTC or behind the counter (BTC) availability of emergency contraception products; also provide data on age restrictions if there are any for each country.
5. Any proposed changes or further details in the CARE Program
6. All recent articles from the medical literature or other data sources not previously submitted to the Division concerning:
 - a. overall safety of levonorgestrel for emergency contraception, especially relating to ectopic pregnancy, hospitalizations for bleeding or serious adverse events, and birth defects (congenital anomalies) possibly associated with levonorgestrel use
 - b. use of emergency contraception in young women under age 18 and especially under age 16
 - c. use of emergency contraception and the incidence of STIs
 - d. use of emergency contraception in OTC-like settings

We would like a response to this information request by the COB on Thursday, January 6, 2005.

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this page is the manifestation of the electronic signature.**

/s/

Karen Kirchberg
1/3/05 04:23:41 PM
CSO

Daniel Davis
1/3/05 04:33:03 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045\S-011

INFORMATION REQUEST LETTER

Barr Research, Inc. [U.S. Agent for Duramed Pharmaceuticals, Inc.]
Attention: Joseph Carrado, M.Sc., R.Ph
Senior Director, Regulatory Affairs
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your April 16, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B (0.75mg levonorgestrel) tablets.

We also refer to your submission dated July 21, 2004.

We are prepared to begin negotiations regarding the proposed draft labeling for this product even though we have not completed all aspects of our analysis of your proposal for marketing. We request that you submit revised labeling that incorporates the following revisions and recommendations. We may raise additional concerns and make additional recommendations once all aspects of our analysis of your proposal have been completed.

Principal Display Panel (PDP) on the Carton

1. Rename the pharmacological category "Emergency Contraceptive" instead of "Emergency C] to be consistent with other OTC contraceptive drug products.
2. Include more information on the PDP to help consumers with self-selection and to clarify what emergency contraception is. In addition to your current statements that read, "Not Intended to Replace Regular Birth Control" and "Plan B Should Be Used Only in Emergencies", you should consider including other statements to reinforce consumer understanding, such as:

"Reduces the chance of pregnancy after unprotected sex (i.e., if a regular birth control method fails or after sex without birth control)".
3. Delete the periods from the end of the statements "Not Intended To Replace Regular Birth Control." and "Plan B Should Be Used Only In Emergencies.".
4. The advisory committee recommended that the labeling convey the urgency about taking the first pill right away. Add the sentence, "The sooner you take the first tablet, the more

effective Plan B will be” after the statement “Take the first pill as soon as possible within 72 hours of unprotected sex”.

5. Add the phrase “Prescription only for women age 15 and younger” to the PDP.

Drug Facts

6. 21 CFR 201.66 (d) provides the format requirements for **Drug Facts**. Submit your font size and type specifications for title, headings, subheadings, text, and bullets.
7. Delete “Plan B” anywhere it appears in the **Drug Facts** labeling and substitute “this product”. Although it is our policy not to allow brand names of drug products in the **Drug Facts** labeling, we are making an exception for the website address (refer to item # 32 listed below).
8. Under **Active Ingredient**, revise the first “I” in “Ingredient” to be lower case.
9. Under **Purpose**, substitute the word “contraceptive” for the word “contraception” in “Emergency contraception” in order to be consistent with the OTC contraceptive drug products.
10. Under **Use**, revise the letter “R” in “Reduces” to be lower case.
11. Under **Use**, revise the space between the heading “Use” and the word “Reduces” in accordance with 201.66 (d)(4).
12. Under **Use**, delete the period after the word “sex”.
13. Under **Warnings**, move the subheading “Do Not Use” from the same line as “Warnings”, in accordance with 201.66 (d)(6).
14. Under **Warnings**:
 - a) revise the order of the warnings so that the “Allergy alert” is listed first, in accordance with 201.66 (c)(5)(b).
 - b) revise the allergy alert to read, “Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel”.
 - c) delete the second bulleted allergy statement.

This “Allergy alert” replaces your allergy statement which is currently located under **Warnings**, “Do not use”.

15. Under *Warnings*, insert a “Sexually transmitted diseases (STDS) alert” after the Allergy alert to read as follows: “**Sexually transmitted diseases (STDs) alert:** This product does **not** protect against HIV/AIDS or other STDs”. Delete the statement under *Warnings* that reads, “[]’.
16. Under *Warnings*, delete the colon from the subheading “**Do not use**”.
17. Under *Warnings*, revise “DO NOT USE” to read “**Do not use**” (change to upper and lower case letters and no italics) in accordance with 201.66 (d)(1).
18. Under “**Do not use**”, add the bulleted statement “for regular birth control”.
19. Under “**Do not use**”, relocate the statement “Plan B is not recommended for regular contraception” to *Other information*.
20. Delete the phrase “Rx only for women age 15 and younger” from where it is currently positioned in *Drug Facts*.
21. Under *Warnings*, “**When using this product**”, delete the comma from the subheading “When using this product, you may have”. Also, remove the bolding from the words “you may have”.
22. Under *Warnings*, “**When using this product**”, begin each bulleted word with a lower case letter.
23. Include the accidental overdose/ingestion warning as set forth in 330.1(g) to read “**Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control center right away.”
24. Under *Directions*, add the following bulleted statement as the first statement in this section: “adults 16 years of age and over.”.
25. Under *Directions*, revise the first bulleted statement (which is now the second bulleted statement) as follows: begin the first statement with a lower case “t”, bold both statements that comprise this bullet, and delete “Plan B” from the second statement and substitute “it”.
26. Under *Directions*, revise the second bulleted statement (which is now the third bulleted statement) as follows: delete the period at the end of the statement, and bold the phrase “12 hours” in direction “take the second tablet **12 hours** after you take the first tablet”.

27. Under ***Directions***, add a new fourth bulleted statement to read: “prescription only for age 15 and under. If age 15 and under, see a healthcare provider.”
28. Create a new section entitled ***Other information*** (content follows below).
29. Under ***Other information***, add the following bulleted statements:
 - “before using this product read the enclosed consumer information leaflet for complete directions and information”
 - “this product is not recommended for regular birth control. It does not work as well as most other birth control methods used correctly.”
 - “this product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of sperm and egg) or attachment of a fertilized egg to the uterus (implantation). See consumer information leaflet.”
 - “correct use of a latex condom by your partner with every sexual act will help reduce the risk of getting HIV/AIDS and other STDs from infected partners.”
 - describe the tamper-evident statement. In accordance with 211.132(b)(1) and (c)(2), you need to identify a characteristic (e.g., a printing, trademark, logo, or picture) which, when breached or missing, would provide visible evidence to consumers that tampering has occurred. Refer to that characteristic in your labeling.
 - “store at 20-25°C (68-77°F)”
30. Under ***Inactive ingredients***, list the ingredients in alphabetical order to comply with 201.66(c)(8).
31. Revise the “I” in the word “Ingredients” in ***Inactive ingredients*** to be lower case.
32. Under ***Questions or comments?***, bold the phone number. We recommend that you include the days of the week and time of day when a person is available to respond to questions. We will allow you to include your trade name, “plan B”, in your website address.

For your convenience, we have included a sample ***Drug Facts*** label at the end of this letter that incorporates the comments above.

Inner Carton Panels (Blister Packaging for Plan® B Tablets) and other Panels

33. It is not clear to us how consumers would use the “Time Reminder” mechanism you included in this labeling submission. Justify the utility of this tool, or propose one that is more consumer friendly.

34. Revise the indication on the front of the packaging from “Emergency [] }
[] } to “Emergency Contraceptive” to be consistent with outer carton labeling.
35. Include a statement to the effect that the sooner the first pill is taken, the more effective the product is, to be consistent with the directions in *Drug Facts*.
36. Provide a mechanism to ensure that women read the labeling on the back of the inner carton panel (i.e., lift, ▼, etc.).
37. Remove the four bulleted statements on the back of the inner carton package and repeat *Drug Facts* instead.

Consumer Information Leaflet (pages 2-3)

38. We recommend that you substitute pages 2 and 3 of your Patient Brochure (which should be called a Consumer Information Leaflet) with the following content:

What is Plan B[®]?

Plan B[®] is emergency contraception. Emergency contraception is a **backup** method of preventing pregnancy and is not for routine use. Drugs used for emergency contraception are called emergency contraceptive pills, postcoital pills, or morning after pills.

Plan B[®] can reduce your chance of pregnancy after unprotected sex (if your regular birth control method fails or if you have had sex without birth control). For example, if you were using a condom and it breaks or if you forgot to take two or more birth control pills this month, or if you did not use any birth control method, Plan B[®] may work for you.

How does Plan B[®] work?

Plan B[®] contains a dose of the hormone levonorgestrel that is higher than in a single birth control pill. Levonorgestrel has been used in birth control pills for over 35 years. 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.

When is it appropriate to use Plan B[®]?

You can use Plan B[®] **after** you have had unprotected sex one or more times in the last three days (72 hours), and you don't want to become pregnant.

Plan B[®] can be used as a backup method to birth control if, for example,

- Your regular birth control failed (your partner's condom broke or slipped).
- You made a mistake with your regular method (you missed two or more birth control pills this month).
- You did not use any birth control method.

When is it not appropriate to use Plan B[®]?

- Plan B[®] should not be used as a regular birth control method. It does not work as well as most other forms of birth control when they are used consistently and correctly. Plan B[®] is a backup or emergency method of contraception.
- Plan B[®] should not be used if you are already pregnant because it will not work.
- Plan B[®] should not be used if you are allergic to levonorgestrel.
- Plan B[®] does not protect against HIV (the virus that causes AIDS) or other sexually transmitted diseases (STDs). The best ways to protect yourself against getting HIV or other STDs are to use a latex condom correctly with every sexual act or not to have sex at all.

How can I get the best results from Plan B[®]?

You have only a few days to prevent pregnancy after unprotected sex. **Plan B[®] works better the sooner you take it.** Take the first Plan B[®] tablet **as soon as possible but not later than three days (72 hours)** after unprotected sex. Take the second tablet **12 hours** later.

How effective is Plan B[®]?

Plan B[®] works best the sooner you use it. If it is taken within 72 hours (3 days) after sex, it will significantly decrease the chance that you will get pregnant. **Plan B[®] works even better than this if taken within the first 24 hours after sex.**

How will I know if Plan B[®] worked?

Most women will have their next menstrual period at the expected time or within a week of the expected time. If your menstrual period is delayed beyond one week, you may be pregnant and you should get a pregnancy test and follow up with your doctor.

What if I am already pregnant and use Plan B®?

There is no medical evidence that Plan B® would harm a developing baby. If you take Plan B® accidentally after you are already pregnant, or it does not work and you become pregnant, it is not likely to cause any harm to you or your pregnancy. Plan B® should not have any effect on a pregnancy after implantation.

Can I use Plan B® for regular birth control?

Plan B® should not be used for regular birth control. Plan B® is not as effective as using a regular birth control correctly and consistently. It is a backup method to be used if your regular birth control fails or if you have sex without birth control.

How often can I use Plan B®?

Plan B® is meant for infrequent emergency protection. If you need to use emergency contraception often, you should consult with your health care professional for your best methods of birth control and STD prevention.

Will I experience any side effects from Plan B®?

When used as directed, Plan B® is safe for women. Plan B® has no serious or lasting medical side effects. Some women will experience non-serious side effects, such as nausea, stomach pain, headache, dizziness, or breast tenderness. These are similar to the side effects of regular birth control pills. Some women have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late. **If your period is more than a week late, you should get a pregnancy test.**

What warnings should I know about when using Plan B®?

Plan B® does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs).

Do not use:

- if you already pregnant (because it will not work)
- if you are allergic to levonorgestrel or any of the ingredients in Plan B[®]
- for regular birth control

When using this product you may have:

- nausea
- vomiting
- stomach pain
- tiredness
- diarrhea
- dizziness
- breast pain
- headache

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

What are the directions for using Plan B[®]?

- **adults 16 years of age and over:**
 - **take the first tablet as soon as possible but not later than 72 hours (3 days) after unprotected sex**
 - take the second tablet **12 hours** after you take the first tablet
 - if you vomit within one hour of taking either dose of medication, call a health care professional to discuss whether to repeat the dose.
- prescription only for age 15 and under. If age 15 or under, see a healthcare provider

What should I do if I have questions about Plan B[®]?

If you have questions or need more information about this product, call our toll-free number, 1-800-330-1271, or visit our website at www.go2planb.com.

Other information

- (Describe the tamper-evident feature of the package, i.e., “each Plan B[®] package is sealed in plastic wrap and secured with a printed seal. **Do not use if the printed seal has been either removed or broken.**”)

- store at 20-25°C (68-77°F)

Active ingredient: levonorgestrel, 0.75 mg in each tablet

Inactive ingredients: colloidal silicon dioxide, corn starch, gelatin, lactose monohydrate, magnesium stearate, potato starch, talc

Consumer Information Leaflet (pages 4-5)

39. Replace pages 4-5 of your Patient Brochure with the following content for the “Consumer Information Leaflet”:

Protect Yourself in More Ways Than One!

If you are sexually active, but you're not ready for a pregnancy, it is important to use routine pregnancy protection. There are many types of birth control. Whichever type you choose, it's important to use your routine birth control method as directed. This ensures that you have effective protection against pregnancy every time you have sex.

But, things do not always go as planned. You might have forgotten to take your pill, or another birth control method you use might have failed (for example, a condom can break during sex). That is why there is Plan B®. Plan B® is an emergency contraceptive that offers you a second chance to prevent pregnancy after unprotected sex or when you fail to use your birth control method correctly.

Remember, Plan B® is only for emergency pregnancy prevention. We know it works well for this purpose. There are many other products that we know work very well for routine birth control. The most effective of these are available by prescription from your health care provider. Other effective methods are available for purchase without a prescription.

There is also another form of protection to think about when you have sex: protection against sexually transmitted diseases (STDs). Some common STDs are HIV/AIDS, chlamydia, genital herpes, gonorrhea, hepatitis, human papilloma virus (HPV), genital warts, syphilis, and trichomonas. Some of these STDs can be very serious and can lead to infertility (permanent inability to have a baby), problems during pregnancy, chronic illness, and even death. All sexually active women are at risk of catching STDs because they may not be able to know that their partner has an STD (the partner himself may not know). If your partner uses a latex condom **correctly each and every time you have sex with him, this will help reduce the chance that you will catch an STD.** No other birth control methods will protect you from STDs. The female condom may give some STD protection, but it is not as effective as a male

latex condom. For more information on STDs call the Centers for Disease Control and Prevention (CDC) AIDS/STD Hotline. The CDC phone numbers are 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

Be sure to protect yourself against pregnancy and STDs by using some form of birth control plus a latex condom. Of course, not having sex is the most effective way to prevent pregnancy and stay free of STDs. We hope this information will help you make the right choices to stay healthy for your future.

Consumer Information Leaflet (pages 6-9)

40. Delete the section "
[

]
]

Consumer Information Leaflet (pages 10-14)

41. Delete the section " We believe the subject is covered sufficiently in the section "Protect Yourself in More Ways than One!"

Consumer Information Leaflet (Back Cover)

42. Revise the statements on the back cover to be more consumer-friendly and to resemble statements in a consumer information leaflet rather than a prescription package insert. For example, we suggest the following changes.

- ✓
-
-
-
-
-

]

Attachment 2.

Sample Drug Facts Labeling for Plan B®
This label provides content information only. It incorporates the recommendations made in Attachment 1 which are intended to make the Plan B labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive labeling. The font sizes for title, headings, subheadings, condensed text, bullets and other graphic features must be in accordance with 21 CFR 201.66.

Drug Facts											
Active ingredient (in each tablet) Levonorgestrel 0.25 mg		Purpose Emergency contraceptive									
Use reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)											
Warnings Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel Sexually transmitted diseases (STDs) alert: The product does not protect against HIV/AIDS or other STDs											
Do not use <ul style="list-style-type: none">■ if you are already pregnant (because it will not work)■ for regular birth control											
When using this product you may have <table border="0"><tr><td>■ nausea</td><td>■ vomiting</td><td>■ stomach pain</td></tr><tr><td>■ dizziness</td><td>■ diarrhea</td><td>■ bloating</td></tr><tr><td>■ menstrual changes</td><td>■ breast pain</td><td>■ headache</td></tr></table>			■ nausea	■ vomiting	■ stomach pain	■ dizziness	■ diarrhea	■ bloating	■ menstrual changes	■ breast pain	■ headache
■ nausea	■ vomiting	■ stomach pain									
■ dizziness	■ diarrhea	■ bloating									
■ menstrual changes	■ breast pain	■ headache									
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.											
Directions <ul style="list-style-type: none">■ adults 15 years of age and over<ul style="list-style-type: none">■ take the first tablet as soon as possible but not later than 72 hours (3 days) after unprotected sex. The sooner you take the first tablet, the more effective it will be.■ take the second tablet 12 hours after you take the first tablet■ prescription only for age 15 and under. If age 15 and under, see a healthcare provider.											
Other information <ul style="list-style-type: none">■ before using this product, read the enclosed consumer information leaflet for complete directions and information■ this product is not recommended for regular birth control. It does not work as well as most other birth control methods used consistently and correctly.■ this product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of the sperm and the egg) or attachment of a fertilized egg to the uterus (implantation). See consumer information leaflet.■ correct use of a latex condom by your partner with every sexual act will help reduce the risk of getting HIV/AIDS and other STDs from infected partners■ describe tamper evident statement (i.e., "this package is sealed in plastic wrap and secured with a printed seal. Do not use if the seal has been removed or broken.")■ store at 20-25°C (68-77°F)											
Inactive ingredients: colloidal silicon dioxide, corn starch, gelatin, lactose monohydrate, magnesium stearate, potato starch, talc											
Questions or comments? 1-800-338-1271 www.gonplan.com											

If you have any questions, call Tia Frazier, Project Manager, at 301-827-2271.

Sincerely yours,

{See appended electronic signature page}

Curtis Rosebraugh, M.D. M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
12/22/04 01:38:01 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S011

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

Dear Mr. Carrado:

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

On February 9, 2004, we received your February 6, 2004 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 21, 2004.

If you have any questions, call Karen Anderson-Kirchberg, N.P., Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

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

Dear Mr. Carrado:

We acknowledge receipt on July 22, 2004 of your July 21, 2004 resubmission to your new drug application for Plan B[®] (levonorgestrel) Tablets, 0.75 mg.

We consider this a complete, class 2 response to our May 6, 2004 action letter. Therefore, the user fee goal date is January 20, 2005.

If you have any question, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

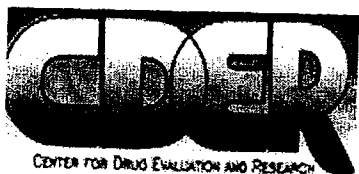
{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
8/11/04 11:16:05 AM
signed for Jennifer Mercier



OTC Drug Labeling Review Addendum

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Date: July 21, 2004 (CDER stamp date July 22, 2004)

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Barr Research Inc.

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: December 20, 2004

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Tia Frazier

Background


The label review for NDA 21-045 S-011 (BL), Plan B®, submitted July 21, 2004, was put into DFS on November 23, 2004. On December 16, 2004, the Division of Reproductive and Urologic Drug Products (HFD-580) requested that a statement in the review be revised to be more factual. This addendum documents the change.

Reviewer's Revision

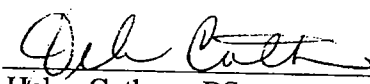
In Attachment 3, under the heading "**How does Plan B® work?**" in the consumer information leaflet, the sentence which reads "It is possible that Plan B® may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb), which usually occurs within 3 days after release of an egg from the ovary." is revised to read as follows:

"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."

This comment can be conveyed to the sponsor.

 12/20/04

Arlene Solbeck, MS
IDS - HFD 560

 12/20/04

Helen Cothran, BS
IDS Team Leader - HFD 560

NDA 21-405

HFD-580: Griebel/Davis/Monroe/Kirchberg/Shames

HFD-560: Division File

HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/Chen/Frazier

DOCID: AddendumPlanBlabel_12_20.doc

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/s/

Arlene Solbeck
12/20/04 02:03:20 PM
INTERDISCIPLINARY

Helen Cothran
12/20/04 02:52:51 PM
INTERDISCIPLINARY



OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011 (BL)

Submission Date: July 21, 2004 (CDER stamp date July 22, 2004)

Type of Submission: Supplement, Rx-to-OTC Switch

Sponsor: Barr Research Inc.

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: November 15, 2004

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Tia Frazier

Background

Plan B® is emergency contraception, a backup method of birth control. It can reduce the risk of pregnancy after unprotected sex (i.e. if a regular birth control method fails or after sex without birth control). Plan B® contains a concentrated dose of levonorgestrel, a synthetic hormone used in birth control pills for over 35 years. FDA approved Plan B® for prescription use on July 28, 1999 under NDA 21-045. On April 16, 2003, the sponsor submitted an NDA to switch Plan B® from prescription status to OTC. The sponsor also submitted revised carton and package insert labeling on October 15, 2003 (CDER stamp date October 24, 2003). Plan B® was reviewed jointly by the Advisory Committee on Reproductive and Urologic Drugs and the Nonprescription Drugs Advisory Committee on December 16, 2003, and approval for this application was recommended by the committees. The sponsor received a not approvable letter for Plan B® on May 6, 2004.

This current submission is an amendment to S-011 providing support for the marketing of Plan B® as a nonprescription product for women 16 years and older and as a prescription-only product for women 15 years and younger. The sponsor submitted outer carton labeling including Drug Facts, inner carton labeling including a "time reminder" strategy for remembering when to take the second pill, a consumer brochure, and a package insert.

Reviewer's Comments and Recommendations

- A. Attachment 1 contains comments on the sponsor's proposed Plan B® OTC carton labeling (principal display panel (PDP), Drug Facts, and other panels). These comments are intended to make the Plan B® labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive labeling. These comments also address any labeling changes suggested by the advisory committee on 12/16/03.
- B. Attachment 2 contains a mock Drug Facts label incorporating the recommendations made by FDA in Attachment 1 to make the carton and Drug Facts labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive labeling.
- C. Attachment 3 is FDA's revised version of pages 2-5 of the sponsor's proposed Consumer Information Leaflet, "Important Information for Women About Plan B®, Birth Control & Sexually Transmitted Diseases". It also contains comments on "Methods of Birth Control" (pages 6-9) and Sexually Transmitted Diseases (pages 10-14).

Attachment 1.**A1. Principal Display Panel (PDP)**

1. Change the pharmacological category from "Emergency Pregnancy Prevention" to "Emergency Contraceptive" to be consistent with other OTC contraceptive drug products.
2. We recommend that more information be placed on the PDP to help the consumers in their self-selection and to clarify what emergency contraception is, such as the following, which can be added to the statements "Not Intended To Replace Regular Birth Control." and "Plan B Should Be Used Only In Emergencies":

"Reduces the chance of pregnancy after unprotected sex (i.e., if a regular birth control method fails or after sex without birth control)".
3. Delete the periods from the end of the statements "Not Intended To Replace Regular Birth Control." and "Plan B Should Be Used Only In Emergencies."
4. The advisory committee recommended that the labeling convey the urgency about taking the first pill right away. We recommend adding the phrase "The sooner you take the first tablet, the more effective Plan B will be" after the statement "Take the first pill as soon as possible within 72 hours of unprotected sex".
5. Add the phrase "Prescription only for women age 15 and younger" to the PDP.

A2. Drug Facts

6. 21 CFR 201.66 (d) provides the format requirements for Drug Facts. Please submit your font size and type specifications for title, headings, subheadings, text, and bullets.
7. Delete "Plan B" anywhere in the Drug Facts labeling and substitute "this product". It is FDA's policy not to allow brand names of drug products in the Drug Facts labeling.
8. **Active Ingredient (in each tablet):** make the letter "I" in "Ingredient" lower case.
9. **Purpose:** the word "contraception" in "Emergency contraception" should be changed to "contraceptive" to be consistent with other OTC contraceptive drug products.

10. Use:
 - Make the letter “R” in “Reduces” lower case.
 - In accordance with 201.66 (d)(4), revise the space between the heading “Use” and the word “Reduces”.
 - Delete the period after the word “sex”.
11. Warnings: in accordance with 201.66 (d)(6), move the subheading “Do Not Use” from the same line as “Warnings”.
12. Warnings: the first statement under *Warnings* should be the “Allergy alert” (in accordance with 201.66 (c)(5)(b)). Insert the following: “Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel”. The current allergy statement in the “Do not use” section of the labeling should be deleted.
13. Warnings: insert a “Sexually transmitted diseases (STDs) alert” after the Allergy alert to read as follows: “Sexually transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs”. FDA has also proposed this alert for OTC vaginal contraceptives containing nonoxynol-9. The sponsor's similar warning which is not designated as an alert needs to be deleted.
14. Do not use:
 - Delete the colon from this subheading.
 - In accordance with 201.66 (d)(1), revise “**DO NOT USE**” to read “Do not use” (change to upper and lower case letters and no italics)
 - Delete the second bulleted statement about being allergic to Plan B. It is covered by inserting the “Allergy alert” (see A2.12 above).
 - Add the bulleted statement “for regular birth control”, which becomes the second bulleted statement in this section.
15. Move “Plan B is not recommended for regular contraception” to “*Other information*”. Also, delete “Plan B” from the statement. Substitute “this product” (see A2.7 above)
16. Replace “Plan B does not protect against HIV (the virus that causes AIDS) or any other sexually transmitted diseases” with the “Sexually transmitted diseases (STDs) alert” (see A2.13. above).

17. Delete the phrase "Rx only for women age 15 and younger" from Drug Facts (move to PDP – see A1.5 above).
18. **When using this product:**
 - Delete the comma from the subheading "**When using this product, you may have**". Also, the words "you may have" should not be bolded.
 - Begin each bulleted word with a lower case letter.
19. **Pregnancy/breast-feeding warning:** The sponsor excluded the pregnancy and breastfeeding warning "**If pregnant or breast-feeding, ask a health professional before use**". Technically, the pregnancy warning is unnecessary because the label tells women not to use the product if they are pregnant because it will not work. The advisory committee felt that a breast-feeding warning was not necessary. Therefore, the sponsor is exempted from including a pregnancy/breast-feeding warning.
20. Include the accidental overdose/ingestion warning as set forth in 330.1(g) to read "**Keep out of reach of children. If swallowed, get medical help or contact a Poison Control center right away.**"
21. **Directions:**
 - Add a bulleted statement which becomes the first bulleted statement to read: "adults 16 years of age and over."
 - The first bulleted statement then becomes the second bulleted statement. Revise as follows: begin the first statement with a lower case "t", bold both statements that comprise this bullet, delete "Plan B" from the second statement and substitute "it".
 - The second bulleted statement then becomes the third bulleted statement. Delete the period at the end of the statement. Bold "12 hours".
 - Add a new bulleted statement which becomes the fourth bulleted statement to read: "prescription only for age 15 and under. If age 15 and under, see a healthcare provider."
22. Add a new section "***Other information***" (and see below).
23. **Other information:** Add the following bulleted statements:
 - a. **before using this product read the enclosed consumer information leaflet for complete directions and information**

- b. this product is not recommended for regular birth control. It does not work as well as most other birth control methods used correctly.
- c. **this product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of sperm and egg) or attachment of a fertilized egg to the uterus (implantation). See consumer information leaflet.**
- d. correct use of a latex condom by your partner with every sexual act will help reduce the risk of getting HIV/AIDS and other STDs from infected partners.
- e. *(Describe the tamper evident statement. In accordance with 211.132(b)(1) and (c)(2), the product needs an identifying characteristic (e.g., a printing, trademark, logo, or picture) which, when breached or missing, would provide visible evidence to consumers that tampering has occurred, and that characteristic must be referenced in the labeling)*
- f. store at 20-25°C (68-77°F)

24. **Inactive ingredients:**

- List in alphabetical order to comply with 201.66(c)(8).
- Change the “I” in the word “Ingredients” in the heading “*Inactive ingredients*” to lower case.

25. **Questions or comments?** Bold the phone number. We recommend that you include the days of the week and time of day when a person is available to respond to questions. (It is the agency’s policy to not include brand names in the Drug Facts box. However, we may grant an exemption to this policy and allow use of this website address in the Drug Facts box if the sponsor provides adequate justification).

A sample Drug Facts label for Plan B incorporating the above comments is found in Attachment 2.

A3. Inner Carton Panels (Blister Packaging for Plan® B Tablets) and other panels

26. **Time Reminder:** It is not clear how consumers would use this “Time Reminder” mechanism in the labeling. Please clarify. Alternatively, the sponsor should come up with an easier time reminder method, perhaps a “scratch off clock”.
27. Revise the indication on the front of the packaging from “Emergency Pregnancy Prevention” to “Emergency Contraceptive” to be consistent with outer carton labeling.

28. Revise the directions on the front of the packaging to be consistent with the directions in *Drug Facts* (i.e., include a statement to the effect that the sooner the first pill is taken, the more effective the product is).
29. The inner carton package consisting of the tablets has a front and a back. The sponsor should provide a mechanism to ensure that women read labeling on the back of the inner carton panel (i.e., lift, ▼, etc.).
30. Remove the four bulleted statements on the back of the inner carton package and repeat *Drug Facts* instead.

Arlene Solbeck 11/22/04

Arlene Solbeck, MS
IDS - HFD 560

Helen Cothran 11/22/04

Helen Cothran, BS
IDS Team Leader - HFD 560

NDA 21-405

HFD-550: Griebel/Davis/Monroe/Kirchberg/Shames

HFD-560: Division File

HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/ Chen/Frazier

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/s/

Arlene Solbeck
11/22/04 04:39:58 PM
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Helen Cothran
11/23/04 11:20:59 AM
INTERDISCIPLINARY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

Barr Laboratories, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
5040 Lester Road
Cincinnati, OH 45213

Dear Mr. Carrado:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B® (levonorgestrel) Tablets.

We also refer to your June 30, 2004, correspondence, received July 6, 2004, requesting a meeting to discuss your proposed resubmission to your Not Approvable (NA) letter dated May 6, 2004.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: August 19, 2004

Time: 1:00 – 3:00 PM EST

Location: Parklawn Building, 3rd Floor Conference Rooms, Potomac

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at mercierj@CDER.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Karen Kirchberg, 301-827-4254; the division secretary, 301-827-4260.

Provide the background information for this meeting (three copies to the NDA and 25 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by August 5, 2004, we may cancel or reschedule the meeting.

NDA 21-045/S-011

Page 2

If you have any questions, call Karen Kirchberg, Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
7/9/04 09:52:01 AM

TELECONFERENCE MINUTES

Date: May 5, 2004, 12:00 – 12:30 PM

NDA 21-045/S011 Drug: Plan B (levonorgestrel) Tablets, 0.75 mg

Indication: Emergency Contraception (OTC use)

Sponsor: Barr Research, Inc.

Type of Meeting: Internal

Meeting Chair: Steven Galson, MD – Acting Director, CDER

Meeting Recorder: Florence Houn, MD, Director, ODE III

Attendees:

Office of the Center Director (HFD-001)

Steven Galson MD, Acting Director

Office of Regulatory Policy (HFD-005)

Jane Axelrad JD, Associate Director for Policy

Office of New Drugs (HFD-020)

John Jenkins MD, Director

Sandra Kweder MD, Deputy Director

Office of Drug Evaluation III (ODE III; HFD-103)

Florence Houn MD, Director

Julie Beitz MD, Deputy Director

Bronwyn Collier, Associate Director for Regulatory Affairs

Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Daniel Shames MD, Director

Office of Drug Evaluation V (ODE V; HFD-105)

Jonca Bull MD, Director

Terri Rumble, Associate Director for Regulatory Affairs

Division of Over the Counter Drug Products (DOTCDP; HFD-560)

Charles Ganley MD, Director

Curt Rosebraugh, MD, Deputy Director

Background: Supplement 011 proposes a switch in marketing status for Plan B from prescription to over-the-counter (OTC). Final review and action on the application will be in the Office of the Center Director. Dr. Galson requested this meeting to update DRUDP, DOTCDP, ODE III and ODE V on the pending action.

Discussion:

Dr. Galson informed the participants on the call that:

- The action letter for the Plan B OTC switch will be a Not Approvable letter. The letter is anticipated to be signed May 6, 2004 in the afternoon.

- The reason for the Not Approvable action is lack of data in the age group <16, particularly the total absence of data in <14 years olds, in which there is an urgent need to prevent pregnancy.
- Dr. Dianne Murphy, after conferring with staff in the Division of Pediatric Drug Development provided input on the difficulty of extrapolating safety and effectiveness in older populations to young adolescents.
- The literature cited in OND reviews do not sufficiently approximate actual OTC use to support approval. No study tests the hypothesis that typical adolescent users with no extra information will use the product correctly.
- Non-medical or political views about the drug and sexual behavior did not factor into the decision.

Dr. Galson will call Barr prior to the action to ask permission to publicly discuss the action in general terms and to post the not approvable letter on the CDER web site. The agency will issue statements concerning the action including a press release, posting Qs & As and the not approvable letter (given permission from Barr) on the web, and conduct a press interview on Friday morning (spokesperson- Dr. Galson). The staff's disagreement with the NA action will be acknowledged publicly.

Certain members of the Joint Advisory Committee held on December 16, 2003 will be contacted prior to the action. Peter Pitts will be asked to help identify appropriate members to contact.

Barr's March .11, 2004, submission of a marketing plan for OTC availability for older women and prescription for adolescents under 16 years was forwarded to the Office of the Chief Counsel (OCC) but no final review was done. Any future marketing plan that proposes dual marketing status would need OCC review within PDUFA time frames.

Minutes prepared by ODE III: F. Houn, J. Beitz, B. Collier

Reviewed/Revised: J.Bull, T.Rumble, D.Shames, S.Galson, J.Jenkins, C.Rosebraugh

Final Review/Revision: F.Houn 6/21/04, J.Axelrad 6/16/04, J.Bull 6/17/04, T.Rumble 6/17/04,

C.Rosebraugh 6/17/04, D.Shames 6/17/04, S.Galson 6/17/04, J.Beitz 6/17/04, J.Jenkins 6/30/04

Chair Concurrence: S. Galson 6/17/04

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/s/

Steven Galson

6/30/04 05:34:48 PM

February 26, 2004

Administrative memorandum

Drug Product: Plan B®

Indication: emergency contraception

Applicant: Barr Laboratories, Inc., Women's Capital Corporation

RE: Explanation of administrative closure of a minor labeling amendment dated October 15, 2003, received by FDA on October 24, 2003

FDA requested copies of the labeling for the Plan B product used in the label comprehension study, the actual use study, and the proposed OTC labeling for Supplement 011. The applicant submitted this amendment to educate the FDA about the iterative development of the label proposed in Supplement 011. The October 15, 2003, submission did not require a labeling review, and thus is administratively closed with this memorandum.

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/s/

Tia Frazier
2/26/04 01:15:11 PM
CSO

Meeting Minutes

Date: February 18, 2004 **Time:** 2:00 PM – 3:00 PM **Location:** PKLN; Conference Rm 13-57

NDA 21-045/S011 **Drug:** Plan B® (levonorgestrel) Tablets, 0.75 mg

Indication: Emergency Contraception (OTC use)

Sponsor: Barr, Inc. / Women's Capital Corporation

Type of Meeting: Internal

Meeting Chair: Steven Galson, M.D. –Acting Director, CDER

Meeting Recorder: Karen Anderson, N.P. - Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)

Attendees:

Office of the Commissioner of Food and Drugs

Mark McClellan, M.D. - Commissioner

Office of the Center Director (HFD-001)

Janet Woodcock, M.D. - Director, Cross Center Initiatives Task Force, OC

Steven Galson, M.D. - Acting Director

Office of New Drugs (OND; HFD-020)

John Jenkins, M.D. - Director

Sandra Kweder, M.D. - Deputy Director

Office of Executive Programs (OEP; HFD-006)

Maureen Hess, M.P.H., R.D. - Science Policy Analyst, Executive Operations Staff

Lee Lemley - Policy Analyst, Executive Operations Staff

Office of Drug Evaluation III (ODE III; HFD-103)

Florence Houn, M.D. - Director

Julie Beitz, M.D. - Deputy Director

Bronwyn Collier, R.N. - Associate Director for Regulatory Affairs

Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Daniel Shames, M.D. - Director

Donna Griebel, M.D. - Deputy Director

Margaret Kober, R.Ph. - Chief, Project Management Staff

Scott Monroe, M.D. - Medical Team Leader

Daniel Davis, M.D. - Medical Officer

Karen Anderson, N.P. - Project Manager

Office of Drug Evaluation V (ODE V; HFD-105)

Jonca Bull, M.D. - Director

Terri Rumble, R.N., B.S.N. - Associate Director for Regulatory Affairs

Division of Over the Counter Drug Products (OTC; HFD-560)

Charles Ganley, M.D. - Director

Curtis Rosebraugh, M.D., M.P.H. - Deputy Director

Andrea Leonard Segal, M.D., M.S. - Medical Team Leader

Jin Chen, M.D., Ph.D. - Medical Officer

Helen Cothran, B.S. - Interdisciplinary Scientist, Team Leader

Arlene Solbeck, M.S. - Interdisciplinary Scientist

Tia Frazier, R.N., M.S. - Project Manager

Division of Surveillance, Research, & Communication Support (DSRCS; HFD-410)

Karen Lechter, J.D., Ph.D. - Social Science Analyst

Meeting Objective: To inform and update the Office of the Commissioner (OC) on the Division of Over the Counter Drug Product's (OTC) and the Division of Reproductive and Urologic Drug Product's (DRUDP) positions on the acceptability of the application after reviewing numerous studies on adolescents.

Background: Plan B was approved as a prescription medication for emergency contraception on July 28, 1999. Barr, Inc. / Women's Capital Corporation has applied for an over-the-counter (OTC) switch. A joint meeting of the Non-Prescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs took place on December 16, 2003. The Committee voted 23-4 in favor of the OTC switch. The Action date for this application was extended to May 21, 2004.

Discussion:

DRUDP reviewed the sponsor's Actual Use study (AUS) and additional data from 4 studies on use of emergency contraception that was submitted after the December 2003 Advisory Committee meeting. Particular emphasis was placed on use in adolescents in order to address concerns that had been conveyed to the Divisions and Offices from senior management regarding timing of doses, safety, and behavior changes that might result if product access increased.

The Divisions and Offices stated that they had concluded that the benefits of timely access outweighed any risk for all women, including adolescents, and support OTC availability without age restriction. The slides presented are attached.

The discussion encompassed the following points:

- Benefits of improved access to emergency contraception to women in general.
- Impact of improved access on unplanned pregnancy and abortion, especially for adolescents who are at high risk for unplanned pregnancy.

- Potential impact of OTC availability on sexual and contraceptive behavior of women, including adolescents.
- The evidence supporting OTC switch from the AUS and from additional US studies conducted in a variety of settings and involving over 11,000 women, of whom over 1400 were adolescents.
- Data from these studies supporting that women, regardless of age, can properly dose and self-select and do not exhibit changes in sexual or contraceptive behavior that are cause for concern.
- The relative strengths and weaknesses of the available evidence, particularly the level of relevance of the studies to the unrestricted OTC availability proposed in the application.
- The relatively low numbers of adolescents aged 16 years and younger who provided data on Plan B use in the AUS, which doubled when the adolescents who were aged 17 were included, and the proper weight that should be placed on data for adolescents from other studies.
- Feasibility of conducting studies in teens younger than 15, given local IRB restrictions.
- Label comprehension data for adolescents and adults was reviewed and considered from the perspective that label comprehension study findings are used in non-prescription drug development programs to design the label for future actual use studies, which are the definitive trials to test label performance.

At the conclusion of the meeting, the Commissioner expressed the following:

- He noted a trend toward a potential difference in various parameters between adults and adolescents in the Tina Raine study.
- The potential exists for changes in future contraceptive behaviors after adolescents take Plan B.
- He was not convinced the studies had enough power to determine if there were behavioral differences between adults and adolescents.
- Counseling by a learned intermediary may be of benefit, particularly to young teens.

Action Items:

- CDER was directed to continue to work with the sponsor on a marketing plan to limit availability of the product over the counter and to consider the most appropriate age groups to be restricted from access to the product.
- The Commissioner expressed that restricted distribution would deserve another discussion in a public forum before implementation.
- The Commissioner requested a rapid action on the application.

Minutes prepared: K. Anderson, N.P., Project Manager, DRUDP
Chair Concurrence: S. Galson, M.D. - Acting Director, CDER

Concurrence:

M. McClellan
J. Woodcock 2.24.04
S. Galson 3.15.03
J. Jenkins
S. Kweder 2.24.04
M. Hess
L. Lemley 2.24.04
F. Houn
J. Beitz 3.15.04
B. Collier 2.24.04
D. Shames
D. Griebel 2.24.04
M. Kober 2.23.04
S. Monroe
D. Davis
J. Bull 2.24.04
T. Rumble
C. Ganley
C. Rosebraugh 2.24.04
A. Solbeck
A. Leonard-Segal
H. Cothran
J. Chen
T. Frazier
K. Lechter 2.24.04

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 (HCP)**



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 childbirth morbidity**
- **Avoid abortion**
 - **For < 15 yo in US: 700 abortions/1000 live births**
 - **WA State abortion/ live birth ratios lower after pharmacy access (1997), including ratios for 15-19**
 - **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 year; 2% at 2 years

Outcomes Among Adolescents

- **Pregnancy**
 - 94 pregnancies/1000 females aged 15-19
 - Birth rates in 15-19 yo's declined by 39% in WA, 44% in CA, 40% in AK (pharmacy access states)
- **Fetal complications**
 - Pre-term birth
 - Low birth weight
 - Small for gestational age
- **STIs**
 - Chlamydia infection rates similar for ages 15-19 and 20-24
 - WA State and Seattle rates track with national rates

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 evaluating data from:**
 - **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**



Commissioner Briefing
February 18, 2004

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%

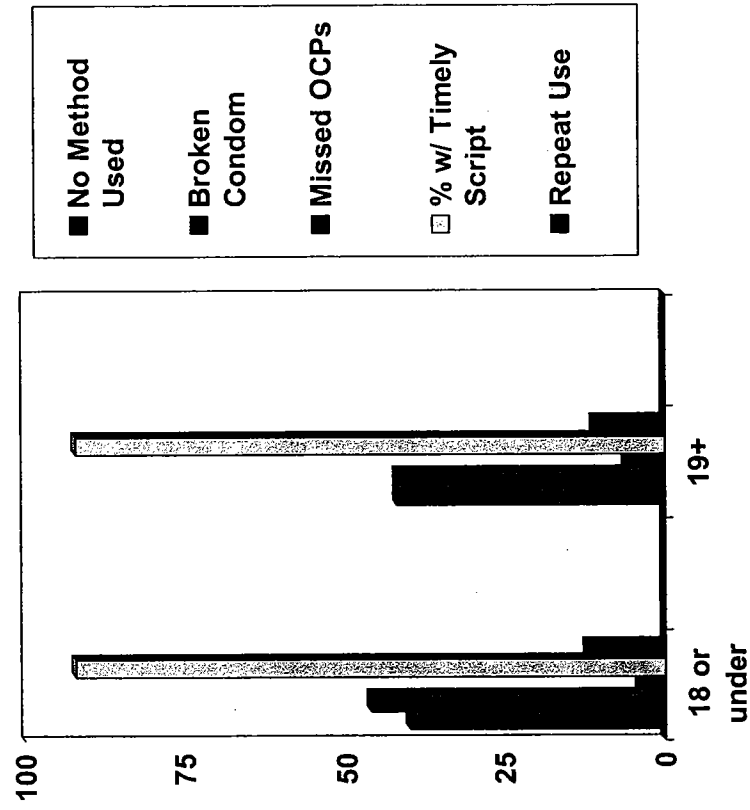
Behavior Changes in AUS: No Impact of Prior EC Use (Learned Intermediary/ HCP)

Behavior Change (% of Subjects)	Prior EC Use	
	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

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 \leq 72 hr
 - % requesting 2nd script

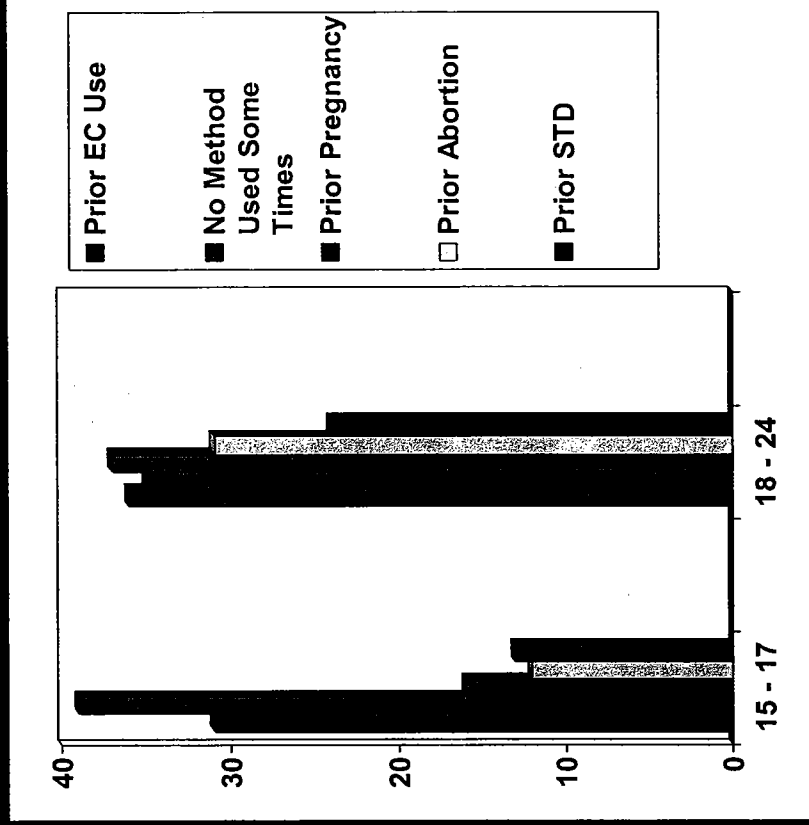
Percent of Subjects



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

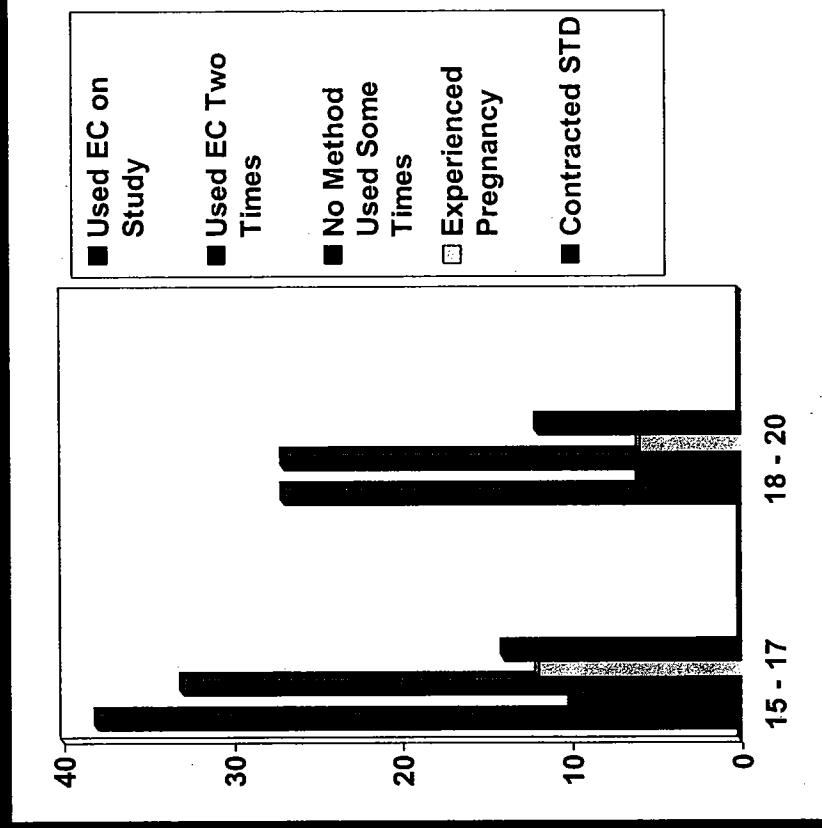
Percent of Subjects



Raine Follow-Up: No Age Differences in EC Use, Sexual Behavior, Outcomes

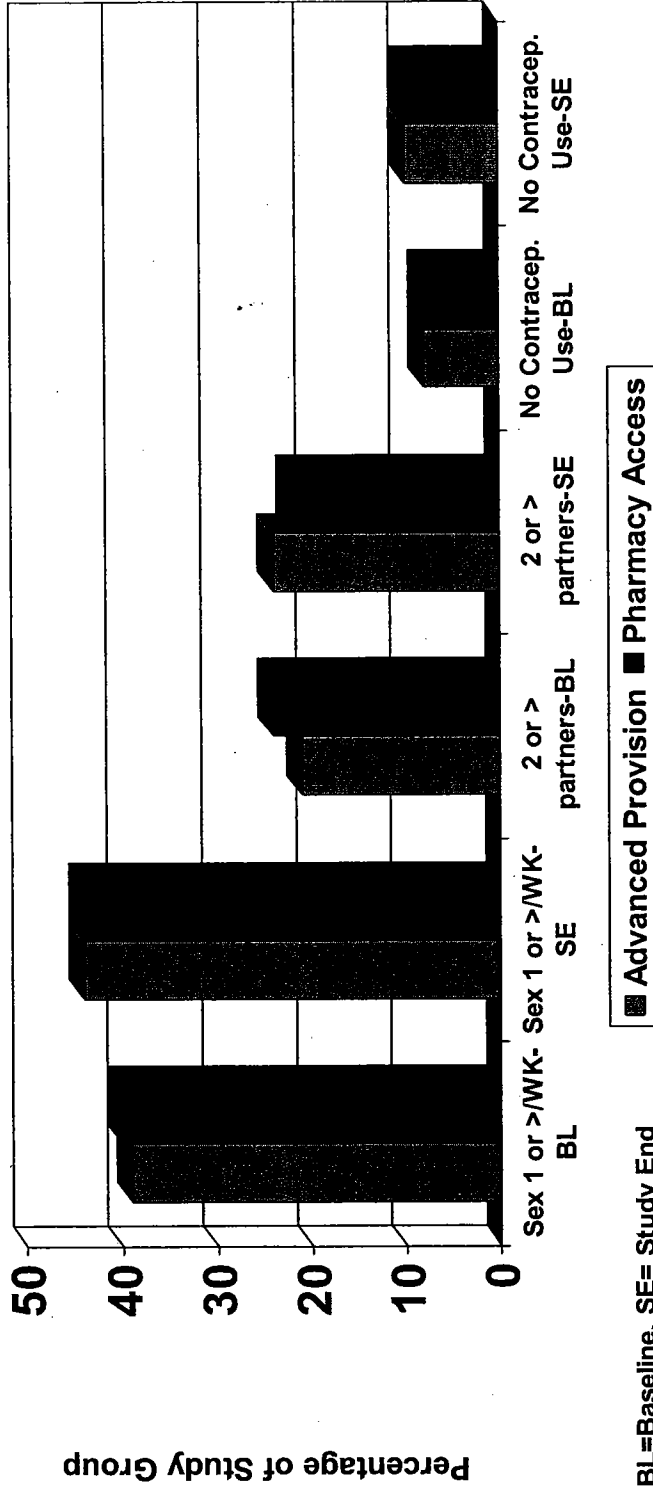
- **At 6 mo follow-up:**
 - 455 aged 15-17
 - 1,485 aged 18-24
- **Adolescents had no significant differences in:**
 - EC use on study
 - Timing of first dose
 - 80% within 24 h
 - EC use a second time
 - Unprotected sex
 - Pregnancies
 - STDs

Percent of Subjects



Raine Study: Behavioral Trends Ages 15-17

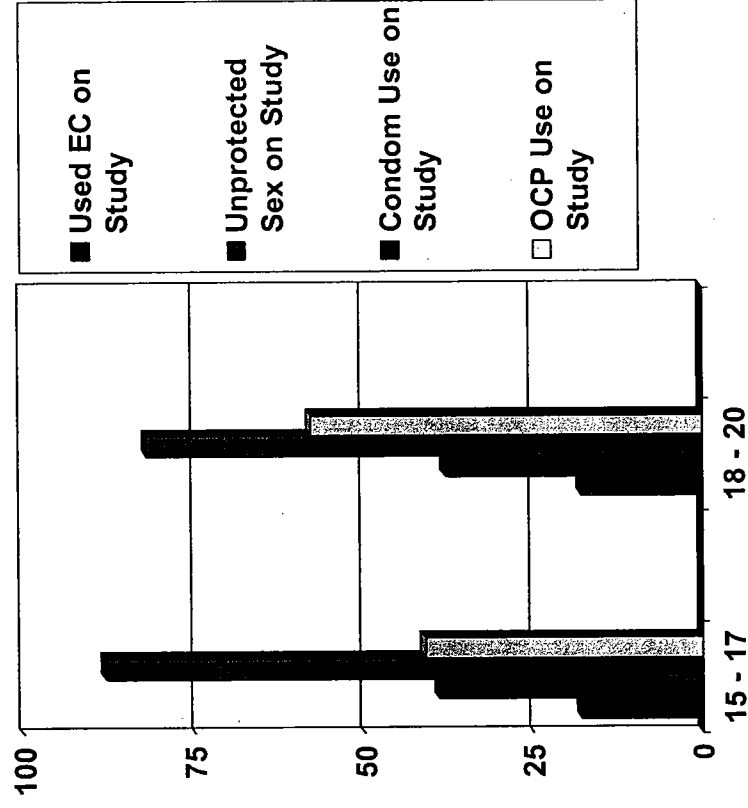
Behavioral Trends Over 6 Months



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

Percent of Subjects



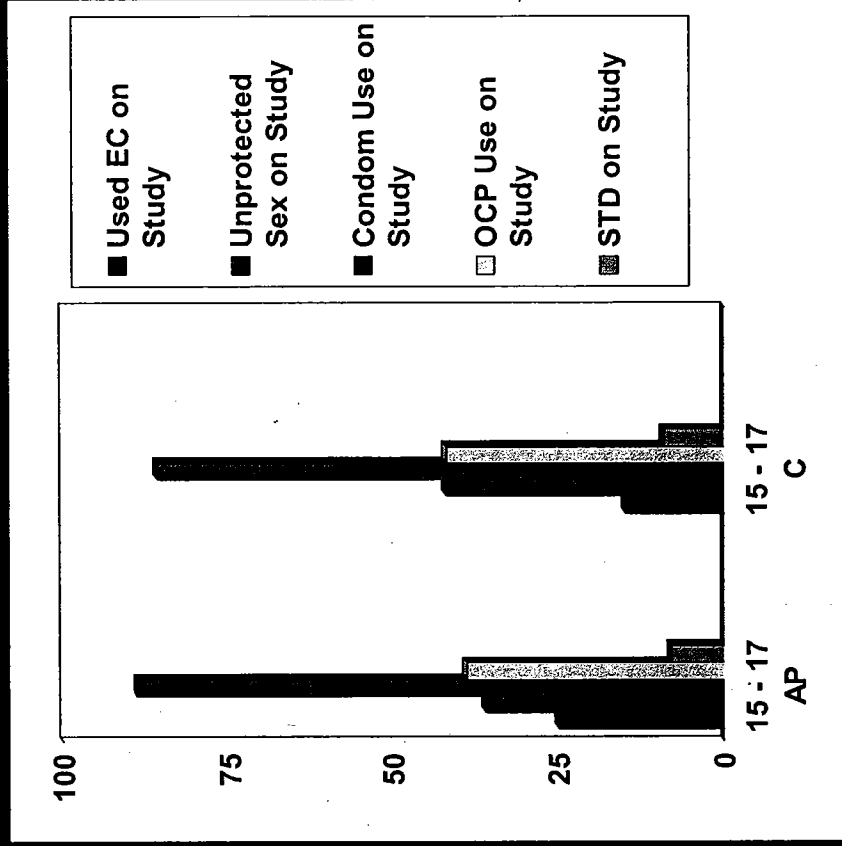
Gold Study: Timing of First and Second Dose

	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

Percent of Subjects



Plan B: Overall Risk-Benefit

- **Plan B meets criteria for OTC switch for all ages**
- **Benefit of timely access (with improved efficacy) to**
 - **Avoid unplanned pregnancy**
 - **Avoid abortion**
- **Benefit outweighs the risks for all ages**
 - **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**
- **No additional studies are needed**

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/s/

Steven Galson
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NDA 21-045/S011

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

Dear Mr. Carrado:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel) Tablets, 0.75 mg for emergency contraception.

We request that you submit the following additional data. In a cross-study comparison, the mean plasma C_{max} and AUC values of levonorgestrel following a single oral administration of Plan B tablet were about 47% and 23% lower in healthy adolescent females compared to healthy adult females, respectively. Please address the possible clinical significance of these apparent differences and discuss any factors that you believe may have contributed to the observed differences between the two populations. Include in your response any available data, including literature data, which support your conclusions.

If you have any questions, call Karen Anderson-Kirchberg, N.P., Project Manager, at (301) 827-4259.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
2/5/04 10:09:39 AM



NDA 21-045

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

Dear Mr. Carrado:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel) Tablets, 0.75 mg for emergency contraception.

We request that you submit additional data further supporting the use of Plan B in an adolescent population, specifically in the age range under 18 years. Of particular interest is additional supportive data that addresses 1) correct use (timing and self selection) of Plan B in a setting of minimal educational intervention; 2) repeat use, and 3) impact of access on routine contraceptive use and acquisition of sexually transmitted diseases in this population.

This supportive information may include the following:

1. 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.
2. Updated data from the study reported by Dr. Marvin Belzer, which was presented in abstract form in the NDA submission, with presentation of data analyses for the age subset of interest (<18 years).
3. Educational materials, including pamphlets and scripts, used in the 3-arm pharmacy vs. advanced access study by Tina Raine, which was presented as an interim study report in the NDA submission. Updated subset analyses by age group, examining the subset <18 years of age are of particular interest, including comparisons to the older age group.
4. Summary use data by the adolescent population in European countries where Plan B is available via pharmacy access and in those countries where it is available as an over the counter product, i.e. Sweden and Norway. Data of interest would include numbers of adolescent uses and use relative to use in the adult population. Any epidemiological data available from those countries on the impact that access to emergency contraception has

had on adolescent contraceptive behaviors and acquisition of sexually transmitted infections in this population is of interest.

5. Please provide information on whether age restrictions to access to emergency contraception exist in countries where it is available through pharmacy access. If age restrictions exist, provide the details of those restrictions – age limits, why they were imposed, and how these limits are enforced.

In addition, please provide information to address the following issues:

1. Impact of food on the pharmacokinetics of levonorgestrel.
2. Summaries of studies that document the dose selection of levonorgestrel for emergency contraception. Are there data that show that lower doses are effective? Are there data that define dose levels that are not effective?
3. Please provide the ages of the women whose pregnancies were included in the post-marketing levonorgestrel safety database you accessed and presented in the NDA (i.e., the database that reported 123 pregnancies).
4. Please summarize any changes you propose to the CARE program in response to comments made by the 28 members during the December 2003 Joint Advisory Committee Meeting.

If you have any questions, call Karen Anderson, NP, Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
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For Internal Use Only

Meeting Request Denied Form**

(Use this form to document the meeting denied via telephone.)

Complete the information below and check form into DFS.

Application Type	<input type="checkbox"/> P-IND <input type="checkbox"/> IND <input checked="" type="checkbox"/> NDA
Application Number	21045 S011
DATE Meeting Denied (per communication with requester)	August 13, 2004
Reason for Denial	The Division canceled the meeting. It was determined that it was not necessary because the sponsor decided to submit a written complete response to an AE action for this efficacy supplement instead of discussing what should be submitted at the scheduled meeting.
Project Manager	Karen Kirchberg

Any follow-up letter must be checked into DFS as an advice letter, **NOT as a meeting request denial letter.

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/s/

Karen Kirchberg
8/17/04 11:32:44 AM

Meeting Minutes

Date: January 23, 2004 **Time:** 12:30 – 2:00 PM **Location:** CORP Rm: 200A

NDA: 21-045 **Indication:** Emergency Contraception

Drug Name: Plan B[®] (levonorgestrel) Tablets, 0.75mg

Sponsor: Barr, Inc. / Women's Capital Corporation

Meeting Type: Guidance

Meeting Chair: Donna Griebel, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Office of New Drugs (OND; HFD-020)

John Jenkins, M.D. - Director

Office of Executive Programs (OEP; HFD-006)

Lee Lemley - Policy Analyst, Executive Operations Staff

Office of Drug Evaluation III (ODE III; HFD-103)

Florence Houn, M.D. - Director

Julie Beitz, M.D. - Deputy Director

Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Daniel Shames, M.D. - Director

Donna Griebel, M.D. - Deputy Director

Scott Monroe, M.D. - Medical Team Leader

Dan Davis, M.D. - Medical Officer

Karen Anderson, N.P. - Project Manager

Office of Drug Evaluation V (ODE V; HFD-105)

Jonca Bull, M.D. - Director

Terri Rumble, R.N. - Associate Director for Regulatory Affairs

Division of Over the Counter Drug Products (OTC; HFD-560)

Curtis Rosebraugh, M.D., M.P.H. - Deputy Director

Jin Chen, M.D., Ph.D. - Medical Officer

Helen Cothran, B.S. - Interdisciplinary Scientist, Team Leader

Arlene Solbeck, M.S. - Interdisciplinary Scientist

Division of Surveillance, Research, & Communication Support (DSRCS; HFD-400)

Karen Lechter, J.D., Ph.D. – Social Science Analyst

External Attendees:

Carole Ben-Maimon, M.D. - President and COO, Barr Research, Inc.

Joe Carrado, M.Sc., R.Ph. - Senior Director, Clinical Regulatory Affairs

Deborah Wilkerson, Ph.D. – Director, Scientific Affairs, Women's Capital Corporation

Background: Plan B[®] (levonorgestrel 0.75 mg) is indicated for Emergency Contraception. In April 2003, the sponsor, Women's Capital Corporation (WCC), submitted an SE6 Efficacy Supplement to market Plan B[®] as an over-the-counter product. The action goal date is February 20, 2004. A joint meeting of the Non-Prescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs took place on December 16, 2003 to discuss the application and voted 23 to 4 in support of the over-the-counter switch. The Division of Reproductive and Urologic Drug Products (DRUDP) with the Division of Over-the-Counter Drug Products (OTC) and the sponsor are ready to begin label negotiations. These negotiations have been pre-empted due to concerns from the Office of the Commissioner (OC) to be conveyed through CDER management at this meeting.

Discussion:

Statement from CDER/ DRUDP and OTC for the sponsor:

1. The Divisions were ready to negotiate labeling with you today, but on January 15, 2004, we were informed by the Acting Center Director, Dr. Steven Galson, that the regulatory decision for the action on your application would be made by CDER upper management (above the ODE level). This is not the usual or typical CDER process for determining the approvability of an NDA. He also informed us that there were unresolved issues of concern to upper level management that would require their discussion.
2. The Divisions and ODEs are in the process of completing their reviews and will forward them with their final recommendations to CDER upper management. The Divisions and ODEs will continue to communicate with upper management on any issues that upper management believes are in need of further explanation.
3. You will need to request a meeting directly with the Office of the Center Director or the Office of New Drugs Director to understand their concerns. This will allow you to obtain the best information to decide how to proceed. We also are meeting with upper level management to better understand their concerns. Until instructed to do otherwise, we will schedule no meetings with you to discuss labeling.
4. We understand the current circumstances may be confusing. Dr. Jenkins is here to answer your questions as best he can at this point.

General Comments:

- Dr. Jenkins stated that the Office of the Commissioner and CDER management have raised concerns about the application to switch Plan B to OTC. The primary area of concern appears to be whether there are adequate data to establish that minors (i.e., those

under 18 years) will use Plan B appropriately in the absence of a learned intermediary. It has been noted that the number of subjects under 18 in the Actual Use Study (AUS) and label comprehension studies was small. The divisions plan to meet with FDA and CDER management in the near future to review the available data from the application and to determine the path forward. Potential options that have been suggested from FDA and CDER management include the possible need to collect additional data, perhaps from another AUS targeted to minors, or to impose an age restriction on OTC sale of the product. Since we have not had a chance to have these internal discussions, we recommended that the sponsor not attempt to submit new data or plans to address these concerns until we better understand the issues and the possible path(s) forward.

The sponsor stated that they understand the current situation and reiterated their commitment to the Plan B application. Barr noted that they plan to proceed with the acquisition of the NDA from WCC and that they want to work with FDA to find a resolution to any deficiencies in the current application. The sponsor asked that they be allowed to discuss with the agency possible remedies to address the current concerns and noted that they are willing to be flexible to find pragmatic solutions.

Decisions:

- DRUDP and OTC will go forward with a meeting with FDA and CDER management as soon as that meeting can be arranged
- The sponsor agreed to be responsive to any requests for additional information that may help to address the concerns regarding the application.
- The divisions will be working to finalize reviews in a timely manner.
- The sponsor may attempt to contact CDER management for further discussions
- Label negotiations are postponed until further notice.

Action Items:

- None

Minutes prepared by: Karen Anderson, N.P. – Project Manager, DRUDP
Concurrence of Meeting Chair: Donna Griebel, M.D. –Deputy Director, DRUDP

NDA 21-045/S011

Reviewed by

J. Jenkins 2.3.04

L. Lemley

F. Houn 2.2.04

J. Beitz 2.2.04

D. Shames

D. Griebel

S. Monroe 2.2.04

D. Davis

J. Bull

T. Rumble

C. Rosebraugh

J. Chen

H. Cothran

A. Solbeck

K. Lechter 2.2.04

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/s/

Daniel A. Shames
3/4/04 04:30:07 PM

MEMORANDUM OF TELECON

DATE: January 16, 2004

APPLICATION NUMBER: NDA 21-045/S-011, Plan B (0.75mg levonorgestrel) tablet

BETWEEN:

Name: Joseph Carrado, M.Sc., R.Ph., Regulatory Agent
Phone: 610-668-2989
Representing: Women's Capital Corporation

AND

Name:
Charles Ganley, Director
Curtis Rosebraugh, MD, MPH, Deputy Director
Tia Frazier, Regulatory Project Manager
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: Review issues related to Plan B

Following greetings, Dr. Charles Ganley proceeded to convey the following information to Mr. Joseph Carrado:

- We had a meeting with CDER upper management (Drs. Galson, Jenkins, and Kweder) yesterday regarding the Plan B application and were instructed to complete our written reviews for the application. All of the reviews have not been completed. There were some issues raised in the meeting that will require us to provide additional information and have additional discussions with CDER upper management.
- We are not going to be sending labeling revisions at this time. For the meeting scheduled for January 23, 2004, we do not plan to discuss labeling. It would be premature to have any labeling discussions with you at this point in time. The review process has to be completed and move forward.
- We can keep the meeting scheduled for January 23 on the books. You have the option of participating by t-con or in person. At the meeting, we will provide an update of the status of review of the application. If there is a need for additional information from you, we can discuss it at that time.

Mr. Carrado asked FDA when he might to learn what issues would be discussed at the meeting on January 23, 2004. The FDA informed Mr. Carrado that it was not certain whether or not it would be able to provide a list of issues to the sponsor prior to the meeting.

The meeting concluded cordially.

Curtis Rosebraugh, MD, MPH
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Tia Frazier
1/16/04 12:47:00 PM
CSO

Curtis Rosebraugh
1/16/04 04:29:54 PM
MEDICAL OFFICER

Meeting Minutes

Date: January 15, 2004 **Time:** 2:00 PM – 3:30 PM **Location:** PKLN; Conference Rm 13B45

NDA 21-045/S011 Drug: Plan B[®] (levonorgestrel) Tablets, 0.75 mg

Indication: Emergency Contraception (OTC use)

Sponsor: Barr, Inc. / Women's Capital Corporation

Type of Meeting: Internal

Meeting Chair: Steven Galson, M.D. –Acting Director, CDER

Meeting Recorder: Karen Anderson, N.P. - Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)

Attendees:

Office of the Center Director (HFD-001)

Steven Galson, M.D. – Acting Director

Mark Goldberger, M.D. – Deputy Director

Office of Regulatory Policy (HFD-005)

Jane Axelrad, J.D. - Associate Director for Policy

Office of New Drugs (HFD-020)

John Jenkins, M.D. – Director – by telephone

Sandra Kweder, M.D. - Deputy Director – by telephone

Office of Executive Programs (HFD-006)

Maureen Hess, M.P.H., R.D. - Science Policy Analyst, Executive Operations Staff

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D. - Director

Julie Beitz, M.D. - Deputy Director

Division of Reproductive and Urologic Drug Products (HFD-580)

Daniel Shames, M.D. - Director

Donna Griebel, M.D. - Deputy Director

Margie Kober, R.Ph. - Chief, Project Management Staff

Scott Monroe, M.D. - Medical Team Leader

Dan Davis, M.D. - Medical Officer

Karen Anderson, N.P. - Project Manager

Jennifer Mercier - Project Manager

Office of Drug Evaluation V (HFD-105)
Jonca Bull, M.D. – Director - by telephone

Division of Over the Counter Drug Products (HFD-560)
Charles Ganley, M.D. - Director
Curtis Rosebraugh, M.D., M.P.H. - Deputy Director

Meeting Objective: To inform ODE III and ODE V of the Office of the Commissioner's (OC) position on the acceptability of the application.

Background: Plan B was approved as a prescription medication for emergency contraception on July 28, 1999. Barr, Inc. / Women's Capital Corporation has applied for an over-the-counter (OTC) switch. A joint meeting of the Non-Prescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs took place on December 16, 2003. The Action date for this application is February 20, 2004.

Discussion/Decisions Made:

Dr. Galson raised the following issues:

- There are very limited data from the AUS and label comprehension studies in the younger age group (less than 16 years of age).
- There are concerns about whether there are adequate data to support appropriate use of Plan B in the younger age group without a learned intermediary.
- Possible options to address these concerns may include asking the sponsor to collect more data to demonstrate appropriate use in ≤ 18 year olds or limit availability of the product (e.g., restrict distribution to minors; pharmacy access restricted to behind the counter, etc.).
- A "non approval" letter is recommended based on need for more data to more clearly establish appropriate use in younger women and/or the need to develop a restricted distribution plan that is monitorable to address use in younger women.
- Plans to proceed with labeling negotiations should be deferred at this time.
- ODE III and ODE V staff may document their views regarding the acceptability of the application in their reviews.

ODE III and ODE V reported that more data exist on use of Plan B in adolescent girls from the NDA and the medical literature and that the OC may not be aware of these additional data. Dr. Galson reported that OC has expressed a willingness to meet with the review team to further discuss the data and these concerns.

Action Items:

- ODE III and ODE V are invited to meet with the Commissioner to discuss Office of the Commissioner (OC) concerns and present more data on use in adolescent girls.
- Proposal to meet in early February.

- In preparation for the meeting with the Commissioner, staff will gather available data on use in younger aged women, including information in the NDA and data that will soon be published.
- ODE III and ODE V staff will finalize their reviews and enter into DFS.
- The previously scheduled labeling meeting with the sponsor for January 23, 2004, will still take place, but the purpose of the meeting would be to convey the concerns of FDA upper management and that labeling negotiations will be deferred.

Minutes prepared: DRUDP - M. Kober, R.Ph., CPMS & K. Anderson, N.P., PM
Chair Concurrence: S. Galson, M.D. --Acting Director, CDER

Concurrence:

S. Galson 2.9.04

J. Jenkins 2.3.04

S. Kweder no comments

J. Axelrad no comments

M. Goldberger no comments

M. Hess 02.02.04

F. Houn 02.02.04

J. Beitz 02.02.04

D. Shames no comments

D. Griebel 2.02.04

M. Kober 02.02.04

S. Monroe 02.02.04

D. Davis no comments

J. Bull no comments

T. Rumble no comments

C. Ganley no comments

C. Rosebraugh no comments

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/s/

Steven Galson
2/20/04 02:47:02 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 12, 2004

TO: Tia Frazier, Regulatory Project Manager, HFD-560
Division of Over-the-Counter Drugs, HFD-560
Karen Anderson, Project manager, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

FROM: Roy Blay, Ph.D.,
Director Regulatory Review Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: 21-045

APPLICANT: Women's Capital Corporation

DRUG: Plan B[®]

STUDY: Protocol #9727 entitled: "Plan B[®] OTC Actual Use Study"

THERAPEUTIC CLASSIFICATION: 3P

INDICATION: Emergency contraception

DSI GOAL DATE: 22 Jan 2004
REVIEW DIVISION GOAL DATE: 22 Jan 2004
ACTION GOAL DATE (PDUFA Date): 22 Feb 2004

I. BACKGROUND:

The clinical site of Dr. Fine submitted data that were essential to the approval of this submission; thus, it was selected for inspection. The study was done to determine whether subjects could appropriately use the emergency contraceptive, Plan B, with minimal professional medical intervention as this drug is proposed for OTC use.

II. RESULTS (by site):

NAME	CITY, COUNTRY	ASSIGNED DATE	INSPECTION DATES	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Paul Fine, M.D.	Houston, TX	5 Sept 03	22 Oct-3 Nov 03	22 Dec 03	NAI/011074

Site #1

Paul Fine, M.D.
Fannin Clinic
3601 Fannin Street
Houston, Texas 77004

See **Assessment and Recommendations**, below

- a. 138 subjects were enrolled in the study. Data points for at least 50 subjects were compared with the source data. The Study Screening Forms, Background Questionnaires, Disposition Form, and One and Four Week Contact Forms, and Study Data Cards were reviewed. No pregnancies were recorded for any subject.
- b. There were no limitations on the inspection.
- c. A Form 483 was not issued.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this NDA by Dr. Fine appear acceptable.

Roy Blay, Ph.D.,
DSI/GCPBI

CONCURRENCE:

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

DISTRIBUTION:

NDA 21-045
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-580/PM/Anderson
HFD-560/PM/Frazier
HFD-46/Blay
HFD-46/CIB File #s 011074
HFD-46/Reading File

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/s/

Michele Lackner

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TECHNICAL

Original CIS was signed by Drs. Blay and U on 1/13/04.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Paul Fine, M.D.
Fannin Clinic
3601 Fannin Street
Houston, Texas 77004

Food and Drug Administration
Rockville MD 20857

JAN 8 2004

Dear Dr. Fine:

Between October 22 and November 3, 2003, Ms. Andrea Branche, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #9727 entitled: "Plan B[®] OTC Actual Use Study") of the investigational drug Plan B[®], performed for Women's Capital Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Branche during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Paul Fine, M.D.

FEI: 3004128297

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

cc:

HFA-224

HFD-560/Doc.Rm./NDA # 21-045

HFD-560/Division Director/

HFD-560/MO/Chin

HFD-560/PM/Frazier

HFD-46/c/r/s/ GCP File #011074

HFD-46/Blay

HFR-SW150/DIB/Thornburg

HFR-SW1540/BIMO Monitor/Martinez

HFR-SW1580/Field Investigator/Branche

GCF-1 Seth Ray

r/d:rab/1/7/04

KMU:1/7/04

F/t:sg: 1/8/04

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O:\rab\fine.doc

Reviewer's Note to Review Division's Medical Officer

138 subjects were enrolled in the study. Data points for at least 50 subjects were compared with the source data. The Study Screening Forms, Background Questionnaires, Disposition Form, and One and Four Week Contact Forms, and Study Data Cards were reviewed. No pregnancies were recorded for any subject. The data appear acceptable in support of the relevant submission.

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/s/

Khin U

1/29/04 02:56:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

SNDA 21-045\S-011

Barr Research, Inc.

Attention: Joseph A. Carrado, M.Sc., Ph.D.

Senior Director, Regulatory Affairs

One Bala Plaza, Suite 324

Bala Cynwyd, PA 19004-1401

Dear Dr. Carrado:

We received your December 9, 2003 correspondence on December 9, 2003 requesting a meeting to discuss label issues and recommendations. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You have requested a type C meeting. The meeting is scheduled for:

Date: January 23, 2004

Start time: 12:30PM

End time: 2:00PM

Location: 9201 Corporate Blvd., Conf room S200A
Rockville, MD 20850

We acknowledge the fact that you have not confirmed your participation on this date, and understand you may request that we reschedule. Please note that, due to the short time frame that we have to schedule this meeting prior to the PDUFA-mandated deadline of February 22, 2004, we may not be able to offer much flexibility to you in the timing of this meeting.

Potential list of CDER participants:

ODE V

Jonca Bull, M.D. - Director

Teri Rumble, R.N., B.S.N. - Associate Director for Regulatory Affairs

Division of Over-the-Counter Drug Products

Charles Ganley, M.D. - Director

Curtis Rosebraugh, M.D., M.P.H. - Deputy Director

David Hilfiker, M.S. - CPMS

Andrea Leonard Segal, M.D., M.S. - Medical Team Leader

Jin Chen, M.D., Ph.D. - Medical Officer

Helen Cothran, B.S. - Interdisciplinary Scientist, Team Leader

Arlene Solbeck, M.S. - Interdisciplinary Scientist

Tia Frazier, R.N., M.S. - Project Manager

ODE III

Florence Houn, M.D., M.P.H. - Director

Julie Beitz, M.D. - Deputy Director

Division of Reproductive and Urologic Drug Products

Donna Griebel, M.D. - Deputy Director

Scott Monroe, M.D. - Medical Team Leader

Dan Davis, M.D. - Medical Officer

Karen Anderson, N.P. - Project Manager

DSRCS

Karen Lechter, Ph.D

Provide the background information (package), including the latest version of the proposed labeling for this product, at least two weeks prior to the meeting. If we do not receive it by January 9, 2004, we may need to reschedule or cancel the meeting.

If you have any questions, call Tia Frazier, Project Manager, at 301-827-2271.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker, M.S.

Chief, Project Management Staff

Division of Over-the-Counter Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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/s/

David Hilfiker
12/19/03 08:28:26 AM

MEETING MINUTES

MEETING DATE: December 2, 2003

TIME: 11:00 AM -12:35 PM

LOCATION: Conference room M (3rd floor Parklawn)
5600 Fishers Lane, Rockville, MD.

APPLICATION: NDA 21-045/Supplement 011

DRUG PRODUCT: Plan B (levonorgestrel) Tablets

TYPE OF MEETING: C

MEETING CHAIR: Dr. John Jenkins

RECORDER: Tia Frazier

FDA attendees:

Office of New Drugs (HFD-002)

John Jenkins, M.D. – Director

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H.. Director

Julie Beitz, M.D. – Deputy Director

Division of Reproductive and Urologic Drug Products (HFD-580)

Donna Griebel, M.D. – Deputy Director

Scott Monroe, M.D. – Medical Team Leader

Dan Davis, M.D., M.P.H. – Medical Officer

Karen Anderson, N.P. – Project Manager

Office of Drug Evaluation V (HFD-105)

Jonca Bull, M.D. – Director

Division of Over-the-Counter Drug Products (HFD-560)

Curtis Rosebraugh, M.D., M.P.H. - Deputy Director

Andrea Leonard Segal, M.D., M.S. - Medical Team Leader

Jin Chen, M.D., Ph.D. - Medical Officer

Helen Cothran, B.S. - Interdisciplinary Scientist, Team Leader

Arlene Solbeck, M.S.- Interdisciplinary Scientist

Tia Frazier, R.N., M.S. - Project Manager

Division Surveillance Research and Communication Support (HFD-410)

Karen Lechter, J.D., Ph.D. – Social Science Analyst

Advisors and Consultants Staff

Jayne Peterson, R.Ph., J.D. – Team Leader

Karen Templeton-Somers, Ph.D. – Team Leader

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Barr Laboratories, Incorporated

Carole Ben-Maimon, M.D. – President and COO, Barr Research, Inc.

Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.

Joe Carrado - Senior Director, Clinical Regulatory Affairs

Wayne Mulcahy – Vice President, Clinical Operations

Womens Capital Corporation

Debbie Wilkerson, Ph.D. – Director, Scientific Affairs

Background:

- On April 22, 2003, a supplemental NDA was submitted by Women's Capital Corporation to switch Plan B from prescription to over-the-counter. On September 26, 2003, Women's Capital Corporation (WCC) informed FDA that Barr Laboratories, Inc. had purchased the supplemental new drug application (sNDA) for Plan B. Barr Laboratories was named as the regulatory agent for the NDA in October, 2003.
- On December 16, 2003, members from the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs will meet to consider the safety and effectiveness of the supplemental NDA proposing over-the-counter (OTC) use for Plan B.
- On October 31, 2003, Barr requested a meeting to discuss major issues in the review of the actual use and label comprehension studies. Labeling issues related to the label comprehension study, and modifications needed to conform to OTC Drug Facts requirements, were cited as a part of Barr's proposed agenda. Barr also wished to discuss the post-marketing roll-out plan for the product, and other advisory committee planning issues.
- On November 25, 2003, Barr agreed to postpone discussion about the labeling for the product to a future meeting. Both Barr and FDA agreed that many of the originally proposed discussion topics have been addressed in subsequent teleconference meetings and discussions with FDA personnel.
- On November 28, 2003, Barr clarified that their only question for FDA at this point in time concerned the agency's thoughts on existing and potential non-prescription distribution mechanisms.

.....
Start of meeting

First, FDA acknowledged Barr's request to discuss the single question listed above. FDA informed Barr that it may not be able to present a clear regulatory path for alternate non-prescription distribution mechanisms for Plan B in time for the December 16, 2003, Advisory Committee meeting.

FDA emphasized that it was crucial for the sponsor to present the best possible proposal for OTC distribution of Plan B at the upcoming December 16, 2003, Advisory Committee meeting.

- The sponsor agreed, and stated that the purpose of their Convenient Access, Responsible Education (CARE) program was to ensure the product's appropriate and responsible use. They acknowledged that the program could be further developed.
- Barr clarified their view that a single appropriate target population existed for Plan B. Barr later clarified their intention not to expand the population for which this product is targeted.
- The applicant requested that FDA share a copy information of the American Pharmaceutical Association's January 7, 2003, summary entitled, "Policy Analysis of Options for Achieving 'At-the-Counter' Status for Emergency Contraception", and FDA agreed.
- Barr agreed to research the success of voluntary BTC distribution of Mucinex. (This distribution was not required or recommended by FDA).

FDA requested that Barr address distribution of the product to young women carefully.

Barr agreed to present the data they have to support the product's safety in populations less than 18 years of age at the upcoming Advisory Committee meeting.

FDA asked Barr where they had obtained the state distribution data contained in the table entitled "Response to 3 November 2003 Request".

Barr replied that these data were provided by Pharmacy Access Institute, a division of the Public Health Institute.

The applicant agreed to verify the accuracy of these data, remove the editorial comments in the comments column, and submit the revised version to their supplemental New Drug Application.

Barr announced that special labeling for victims of rape and sexual assault would be incorporated into the labeling for Plan B. They stated that their labeling would warn the user that sexually transmitted infections could not be prevented by taking Plan B.

FDA communicated its concern with Barr's plan to target victims of rape or sexual assault who might not seek appropriate medical and police attention after the crime if they simply purchase OTC Plan B and do nothing else. FDA also noted that the sponsor did not target rape victims in their studies.

FDA asked if women in the Actual Use Study (AUS) had purchased the product for immediate, or future, use.

Barr informed FDA that the study did not capture information that would answer this question.

FDA suggested that Barr consider extending its distribution program (CARE) out well beyond approval, if the product should be approved for OTC use.

Barr had earlier agreed that Phase IV commitments could be incorporated into their distribution and roll-out plans, but expressed concern about their ability to monitor Plan B's post-marketing experience for an indefinite period of time.

Barr inquired about FDA's position on omitting "unexplained vaginal bleeding" as a contraindication from their labeling, and the Division of Reproductive and Urologic Drug Products agreed that the labeling no longer needed to include this particular contraindication.

The meeting concluded cordially.

End of meeting

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/s/

John Jenkins

12/23/03 12:53:57 PM

MEMORANDUM OF TELECON

DATE: 05 Nov 2003

APPLICATION NUMBER: NDA 21-045/S-011, Plan B (0.75mg levonorgestrel) tablet

BETWEEN:

Name: Joseph Carrado, M.Sc., R.Ph., Regulatory Agent
Phone: 610-668-2989
Representing: Women's Capital Corporation

AND

Name: Tia Frazier, Project Manager
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: Sponsor's October 31, 2003, request for a meeting with FDA

The sponsor telephoned me concerning his request for a Type A meeting with FDA. I informed Mr. Carrado that FDA regarded this meeting as a Guidance meeting, and therefore classified it as a Type C meeting. I also informed the sponsor that the meeting would occur on December 2, 2003 between 10:30 A.M.-12:30 P.M.

I reiterated FDA's willingness to review and comment on the sponsor's presentations for the December 16, 2003, Advisory Committee held to discuss the proposed OTC switch for Plan B. I informed the sponsor that, if they wished FDA to provide feedback on their presentations, they should be ready to present this information on December 2, 2003.

The meeting concluded cordially.

Tia Frazier
Project Manager

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/s/

Tia Frazier
11/17/03 01:50:09 PM
CSO

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

DATE: November 2, 2003

TO: Daniel Shames, M.D., Director
 DRUDP, HFD-580

FROM: Karen Lechter, J.D., Ph.D.
 Social Science Analyst
 Division of Surveillance, Research,
 and Communication Support, HFD-410
 Office of Drug Safety (ODS)

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
 Division of Surveillance, Research,
 and Communication Support, HFD-410
 Office of Drug Safety

SUBJECT: Plan B Label Comprehension Study Review
 NDA 21-045

The following is a review of the label comprehension study for Plan B, conducted in support of the application for OTC approval.

{See appended electronic signature page}

DSRCS REVIEW

NDA#: 21-045
Drug: Plan B (levonorgestrel) Tablets
Sponsor: Women's Capital Corporation
Study: Plan B Over-the-Counter Label Comprehension Study Final Report. Study Number 9728
Study Report Date: November 5, 2001 (Submission Date April 2003)
Reviewer: Karen Lechter, J.D., Ph.D.
Reviewing Div: HFD-410
Review Completed: November 2, 2003

Executive Summary

In a label comprehension study of the labeling on the outside and inside of the package, study participants demonstrated good understanding of some concepts and low understanding of a few concepts. Results for other concepts were inconclusive due to the wording of some of the questions and the sponsor's scoring system for open-ended questions. Despite some shortcomings in the questionnaire and some scores that were lower than desirable, the Division of Surveillance, Research, and Communication Support (DSRCS) believes that labeling changes are likely to result in acceptable levels of comprehension. Results of the Actual Use Study should weigh more heavily in evaluating the labeling.

Concepts that received relatively high comprehension scores are the following:

- Plan B is for contraception.
- Plan B does not protect against STD's, including HIV/AIDS.
- Do not take the product while pregnant; Plan B cannot end a pregnancy.
- Do not use Plan B if you are allergic to its ingredients.
- Nausea and vomiting are side effects.

Concepts with moderate levels of understanding include the following:

- Take the first tablet within 3 days of intercourse.
- Get medical help if severe abdominal pain develops.

Concepts that may not be clearly understood or for which the data are inconclusive are the following:

- Plan B is not for regular use for contraception.
- Take the first tablet as soon as possible after intercourse.
- Take the second tablet 12 hours after the first one.
- Do not use Plan B if you have unexplained vaginal bleeding
- Use Plan B **after** intercourse.
- Plan B can be used even if the woman has medical conditions not mentioned on the label. (Asthma was mentioned in the question.)

As a result of these findings, DSRCs believes that comprehension of the critical messages is adequate or would be adequate after changes to the labeling. Therefore, DSRCs has the following recommendations based on the study:

- Strengthen the following messages:
 - Not for regular use (sponsor has bolded this)
 - Timing of first dose
 - Timing of second dose (sponsor has bolded this)
 - If severe abdominal pain develops, seek immediate medical care
 - Do not use if unexplained vaginal bleeding (if kept in the labeling)
- State on the label if there is a window of time for the second tablet, rather than just the 12 hour time already given.

In addition, DSRCs has a recommendation to help women time the second dose appropriately:

- Have a place on the label for the woman to write the time she took the first pill and the time she should take the second pill.

Inclusion of a package insert might be helpful for consumers.

REVIEW

The purpose of this study was to evaluate comprehension of a prototype OTC package label for Plan B emergency contraceptive pills.

Communication Objectives

The study tested 11 Communication Objectives important for safe and effective use of the product:

1. Plan B is indicated for prevention of pregnancy after unprotected sex.
2. Plan B is intended as a back up method and should not be used for regular contraception.
3. Plan B does not prevent sexually transmitted diseases or HIV/AIDS.
4. The first pill should be taken as soon as possible after intercourse.
5. The first pill should be taken within 72 hours after intercourse.
6. The second pill should be taken 12 hours after the first.
7. Plan B should not be used by women who are already pregnant (because it will not be effective).
8. Plan B should not be used by women with unexplained vaginal bleeding.
9. Plan B should not be used by women with allergy to any ingredient in the product.
10. Side effects of Plan B include nausea and vomiting.
11. If severe abdominal pain develops, the user should seek medical care immediately.

Methodology

Participants

Participants were 663 females, age 12-50 years old. Sample size was based on using a 95% confidence interval of ± 5 percentage points, conservatively assuming the proportion of correct responses would be 50%. Based on these requirements, a minimum sample size was 385. To ensure adequate demographic representation and a sufficient number of low literacy women for subset analyses, the target sample was increased to 575. In actuality, data for 656 participants were reported.

Distribution by age was as follows:

Age Range	%
12-16	12
17-25	54
26-50	34

Black and Hispanic women were overrepresented with respect to the general population as follows:

Race	Study population %	General population %
Black	24	12
Hispanic	24	13
White	49	75

More than $\frac{3}{4}$ of participants were sexually experienced. Most of them had had unprotected intercourse despite a desire not to become pregnant. More than half of participants who had used oral contraceptive pills reported having missed taking pills, and 40% of those who had used condoms had had a condom break. At least 82% of the sexually experienced participants had had either a pregnancy scare or sex not adequately protected by contraception. Only 32 of the sexually experienced participants had ever used emergency contraceptive pills.

Literacy levels among those age 18 or older who had not completed college were as follows:

Literacy Level	% (n=395)
3 rd grade or less	<1
4 th -6 th grade	4
7 th -8 th grade	31
High school	64
Missing	<1

The highest level of school completed was as follows:

Highest grade completed	% (n=656)
6 th grade or less	1
7 th or 8 th grade	4
9 th -11 th grade	23
High school or GED	30
Vocational/technical school	3
Less than 4 years of college	18
College	16
Graduate school	6
Refused/missing	<1

Procedure

Interviews were conducted in shopping malls and family planning clinics in eight US cities. Minor participants recruited from clinics did not require parental consent to participate.

Before the interviews began, participants who were age 18 or older who had not completed college were tested for literacy level using the Rapid Estimate of Adult Literacy in Medicine (REALM) test.

For the main questionnaire, participants were asked to look at the outside of the Plan B package as if they were thinking about whether to purchase the product. The interviewer then removed the package while the participant answered the first question. The participant was permitted to look at the outside of the package while answering five additional questions. Participants were then told to open the package and review the contents as if they were about to use the product. Participants could refer to the package as well as the contents for the remaining questions.

The only information on the front outside of the package was the name of the product, the statement "Emergency Contraception," and the number and strength of the tablets. On the back was the Drug Facts format containing the most important information about the indication, warnings, directions, and ingredients. The back also included storage and manufacturing information. Additional information that reinforced the Drug Facts information was on the inside of the package.

At the end of the main questionnaire, participants were given a questionnaire asking information about their sexual activities.

Comments: The sponsor did not give the REALM literacy test to women who had graduated college or to participants younger than 18 years. It would have been better to test everyone, to make their study experience similar and to test literacy at all education levels, as all of these women represented potential product users. The sponsor noted that even at the level of some college education, there were some who tested as low literate.

In correspondence with the agency (Serial No. 110), the sponsor explained its decision not to test the younger participants for two reasons: (1) the REALM is designed for adults, and (2) the sponsor assumed that women under the age of 18 would not be well-educated. The college graduates were not tested because the sponsor assumed that college graduates would have at least a 9th grade literacy level. In hindsight, the sponsor notes that this assumption may not have been correct. The sponsor also pointed out that about 25% of the entire study population was either poorly educated or tested in the lower literacy group on the REALM. Twenty-eight aged 17 or younger had not gotten past 8th grade in school, and 139 who were tested were in the lower literate category.

As only the 393 women age 18 or older who had not graduated from college were categorized by literacy level, we do not have results by literacy level for the entire sample. We do not know what effect, if any, this fact had on the results of the analyses by literacy groups. However, because the results suggest a literacy effect for almost all of the communication objectives, we should proceed as if literacy has an effect on almost everything tested, and try to improve those aspects of the label for which the lower literate group seemed to have particular problems.

Questionnaires

Questions included multiple choice and open-ended questions. The latter are questions for which choices are not provided by the questioner. Many questions presented a hypothetical scenario and asked participants if Plan B use would be correct to use in the situation.

Comment: Scenario-type questions require more cognitive processing than more direct questions about information on the labeling because scenario questions require participants to apply the information.

Main Questionnaire

Question 7 was the first question asked about the product. It was asked after only the outside of the package had been read and after the package was removed. Therefore, this response was based on recall. Questions 8-12 were asked with only the outer carton available for reference. For the remaining questions, participants could open the carton and inspect the contents before responding.

At the end of the questioning about the labeling, participants were asked for demographic information and took a self-administered test ("Confidential Information Questionnaire") about sexual and contraceptive history.

Comments: The scenario questions asked, in essence, if the hypothetical person was using the product correctly or not. Many questions were of the yes/no or correct/incorrect variety. Such questions have a 50% chance of a correct response by chance. It would have been better to follow all of these questions with a probe asking

participants why they answered as they did. We therefore do not know if participants answered correctly by chance or because they knew the information.

Personal information questions about marital status and income did not seem useful to ask for comprehension purposes.

Confidential Information Questionnaire

This questionnaire asked about the participants' experience with sex and birth control. Results were used to further analyze responses to the main questionnaire by categorizing participants according to their responses to these questions.

Comment: The question "Have you ever had sex?" (Q. 1) would have benefited from providing a definition for "sex." Without such a definition, we must assume participants knew it meant sexual intercourse, but we cannot be sure. Q. 6 asked if the participant had ever used birth control pills and had missed taking two or more from one pack. The results were used to conclude that participants responding affirmatively to this question might have experienced anxiety about the possibility of being pregnant. Q. 10 asked if the woman had ever used emergency contraceptive pills. It would have been best to exclude these women from the study, as their experience, possibly with Plan B, might have raised their scores artificially. However, the results showed that there were only 32 in this group, and thus, they may have had little influence on the overall results. An analysis by the sponsor showed no effect of this prior experience on understanding the Communication Objectives. However, the small size of this group may be responsible for the lack of apparent effect. Thus, we cannot conclude that women with prior experience with emergency contraception would not understand the information better than others.

Results by Communication Objective

Results for the total sample were provided for each question. In addition, results for each Communication Objective were provided based on the following characteristics: literacy level, age, race, ethnicity, interview location, type of site (mall or clinic), income, education, previous sexual experience, sexual experience in the past three months, experience with pregnancy scare (condom break, missed pills, unprotected intercourse, worry about unwanted pregnancy), and experience using emergency contraceptive pills. Literacy level and location of the interview had an effect on most responses. Literacy level affected nine of the Communication Objectives. Location affected all of them. Other characteristics had far fewer effects. Any significant findings based on particular characteristics are mentioned in the appropriate sections that follow. The sponsor did not make adjustments for multiple confidence interval estimations.

The sponsor determined whether Communication Objectives had been met by participants based on formulas that differed among the Communication Objectives. For some objectives, correct responses to only half of the questions under that Communication Objective were deemed sufficient to indicate understanding of that

Communication Objective. For others, 75% or 100% of the questions needed to be correct to satisfy the sponsor's criteria for successful understanding.

Based on the sponsor's scoring method for Communication Objectives, more than 85% of participants understood seven of the 11 Communication Objectives, if both acceptable and correct answers were counted. Ninety-three percent (93%) understood that Plan B is indicated for prevention of pregnancy after unprotected sex (Objective 1), 94% understood it does not prevent HIV or AIDS (Objective 3), and almost all (98%) understood that it should not be used by pregnant women (Objective 7). Less than 80% understood two objectives: 67% understood Objective 2 (Plan B is intended as a back up method and should not be used for regular contraception), and 75% understood objective 8 (Plan B should not be used by women with unexplained vaginal bleeding.). The results by Communication Objective appear in Table 1.

Table 1. Results by Communication Objective.

Communication Objective	% Understanding* (N=656)
1. Plan B is indicated for prevention of pregnancy after unprotected sex	90/93**
2. Plan B is intended as a back up method and should not be used for regular contraception	67
3. Plan B does not prevent sexually transmitted diseases or HIV/AIDS	94
4. The first pill should be taken within 72 hours after intercourse	85
5. The first pill should be taken as soon as possible after intercourse	82
4. or 5. The first pill should be taken within 72 hours or as soon as possible after intercourse.	97
6. The second pill should be taken 12 hours after the first	69/85†
7. Plan B should not be used by women who are already pregnant	98
8. Plan B should not be used by women with unexplained vaginal bleeding	75
9. Plan B should not be used by women with allergy to any ingredient in the product	91
10. Side effects of Plan B include nausea and vomiting	89
11. If severe abdominal pain develops, the user should seek medical care immediately	81

*Based on sponsor's criteria of 50%-100% correct on questions relevant to each Communication Objective.

**First number based on correct responses for Q. 7 (Sponsor's interpretation). Second number based on correct/acceptable responses for Q. 7 (Sponsor's interpretation).

† First number based on correct responses for Q. 30. Second number based on correct/acceptable responses for Q. 30. (Sponsor's interpretation.)

More than 80% of lower literate women were able to understand eight of the 11 objectives. Women aged 16 years or younger were less likely than older women to understand many of the objectives, but the differences were not statistically significant in most cases, and more than 80% of the younger women understood seven objectives.

Comment: In correspondence with the Agency (facsimile dated 10/21/03), the sponsor stated that it developed the criteria for each communication objective prior to conducting the study. The sponsor said "it would be inappropriate to require subjects to answer all of the questions related to a particular objective 'right' (i.e., correctly or acceptably) for several reasons." These reasons included the fact that the sponsor knew that some questions and some answers, particularly responses to open-ended questions, would be ambiguous. Other reasons included the fact that "people do not always answer questions

correctly even when they know the correct answer," and that some questions were asked before participants saw the whole package.

In some instances, these criteria made it easier to reach the objective by using correct responses for less than all of the questions in an objective. Because there may be disagreement as to what criteria would be appropriate for each Communication Objective, this review will examine results of questions individually, as well as results by Communication Objective.

DSRCS would not necessarily agree with the scoring of some of the "acceptable" responses. Thus, scores for some Communication Objectives may be lower under DSRCS's scoring.

Of the subgroups, DSRCS is most interested in results by literacy level. As noted earlier, the sponsor did not include all participants in the analyses of Communication Objectives based on literacy levels. Instead, only participants age 18 or older who had not completed college were included. Thus, because we do not have a complete comparison of the entire sample of the lower literate (reading level 8th grade or below) with those of a higher reading level, any conclusions we draw from the literacy analysis should be viewed with the understanding that the sample had limitations. Presumably, many of those below age 18 (at least 12%) would test as lower literate, because they had not completed high school. On the other hand, those who had graduated from college (22%) were more likely to be in the higher literacy group. Thus, we cannot be sure how well the literacy results reflect the range of potential product users.

Communication Objective 1: Plan B is indicated for prevention of pregnancy after unprotected sex. (Q 7, 14, 16, 19) [Communication Objective satisfied if at least two answered correctly]

The first question in this set (Q. 7) was open-ended (not multiple choice). The other three were all of the yes/no variety, asking if the hypothetical situation described was a correct use of the product.. For these three questions, the correct response was that it was a correct use.

Q. 7 asked what Plan B is used for. The response was based on recall, as the carton was removed before the question was asked. Forty-five percent (45%) responded that the product is for contraception after sex. Thirty-nine percent (39%) stated only that it is for contraception. The sponsor counted both of these as acceptable responses. Therefore, a total of 84% provided correct or acceptable responses to this question under the sponsor's scoring system. For this question, the lower literate group scored 73%, compared with 87% for the higher literate group.

For this Communication Objective, there was a statistically significant difference between the adult (age 18 or older) lower literate (8th grade or lower) and those with a higher reading level. As noted earlier, participants under age 18 and college graduates were not included in this analysis. The results show that 84% of the adult lower literate

met the sponsor's criterion for success on this objective, while 96% of the adult higher literate were successful. Table 2 summarizes the most common responses to Q.7.

Table 2. Responses to open-ended question about purpose of product (Q.7)

Response	% Responding (N = 656)
contraception after sex*	45
contraception**	39
after sex, purpose unspecified	4
STI/HIV	1
emergency (sex not mentioned)	1
other	4
don't know/refused	6

*correct under sponsor's scoring

** acceptable under sponsor's scoring

Comment: For Q. 7, it is not clear that those who mentioned only that the product was for contraception, and did not mention "after sex," truly understood the full nature of the indication. It would have been better if this question had probed for more responses by asking if there was anything else the participant wanted to add. Therefore, the total figure of acceptable responses for that question of 84% may be overstating the level of understanding of the participants on this issue. On the other hand, it is likely that some, perhaps many, of those who mentioned only contraception actually understood that the product is used after sex, but failed to mention that detail. We should keep in mind that Q. 7 was answered without participants being able to refer to the carton. For that reason, the relatively low totally correct score (contraception after sex) for this item should not be cause for concern, particularly when viewed in conjunction with other questions about specific uses for the product.

Q. 14 was a scenario about a woman who wanted to use Plan B after a condom broke. Participants were asked if this was an appropriate use according to the package. Ninety-one percent (91%) responded correctly that it was an appropriate use. Eighty-one percent (81%) of the lower literate were correct, while 95% of the higher literate were correct.

Q. 16 stated that a woman with asthma had unprotected sex and took Plan B the next day to prevent pregnancy. Participants were asked if this was a correct use. Sixty-three percent (63%) responded correctly that it was an appropriate use.

Q. 19 asks about using the product two days after unprotected sex. Eighty-seven percent (87%) correctly stated that it was an appropriate use. For this question, 78% of the lower literate and 90% of the higher literate were correct.

Table 3 summarizes responses to the three scenario questions for these Communication Objectives for the total sample.

Table 3. Correct responses to scenario questions about the indication

Question	% Correct (N = 656)
14. condom broke	91
16. asthma/unprotected sex	63
19. unprotected sex 2 days ago	87

The sponsor stated that 90% of participants met the criterion for understanding this Communication Objective. The criterion for success was to answer at least two of the four questions correctly or acceptably.

Comment: The relatively low rate of correct responses for the question about the woman with asthma suggests that there may be a tendency for participants to be confused if other medical conditions are mentioned. This may be due to an inclination to respond conservatively to the questions, so that when in doubt, the participant would state that product should not be used. In correspondence with the Agency (Serial No. 110), the sponsor speculates that some women may not fully understand the term "asthma" and some women may have been flustered by this question. Further study would be necessary to determine what caused so many incorrect responses for the question mentioning asthma. Asking participants why they responded as they did might have clarified the situation.

Overall, results for this Communication Objective suggest the following:

- About 90% understand some specific situations in which it is appropriate to use the product.*
- There is a tendency to state, incorrectly, that certain medical conditions might preclude use. However, incorrect responses may be an artifact of the testing situation. Moderately high proportions of participants were able to identify two situations under this Communication Objective in which the product would be appropriate.*
- Many participants did not clearly express the full indication for the product when asked from memory without further prompting.*
- The sponsor's criterion for success on this Communication Objective (two of the four responses correct or acceptable) seems rather low. With a higher criterion for success, fewer than 90% would have been considered to have answered correctly.*

Communication Objective 2: Plan B is intended as a back-up method and should not be used for regular contraception. (Q. 9, 21, 22, 25) [Communication Objective satisfied if at least three answered correctly]

For this series of questions, the three scenarios all depict inappropriate uses, and one question is direct. Q. 9 asks the direct question whether Plan B should be used as regular birth control. Eighty-five percent (85%) answered correctly. Only 71% of the lower literate were correct, while 93% of the higher literate were correct.

Q. 21 presents a scenario in which a woman's husband complains about using condoms and asks if it is correct to use Plan B in this situation. The correct response is that it is not an appropriate use. Only 47% correctly responded here. The sponsor suggests this may be due to the fact that some of the questions used to define this objective "may have required excessively strict or unrealistic interpretation of the concept of 'emergency' contraception." The intent of Q. 21 was that the woman should find another contraceptive method or refuse to have sex when her husband refuses to use condoms. The sponsor stated that this choice might be improbable in the minds of many women, who may have assumed unprotected sex was inevitable and therefore using Plan B would be appropriate. The sponsor will bold the label text "Plan B should not be used in place of regular contraception" to emphasize this point. The lower literate scored 37% for this question, while the higher literate scored 53%.

Q. 22 is a scenario about someone who inappropriately uses Plan B daily instead of usual birth control. Ninety-one percent (91%) were correct on this question. The lower literate scored 76%; the higher literate scored 95%.

Q. 25 is about a couple that wants to use Plan B as the main contraceptive method. Only 68% answered this one correctly. The lower literate scored 50%; the higher literate scored 78%.

The sponsor concluded that the Communication Objective was met by a participant if three of the four questions were answered correctly. Sixty-seven percent (67%) of participants met this criterion. There was a statistically significant difference between the lower and higher literacy participants for this Communication Objective. Forty-six percent (46%) of the adult lower literate met the criterion for success, while 78% of the adult higher literate were successful. Table 4 presents the results for these four questions for the total sample.

Table 4. Correct responses to scenario questions about Using Plan B for regular contraception

Question	% Correct (N = 656)
9. Direct question about use for regular birth control	85
21. Husband complains about condoms	47
22. Use Plan B daily instead of usual birth control	91
25. Couple uses Plan B as main contraceptive method	68

Comment: Results for these questions would have been easier to interpret if each question had been followed by another question asking why the woman responded as she did. We do not know if correct responses were correct for the right reasons, or if the incorrect ones were incorrect due to misunderstanding or for some other reason.

In response to the direct question about use for regular contraception, a respectable proportion of participants (85%) answered correctly. However, far fewer were correct about use if one's partner does not want to use protection. The scenario for that question (Q.21) stated that "This time she plans to use plan B." The implication could be that this is a one-time event. Thus, it may not be unreasonable for the women to believe that Plan B is appropriate. Therefore, the relatively low results of this question (Q.21) should not be counted heavily.

However, there does not seem to be a clear rationale for the relatively low scores (68%) for the scenario about using Plan B as the main contraceptive method (Q.25), despite the fact that many more (85%) were correct in saying the product should not be used for regular birth control (Q.9), and a high proportion (92%) answered correctly for a different scenario (Q. 22) that the product should not be used daily instead of usual birth control. In correspondence with the Agency (Serial No. 110), the sponsor suggests that Q. 25 required "more extended thought processes" than the other questions, which may have contributed to the lower correct response rate.

Even using the sponsor's criterion for achieving the Communication Objective (3/4 correct), a relatively low number of participants (67%) seemed to understand clearly and consistently that the product is not to be used as the main form of contraception. Even fewer lower literate participants seemed to understand this concept.

The conflicting results for questions under this Communication Objective suggest that the message that this product is not for regular use should be strengthened on the label.

Communication Objective 3: Plan B does not prevent sexually transmitted diseases or HIV/AIDS. (Q. 13 and 27) [Communication Objective satisfied if both answered correctly.]

The two questions in this group include a scenario question and a direct question. Responses to both of these questions should be that Plan B does not protect against STD's. Q. 13 is a scenario about a woman using Plan B to avoid STD's. Ninety-six percent (96%) answered correctly. Among the lower literate, 88% were correct, while among the higher literate, 99% were correct. Q. 27 is a direct question asking if Plan B protects against HIV and other STD's. Ninety-eight percent (98%) answered this correctly.

For this Communication Objective, there was a statistically significant difference between the lower literate and higher literate. Eighty-four percent (84%) of the adult lower literate met the sponsor's criterion for success for this question, while 99% of the adult higher literate were successful. Table 4. summarizes these results for the total sample.

Table 5. Correct responses to questions about use for STD's

Question	% Correct (N = 656)
13. scenario about use to avoid STD's	96

27. direct question about protection against HIV and other STD's	98
------------------------------------------------------------------	----

Comment: Participants understood at high rates that Plan B cannot protect against STD's. Although the lower literate scored lower than the higher literate, scores for the lower literate were not very low.

Communication Objective 4: The first pill should be taken within 72 hours after intercourse. (Q. 10, 29, 19, 20) [*Communication Objective satisfied if at least two answered correctly: 10 (if response mentions 72 hours or 3 days), 29, (19 and 20)*]

Q. 10 asks what the best time is to take the first pill. If the participant has not already said both "within 3 days" **and** "as soon as possible," Q. 10 also includes a second part that asks if the label says anything more specific. The correct answer is "as soon as possible **and** within 72 hours or three days." Twenty-three percent (23%) gave this response. Acceptable responses were the following: "within 72 hours or three days" (31%), **or** "as soon as possible" (26%). Thus, a total of 80% had correct or acceptable responses. An additional 10% said "72 hours or 3 days." These responses were not scored as correct because they did not indicate that was the maximum time.

Q. 29 asks how many days is the longest after sex that a woman should wait before taking the first pill. Ninety-one percent (91%) correctly responded 72 hours. Eighty-four percent (84%) of the lower literate and 95% of the higher literate were correct on this question.

Q. 19 applies also to the first Communication Objective, discussed earlier. Eighty-seven percent (87%) correctly said it was correct to use Plan B if the woman had unprotected sex two days earlier.

Q. 20 asks about use if unprotected sex was a week ago. Ninety-five percent (95%) correctly stated that this was an incorrect use.

The sponsor scored this objective as having been met if participants answered at least two of the four questions correctly. Eighty-five percent (85%) met this criterion. There was a statistically significant difference between the literacy groups in attaining the criterion for success for this Communication Objective. Seventy-one percent (71%) of the adult lower literate and 90% of the adult higher literate met the criterion. Table 6 presents the results for this Communication Objective for the full sample.

Table 6. Correct/acceptable responses to questions about taking the tablet within 72 hours after intercourse

Question	% Correct/acceptable (N = 656)
10. Best time to take first tablet	80
29. The longest one should wait before first tablet	91
19. Use 2 days after unprotected sex	87
20. Use 1 week after unprotected sex	95

Comment: If we deem as acceptable for Q. 10 those 10% of responses that mentioned 72 hours or three days, but did not indicate that was the maximum time, then the correct/acceptable score for Q. 10 would be 90%. It is likely that many in this 10% group had the correct understanding, but were sloppy in expressing it. Overall, the results for this Communication Objective suggest moderately high understanding of the timing of the first tablet. However, to be sure that more lower literate women understand this issue, the timing of the first tablet should be emphasized if possible.

Communication Objective 5: The first pill should be taken as soon as possible after intercourse. (Q.10, 26) [*Communication Objective satisfied if either answered correctly, where response to Q. 10 mentions as soon as possible*]

As noted earlier, Q. 10 asked the best time to take the first tablet. Twenty-three percent (23%) scored correctly (as soon as possible **and** within 72 hours or 3 days). A total of 57% scored acceptably (either within 72 hours or 3 days, **or** as soon as possible, without providing a time frame). Acceptable responses included 26% who said as soon as possible. Therefore, for Q. 10, 80% scored correctly or acceptably. Q. 26 asks if Plan B will be more effective if taken one day after unprotected sex or two days after unprotected sex. Seventy-one percent (71%) correctly said one day. Sixteen percent (16%) said both were the same, and 12% incorrectly said two days. Among the lower literate, 64% were correct, compared with 75% of the higher literate.

The sponsor counted people as responding correctly for this Communication Objective if for Q. 10 they mentioned "as soon as possible" or answered correctly to Q. 26. Eighty-two percent (82%) met this criterion. For this Communication Objective, there were no significant differences between the adult lower literate and higher literate participants. Table 7 presents these results.

Table 7. Correct/acceptable responses about timing of the first tablet

Question	% Correct/acceptable (N = 656)
10. Best time to take first tablet	80
26. Better to take at 1 days or two?	71

Comment: The moderate overall correct response rate for Q. 10, and the even lower rate among the lower literate, combined with the somewhat lower overall correct response

rate for Q. 26 make it advisable to strengthen the labeling for this issue. Approximately 1/3 seem not to have understood the message about using the product as soon as possible, although there seems to be good understanding, based on other questions, that it should be taken within three days of unprotected intercourse.

Communication Objective 6: The second pill should be taken 12 hours after the first (Q. 30)

Q. 30 asks directly when a woman should take the second tablet. Sixty-nine percent (69%) correctly said 12 hours after the first tablet. The sponsor counted as acceptable those who mentioned 12 hours but said something other than the full correct response. Seventeen percent (17%) responded in this way. An additional person (<1%) gave the response of the next morning, which the sponsor counted as acceptable. Thus, 87% answered correctly or acceptably under the sponsor's scoring system. For this question, there was a statistically significant difference among the literacy groups, with 82% of the adult lower literate and 93% of the higher literate responding correctly or acceptably. Table 8 presents these results for the full sample.

Table 8. Responses about when to take the second tablet (Q. 30)

Response	% Responding (N=656)
12 hours after first tablet*	69
12 hours (but did not give full response)*	17
the next morning*	<1
other	12

*Scored as correct or acceptable by sponsor

Comment: It is not clear whether those mentioning 12 hours but not saying "12 hours after the first tablet" truly understood the concept. It is possible that some of them did not, but it is also likely that many of them did. In correspondence with the Agency (facsimile of 10/21/03), the sponsor stated that "...some participants had difficulty communicating in standard English." The sponsor counted as acceptable "responses we suspected were probably correct but were slightly ambiguous, so we could not be sure." They included answers such as "after 12 after the first one," "before your 12 hours is up," "up to 12 hours after the first," "within 12 hours." Thus, it is possible that some responses scored as acceptable by the sponsor did not reflect correct understanding. Also, although it is a minor point, DSRCs would not have scored "the next morning" as an acceptable response. We do not know when the first pill was taken in that case.

Based on only the completely correct responses, only 69% conveyed clear understanding of when to take the second pill. Because it is possible a number of those participants who were scored as acceptable for this question did not truly understand, the timing of the second pill should be emphasized in the materials. We recommend also that the label state what to do if the dose is not taken at exactly 12 hours. If possible, the label should indicate if there is a window of time in which the second dose can be taken.

To assist women in determining exactly when to take the second tablet, we suggest there be a space on the package for the woman to fill in with the time when she took the first tablet and the time when she should take the second tablet.

Q. 23 was not specifically associated with this Communication Objective. However, it is related to the timing of the second dose. Q. 23 asked if it was correct for a woman to take both tablets at the same time. Ninety-six percent (96%) answered correctly that it was not correct.

Comment: A more detailed scenario providing the reasons why the woman might have taken both at the same time would have been more realistic and perhaps would have provided a better question to test this concept.

Communication Objective 7: Plan B should not be used by women who are already pregnant (because it would not be effective). (Q. 11 or Q. 17) [*Communication objective met if either answered correctly.*]

Q. 11 asks whether a woman who is two months pregnant should use Plan B. Ninety-two percent (92%) correctly responded. Q. 17 asks if it was correct for a pregnant woman to use Plan B because she didn't want to become pregnant. Eighty-nine percent (89%) answered this question correctly. Ninety-eight percent (98%) answered at least one of these correctly, which was the sponsor's criterion for having understood the concept. While scores for both literacy groups were high, there was a statistically significant difference between them. The adult lower literate scored 95% on this criterion for success, while the adult higher literate scored 99%.

Q. 12 was not associated with a specific Communication Objective by the sponsor. It is a follow-up to Q. 11, which asked if a woman who is two months pregnant should use Plan B. Q. 12 asks for the reason behind the response to Q. 11. Ninety-four percent (94%) responded correctly that she was already pregnant, the product won't work, or it is too late to use it. Table 9 presents the results for questions related to this Communication Objective.

Table 9. Correct/acceptable responses about use by pregnant women

Question	% Correct/Acceptable (N=656)
11. Use by woman 2 months pregnant	92
12. Reason for response to Q. 11	94
17. Use if have positive pregnancy test	89

Comment: As stated in the protocol, one aspect of this Communication Objective was that the product is not effective in pregnant women. This issue was not specifically tested, but it did surface in responses to Q. 12. It appears that a relatively high proportion of participants understood that the product is not appropriate during pregnancy. Responses to Q. 12 suggest that the reasoning for responses to Q. 11 is appropriate.

Communication Objective 8: Plan B should not be used by women with unexplained vaginal bleeding. (Q. 15)

Q. 15 is a scenario about a woman who had unusual vaginal bleeding during the week and who took Plan B to prevent pregnancy after unprotected sex. Participants were asked if this was a correct use of Plan B. Seventy-six percent (76%) answered correctly. Again, there was a statistically significant difference between the literacy groups. The adult lower literate scored 69%, while the adult higher literate scored 82%.

Comment: Clearly, this concept was not highly understood. If it is kept in the labeling, it should be emphasized further, either by bolding or by explaining its importance, or both.

Communication Objective 9: Plan B should not be used by women with allergy to any ingredient in the product. (Q. 18)

Q. 18 is a scenario about a woman allergic to an ingredient in Plan B who used it because she noticed that her partner's condom broke during sex. When asked if this was a correct use of Plan B, 91% answered properly that it was an incorrect use. The differences between literacy groups were statistically significant. The adult lower literate scored 82%, while the higher literate scored 96%.

Communication Objective 10: Side effects of Plan B include nausea and vomiting. (Q. 32-37) [Communication Objective satisfied if correct on Q. 32 and Q. 34, or nausea/vomiting mentioned in answer to Q. 37. Scored as not meeting Objective if she answered "yes" to all of Q. 32-36.]

Q. 32-35 ask if different symptoms can be side effects of Plan B (32-nausea; 33-trouble breathing; 34-vomiting; 35-fever). Q. 36 asks if there are any other possible side effects, and Q. 37 asks participants to name one of the possible side effects.

The sponsor considered participants as having understood the Communication Objective if they answered Q. 32 and Q. 34 correctly or if nausea and vomiting were mentioned in answer to Q. 37, unless all of Q. 32-36 were answered "yes." Based on these criteria, 89% understood this Communication Objective. For this Communication Objective, there were statistically significant literacy differences. The adult lower literate scored 84%, while the adult higher literate scored 96%. For Q. 37, 81% of the lower literate were correct and 93% of the higher literate were correct.

When those who said there were other possible side effects were asked to name one additional side effect, 87% provided a correct response. Table 10 presents the results for this set of questions.

Table 10. Correct responses to side effects questions.

Question	% Correct (N = 656)
32. nausea a side effect?	99
33. trouble breathing a side effect?	83
34. vomiting a side effect?	96
35. fever a side effect?	80
36. other possible side effects?	94
37. name one other side effect	87

Comment: These results show that participants generally understand the side effects of vomiting and nausea. However, there is a slight tendency to say that everything is a side effect, as evidenced by incorrect scores of about 15-20% for the questions about symptoms that are not real side effects. Such a tendency may have slightly elevated the scores for the nausea and vomiting items. The question asking for another side effect does not seem to contribute much to our understanding of participants' knowledge of the full range of side effects. However, there were no Communication Objectives addressing specific side effects other than nausea and vomiting

Communication Objective 11: If severe abdominal pain develops, the user should seek medical care immediately. (Q. 31)

The question for this Communication Objective presented a scenario asking what a woman should do if she gets severe stomach pain after using Plan B. Seventy percent (70%) said to see or call a doctor, with no time frame mentioned. Eleven percent (11%) said to see or call a doctor immediately. Four percent (4%) said to see a doctor, but not immediately, and 10% said to stop using the product. The sponsor scored as correct responses to see or call a doctor immediately or to see a doctor with the time not mentioned. On that basis, 81% responded acceptably. There were no differences between literacy groups. Table 11 presents the results.

Table 11. Responses about what to do for severe abdominal pain (Q. 31)

Response	% Responding (N=656)
See/call a doctor (time not specified)*	70
See/call a doctor immediately*	11
See/call a doctor, not immediately	4
Stop using	10
Other	1
call number on box	<1

*Scored as correct or acceptable.

Comment: Based on these results, it is not clear that participants understand that they should get immediate medical help for severe abdominal pain. However, as the sponsor suggests, perhaps in real life, it is likely that women who experience this pain would seek medical help quickly. The sponsor should consider emphasizing this message.

Additional Results

Some questions were not associated by the sponsor with particular Communication Objectives. Q. 8 asks if Plan B is the same or different from ordinary birth control pills. Eighty two percent (82%) answered correctly. For this question, 73% of the lower literate and 87% of the higher literate answered correctly.

Comment: Unfortunately, the questionnaire did not ask how this product is different, to enable us to further understand the responses.

Q. 24 was eliminated by the sponsor. It asked "A woman stopped taking her birth control pills a week ago and then she had sex with no other birth control method. She then used Plan B to prevent pregnancy. Was this a correct use of Plan B?" The sponsor said the question was "excluded from the analysis because it was recognized to have been ambiguous after the survey was concluded." No additional explanation was provided.

Comment: We do not know why the sponsor dropped this question, yet retained Q. 21, which also may have been ambiguous. A better explanation of the criteria used to drop a question would have been helpful here.

Q. 28 was a multiple choice question that asked when a woman should expect her next period after taking Plan B. The correct response, at about the normal time, was given by 79% of participants. The sponsor considered the response of one week later as acceptable because the label said "**...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.**" An additional 10% gave the acceptable response, making a total of 89% correct or acceptable. Five percent (5%) said she should expect her period immediately, and about 1% said she never should expect it. Table 12 shows these results.

Table 12. Responses to when to expect the next period (Q. 28)

Response	% Responding (N = 656)
About normal time*	79
1 week late*	10
immediately	5
refused	5
never	1

*Correct or acceptable

Comment: These results suggest a fairly good understanding of the effect of the medication on women's menstruation. The choice of "never" seemed unlikely to be correct on its face, and should have been replaced with another choice.

Results by demographic characteristics

Age. Using the sponsor’s criteria for demonstrating comprehension of each Communication Objective, age made a statistically significant ($p \leq .05$) difference for four of the objectives. Table 13 presents those differences.

Table 13. Statistically significant differences for Communication Objectives by age

Communication Objective	Age 12-15 Correct/ acceptable (%) (n=76)	Age 17-25 Correct/ acceptable (%) (n=355)	Age 26-50 Correct/ acceptable (%) (n=255)	Total Correct/ acceptable (%) (n=656)
1. Plan B indicated for prevention of pregnancy after unprotected sex*	86	93	95	93
3. Plan B does not prevent sexually transmitted diseases or HIV/AIDS	93	96	92	94
6. Second pill should be taken 12 hours after the first**	77	90	82	86
10. Side effects include nausea and vomiting	90	93	84	89

*includes correct and acceptable responses for Q. 7

**includes correct and acceptable responses for Q. 30

Comment: We should keep in mind that there were no adjustments for multiple comparisons. Therefore, some of these apparently statistically significant differences might have occurred by chance. For 3/4 of these Communication Objectives, the youngest age group scored lowest. For 3/4 of the objectives, the oldest age group scored lower than the middle group. Thus, there is no clear linear effect of age on increasing or decreasing comprehension. It is possible that there is a quadratic relationship, with the youngest and oldest understanding less than those in the mid-range. It is likely that because of the varying age ranges for the three age categories, particularly the very wide (26-50) range for the oldest group, some age-related differences were not detected. Even with these differences, the youngest group (Age 12-15) did not score extremely low.

Race. For three of the Communication Objectives, race made a statistically significant difference. Table 14 presents these results. There was not a consistent trend for any

particular racial group to do better than others. In two of the three objectives, whites did better than blacks. However, in another, blacks did better than whites and the "other" group.

Table 14. Statistically significant differences for Communication Objectives by race

Communication Objective	White % Correct/ Acceptable	Black % Correct/ Acceptable	Other % Correct/ Acceptable	Total % Correct/ Acceptable
2. Plan B is intended as a back up method and should not be used for regular contraception	75	57	61	67
8. Plan B should not be used by women with unexplained vaginal bleeding	77	68	79	75
11. If severe abdominal pain develops, the user should seek medical care immediately	79	88	81	81

Literacy. Literacy level had a statistically significant effect on nine of the 11 Communication Objectives. Table 15 presents the Communication Objectives that showed these differences.

Table 15. Statistically significant differences for Communication Objectives by literacy level.

Communication Objective	Lower Literate % Correct/Acceptable (N=139)	Higher Literate % Correct/Acceptable (N=254)	Total (N=393)
1. 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
6. 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	84	96	92

*Includes correct and acceptable responses for Q. 7.

**Includes correct and acceptable responses for Q. 30.

In addition to literacy differences by Communication Objective, there were many instances of differences between the literacy groups for the individual questions. Differences between the groups for correct and acceptable responses varied from 1 percentage point to 28 percentage points, with a mean of 11 points. In all cases, the lower literate group scored lower than the higher literate group. The sponsor did not report which of these differences may have been statistically significant. Responses for the two literacy groups are reported in Table 16.

Table 16. Correct/acceptable results for questions by literacy groups.

Question	Lower Literate % Correct/Acceptable (N=139)	Higher Literate % Correct/Acceptable (N=254)
7. Tell what Plan B is used for	73	87
8. Different from ordinary birth control?	73	87
9. Should Plan B be used as regular birth control?	71	93
10. Best time to take 1 st tablet	21/75*	26/83*
11. Use if 2 months pregnant	88	93
13. Correct to use to avoid STD's?	88	99
14. Use after condom broke	81	95
15. Use if unusual vaginal bleeding	69	82
16. Use if have asthma	61	66
17. Use if positive pregnancy test	84	92
18. Use if allergic and condom broke	82	96
19. Use 2 days after sex	78	90
20. Use after 1 week	88	96
21. Husband complains about condoms; woman wants to use Plan B	37	54
22. Use Plan B every day instead of usual birth control pills	76	95
23. Take both tablets together	89	98
25. Couple wants to use Plan B as main contraceptive method	50	78
26. Is plan B more effective 1 day or 2 days after sex?	64	75
27. Protection against STD's	94	100
28. When expect next period	65/84*	85/91*
29. What is longest woman can wait to take first tablet?	84	95
30. When take second tablet?	64/82*	77/93*
31. What do if severe stomach pain?	7	10
32. Nausea a side effect?	96	100
33. Trouble breathing a side effect?	78	88
34. Vomiting a side effect?	97	98
35. Fever a side effect?	77	82
36. Other side effects not mentioned?	91	95
37. Name other side effects not mentioned in previous questions	81	93

*First number correct; second number correct plus acceptable by sponsor's scoring

Comment: Literacy level had a definite effect on the results of the study. For most Communication Objectives and for most questions, there were substantial differences in scores between the two literacy groups. Comprehension among the lower literate was

particularly low for Communication Objective 2, concerning use of Plan B as a back up method and not for regular contraception. These results suggest that any strengthening of the messages in the labeling might increase comprehension among the lower literate, but particular attention should be paid to messages about not using the product for regular contraception and not using it if there is unexplained vaginal bleeding, as the lower literate scores were the worst for these two concepts.

We should keep in mind that the only participants included in the literacy analyses were those who were age 18 or older who had not graduated from college. Therefore, all college graduates were eliminated, as were teen-agers. Twenty-two percent (22%) of the full sample had graduated college, and more than 12% were under age 18. (The sponsor reported age ranges of 12-16, 17-25, and 26-50. Therefore, we do not know exactly how many were below age 18.) As a result of this analysis of fewer than the full sample, the literacy results may be atypical, as only adults who had not graduated from college were included. Because college graduates were excluded, it is possible that the higher literacy group had lower literacy than a typical higher literate group taken from the population as a whole, and differences between the literacy groups may therefore be minimized. However, balancing that possibility is the possibility that participants under age 18 would lower the literacy level of the lower literate group, again widening the differences between the groups.

It would have been better to include all participants in the literacy analyses to get a better picture of how literacy would affect the full range of potential product users. Nevertheless, the results do show that literacy had an effect on almost every Communication Objective, making it apparent that lower literate women may have more trouble in understanding the labeling than higher literate women.

Previous sexual experience. There were no statistically significant differences based on whether or not the participants had had sexual experience.

Experience using emergency contraceptive pills. There were not statistically significant differences based on previous use of emergency contraception.

Comment: As there were only 32 in this group, we should not conclude that they would not answer differently than other women if there had been a larger sample.

Location of interview. There were statistically significant differences based on geographic interview location for all of the Communication Objectives.

Comment: This result is not surprising, as locations are chosen to add variety to the socioeconomic and demographic characteristics of participants.

Other demographic and location effects. Race had an effect on three Communication Objectives, and ethnicity on two. Income affected three Communication Objectives and education affected four. Previous sexual experience had no effect, and experience with a

pregnancy scare and sex within the past three months affected only one Communication Objective, as did site (mall vs. clinic).

Comment: These differences were too few to lead to conclusions that there were systematic effects of these participant characteristics.

Discussion and Conclusions

Based on the sponsor's assessment, two Communication Objectives were understood by less than 80% of the sample. One was that Plan B is intended as a back up method and should not be used for regular contraception. The sponsor attributes this as possibly due to the wording of the questions. However, to help communicate this message, the sponsor will bold the text "Plan B should not be used in place of regular contraception." The other Communication Objective that was understood by less than 80% stated that the product should not be used by women with unexplained vaginal bleeding. The sponsor does not believe this contraindication is appropriate and has stated that it will seek to remove it from the label.

Based on the sponsor's analyses of Communication Objectives, two objectives were understood by 80% and 85% of participants. One was that the first pill should be taken as soon as possible after intercourse and the other one was about what to do if severe abdominal pain develops. The sponsor states that the timing of the first pill should not be viewed in isolation, as the product is still highly effective if use is delayed up to 72 hours. Almost all (97%) understood the product should be used within 72 hours, or as soon as possible after sex. The sponsor believes that failing to demonstrate understanding of what to do if there is severe abdominal pain is not of "extreme clinical concern," because women "do not need written instructions to know that they should see a doctor if severe pain develops." The sponsor plans to bold "as soon as possible" and "a serious medical problem (describing ectopic pregnancy) in the next version of the labeling.

Comment: DSRCS does not agree with the sponsor's scoring of some responses as acceptable. Further, some of the Communication Objectives could be satisfied if fewer than 100% of the questions in the objective were answered correctly. Thus, the sponsor's overall conclusions about the level of comprehension based on Communication Objectives are probably higher than those of DSRCS.

However, DSRCS believes that comprehension of critical messages was generally adequate or could be improved by label changes. Misunderstandings about regular use would be affected by the cost of the product and would not present public health issues.

The following summarizes DSRCS's findings for each Communication Objective:

1. Participants tended to understand that the product is for contraception. However, it was not clear if it was on the top of their mind that the product is for use **after** sex. As the question asked for information from memory and participants who gave partial responses were not probed for further information, it is possible that many

participants may have known that the product was for use after sex but did not express that fact.

Participants understood a variety of situations in which to use the product, but there was a tendency to say that it should not be used if one has other medical conditions. This tendency may have been an artifact of the questioning situation.

2. There were inconsistent responses about use for regular contraception. These conflicting results may be due to weaknesses in the questionnaire rather than to lack of comprehension.
3. There is a high level of understanding that Plan B does not protect against STD's, including HIV/AIDS.
4. There is moderate to high understanding of when to take the first tablet. About 90% understood that users should wait no more than 3 days.
5. The fact that the first pill should be taken as soon as possible after intercourse was not understood at high levels. Of the two questions in this Communication Objective, one scored 80% and the other 71%.
6. The fact that the second tablet should be taken 12 hours after the first was not highly understood, or the results are ambiguous.
7. A fairly high majority understood not to take the product while pregnant and that the product could not end a pregnancy.
8. There was relatively low understanding (76%) not to use the product if there is unexplained vaginal bleeding. The sponsor stated that it plans to request that this information be removed from the label.
9. There is fairly high understanding not to use the product by persons allergic to its ingredients.
10. There is high understanding of nausea and vomiting as side effects.
11. There is moderate (81%) understanding that one must get medical help if severe abdominal pain develops. The sponsor states that women "do not need written instructions to know they should see a doctor if severe pain develops."

This study suggests that there may be some lack of clarity about some issues. Failure to attain high scores for some questions may be due to actual knowledge deficits or to shortcomings of the questionnaire. As we cannot be sure of the source of the lower scores, we recommend stressing the messages that did not score in the high ranges. Messages in the labeling that may not have been communicated at the highest levels include the following:

- Do not use for regular contraception
- Use after intercourse
- Timing of doses
- Do not use if experiencing unexplained vaginal bleeding
- Get medical help for severe abdominal pain

Based on the results of this study, the sponsor has recognized some of the shortcomings of the label and stated that it planned to bold certain information in the label in an effort to communicate that information more effectively.

Results of this study and the ensuing changes to the label to emphasize information that had not been understood at very high levels should be viewed in conjunction with the Actual Use Study. That study provides insight as to whether the revised labeling was sufficient to enable women in the use trial to use the product appropriately.

Recommendations

Based on these results, DSRCS has the following recommendations for changes to the label that had been used in this study:

- Strengthen the following messages:
 - Not for regular use (sponsor has bolded this)
 - Timing of first dose
 - Timing of second dose (sponsor has bolded this)
 - If severe abdominal pain develops, seek immediate medical care
 - Do not use if unexplained vaginal bleeding (if kept in the labeling)
- State if there is a window of time for the second tablet, rather than just the 12 hour time.

In addition, DSRCS has a recommendation to help women time the second dose appropriately:

- Have a place on the label for the woman to write the time she took the first pill and the time she should take the second pill.

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/s/

Karen Lechter
11/5/03 10:37:25 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
11/5/03 05:20:36 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: October 15, 2003

FROM: Tia Frazier, R.N., M.S.
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2271 FAX: 301-827-2315

TO: Dr. Carole S. Ben-Maimon

FAX #: 610-688-2991 No. of pages (including cover) 2

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Message: We have the following questions concerning your pending supplemental NDA for Plan B (0.75mg levonorgestrel) Tablets.

- 1) Explain the rationale for excluding women under age 18 and college graduates from the literacy analyses. Explain the extent to which the literacy data that were collected reflect the literacy levels of potential product users.
- 2) Explain why it was an acceptable response to Question 7 to say the product was for contraception, without stating that it is for use after intercourse or for emergency situations only.
- 3) Do you have an explanation for the relatively low percentage of correct response to Question 17, about the woman with asthma?
- 4) How do you explain the differences in scores for similar questions—e.g. Question 25 (68%), compared with Question 22 (91%) and Question 9 (85%)?
- 5) What is the rationale for accepting different proportions of correct responses as having satisfied various communication objectives? (Refer to our previous set of questions sent to you on September 11, 2003.)
- 6) Explain the criteria used for concluding that Communication Objective 10 had been met. What does "unless she answered yes to all of 32-34" mean? If she had answered yes to 32-34, wouldn't she have already satisfied the communication objective because she had answered yes to 32 and 34? (Refer to our previous set of questions sent to you on September 11, 2003.)
- 7) What did you hope to learn from responses to Question 8, that asks whether the product is different from others, as there is no follow-up question asking how it is different?
- 8) As 9 of the 11 Communication Objectives were affected by literacy level, what changes to the label, other than those already mentioned, could help to increase the effectiveness of the label for the low literacy users, as well as for others?

A comprehensive list of the major issues regarding the label comprehension study is being developed, and will be sent to you as soon as possible. If you find our recent information requests unduly burdensome, or if you have questions, please contact me at 301-827-2271.

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/s/

Tia Frazier
10/15/03 11:52:51 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: October 10, 2003

FROM: Tia Frazier, R.N., M.S.
Regulatory Health Project Manager
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2271 FAX: 301-827-2315

TO: Dr. Carole S. Ben-Maimon

FAX #: 610-688-2991 No. of pages (including cover) 2

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Message: We have the following questions concerning your pending supplemental NDA for Plan B (0.75mg levonorgestrel) Tablets.

- 1) The subjects recruited in the label comprehension study were from shopping malls and family planning clinics. Please compare the demographics and the comprehension results from mall subjects with those of family planning clinic subjects.

If you have any questions, please contact Tia Frazier, Regulatory Project Manager, at 301-827-2271.

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/s/

Tia Frazier
10/10/03 12:34:45 PM
CSO

MEMORANDUM OF TELECONFERENCE MEETING

MEETING DATE: October 9, 2003

TIME: 2:07-3:05pm

APPLICATION: NDA 21045/S-011

MEETING CHAIR: Scott Monroe, M.D.

RECORDER: Tia Frazier

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Office of Executive Programs (OEP; HFD-006)

Lee Lemley - Policy Analyst, Executive Operations Staff

Office of Drug Evaluation V (ODE V; HFD-105)

Brian Harvey, M.D., Ph.D. - Deputy Director

Office of Over the Counter Drug Products (OTC; HFD-560)

Charles Ganley, M.D. - Director

Jin Chen, M.D., Ph.D. - Medical Officer

Helen Cothran, B.S. - Interdisciplinary Scientist, Team Leader

Arlene Solbeck, M.S. - Interdisciplinary Scientist

Youngman Kim, Pharm D. - Statistician

Keith Olin - Project Manager

Tia Frazier, R.N., M.S. - Project Manager

Office of Drug Evaluation III (ODE III; HFD 103)

Florence Houn, M.D., M.P.H. - Director

Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Dan Shames, M.D. - Director

Scott Monroe, M.D. - Medical Team Leader

Dan Davis, M.D. - Medical Officer

Lisa Soule, M.D. - Medical Officer

Karen Anderson, N.P. - Project Manager

Division of Surveillance, Research, & Community Support (DSRCS; HFD-400)

Karen Lechter, J.D., Ph.D. - Social Science Analyst

Advisors and Consultants Staff

Jayne Peterson, R.Ph., J.D. - Team Leader

Karen Templeton-Somers, Ph.D. - Team Leader

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Barr Labs.

Carole Ben-Maimon, M.D. – President and COO, Barr Research, Inc.

Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.

Joe Carrado - Senior Director, Clinical Regulatory Affairs

Womens Capital Corporation

Debbie Wilkerson, M.D. – Director, Scientific Affairs

Jessica Rosenberg – Operations and Research Associate

BACKGROUND:

On September 26, 2003, Women's Capital Corporation (WCC) informed FDA that Barr Laboratories, Inc. had purchased the new drug application (NDA) for Plan B. At that time, they announced that Barr Laboratories, Inc. would assume responsibility for the NDA and advisory committee meeting at some time in the near future.

This meeting was held at the applicant's request. The purpose of the meeting was to plan for an upcoming Advisory Committee meeting addressing the applicant's proposal for over-the-counter availability of the emergency contraceptive, Plan B (0.75mg levonorgestrel tablets).

At the outset of this meeting, WCC gave permission for Barr Laboratories, Inc. to participate in this teleconference. FDA requested that a formal letter identifying the applicant's new owner and/or U.S. agent be submitted to the NDA and be sent by facsimile to both the Division of Reproductive and Urologic Drug Products and the Division of Over-the-Counter Drug Products as soon possible.

Questions asked during the teleconference:

- 1. FDA asked: Have you identified speaker(s) for the Advisory Committee meeting, and would you share these with FDA?**

Dr. Ben-Maimon reported that she would address the mechanism of action, label comprehension study, and risk/benefit issues involved in the proposed OTC switch for this Plan B product at the December, 2003 Advisory Committee meeting.

Dr. Ben-Maimon confirmed that Dr. Vivian Dickerson, M.D., President, American College of Obstetrics and Gynecologists had accepted WCC's invitation to speak on their behalf at the Advisory Committee meeting.

Potential speakers still unconfirmed included:

1. Dr. David Grimes, M.D., Family Health International
2. Dr. Tina Raine, M.D., M.P.H., Department of Obstetrics, Gynecology and Reproductive Science, Center for Reproductive Health Research and Policy, University of California, San Francisco
3. Dr. Elizabeth Raymond, M.D., Associate Medical Director, Family Health International

2. FDA inquired about the applicant's intended list of subjects to be addressed at the Advisory Committee meeting.

Barr Laboratories responded that potential topics included:

- Regulatory history and overview
- Review of supportive trials for prescription status approval
- Global safety, time and extent of worldwide marketing
- Unmet health need for OTC availability of an emergency contraceptive

FDA requested that the applicant consider Dr. Horacio Croxatto, M.D. for expertise on the mechanism of action of Plan B tablets.

Carole Ben-Maimon of Barr Laboratories, Inc. agreed to invite Dr. Croxatto to be a guest in the audience at the Advisory Committee meeting.

3. FDA inquired about the sponsor's thoughts on age restrictions for use of Plan B.

Barr Laboratories expressed that they intended to offer their product to women down to age 15. They expressed confidence that the clinical data submitted in the application supported use of the product by young women.

FDA and the applicant discussed various challenges related to age restriction for sale of the product. The potential hurdles in restricting the sale of Plan B included the fact that teens may not possess identification that serves as proof of age.

4. FDA inquired about the applicant's distribution plan for the Plan B product.

Barr Laboratories voiced its plan to restrict the sale of Plan B to retail locations licensed to sell prescription drug products.

~~4~~

FDA voiced concern that pharmacists may not be present during late-night hours when women might want to purchase the product, particularly in pharmacies located in grocery stores.

Barr Laboratories informed FDA that they intended to explore the possibility of conducting pilot tests with cooperating pharmacies that ensured the product was being distributed according to the approval conditions.

5. FDA asked whether or not the applicant's distribution plan considered extra-contractual relationships (e.g. relationships between retail outlets with pharmacies and other distributors) that might result in the sale of Plan B in convenience locations such as vending machines and convenience stores.

Barr Laboratories agreed to look into whether these relationships may exist.

6. FDA inquired about the sponsor's plan for educating women who might purchase the product and all levels of healthcare providers on the intended use of the product as an emergency contraceptive.

Barr Laboratories discussed potential plans for educating healthcare providers in the proper use of the product through continuing medical education (CME) credits, sales representatives' details, and information in patient waiting rooms.

FDA inquired about whether or not the sponsor included a telephone number for patient inquiries, and Barr Laboratories agreed to report the answer to FDA.

Meeting Outcomes:

- 1) Barr Laboratories agreed to explore and report back to FDA its research on contractual relationships, behind-the-counter marketing (may be available only in select states), and age limitations on the sale of the product.
- 2) Joe Carrado, Senior Director, Clinical Regulatory Affairs, Barr Laboratories- was named the new contact for Advisory Committee planning.
- 3) Barr Laboratories confirmed that their responses to FDA's requests for information on the label comprehension and actual use studies would be sent to the review Divisions by October 17, 2003.
- 4) Barr Laboratories agreed to submit recent professional articles on the Plan B product to the supplemental NDA as an amendment to their application.

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/s/

Charles Ganley
11/7/03 03:20:11 PM

NDA 21-045/S-011

INFORMATION REQUEST FACSIMILE

Dear Dr. Camp:

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

We are reviewing the actual use study results in your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Most results (except AEs) were driven from the follow-up contacts (by phone mostly) in this study. What were results (such as the incorrect use, contraindication use) of Plan B derived from the Study Data Card only? What steps, if any, did you take to collect the Study Data Cards from the 43% of subjects who did not return the cards?
2. In those subjects experiencing vomiting after taking Plan B, did the vomiting occur right after Plan B (within 1 hour?)? Was there a relationship between vomiting within 1 hour after Plan B and becoming pregnant?
3. What kind of computer hardware problem did you notice during the study (p029, vol 27)? Which data sets do you think were impacted by the computer problem? How were they impacted? What was the rationale of considering "> 0.05% error rate" as failed during the audit?
4. How did you define "exactly 12 hours" for the correct vs. incorrect use analysis for the second pill?
5. Explain how the enrolled subjects were able to use Plan B themselves and yet give Plan B to an acquaintance (see page 31 of volume 27). How many subjects were involved?
6. There was a discrepancy between the number of subjects enrolled and the number of people to whom race and ethnicity were assigned, for example, in Tables 2.10d, 2.10e, and 5.1 (vol 28). Please explain.
7. Please explain what you mean by "data from card only" and "data from contact only" in Tables 4.1 and 4.2 (page 093, vol 28).
8. The number of the Lost to Follow-up was inconsistent between Figure 2 and Table 1.4a. Please clarify.
9. The number of subjects with insufficient data varies with different analyses (alternates I-III); refer Table 5.8a (vol 28, p131), Table 5.11a (vol 28, p141), Table 5.14a (vol 28, p151) and Table 5.17a (vol 28, p160a). Please clarify.
10. Please explain how "533 total product uses" were calculated in Table 5.2a? What happened to the other 7 users?
11. In Table 2.10a "Reasons to request Plan B", did "prevent pregnancy" include Plan B use before sexual intercourse?

Actual Use Study
Reviewer Questions
October 1, 2003
2

12. The results of "consultation with health care provider" presented in Section 9.7 (AU study report, p48, vol 27), Section 11.3 (AU study report, p57, vol 27), and Table 23 of *Addendum to Final Study Report* (p27) appear to be inconsistent. Please clarify.
13. Of 585 subjects who received Plan B, 45 (8%) did not use it. Did you have information about their reason for not using Plan B.

If you have any questions, call me at 301-827-2271.

Tia Frazier
Regulatory Health Project Manager
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Tia Frazier
10/1/03 03:23:44 PM
CSO

MEMORANDUM OF TELECONFERENCE MEETING

MEETING DATE: Friday, September 26, 2003

TIME: 2:30-2:45PM, resumed and continued 3:00-3:32PM

APPLICATION: NDA 21-045/S-011

MEETING CHAIR: Tia Frazier

RECORDER: Tia Frazier

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name and HFD#</u>
1. Curtis Rosebraugh, M.D., M.P.H.	Deputy Director	Division of Over-the-Counter Drug Products HFD-560
2. Tia Frazier, R.N., M.S.	Regulatory Project Manager	Division of Over-the-Counter Drug Products HFD-560
3. Andrea Leonard-Segal, M.D.	Medical Team Leader	Division of Over-the-Counter Drug Products HFD-560
Jin Chen, M.D.	Medical Reviewer	Division of Over-the-Counter Drug Products HFD-560
5. Helen Cothran	Interdisciplinary Scientist Team Leader	Division of Over-the-Counter Drug Products HFD-560
6. Arlene Solbeck, M.S.	Interdisciplinary Scientist	Division of Over-the-Counter Drug Products HFD-560
7. Yongman Kim, Ph.D.	Statistical Reviewer	Division of Analgesic and Ophthalmic Drug Products, HFD-550
8. Donna Griebel, M.D.	Deputy Director	Division of Reproductive and Urologic Drug Products, HFD-580
9. Daniel Davis, M.D.	Medical Officer	Division of Reproductive and Urologic Drug Products, HFD-580
10. Karen Anderson, R.N., N.P.	Regulatory Project Manager	Division of Reproductive and Urologic Drug Products, HFD-580
11. Karen Templeton-Somers, Ph.D.	Supervisory Health Science Administrator	Office of Executive Programs, Advisors and Consultants Staff
12. Jayne Peterson, R.Ph., J.D.	Supervisory Health Science Administrator	Office of Executive Programs, Advisors and Consultants Staff
13. Lee Lemley	Executive Secretary	Office of Executive Operations, HFD-006
14. Maureen Hess, M.P.H, RD	Science Policy Analyst	Office of Executive Operations, HFD-006

5. Julie Beitz, M.D.	Deputy Director	ODE III, HFD-103
6. Karen Lechter, J.D., Ph.D.	Social Science Analyst	Division of Surveillance, Research, & Community Support (DSRCS); HFD-400
17. Brian Harvey, M.D., Ph.D.	Deputy Director	ODE V, HFD-105

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. John Pinney	President	Pinney Associates (consultant)
2. Sharon Camp, Ph.D.	Chief Executive Officer	Women's Capital Corporation
3. Debbie Wilkerson, M.D.	Director, Scientific Affairs	Women's Capital Corporation
4. Jessica Rosenberg	Operations and Research Associate	Women's Capital Corporation
5. Lauren Lind	Director of Operations	Women's Capital Corporation

BACKGROUND:

The agenda for the meeting consisted of questions about Women's Capital Corporation's plans for the December 16, 2003, Advisory Committee meeting to address the supplemental new drug application for Plan B (0.75mg levonorgestrel) tablets. FDA also planned to inquire about the applicant's timeline for responding to FDA's September 11, 2003 information requests.

At the beginning of the meeting, Women's Capital Corporation (WCC) read a prepared statement announcing that on September 23, 2003, a majority of its board voted to sell the entire new drug application for the Plan B product to Barr Laboratories. WCC voiced uncertainty about when Barr Laboratories would assume control of the application and responsibility for developing presentations for the upcoming December Advisory Committee meeting.

After a 15 minute interruption in the teleconference, WCC provided the following tentative list of speakers. WCC stated that they had not yet finalized their speakers list.

List of Potential Speakers

1. Vivian Dickerson, M.D., American College of Obstetricians and Gynecologists, President
2. Horacio Croxatto, M.D., Instituto Chileno de Medicina Reproductiva, Santiago, Chile
3. Sharon Camp, Ph.D., President and CEO, Women's Capital Corporation

4. Elizabeth Raymond, M.D., M.P.H., Family Health International, Associate Medical Director, Clinical Research Division
5. Tina Raine, M.D., M.P.H., Department of Obstetrics, Gynecology, and Reproductive Science, Center for Reproductive Health Research and Policy, University of California, San Francisco

FDA requested that the applicant respond to our information requests by October 17, 2003, in order allow us to consider these responses in our presentations during the Advisory Committee meeting.

FDA had the following additional information request:

1. Provide the label used for the label comprehension studies, the actual use study, and the label proposed for approval in this supplemental new drug application in a format that allows FDA to compare and contrast each of the labels.

The meeting concluded cordially, and the sponsor voiced plans to request a follow-up meeting including representatives from Barr Pharmaceuticals, Inc.

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/s/

Curtis Rosebraugh
10/27/03 02:32:36 PM

Telephone-Conference Meeting Minutes

Date: August 22, 2003 **Time:** 11:30 AM – 12:00 noon **Location:** PKLN; 17B43

NDA: 21-045 **Indication:** Emergency Contraception

Drug Name: Plan B[®] (levonorgestrel 0.75mg) Tablet

Sponsor: Women's Capital Corporation

Meeting Type: T-Conference / Guidance

Meeting Chair: Daniel Shames, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. – Project Manager, DRUDP (HFD-580)

Division of Reproductive and Urologic Drug Product Attendees:

Daniel Shames, M.D. - Director, DRUDP (HFD-580)

Donna Griebel, M.D. - Deputy Director, DRUDP (HFD-580)

Margie Kober, R.Ph. – Chief, Project Management Staff, DRUDP (HFD-580)

Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

Division of Over the Counter Drug Products

Curtis Rosebraugh, M.D. – Deputy Director, OTC (HFD-560)

Office of Drug Evaluation III

Julie Beitz, M.D. – Deputy Director (HFD-103)

Bronwyn Collier, B.S.N. – ADRA (HFD-103)

External Attendees:

Sharon Camp, Ph.D. – President and Chief Executive Officer, Women's Capital Corporation

Deborah Wilkerson, Ph.D. – Director, Scientific Affairs, Women's Capital Corporation

David Adams – Chief Regulatory Counsel

Background: Plan B[®] (levonorgestrel 0.75 mg) is given in 2 doses, 12 hours apart, for Emergency Contraception. The sponsor has submitted an SE6 Efficacy Supplement to market Plan B[®] as an over-the-counter product.

Discussion:

- Assurance that DRUDP will begin working with the sponsor on plans for the December Advisory Committee meeting to be held Tuesday, December 16, 2003.
- Prepared statement given to the sponsor concerning a voluntary distribution plan to ensure that Plan B is introduced in a responsible manner to the over the counter market. The plan is to be submitted to DRUDP. The statement follows:

“This is Dan Shames calling about your application to DRUDP and DOTCDP regarding Plan B going OTC.

We are calling for two reasons. One is to discuss issues surrounding the AC which will occur on mid December and the other is to ask that you submit information that you have previously discussed with us limiting the OTC distribution of your product by involving a learned intermediary.

The date of the AC meeting regarding your product is December 16, 2003. We will be working with you on plans regarding the logistics and presentations (time required, participants and topics covered during their talks etc.) to ensure adequate coverage of important issues and an effective meeting.

Secondly, we are currently actively reviewing your application in both divisions and believe that additional material may be helpful for our evaluation of your product.

Specifically, while the approval of your package depends on our finding of whether this drug regimen is safe and appropriate for the OTC market, we believe that it would be in the interest of the American public, and in your business interest, that a product of this nature is introduced in a responsible manner. Measures to accomplish this may include the initial use of a learned intermediary such as a pharmacist (behind the counter), availability at selected types of stores, or other methods that address initial public sensitivities and concerns regarding your product.

Your voluntary plan might also address issues such as age, literacy or misunderstandings regarding the administration of your product. We urge you to submit such a plan as soon as possible so that we can discuss it with you. We anticipate that introduction of your product will be an important topic for discussion at the advisory committee meeting.”

Action Items:

- Begin working within DRUDP to develop an agenda for the Advisory Committee.
- A letter quoting the statement will be sent to the sponsor.
- The sponsor will send in a draft plan for product distribution to DRUDP for comment
- Minutes, quoting the statement, to the sponsor within 30 days.

Minutes prepared by: Karen Anderson, N.P. – Project Manager
Concurrence of Meeting Chair: Daniel Shames, M.D. –Director, DRUDP

Reviewed by

D. Shames 9/15/03

D. Griebel no comments

M. Kober 9/15/03

C. Rosebraugh no comments

J. Beitz no comments

B. Collier 8/25/03

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/s/

Daniel A. Shames
9/17/03 05:15:13 PM



NDA 21-045/S-011

INFORMATION REQUEST LETTER

Women's Capital Corporation
Attention: Sharon Camp, Ph. D.
President and Chief Executive Officer
1990 M Street, N.W., Suite 250
Washington, DC 20036

Dear Dr. Camp:

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

We are reviewing the label comprehension results in your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide results for each question based on literacy levels, rather than literacy results based on communication objectives.
2. For Question 7, indicate what percent answered that the product was for emergency contraception. Table 5 in the report provides percentages for "contraception after sex," "contraception," "emergency," and a few other categories, but not for emergency contraception.
3. For Question 30, explain how responses given Code #4 were scored (see page 153). Were these scored as "acceptable"? If so, why are there only 43 items listed as Code 4, yet Table 5 (page 025), providing results for this question, states there were 110 participants giving responses of "other but mentioned 12 hours." Normally, we would assume that more than one person gave the same response, which would account for a shorter list of codes than persons in this category. However, some of the codes are identical, suggesting that each response in the Code 4 category was listed separately. Also, how does the coding for Question 30 on page 098 relate to the coding for that question that begins on page 149?
4. For Question 30, discuss whether items coded as 4 were considered to be acceptable, and if they were, why they were acceptable. Were these the "other but mentioned 12 hours"?
5. Was there an insert in the package or writing on the blister pack? Explain what information participants saw if they opened the carton before responding to questions 13 and above.
6. In some places, does the count of "acceptable" responses also include "correct" responses? For example, on page 027, if we add the correct and acceptable numbers for the items that have both, they

are more than 100%. Therefore, does "acceptable" include "correct" as well? If so, does this occur elsewhere in the report? If so, where? Is Table 7 (page 029) also included?

7. On page 029 (Table 7), explain the separate listings for "all five questions," "four of five questions," "all 24 questions" and "21/24 questions." Why were fewer than the full number in each category reported like this? What is the rationale for selecting 4 out of 5 and 21 out of 24?
8. Discuss in detail the criteria used to determine if a communication objective was met. Why select less than 100%? If less than 100% was the objective, how was the % used determined? (Refer to page 010.)
9. For the list of questions associated with the communication objective (page 010), why are some questions (e.g., #4, #10) in parenthesis in the right hand column? What does this signify?
10. There seem to be a relatively significant number of refusals to respond, even on non-sensitive questions. Can you explain this? Were the same people refusing on these questions, or were refusals widely distributed among participants? Why were there refusals to answer non-sensitive questions?
11. Explain the revised numbering for communication objectives 1 and 6 (1A and 6A) that appear in some tables (e.g., tables 8-10). The wording seems to be the same for the objectives, so what do the number changes mean?
12. Are the footnotes for Table 16 misplaced? Why is the asterisk discussing the REALM results placed after item 1A? What does the footnote mean for 6A ("using acceptable definition for Question 7")? Question 7 is not involved in the communication objective to which this footnote connects. Further, does the footnote "using acceptable definition for Question 30" mean the response was correct or acceptable, or just acceptable?

If you have any questions, call Tia Frazier, Project Manager, at 301-827-2271.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker
Chief, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

David Hilfiker
9/11/03 11:31:59 AM



NDA 21-045\S-011
Women's Capital Corporation
Attention: Sharon Camp, Ph. D.
President and Chief Executive Officer
1990 M Street, N.W., Suite 250
Washington, DC 20036

Dear Dr. Camp:

Please refer to your supplemental new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel) Tablets, 0.75 mg.

We also refer to the phone communication, August 22, 2003, discussing the upcoming Advisory Committee meeting set for Tuesday, December 16, 2003, and a request that your proposed voluntary distribution plan be submitted to the agency. This communication is reiterated for your convenience as follows:

“We are calling for two reasons. One is to discuss issues surrounding the AC which will occur on mid December and the other is to ask that you submit information that you have previously discussed with us limiting the OTC distribution of your product by involving a learned intermediary.

The date of the AC meeting regarding your product is December 16, 2003. We will be working with you on plans regarding the logistics and presentations (time required, participants and topics covered during their talks etc.) to ensure adequate coverage of important issues and an effective meeting.

Secondly, we are currently actively reviewing your application in both divisions and believe that additional material may be helpful for our evaluation of your product.

Specifically, while the approval of your package depends on our finding of whether this drug regimen is safe and appropriate for the OTC market, we believe that it would be in the interest of the American public, and in your business interest, that a product of this nature is introduced in a responsible manner. Measures to accomplish this may include the initial use of a learned intermediary such as a pharmacist (behind the counter), availability at selected types of stores, or other methods that address initial public sensitivities and concerns regarding your product.

Your voluntary plan might also address issues such as age, literacy or misunderstandings regarding the administration of your product. We urge you to submit such a plan as soon as possible so that we can discuss it with you. We anticipate that introduction of your product will be an important topic for discussion at the advisory committee meeting.”

If you have any questions, call Karen Anderson, NP, Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
9/2/03 04:36:20 PM



NDA 21-045/S011

Women's Capital Corporation
Attention: Sharon Camp, Ph.D.
President and Chief Executive Officer
1990 M St. N.W., Suite 250
Washington, D.C. 20036

Dear Dr. Camp:

Please refer to your April 16, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel) Tablets, 0.75 mg for emergency contraception.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 20, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and request that you submit the following information:

Clinical

1. Please re-organize the "Methods" of the Actual Use Study into the following sections: study design (procedure), subject enrollment and treatment (clearly indicating inclusion/ exclusion criteria, product dispensing/purchasing), data collection/process/analyses, self-selection/de-selection assessment, efficacy assessment (including pregnancy outcome), safety assessment (all Adverse Events). Provide any deviations from the Actual Use Study protocol separately from the other sections.
2. The following pages in Volume 59 (the case reports for Actual Use study) are not legible: 016, 017, 026, 030, 036, 047, 048, 049, 056, 063, 072, 075, 089, 106, 109, 110, 133, 141, 160. Please re-submit.
3. Appendices 18.1.1 to 18.1.8 cited in the Actual Use study report (Volume 27) can not be found. Are they Appendices 16.1.1 to 16.1.8? Please clarify.

Labeling

1. Please submit the graphic specifications for your Drug Facts Labeling, in accordance with 21 CFR 201.66(d). Specify the font type and size for the title, headings, subheadings, text, barlines, hairlines, etc., and also font type and size for bullets.
2. On initial review, problems with the Drug Facts contents, patient package insert, and general formatting were identified. We will forward to you a complete set of comments from the review of the proposed labeling later in the review cycle. We noted that your patient package insert was written to be more like a prescription product package insert than an OTC package insert (consumer information leaflet). A consumer information leaflet provides an opportunity for you to expand on the uses, directions, warnings and other information that a consumer should know when using your product. In revising your patient package insert to a consumer information leaflet, you may want to refer to the leaflets from other OTC products as guides (i.e., vaginal antifungals, acid reducers).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. Please note that although these requests were not filing issues, response to them is requested.

If you have any questions, call Karen Anderson, N.P., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
7/2/03 11:37:17 AM

Meeting Minutes

Date: June 20, 2003 **Time:** 9:00 – 9:40 AM **Location:** PKLN; 17B43

NDA: 21-045 **Indication:** Emergency Contraception

Drug Name: Plan B[®] (levonorgestrel 0.75mg) Tablet

Sponsor: Women's Capital Corporation

Meeting Type: T-Conference / Guidance

Meeting Chair: Scott Monroe, M.D. - Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Dan Davis, M.D. - Medical Officer, DRUDP (HFD-580)

FDA Attendees:

Donna Griebel, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)

Dan Davis, M.D. - Medical Officer, DRUDP (HFD-580)

Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Sharon Camp, Ph.D. – President and Chief Executive Officer, Women's Capital Corporation

Deborah Wilkerson, Ph.D. – Director, Scientific Affairs, Women's Capital Corporation

Background: Plan B[®] (levonorgestrel 0.75 mg) is given in 2 doses, 12 hours apart, for Emergency Contraception. In April 2003, the sponsor submitted an SE6 Efficacy Supplement to market Plan B[®] as an over-the-counter product. The sponsor is now interested in exploring options for changing the dosing regimen to a single dose of 1.5 mg for this indication.

Discussion of the sponsor's questions:

Are literature references acceptable for safety and efficacy? Would the clinical trial sites (WHO and Nigeria) in the literature be subject to inspection by the FDA?

Answer: We need additional information over that described in the briefing packet. To use the two large trials to support an NDA, Plan B 1.5 mg Tablets (or 2 Plan B 0.75 mg tablets administered at the same time) must be demonstrated to be bioequivalent to the levonorgestrel 1.5-mg tablets used in each trial. The WHO trial alone might be sufficient to support a NDA. However, we would need to review the data before making this determination. We would require a full study report, including protocol, complete by-patient

data listings, and case report forms for serious adverse events and pregnancies. For the Nigerian trial, we also would like a full study report and complete by-patient data listings if possible. However, the Nigerian data, alone, would not be sufficient.

The clinical trial sites would be subject to FDA inspection.

General Comments:

In case the data from the WHO and Nigerian trials are unobtainable, the Division would like the following:

- At least 1000 women treated with Plan B[®] 1.5 mg [or Plan B[®] 0.75 mg- 2 tablets at the same time]
- One large, multicenter trial or two smaller multicenter trials of similar design
- Inclusion of at least several American sites
- Accurate pregnancy testing on all subjects at the follow-up visit
- Follow-up all on pregnancies for outcome
- A comparative design with a U.S.-approved product as comparator

The Division also recommended that you send the protocol(s) to the FDA for review before starting any Phase 3 trials.

Decisions:

None

Action Items:

Minutes to the sponsor within 30 days.

Minutes prepared by: Karen Anderson, N.P. – Project Manager

Concurrence of Meeting Chair: Scott Monroe, M.D. – Medical Team Leader, DRUDP

Reviewed by
D. Davis 6/20/03
S. Monroe 6/20/03
D. Griebel 6/23/03

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/s/

Scott Monroe
6/24/03 04:35:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S011

Women's Capital Corporation
Attention: Sharon Camp, Ph.D.
President and Chief Executive Officer
1990 M St. N.W., Suite 250
Washington, D.C. 20036

Dear Dr. Camp:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Plan B [®] (levonorgestrel) tablets, 0.75 mg
NDA Number:	21-045
Supplement number:	011
Review Priority Classification:	Standard (S)
Date of Supplement:	April 16, 2003
Date of Receipt:	April 22, 2003

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 20, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 20, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-045/S011

Page 2

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Karen Anderson, N.P., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
6/12/03 06:56:35 PM
Chief, Project Management Staff

Filing Meeting Minutes

Date: June 9, 2003 **Time:** 8:30 – 9:15 AM **Location:** PKLN; Conference Rm “K”

NDA 21-544 **Drug:** Plan B[®] (levonorgestrel) Tablets, 0.75 mg

Indication: Emergency Contraception (OTC use)

Sponsor: Women’s Capital Corporation

Type of Meeting: Filing

Meeting Chair: Scott Monroe, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Project Manager, DRUDP (HFD-580)

Attendees:

ODE III (HFD-103)

Julie Beitz, M.D. – Deputy Director

Bronwyn Collier, R.N. – Associate Director for Regulatory Affairs (ADRA)

Division of Reproductive and Urologic Drug Products (HFD-580)

Daniel Shames, M.D. – Director

Donna Griebel, M.D. – Deputy Director

Margie Kober, R.Ph. – Chief, Project Management Staff

Scott Monroe, M.D. – Medical Team Leader

Dan Davis, M.D. – Medical Officer

David Lin, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP

Jean Salemme, Ph.D. – Chemist, DNDCII @ DRUDP

Sonia Castillo, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP

Ameeta Parekh, Ph.D. – Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP

Myong Jin Kim, Pharm.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP

Karen Anderson, N.P. – Project Manager

Office of Drug Evaluation V (HFD-105)

Jonca Bull, M.D. – Director

Teri Rumble, R.N. – Associate Director for Regulatory Affairs (ADRA)

Division of Over the Counter Drug Products (HFD-560)

Charles Ganley, M.D. - Director

Curtis Rosebraugh, M.D., M.P.H. - Deputy Director

David Hilfiker, M.S. – Chief, Project Management Staff

Andrea Leonard Segal, M.D., M.S. - Medical Team Leader

Jin Chen, M.D., Ph.D. - Medical Officer

Helen Cothran, B.S. - Interdisciplinary Scientist, Team Leader

Arlene Solbeck, M.S.- Interdisciplinary Scientist
Tia Frazier, R.N., M.S. - Project Manager

Division Surveillance Research and Communication Support (HFD-410)

Karen Lechter, J.D., Ph.D. – Social Science Analyst

Meeting Objective: To establish if the submission is fileable.

Background: Plan B was approved as a prescription medication for emergency contraception on July 28, 1999. Women's Capital Corporation would like the product to be made available over-the-counter (OTC) to enhance timely access to treatment. Levonorgestrel emergency contraception is currently available without a prescription in several other countries. If filed, the User Fee goal date for this application will be February 20, 2004.

Discussion/Decisions Made:

Clinical comments:

- This application is fileable.

Clinical Pharmacology and Biopharmaceutics comments:

- This application is fileable.

Chemistry:

- This application is fileable.

Statistical comments:

- This application is fileable.

Toxicology comments:

- No review will be conducted for this application.

Action Items:

- OTC will send any review comments to DRUDP for the 74-day filing letter due to be sent to the sponsor by July 3, 2003.
- DSRCS and OTC will review the label comprehension.
- DRUDP will review the submission for safety information.
- Monthly status meetings will begin in August (month 4).
- An Advisory Committee is tentatively planned for mid-December.

Minutes prepared: K. Anderson, N.P., Project Manager, DRUDP
Chair Concurrence: Scott Monroe, M.D. – Team Leader, DRUDP

Concurrence:

J. Beitz – no comment

B. Collier 6/12

D. Shames 6/17

D. Griebel 6/18

M. Kober 6/12

D. Davis 6/12

D. Lin – no comment

J. Salemme – 6/12

S. Castillo 6/12

A. Parekh 6/18

M.J. Kim 6/18

J. Bull - no comment

T. Rumble – no comment

C. Ganey 6/23

C. Rosenbraugh 6/23

D. Hilfiker 6/23

A. Leonard Segal 6/23

J. Chen 6/23

H. Cothran 6/23

A. Solbeck - no comment

T. Fraizer - no comment

K. Lechter 6/17

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA # 21-045 Supplement # 011 SE1 SE2 SE3 SE4 SE5 **SE6** SE7 SE8
Trade Name: Plan B
Generic Name: levonorgestrel
Strengths: 0.75 mg

Applicant: Women's Capital Corporation

Date of Application: April 16, 2003
Date of Receipt: April 22, 2003
Date of Filing Meeting: June 9, 2003
Filing Date: June 20, 2003

Indication(s) requested: Emergency Contraception / OTC Switch

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA _____
(b)(1) Supplement X (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA
was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P _____
Resubmission after a withdrawal _____ or refuse to file _____
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) OTC

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness
[21 CFR 316.3(b)(13)]? YES NO

Is the application affected by the application integrity policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

User Fee Status: Paid _____ Waived (e.g., small business, public health) X
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # _____
Clinical data? YES X NO _____, Referenced to NDA # _____

Date clock started after UN: _____

User Fee Goal Date: February 22, 2004
Action Goal Date (optional): February 20, 2003

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information included with authorized signature? NA YES NO
- Exclusivity requested? YES, _____ years NO
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? *YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

*Sent in revised Debarment Certification – 6/24/03

NOTE: Debarment Certification must have correct wording, e.g.: “I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure information included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Has the applicant submitted pediatric data and/or deferral request and/or waiver request for all ages and indications? NEED TO REVISE OR DELETE THIS STATEMENT
- If no, explain. Waived YES NO

- Field Copy Certification (that it is a true copy of the CMC technical section)? NA YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? YES NO (If not, have the Document Room make the corrections).
- List referenced IND numbers: NA
- End-of-Phase 2 Meeting? NA Date _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? (discussion of OTC Switch) Date(s) February 5, 2000 NO
If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? NA YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? NA YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? NA YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? NA YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **NA** YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

YES, IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

• Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

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this page is the manifestation of the electronic signature.**

/s/

Scott Monroe
8/12/03 07:00:37 PM

NDA: 21-045 SE6-011

Received: 4-22-03

Application to go Over-the-Counter (OTC)

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		Exact same dose as before
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		1 label comprehension and 1 actual use study
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		This will be a review issue.
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	X		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		

ITEM	YES	NO	COMMENT
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	X		
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	Yes		OTC Division will primarily review the 2 major studies; DRUDP will primarily review the safety data. Both will review the label.
<p>17) Reasons for refusal to file:</p> <p>This will be a joint review of a prescription product [Plan B®], approved in July 1999, that is applying to go OTC.</p>			

Daniel Davis, MD / 6-11-03

 Reviewing Medical Officer / Date

Scott Monroe, MD / 6-11-03

 Supervisory Medical Officer/Date

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/s/

Daniel Davis
6/11/03 02:13:25 PM
MEDICAL OFFICER

Scott Monroe
6/11/03 02:34:36 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 07/25/03 DATE OF DOCUMENT: 04/22/03	DESIRED COMPLETION DATE: 10/06/03	ODS CONSULT #: 03-0220
---------------------------------------------------------------------	------------------------------------------	-------------------------------

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Karen Anderson
Project Manager
HFD-580

PRODUCT NAME: Plan B (Levonorgestrel Tablets) 0.75 mg	NDA SPONSOR: Women's Capital Corporation
NDA #: 21-045	

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Plan B" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name, Plan B. This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DDMAC finds the name Plan B acceptable from a promotional perspective.

Carol Holquist, R.Ph. Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	Jerry Phillips, R.Ph. Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration
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**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 17, 2003

NDA #: 21-045

NAME OF DRUG: **Plan B**
(Levonorgestrel Tablets)
0.75 mg

NDA HOLDER: Women's Capital Corporation

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), for assessment of the proprietary name "Plan B", regarding potential name confusion with other proprietary or established drug names. The efficacy supplement is for an over-the-counter (OTC) switch. The product is currently approved (July 28, 1999) for emergency contraception and the dosage and instructions will remain the same. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Plan B is intended to prevent pregnancy after known or suspected contraceptive failure or intercourse. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later. Each Plan B tablet contains 0.75 mg of levonorgestrel and will be available for a single course of treatment in PVC/aluminum foil blister packages of two tablets each.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Plan B" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/database within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

³ The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

search system (TESS) was conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Plan B. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with Plan B. The product is listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC did not have concerns with Plan B in regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage Form(s), Established name	Usual adult dose	Other
Plan B	Levonorgestrel Tablets 0.75 mg	One tablet to be taken within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose.	
Pred G	Gentamicin Sulfate/ Prednisolone Acetate Ophthalmic Suspension 0.3 %/1 % 2 mL, 5 mL, 10 mL	Instill one drop two to four times daily. During initial 24 – 48 hours, may increase frequency to every 1 hour. (maximum initial dose = 20 mL)	SA
*Frequently used, not all-inclusive **LA (look-alike), SA (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

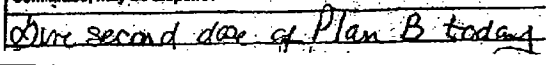

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Plan B with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and

⁴ WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

unapproved drug products and a prescription for Plan B (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

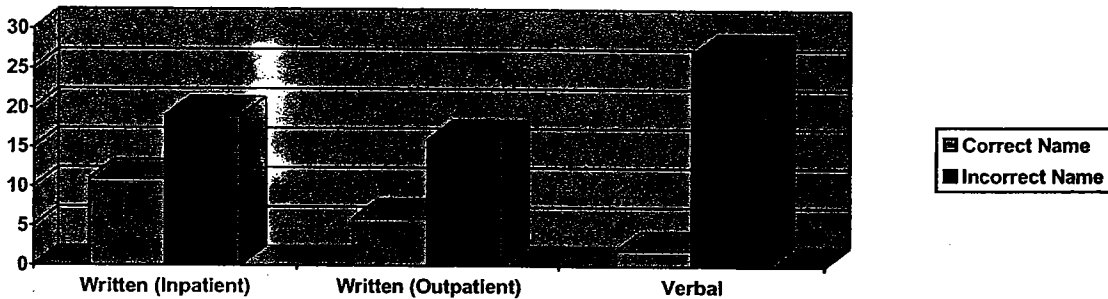
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX: 	Plan B Take 1 tablet now and another tablet in 12 hours. #2
Outpatient RX: 	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	43	28 (65%)	28 (100%)	0 (0%)
Written Outpatient	43	22 (51%)	20 (91%)	2 (9%)
Verbal	41	29 (71%)	29 (100%)	0 (0%)
Total	127	79 (62%)	77 (97%)	2 (3%)



Among the written inpatient prescriptions and the verbal prescription study participants, none of the participants interpreted the name incorrectly.

In the written outpatient prescriptions, 2 of 22 (9%) participants interpreted the name incorrectly. The incorrect interpretations from the prescriptions included Plen B and Plam B, misspelled variations of Plan B. None of the interpretations are similar to a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. AERS Search

Plan B has been marketed since July 28, 1999. Therefore, DMETS searched the FDA Adverse Event Reporting System (AERS) database to determine if any post-marketing safety reports of medication errors associated with *Plan B* were reported. The MedDRA Preferred Terms (PT), "Medication Error," "Overdose," "Accidental Overdose," "Accidental Exposure," and the active ingredient, tradename, and verbatim for "Plan B%" and "levonorgestrel%" were used to perform the searches. This search did not result in the retrieval of any cases relevant to the nomenclature, label, and labeling of Plan B.

2. Look-alike/Sound-alike Names

In reviewing the proprietary name, Plan B, the primary concern raised related to a sound-alike name that currently exists in the U.S. market, Pred G.

The proposed name, Plan B, may sound similar to Pred G depending upon how they are pronounced. Pred G is a topical anti-inflammatory/anti-infective combination product for ophthalmic use. Typically, one drop is instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased, if necessary, up to 1 drop every hour. Pred G is supplied in 2, 5, and 10 mL bottles. Plan B and Pred G have the same number of syllables (one plus a modifier) and have sounds which may overlap with one another. The "Pl-" and "B" sounds in Plan B and the "Pr-" and "G" sounds in Pred G, share phonetic characteristics, however the "-an" in Plan B and the "-ed" in Pred G help differentiate the two names from one another. Plan B and Pred G do not share an overlapping dosage strength, dosage form (tablet vs. suspension), route of administration (oral vs. ophthalmic), or dosing schedule. In addition, the two drugs will not be stored next to one another as Plan B will be an OTC product and Pred G is dispensed by prescription only. Due to these differences, DMETS believes that there is a low risk for confusion and error between Plan B and Pred G.

III. **LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

According to the firm, the labeling and packaging will remain the same as the currently approved (July 28, 1999) product. In the review of the container labels, carton and insert labeling of Plan B, DMETS focused on safety issues relating to possible medication errors. At this time, we have not identified any areas of possible improvement which might minimize potential user error.

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name, Plan B. This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DDMAC finds the proprietary name, Plan B, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Jinhee L. Jahng, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**This is a representation of an electronic record that was signed electronically and
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/s/

Jinhee Jahng
10/7/03 08:47:52 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/7/03 10:15:36 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/7/03 03:21:59 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/7/03 04:30:08 PM
DRUG SAFETY OFFICE REVIEWER
Plan B as an OTC is acceptable ONLY if
the Rx Product is no longer marketed. The
same product can not exist in both marketplaces
with the SAME name.



OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-045 S-011

Submission Date: April 16, 2003 (CDER stamp date April 22, 2003)

Type of Submission: Rx to OTC switch

Sponsor: Women's Capital Corporation, Washington, DC

Drug Product: Plan B® (Emergency Contraception)

Active Ingredient: •Levonorgestrel, 0.75 mg in each tablet

Indication: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 2 tablets, 0.75 mg levonorgestrel in each tablet

Review Date: November 14, 2003

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Tia Frazier

Background

This review provides comments on the sponsor's proposed OTC Plan B® carton labeling (which includes Drug Facts) and 2 package inserts (What You Should Know About Plan B®, and Choosing a Regular Method of Birth Control). These comments are intended to make the Plan B® labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive drug labeling. These comments do not address the labeling changes suggested by the advisory committee. The sponsor needs to address the advisory committees' recommended changes.

Plan B® is emergency contraception, a backup method of birth control. It can reduce the risk of pregnancy after unprotected sex (i.e. if a regular birth control method fails or after sex without birth control). Plan B® contains a concentrated dose of levonorgestrel, a synthetic hormone used in birth control pills for over 35 years. The FDA approved Plan B® for prescription use on July 28, 1999 under NDA 21-045. On April 16, 2003, the sponsor submitted an NDA to switch Plan B® from prescription status to OTC. FDA also references the sponsor's subsequent labeling submission of October 15, 2003 (CDER stamp date October 24, 2003) containing revised carton and package insert labeling. Plan B® was reviewed jointly by the Advisory Committee on Reproductive and Urologic Drugs and the Nonprescription Drugs Advisory Committee on December 16, 2003.

Reviewer's Comments

- A. Attachment 1 contains comments on the sponsor's proposed Plan B® OTC carton labeling (principal display panel (PDP), Drug Facts, and other panels). These comments are intended to make the Plan B® labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive labeling. These comments do not address the labeling changes suggested by the advisory committee. The sponsor needs to address the advisory committees' recommended changes.
- B. Attachment 2 contains a mock Drug Facts label incorporating the recommendations made by FDA in Attachment 1 to make the carton and Drug Facts labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive labeling.
- C. Attachment 3 is FDA's revised version of the sponsor's proposed consumer information leaflet, "What You Should Know About Plan B". FDA recommends that it be written in question and answer format to make it easier to read and locate information.
- D. Attachment 4 contains some comments on the sponsor's proposed consumer information leaflet, "Choosing a Method of Birth Control".

- E. Attachment 5 contains the current version of FDA's Table of Pregnancy Rates. This table is a simplified, easy to read table that is intended to be included in the labeling for all OTC contraceptive drug products. Note that this table needs to be updated.
- F. Attachment 6 contains the Pregnancy Rate table found in Rx contraceptive drug products.

Attachment 1.**A1. Principal Display Panel (PDP)**

1. According to 21 CFR 201.61 (b), the statement of identity shall consist of the OTC drug's established name (USP name) followed by an accurate statement of the general pharmacological category. In the case of Plan B®, the brand name is followed by the pharmacological category; but the established name (levonorgestrel tablets) is located at the bottom of the PDP, not in conjunction with the brand name and pharmacological category. Remove the established name from the declaration of net quantity of contents and place it more in conjunction with the brand name and pharmacological category. Also, change pharmacological category from emergency contraception to emergency contraceptive to be consistent with other OTC contraceptive drug products.
2. According to 21 CFR 201.61 (c), the statement of identity shall be presented in a size reasonably related to the most prominent printed matter on the panel. We recommend that the established name of the drug be more prominent (i.e., ½ the size of the brand name).
3. We recommend that more information be placed on the PDP to help the consumers in their self-selection, such as the indication(s) for this OTC drug product (see below).

Revised Mock PDP

<p>Plan B® Levonorgestrel Tablets (0.75 mg) Emergency Contraceptive</p> <p>Reduces chance of pregnancy after unprotected sex (if a contraceptive failed or you did not use birth control)</p> <p>2 Tablets</p>

A2. Drug Facts

4. **Drug Facts title:** The font size is not in accordance with 201.66 (d)(2) which states that the type size for the Drug Facts title should be in a type larger than the largest type used in the Drug Facts labeling. Enlarge the Drug Facts title.
5. **bullets:** In accordance with 201.66 (d)(4), bullets should be 5-point type size. The bullets in this labeling are 6-point type size. Adjust size of bullets.
6. **hairlines and barlines:** 201.66 (d)(8) specifies the regulations for the use of barlines and hairlines. This drug facts labeling does not comply with the regulations (e.g., distinctive barlines extending to each end of the Drug Facts box providing separation between headings; hairlines extending within either side of the Drug Facts box immediately following the title and preceding each of the subheadings). Provide the correct hairlines and barlines.
7. Delete "Plan B" anywhere in the Drug Facts labeling and substitute "this product". It is the agency's policy not to allow brand names of drug products in the Drug Facts labeling.
8. **Purpose:** It should be right justified in accordance with 201.66 (d)(6). Correct the alignment.
9. **Purpose:** The word "Contraception" in "Emergency Contraception" should start with a lower case "C", in accordance with 201.66 (d)(1) and should be changed to "contraceptive" to be consistent with other OTC contraceptive drug products.
10. **Use:** the word "Reduces" should start with a lower case "R".
11. **Warnings:** the first statement under *Warnings* should be the "Allergy alert" (in accordance with 201.66 (c)(5)(b)). Insert the following: "**Allergy alert:** Do not use if you have ever had an allergic reaction to levonorgestrel". Your current allergy statement in the "**Do not use**" section of the labeling should be deleted.
12. **Warnings:** insert a "Sexually transmitted diseases alert" after the Allergy alert to read as follows: "**Sexually transmitted diseases alert:** This product does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)". FDA has also proposed this alert for OTC vaginal contraceptives containing nonoxynol-9. The sponsor's similar warning which is not designated as an alert needs to be deleted.
13. **Do not use:** delete the colon from this subheading

14. **Do not use:** delete the second bulleted statement about being allergic to Plan B. It is handled by inserting the "Allergy alert" (see A2.11.).
15. **Do not use:** Add the bulleted statement "for regular birth control", which becomes the second bulleted statement in this section.
16. **Do not use:** (*Sponsor has asked that the bullet "if you have unusual vaginal bleeding" be removed. The decision, as part of the review process, is pending*).
17. Move "Plan B is not recommended for regular contraception" to "**Other information**". Also, delete "Plan B" from the statement. Substitute "this product".
18. Replace "Plan B does not protect against HIV (the virus that causes AIDS) or any other sexually transmitted diseases" with the "Sexually transmitted diseases alert" (see A2.12. above).
19. Delete the comma from the subheading "**When using this product**, you may have". Also, the phrase "you may have" should not be bolded.
20. Sponsor excluded pregnancy from the breastfeeding warning because it is unnecessary for women to ask a doctor first if they are pregnant because the label tells them not to use the product if they are pregnant because it will not work. So, the pregnancy/breastfeeding statement can be revised to read: "**If breast-feeding**, ask a health-professional before use." (*The advisory committee discussed not needing a breastfeeding statement. The decision, as part of the review process, is pending*).
21. Include the accidental overdose/ingestion warning as set forth in 330.1(g) to read "**Keep out of reach of children**. If swallowed, get medical help or contact a Poison Control center right away."
22. **Directions:** delete the periods from the end of the two bulleted statements. Begin each bulleted statement with a lowercase letter. When a bulleted statement runs onto the next line, align the continuation with the first word of the statement above, not the bullet.
23. **Directions:** sponsor stated that they decided to bold "12 hours" in the second bullet but it doesn't look like it's bolded in the submission. Bold "12 hours".
24. Add a new section "**Other information**" (and see below).
25. **Other information:** Add the following bulleted statements:

- a. **before using this product read the enclosed consumer information leaflet for complete directions and information**
- b. this product is not recommended for regular birth control. It does not work as well as most other birth control methods used correctly. *(note also that the word "contraception" was changed to "birth control")*
- c. correct use of a latex condom by your partner with every sexual act will help reduce the risk of transmission of the AIDS virus (HIV) and many STDs
- d. Describe the tamper evident statement. *(In accordance with 211.132(b)(1) and (c)(2), the product needs an identifying characteristic (e.g., a printing, trademark, logo, or picture) which, when breached or missing, would provide visible evidence to consumers that tampering has occurred, and that characteristic must be referenced in the labeling statement.)*
- e. store at 20-25°C (68-77°F)

26. **Inactive ingredients:** list in alphabetical order to comply with 201.66(c)(8).
27. **Questions or comments?** Bold the phone number. We recommend that you include the days of the week and time of day when a person is available to respond to questions. Remove "Plan B" from the name of the website. The brand name "Plan B" can be used elsewhere in the labeling outside of the Drug Facts box. *(It is the agency's policy to not include brand names in the Drug Facts box. However, the agency may grant an exemption to this policy and allow use of this website address in the Drug Facts box if the sponsor provides adequate justification).*

A mock Drug Facts label for Plan B incorporating the above comments is found in Attachment 2.

A3. Other Panels

28. Panel 2: Panel 2 does not say anything about vaginal bleeding under Do not use. The sponsor put it into the Drug Facts under Do not use. Labeling should be consistent.
29. Panel 4: Panel 4 says to talk to a doctor if you have "unexplained" vaginal bleeding. The statement in Drug Facts says "unusual" vaginal bleeding. Labeling should be consistent.
30. Panel 6: Include a space for the consumer to write when she took the first tablet and when she needs to take the second tablet (12 hours later).
31. Panel 8: Move the statement "Plan B works better the sooner you use it after unprotected sex" to Panel 6 where the directions for taking the pills are.

32. Include a statement somewhere in the carton labeling to inform the consumer to read the consumer information leaflet for more information.

Attachment 2.

Sample Drug Facts Labeling for Plan B®

This label provides content information only. It incorporates the recommendations made in Attachment 1 which are intended to make the Plan B labeling consistent with the regulations in 21 CFR 201 and other OTC contraceptive labeling. These comments do not address some of the labeling changes suggested by the advisory committee. The font sizes for title, headings, subheadings, condensed text, bullets and other graphic features must be in accordance with 21 CFR 201.66.

Drug Facts		Purpose
Active ingredient (in each tablet) Levonorgestrel 0.75 mg		Emergency contraceptive
Use reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)		
Warnings		
Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel		
Sexually transmitted diseases alert: This product does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)		
Do not use		
<ul style="list-style-type: none"> ■ if you are already pregnant (because it will not work) ■ for regular birth control ■ if you have usual vaginal bleeding 		
When using this product you may have		
<ul style="list-style-type: none"> ■ nausea ■ diarrhea ■ menstrual changes 	<ul style="list-style-type: none"> ■ vomiting ■ dizziness 	<ul style="list-style-type: none"> ■ stomach pain ■ breast pain
<ul style="list-style-type: none"> ■ tiredness ■ headache 		
If breast-feeding, ask a health professional before use. Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.		
Directions		
<ul style="list-style-type: none"> ■ take the first tablet as soon as possible but not later than 72 hours (3 days) after unprotected sex ■ take the second tablet 12 hours after you take the first tablet 		
Other information		
<ul style="list-style-type: none"> ■ before using this product, read the enclosed consumer information leaflet for complete directions and information ■ this product is not recommended for regular birth control. It does not work as well as most other birth control methods used consistently and correctly. ■ correct use of a latex condom by your partner with every sexual act will help reduce the risk of transmission of the AIDS virus (HIV) and many STDs ■ (describe tamper evident statement e.g. "this package is sealed in plastic wrap and secured with a printed seal. Do not use if the seal has been removed or broken.") ■ store at 20-25°C (68-77°F) 		
Inactive ingredients colloidal silicon dioxide, corn starch, gelatin, lactose monohydrate, magnesium stearate, potato starch, talc		
Questions or comments? 1-800-330-1271 www.goto?????.com		

Attachment 3.

General FDA Comments: This leaflet was rewritten (by adding to the sponsor's text) in question and answer format to be more consumer friendly and similar to other OTC drug product consumer information leaflets. However, these comments do not address all of the labeling changes suggested by the advisory committee and some further changes need to be made (see FDA's comments below). FDA additionally recommends that you break the leaflet into sections with headings (such as Product Overview, Important Information for Users, Warnings, Directions, etc.) and group the questions and answers under the appropriate headings to make it easier for the consumer to find the information quickly.

Consumer Information Leaflet

What you should know about Plan B®

What is emergency contraception?

Emergency contraception is a method of preventing pregnancy. It is to be used after a contraceptive fails or after unprotected sex. It is not for routine use. Drugs used for emergency contraception are called emergency contraceptive pills, postcoital pills, or morning after pills.

What is Plan B®?

Plan B® is emergency contraception. It is a backup method of birth control. Plan B® can reduce your risk of pregnancy if you have had unprotected sex (if your regular birth control method fails or if you have had sex without birth control). For example, if you were using a condom and it breaks or if you forgot to take your birth control pills, or if you did not use any birth control method, Plan B® may work for you.

How does Plan B® work?

Plan B® contains a concentrated dose of levonorgestrel, a synthetic hormone used in birth control pills for over 35 years. Plan B® works like other birth control pills to prevent pregnancy. **Because Plan B® prevents pregnancy before it begins, it is not the same as abortion. (FDA Comment: This last statement about abortion should be revised. You should be very exact in your language and explain what Plan B does mechanistically. Women who believe that the term abortion applies to anything following fertilization may not understand that Plan B may affect implantation).**

Plan B® can prevent pregnancy by stopping the release of an egg from the ovary (*ovulation*), or it may prevent the union of sperm and egg (*fertilization*). You are at most risk of pregnancy just before ovulation and on the day of ovulation.

If fertilization does occur, Plan B® may prevent a fertilized egg from attaching to the womb (*implantation*). Plan B® will not work after implantation of a fertilized egg.

Plan B® is **not** the same as the early abortion pill, Mifeprex® (RU486). There is no evidence that Plan B® can disrupt or end an established pregnancy (***FDA Comment: Define established pregnancy***). If you take Plan B® when you are already pregnant it will not work. (***FDA Comment: You need to be clear that if someone already has an implanted fetus, that this will not cause it to be aborted***).

When is it appropriate to use Plan B®?

You can use Plan B® **after** you have had unprotected sex one or more times in the last three days (72 hours), and you don't want to become pregnant.

Plan B® can be used as a backup method to birth control if

- Your regular birth control failed (your partner's condom broke or slipped).
- You made a mistake with your regular method (you missed several birth control pills).
- You did not use any birth control method.

When is it **not** appropriate to use Plan B®?

- Plan B® should not be used as a regular birth control method. It is not as effective as using a regular birth control method correctly and consistently.
- Plan B® should not be used if you are already pregnant because it will not work
- Plan B® should not be used if you are allergic to levonorgestrel.
- Plan B should not be used if you have unusual vaginal bleeding (***FDA Comment: This may not apply anymore. It is a pending review issue and should be consistent with carton labeling***)
- Plan B® does not protect against HIV (the virus that causes AIDS) or other sexually transmitted diseases. Correct use of a latex condom with every sexual act is the best protection against HIV or other sexually transmitted diseases.

- Plan B® should not be used before intercourse. It is a backup method of contraception.

How can I get the best results from Plan B®?

You have only a few days to prevent pregnancy after unprotected sex. **Plan B® works better the sooner you use it.** Take the first Plan B® tablet **as soon as possible but not later than three days (72 hours)** after unprotected sex. Take the second tablet 12 hours later.

How effective is Plan B®?

Plan B® can reduce the risk of pregnancy to about 1 percent, if you use it within the first three days of a single act of unprotected sex. Your risk of pregnancy ranges from 0 to 35 percent, depending on the day of your menstrual cycle. **(FDA comment: The way this data is presented is confusing. The prescription information states that Plan B can reduce the risk of pregnancy by 89% (from about 8 percent to 1 percent) when used correctly. You should revise this section so it is less confusing and include typical use as well as perfect use).**

How will I know if Plan B® worked?

Most women will have their next menstrual period at the expected time or within a week of the expected time. If your menstrual period is delayed beyond one week, you may be pregnant and you should get a pregnancy test and follow up with your doctor.

What if I am already pregnant and use Plan B®?

Plan B® should not have any effect on an established pregnancy. If you take it accidentally after you are already pregnant, or it does not work and you become pregnant, it is not likely to cause any harm to you or your pregnancy. Studies of women who took birth control pills by mistake after they were already pregnant showed no increased risk of birth defects.

Can Plan B® be used for regular birth control?

Plan B® should not be used for regular birth control. Plan B® is not as effective as using a regular birth control correctly and consistently. It is a backup method to be used if your regular birth control fails or if you have sex without birth control. It should not be used as birth control before intercourse.

How often can I use Plan B®?

Plan B® is meant for very infrequent emergency protection. If you need to use emergency contraception more often, you should consult with your health care professional for your best birth control and STD prevention methods.

Will I experience any side effects from Plan B®?

Plan B® has no serious or lasting medical side effects. Some women will experience non-serious side effects, such as nausea, stomach pain, headache, dizziness, or breast tenderness. These are similar to the side effects of regular birth control pills. Some women have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late. **If your period is more than a week late, you should get a pregnancy test.**

When used as directed, Plan B® is safe for most women. Ectopic pregnancy (a pregnancy growing in your fallopian tube) does not appear to be increased with Plan B® use. However, if you use Plan B® and develop severe abdominal pain, consult your health care provider immediately.

What warnings should I know about when using Plan B®

Plan B® does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs).

Do not use:

- if you already pregnant (because it will not work)
- if you are allergic to levonorgestrel or any of the ingredients in Plan B®
- for regular birth control
- if you have any unusual vaginal bleeding

When using this product you may have:

- nausea
- vomiting
- stomach pain
- tiredness
- diarrhea
- dizziness
- breast pain
- headache

If breast feeding, ask a health professional before use.

Keep out of reach of children. if swallowed, get medical help or contact a Poison Control Center right away.

What are the directions for using Plan B®?

- take the first tablet as soon as possible **but not later than 72 hours (3 days)** after unprotected sex
- take the second tablet **12 hours** after you take the first tablet
- if you vomit within one hour of taking either dose of medication, call a health care professional to discuss whether to repeat the dose.

What should I do if I have questions about Plan B®?

If you have questions or need more information about this product, call our toll-free number, 1-800-330-1271, or visit our website at www.go2planb.com.

Other information

- each Plan B® package is sealed in plastic wrap and secured with a printed seal. **Do not use if the printed seal has been either removed or broken.**

- store at 20-25°C (68-77°F)

Active ingredient: levonorgestrel, 0.75 mg in each tablet

Inactive ingredients: colloidal silicon dioxide, corn starch, gelatin, lactose monohydrate, magnesium stearate, potato starch, talc

Attachment 4.

Note to HFD-580: General FDA Comments: This leaflet needs to include FDA's Table of Pregnancy Rates for Birth Control Methods. A copy of the current table is found in Attachment 5. This easy to read table was developed by the Division of OTC Drug Products and is intended to be included in all OTC contraceptive drug product labeling. The data in this table is from Contraceptive Technology, 17th edition (1998). We also notice that the data in the pregnancy rate tables required in the package inserts of Rx contraceptive products reference the 17th edition of Contraceptive Technology. A copy of the Rx pregnancy rate table is found in Attachment 6. The sponsor's leaflet references data from Contraceptive Technology, 18th revised edition (2004). Therefore, FDA's Table of Pregnancy Rates for Birth Control Methods needs to be updated with the most current data for all the birth control methods approved to date. This updated information needs to be included in the Plan B leaflet in addition to the text below. See below for additional comments about this leaflet unrelated to pregnancy rates.

Choosing a Regular Method of Birth Control

Plan B® is a safe and effective emergency contraceptive for use when you need a backup method of birth control.

Plan B® is not a substitute for regular contraception. Using a regular contraceptive correctly and consistently would be more effective and may be less expensive. Plan B® does not protect you against sexually transmitted infections, including HIV/AIDS.

Comment: Revise the second statement to read "Plan B® does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)."

If you are sexually active but you are not using a regular birth control method, or if you are having trouble using your method, you should talk with a healthcare professional. Women who are sexually active and use no birth control method for a year have an 85% risk of becoming pregnant.

Comment: Women who are sexually active and use no birth control method may be also at high risk for STD infection as well as pregnancy.

Listed below are birth control choices that you may want to discuss with your healthcare provider. In some cases, Plan B® may be a good backup for the method you choose.

Abstinence

Sexual abstinence is the most effective way to avoid both unintended pregnancy and sexually transmitted infections, including HIV/AIDS. Sexual abstinence requires commitment and self-control on the part of both partners in a relationship. For women practicing abstinence, Plan B® can be a useful back-up method, if unplanned sex does occur.

Comment: Revise the first sentence to read "Sexual abstinence, i.e., not having sex, is the most effective way to avoid unintended pregnancy and sexually transmitted diseases including HIV, the virus that causes AIDS."

Birth Control Pill

Most birth control pills contain *progestin* and *estrogen*. These active ingredients are synthetic versions of naturally occurring female hormones. *Progestin*-only pills are available for women who should not take estrogen because of cardiovascular or other risk factors. All birth control pills currently require a prescription. Birth control pills are highly effective if they are used correctly and consistently. Because women sometimes forget to take their pills, the typical pregnancy rate in the first year of use is about 8%. Advantages of the pill include more regular periods, less menstrual bleeding, decreased menstrual cramps, and a reduction in the risk of endometrial and ovarian cancer. Side effects may include nausea, breast tenderness, and headaches, but these symptoms often decrease after the first few months of pill use. Birth control pills provide no protection against sexually transmitted infections or HIV/AIDS. Plan B® can be used as a backup contraceptive if you miss two or more pills in a row or if you start a new cycle of pills late. You can start taking your pills again as soon as you finish taking Plan B®.

Comments: The term "birth control pills" needs to be better defined. Plan B tablets are "birth control pills" and will not require a prescription. Change the word "infections" to "diseases" in "sexually transmitted infections".

Condom

Many different types of condoms for men are available in pharmacies without a prescription. Condoms can prevent pregnancy and can also reduce the risk of getting HIV/AIDS or other sexually transmitted infections. To be most effective, condoms must be used correctly and consistently. Condoms break or slip 3% to 5% of the time. As a result of condom accidents and inconsistent use, the typical risk of pregnancy is about 15% in the first year of use. A polyurethane female condom, worn inside the vagina, is also available without a prescription. The female condom can prevent both pregnancy and sexually transmitted infections, including HIV/AIDS. The risk of pregnancy is about 21% in the first year of typical use. Couples depending on male or female condoms for birth control may find it useful to keep Plan B® in the nightstand in case of a condom accident or if unprotected sex occurs.

Comments: Change "sexually transmitted infections" to "sexually transmitted diseases". Add that condoms need to be latex for STD protection. Also include in this section the following: "Except for abstinence, a latex condom is the best protection against STDs, including herpes and HIV/AIDS." and "If a spermicide is used with a condom, be sure that the spermicide is compatible with the condom (won't cause it to weaken or break). Oil-based lubricants (such as petroleum jelly or baby oil) will cause latex to weaken and should not be used with this method."

Diaphragm, Cervical Cap and Sponge (Female Barrier Methods)

Female barrier methods prevent pregnancy by stopping sperm from reaching the uterus. The diaphragm and cap are used with a spermicide; the sponge contains a spermicide. (See "Spermicides" below). These methods do not require a prescription. Plan B® can be a useful backup method when a diaphragm or cervical cap moves out of place during sex, or if unprotected sex occurs.

Comment: Include a statement about STDs and HIV to be consistent with the descriptions of the other methods.

Implant (Contraceptive Implant)

New contraceptive implants, lasting for two or three years, are available in Europe and should be available soon in the United States. Implants allow the steady release of low doses of *progestin*, a synthetic version of a naturally occurring female hormone. Implants are highly effective and convenient for women who want long-term contraception. Pregnancy rates are less than 0.5% in the first year of typical use. Like other *progestin*-only methods, implants can cause irregular menstrual bleeding, including spotting and less frequent periods. Implants must be inserted under the skin and surgically removed by a healthcare professional.

Comment: Include a statement about STDs and HIV to be consistent with the descriptions of the other methods.

Injectable Contraceptive

Injectable contraceptives (birth control shots) are highly effective and more convenient for some women than daily pills. Only 3% of users typically get pregnant in the first year of use. The shots generally work in the same way as birth control pills. There are two types available in the United States. Both require a prescription. Plan B® can be used as a backup if you are late getting your contraceptive injection.

Comment: *Include a statement that there is no protection against HIV and other STDs with this method.*

Intrauterine Device (IUD)

IUDs are contraceptive devices that are inserted into the uterus. They can work for ten years or more, but they must be inserted and removed by a healthcare professional. IUDs provide no protection against sexually transmitted infections, including HIV/AIDS. They are not recommended for women who may be exposed to sexually transmitted infections, such as women with more than one sexual partner. Plan B® can be a useful backup method on those rare occasions when an IUD becomes dislodged or expelled.

Comment: *IUDs are not the only methods that provide no protection against STDs. The same should be said for OCs, injections, implants, diaphragm, cervical cap, sponge, etc.*

Natural Family Planning (Periodic Sexual Abstinence)

Natural family planning (sometimes called "fertility awareness" or "periodic sexual abstinence") generally involves abstaining from vaginal sex during the fertile days of the menstrual cycle. There are a number of different methods. Most couples need some months of training in order to use the methods effectively. Typical pregnancy rates in the first year of use are about 25%. Natural family planning methods provide no protection against sexually transmitted infections, including HIV/AIDS. Plan B® can be used as a backup for natural family planning if, for example, a woman realizes after sex that she has miscalculated the fertile period.

Patch (Transdermal Patch)

One of the newest methods of birth control is a patch that releases low doses of *estrogen* and *progesterin*, synthetic versions of naturally occurring female hormones. Women use one patch per week for three weeks, followed by a break for one week. The patch is worn on the abdomen, buttocks, upper arm or upper torso (except on the breasts). The patch prevents pregnancy in the same way birth control pills do, but may be more convenient for some women. The patch has many of the same advantages and disadvantages as the birth control pill. Side effects and pregnancy rates in the first year of use are expected to be similar to that of the pill. The patch requires a prescription. Plan B® can be a useful backup method if you apply a new patch late.

Comments: *Revise second to last statement to read "Side effects and pregnancy rates in the first year of use are expected to be similar to that of the pill, although the pregnancy rates appear to suggest that the patch is less effective in women weighing more than 198 pounds." Include a statement about no protection from HIV/AIDS.*

Spermicide

Spermicides are often used with female barrier methods, such as diaphragms, but may also be used alone. Spermicides work by attacking sperm. They are available without a prescription, but must be used each time you have sex. Used alone, they have a typical first year pregnancy rate of 29%. Their main advantage is that they are widely available in pharmacies and can be used without a male partner's cooperation. They do not protect against HIV/AIDS. For women who rely solely on spermicides alone or with a barrier method, Plan B® may be a useful backup if unprotected sex occurs.

Comments: *Revise second sentence to read "Currently marketed spermicides contain nonoxynol-9 (N9), which works by attacking and killing sperm." After the statement, "They do not protect against HIV/AIDS," add the following statement "Furthermore, recent studies suggest that N9 may increase the risk of becoming infected with HIV/AIDS from infected partners if used frequently, particularly for women at high risk of HIV infection."*

Vaginal Ring

Another new method of birth control is the vaginal ring. The ring releases low levels of *estrogen* and *progestin*, synthetic versions of naturally occurring female hormones. The ring is worn inside the vagina continuously for three weeks, followed by a break for one week. It does not need to be removed during sexual intercourse. It works the same way as birth control pills and has many of the same advantages and disadvantages. Side effects and failure rates are expected to be similar. The ring requires a prescription. Plan B® can be a useful backup method if you insert a new vaginal ring late.

Comment: *Add "or if the ring is expelled from the vagina" to the last statement. Add a statement about HIV and STDs.*

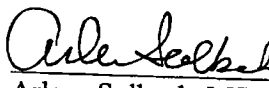
Voluntary Sterilization

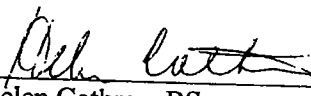
Contraceptive sterilization for women involves blocking off the fallopian tubes by a variety of means to prevent the passage of eggs and sperm. Male sterilization blocks the passage of sperm. Sterilization is highly effective, with a typical first year pregnancy rate of 0.5% for female sterilization and 0.15% for male sterilization. Advantages of female sterilization may include decreased risk of ovarian cancer. Disadvantages may include increased risk of ectopic pregnancy in the event of failure. Neither male nor female sterilization provide any protection against sexually transmitted infections, including HIV/AIDS. Most methods of sterilization involve minor surgery. Sterilization is a permanent method and should be considered only by women and men who are certain they want no more children.

Comment: *Add an HIV/STD risk statement to be consistent with the other methods described above.*

Sources:

1. Hatcher RA, Nelson MA, Ziemann M et al. *A Pocket Guide to Managing Contraception*. Tiger, Georgia: Bridging the Gap Foundation, 2002. <http://www.managingcontraception.com/images/pdfs/managing.pdf>
2. Trussell J. Contraceptive failure. In Hatcher RA, Trussell J, Stewart F, et al. *Contraceptive Technology: Eighteenth Revised Edition*. New York NY: Ardent Media, 2004.

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Attachment 5.
 FDA'S Pregnancy Rate Table - Part of OTC Contraceptive
 Drug Product Labeling.

The following table gives the approximate number of women out of 100 women who are likely to become pregnant while using a particular contraceptive method for one year.

"Typical Use" means that the method either was not always used correctly or was not used with every act of sexual intercourse (e.g., sometimes forgot to take a birth control pill as directed and became pregnant), or was used correctly but failed anyway.

"Perfect Use" means that the method was always used correctly with every act of sexual intercourse but failed anyway (e.g., always took a birth control pill as directed but still became pregnant).

SEE TABLE A

Approximate Number of Women Out of 100 Women Who Became Pregnant in the First Year of Use

TABLE A

Method	Typical Use	Perfect Use
Male Sterilization	fewer than 2	fewer than 1.5
Female Sterilization		
Implant (Norplant™ and Norplant™2)		
Hormone Shot (Depo-Provera™)		
Intrauterine Devices (IUD's)		
Combined Pill (Estrogen/Progestin)	5	fewer than 1
Minipill (Progestin only)		
Male Latex Condom ¹	14	3
Vaginal Sponge ^{2*}	14 - 30	9 - 26
Cervical Cap ^{3*}		
Diaphragm ^{3*}	20 - 21	5 - 6
Female Condom		
Spermicides: (gel, foam, suppository, film)	26	6
Withdrawal	19 - 25	1 - 9
Natural Family Planning (calendar, temperature, cervical mucus)		
No Contraceptive Method:	85	85

¹Used without Spermicide

⁴ Contains Spermicide

² Used with Spermicide

Data adapted from: R.A. Hatcher, J. Trussell, F. Stewart, et al., Contraceptive Technology, 17th Revised edition, New York, NY; Irvington Publishers Inc. New York, NY; Ardent Media, 1998

*Estimates from R.A. Hatcher, J. Trussell et al.

Contraceptive Technology, 17th revised Edition, 1998, Chapter 31, pp. 781-782. Reference cited in text;

J.Trussell, J. Strickler, B. Vaughn: Contraceptive Efficacy of the Diaphragm, the Sponge and the Cervical Cap, Family Planning Perspective, 1993;25:100-105, 135.

Table prepared by FDA:5/13/97, revised 9/17/98 and 9/11/00

For best results, barrier methods, such as the sponge or condom, must be used correctly during every act of intercourse.

Attachment 5.

FDA's Pregnancy Rate Table - part of Rx contraceptive drug product labeling

TABLE III: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR: UNITED STATES.

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year ³
	Typical Use ¹ (2)	Perfect Use ² (3)	
Chance ⁴	85	85	
Spermicides ⁵	28	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal ⁶		2	
Post-Ovulation		1	
Cap ⁷			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm ⁸	20	6	56
Withdrawal	19	4	
Condom ⁹			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Dapo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.¹⁰

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.¹¹

Adapted from Hatcher et al., Contraceptive Technology, 17th Revised Edition, New York, NY: Irvington Publishers, 1998.

¹ Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

² Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

³ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

⁴ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

⁵ Foams, creams, gels, vaginal suppositories, and vaginal film.

⁶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

⁷ With spermicidal cream or jelly.

⁸ Without spermicides.

⁹ The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (one dose is two white pills), Alesse (one dose is five pink pills), Nordette or Levlen (one dose is four yellow pills).

¹⁰ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

NDA 21-405

HFD-550: Griebel/Davis/Monroe/Anderson/Shames

HFD-560: Division File

HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/ Chen

DOCID: 21405PlanBLabelReview.doc

What you should know about Plan B®

Plan B® is a backup method of birth control.

Plan B® is *emergency contraception*, a backup method of birth control. Plan B® can reduce your risk of pregnancy if you have unprotected sex (if your regular birth control method fails or if you have sex without birth control).

Plan B® contains a concentrated dose of *levonorgestrel*, a synthetic hormone used in birth control pills for over 35 years.

Because Plan B® prevents pregnancy before it begins, it is not the same as abortion.

You can use Plan B® if you had unprotected sex one or more times in the last three days (72 hours), and you don't want to become pregnant.

Plan B® is not as effective as using a regular birth control method correctly and consistently. It can be used as a backup method if:

- Your regular birth control failed (your partner's condom broke or slipped)
- You made a mistake with your regular method (you missed several birth control pills)
- You did not use any birth control method

Plan B® works better the sooner you use it.

You only have a few days to prevent pregnancy after unprotected sex. Plan B® works better the sooner you use it. Take the first Plan B® tablet as soon as possible within three days (72 hours) of unprotected sex. Take the second tablet 12 hours later.

Plan B® can reduce the risk of pregnancy to about 1 percent, if you use it within the first three days of a single act of unprotected sex. Your risk of pregnancy ranges from 0 to 35 percent, depending on the day of your menstrual cycle.

Plan B® works like other birth control pills.

Plan B® can prevent pregnancy by stopping the release of an egg from the ovary (*ovulation*), or it may prevent the union of sperm and egg (*fertilization*). You are at most risk of pregnancy just before ovulation and on the day of ovulation.

If fertilization does occur, Plan B® may prevent a fertilized egg from attaching to the womb (*implantation*). Plan B® will not work after implantation of a fertilized egg.

Plan B® is not the same as the early abortion pill, Mifeprex® (RU486). Plan B® cannot disrupt an established pregnancy.

Some women experience short-term side effects?

Plan B® has no serious or lasting medical side effects. Some women will experience non-serious side effects, such as nausea, stomach pain, headache, dizziness, or breast tenderness. These are similar to the side effects of regular birth control pills. Some women have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late. If your period is more than a week late, you should get a pregnancy test.

Plan B will not harm an established pregnancy?

Plan B® should not have any effect on an established pregnancy.. If you take it accidentally after you are already pregnant, or if it does not work, it is not likely to cause any harm to you or your pregnancy. Studies of women who took birth control pills by mistake after they were already pregnant showed no increased risk of birth defects.

Warnings

If you become pregnant after using Plan B®, and you have severe stomach pain, contact a doctor immediately. This may be a sign of an ectopic pregnancy (a pregnancy growing in your fallopian tube).

Keep this and all drugs out of the reach of children. In case of accidental ingestion, call a Poison Control Center, emergency medical facility, or a doctor immediately.

Each Plan B® package is sealed in plastic wrap. If the wrap is missing or torn, return the package to your pharmacy.

Questions or Comments

Call 1-800-330-1271 or visit www.go2planb.com

Choosing a Regular Method of Birth Control

Plan B[®] is a safe and effective **emergency contraceptive** for use when you need a backup method of birth control.

Plan B[®] is not a substitute for regular contraception. Using a regular contraceptive correctly and consistently would be more effective and may be less expensive. Plan B[®] does not protect you against sexually transmitted infections, including HIV/AIDS.

If you are sexually active but you are not using a regular birth control method, or if you are having trouble using your method, you should talk with a healthcare professional. Women who are sexually active and use no birth control method for a year have an 85% risk of becoming pregnant.

Listed below are birth control choices that you may want to discuss with your healthcare provider. In some cases, Plan B[®] may be a good backup for the method you choose.

Abstinence

Sexual abstinence is the most effective way to avoid both unintended pregnancy and sexually transmitted infections, including HIV/AIDS. Sexual abstinence requires commitment and self-control on the part of both partners in a relationship. For women practicing abstinence, Plan B[®] can be a useful back-up method, if unplanned sex does occur.

Birth Control Pill

Most birth control pills contain *progestin* and *estrogen*. These active ingredients are synthetic versions of naturally occurring female hormones. *Progestin*-only pills are available for women who should not take estrogen because of cardiovascular or other risk factors. All birth control pills currently require a prescription. Birth control pills are highly effective if they are used correctly and consistently. Because women sometimes forget to take their pills, the typical pregnancy rate in the first year of use is about 8%. Advantages of the pill include more regular periods, less menstrual bleeding, decreased menstrual cramps, and a reduction in the risk of endometrial and ovarian cancer. Side effects may include nausea, breast tenderness, and headaches, but these symptoms often decrease after the first few months of pill use. Birth control pills provide no protection against sexually transmitted infections or HIV/AIDS. Plan B[®] can be used as a backup contraceptive if you miss two or more pills in a row or if you start a new cycle of pills late. You can start taking your pills again as soon as you finish taking Plan B[®].

Condom

Many different types of condoms for men are available in pharmacies without a prescription. Condoms can prevent pregnancy and can also reduce the risk of getting HIV/AIDS or other sexually transmitted infections. To be most effective, condoms must be used correctly and consistently. Condoms break or slip 3% to 5% of the time. As a result of condom accidents and inconsistent use, the typical risk of pregnancy is about 15% in the first year of use. A polyurethane female condom, worn inside the vagina, is also available without a prescription. The female condom can prevent both pregnancy and sexually transmitted infections, including HIV/AIDS. The risk of pregnancy is about 21% in the first year of typical use. Couples depending on male or female condoms for birth control may find it useful to keep Plan B[®] in the nightstand in case of a condom accident or if unprotected sex occurs.

Diaphragm, Cervical Cap and Sponge (Female Barrier Methods)

Female barrier methods prevent pregnancy by stopping sperm from reaching the uterus. The diaphragm and cap are used with a spermicide; the sponge contains a spermicide. (See

"Spermicides" below). These methods do not require a prescription. Plan B[®] can be a useful backup method when a diaphragm or cervical cap moves out of place during sex, or if unprotected sex occurs.

Implant (Contraceptive Implant)

New contraceptive implants, lasting for two or three years, are available in Europe and should be available soon in the United States. Implants allow the steady release of low doses of *progestin*, a synthetic version of a naturally occurring female hormone. Implants are highly effective and convenient for women who want long-term contraception. Pregnancy rates are less than 0.5% in the first year of typical use. Like other *progestin*-only methods, implants can cause irregular menstrual bleeding, including spotting and less frequent periods. Implants must be inserted under the skin and surgically removed by a healthcare professional.

Injectable Contraceptive

Injectable contraceptives (birth control shots) are highly effective and more convenient for some women than daily pills. Only 3% of users typically get pregnant in the first year of use. The shots generally work in the same way as birth control pills. There are two types available in the United States. Both require a prescription. Plan B[®] can be used as a backup if you are late getting your contraceptive injection.

Intrauterine Device (IUD)

IUDs are contraceptive devices that are inserted into the uterus. They can work for ten years or more, but they must be inserted and removed by a healthcare professional. IUDs provide no protection against sexually transmitted infections, including HIV/AIDS. They are not recommended for women who may be exposed to sexually transmitted infections, such as women with more than one sexual partner. Plan B[®] can be a useful backup method on those rare occasions when an IUD becomes dislodged or expelled.

Natural Family Planning (Periodic Sexual Abstinence)

Natural family planning (sometimes called "fertility awareness" or "periodic sexual abstinence") generally involves abstaining from vaginal sex during the fertile days of the menstrual cycle. There are a number of different methods. Most couples need some months of training in order to use the methods effectively. Typical pregnancy rates in the first year of use are about 25%. Natural family planning methods provide no protection against sexually transmitted infections, including HIV/AIDS. Plan B[®] can be used as a backup for natural family planning if, for example, a woman realizes after sex that she has miscalculated the fertile period.

Patch (Transdermal Patch)

One of the newest methods of birth control is a patch that releases low doses of *estrogen* and *progestin*, synthetic versions of naturally occurring female hormones. Women use one patch per week for three weeks, followed by a break for one week. The patch is worn on the abdomen, buttocks, upper arm or upper torso (except on the breasts). The patch prevents pregnancy in the same way birth control pills do, but may be more convenient for some women. The patch has many of the same advantages and disadvantages as the birth control pill. Side effects and pregnancy rates in the first year of use are expected to be similar to that of the pill. The patch requires a prescription. Plan B[®] can be a useful backup method if you apply a new patch late.

Spermicide

Spermicides are often used with female barrier methods, such as diaphragms, but may also be used alone. Spermicides work by attacking sperm. They are available without a prescription, but must be used each time you have sex. Used alone, they have a typical first year pregnancy rate of 29%. Their main advantage is that they are widely available in pharmacies and can be used without a male partner's cooperation. They do not protect against HIV/AIDS. For women who

rely solely on spermicides alone or with a barrier method, Plan B® may be a useful backup if unprotected sex occurs.

Vaginal Ring

Another new method of birth control is the vaginal ring. The ring releases low levels of *estrogen* and *progestin*, synthetic versions of naturally occurring female hormones. The ring is worn inside the vagina continuously for three weeks, followed by a break for one week. It does not need to be removed during sexual intercourse. It works the same way as birth control pills and has many of the same advantages and disadvantages. Side effects and failure rates are expected to be similar. The ring requires a prescription. Plan B® can be a useful backup method if you insert a new vaginal ring late.

Voluntary Sterilization

Contraceptive sterilization for women involves blocking off the fallopian tubes by a variety of means to prevent the passage of eggs and sperm. Male sterilization blocks the passage of sperm. Sterilization is highly effective, with a typical first year pregnancy rate of 0.5% for female sterilization and 0.15% for male sterilization. Advantages of female sterilization may include decreased risk of ovarian cancer. Disadvantages may include increased risk of ectopic pregnancy in the event of failure. Neither male nor female sterilization provide any protection against sexually transmitted infections, including HIV/AIDS. Most methods of sterilization involve minor surgery. Sterilization is a permanent method and should be considered only by women and men who are certain they want no more children.

Sources:

1. Hatcher RA, Nelson MA, Ziemann M et al. *A Pocket Guide to Managing Contraception*. Tiger, Georgia: Bridging the Gap Foundation, 2002.

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