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FDA News

FOR IMMEDIATE RELEASE

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May 7, 2004

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FDA Issues Not Approvable Letter to Barr Labs; Outlines Pathway for Future Approval

The Food and Drug Administration (FDA) today acknowledged that it has issued a "Not Approvable" letter to the sponsor of an application to make the Plan B emergency contraception product available without a prescription. In its letter to the sponsor, FDA outlined the additional information that would be required to gain approval to market Plan B over-the-counter.

FDA based its action primarily on the lack of data concerning OTC use of the product among adolescents younger than 16 years old. The sponsor's application contained no data in subjects under 14 years of age and very limited data in adolescents 14 to 16 years old.

FDA's letter to the sponsor notes that the application does not provide adequate data to support use of Plan B by young adolescent women without the intervention of a physician. The letter also points out that the sponsor's March 11th amendment of its application to allow marketing of Plan B by prescription only to young women under 16 years of age was not complete. As a result, the agency was unable to do a complete review on that amendment during this review cycle.

Dr. Steven Galson, Acting Director of FDA's Center for Drug Evaluation and Research (CDER), said "Although we did not have sufficient data to approve this application now, I will be working toward the expeditious evaluation of Barr's response to the Not Approvable letter. If Plan B is approved for nonprescription use, it would dramatically increase access to this product and will represent an important incremental step forward in contraceptive availability in the United States. Wide availability of safe and effective contraceptives is important to public health. I look forward to supporting CDER's important continued role in ensuring improved availability of these products."

Although U.S. law prohibits FDA from discussing pending applications because they contain commercial confidential information, in this instance the sponsor of Plan B, Barr Research, has allowed FDA to comment in general terms on the status of Barr's application to make Plan B available as an OTC product, and on the agency's action.

Additional information on FDA's action is available, in question and answer format, on the web at <http://www.fda.gov/cder/drug/infopage/planB/default.htm>.

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FDA Statement

FOR IMMEDIATE RELEASE
Statement
August 26, 2005

Media Inquiries:
Suzanne Treviño, 301-827-6242
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FDA Takes Action on Plan B Statement by FDA Commissioner Lester M. Crawford

Thank you for coming today.

We are announcing the action we took today of sending a letter to Barr Labs concerning their application to allow Plan B to be sold over-the-counter.

I want to start by making sure everyone is clear on what this drug is. Also, it's important that we define what the FDA has been asked by Barr Labs to address with respect to this drug.

Plan B has been referred to as emergency contraception. It contains one of the same active ingredients used in ordinary prescription birth control pills -- only in the case of Plan B -- each pill contains a much higher dose and is taken in a different way.

Like ordinary birth control pills, Plan B is currently available to all women as a prescription drug. There is a second drug called Preven that is similar to Plan B. That drug is also sold with a prescription. Preven was first introduced on the market before Plan B.

The question we have been asked to address is whether Plan B should be available without a prescription on a pharmacy shelf, similar to the way other over-the-counter medicines like some cough syrups and allergy pills are sold, for women age 16 and older, and remain prescription-only for those under the age of 16.

The issues that we were asked to resolve, and the proposal that was put forward by Barr Labs, presented us with many difficult and novel policy and regulatory issues.

In some cases, the questions we were asked to answer were unprecedented for this agency. In particular:

Can age be used as a criterion on which we decide whether a drug should be prescription or over-the-counter, as has been proposed in this case?

Can the prescription and over-the-counter version of the same drug be marketed in a single package?

In addition, if we do use age as the only criterion on which we decide whether a drug is sold as a prescription product, or an over-the-counter product, how, as a practical matter, would such a limitation be enforced?

These are profound regulatory decisions that cut to the heart of our work. The answers to these questions can establish very broad and far-reaching policies that could have a significant effect on

the way FDA regulates many different drugs.

In fact, the answers to these questions could establish pathways that could make many more products available as over-the-counter drugs.

That could be a positive public health step, and one that I would support as the agency's Commissioner if it means we could safely make many more effective medicines more easily available.

We believe these novel regulatory issues should be considered in an open, public process.

Rather than answering these questions in the context of a decision on a single drug, we need to have an open process to solicit public comment.

These regulatory and policy questions are too profound and cut across too many different products to be made behind closed doors.

And so today we are also announcing that we are taking the action of publishing an advance notice of proposed rulemaking to initiate an open public process to consider these important regulatory and policy questions.

This notice will speak only to the regulatory and policy issues raised by this application.

The resubmitted supplemental new drug application that the FDA was asked to review provides for a switch from prescription only status to Over the Counter status only for women ages sixteen years and older.

Plan B would remain prescription only for women under sixteen years of age.

The FDA's drug center, the Center for Drug Evaluation and Research or CDER, 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 over the counter product, but only for women who are 17 years of age and older.

What we are saying today is that the Agency is unable at this time to reach a decision on the approvability of the application because of these unresolved regulatory and policy issues that relate to the application we were asked to evaluate.

We need to resolve these policy and regulatory questions before we can reach a final decision on the underlying science that was presented to us.

FDA is both a scientific and a regulatory agency. And what we are saying today is that there are unique regulatory issues that need to be addressed before we can take a final action on the application.

We are beginning a process that will address the regulatory questions today, but we believe we can only decide these issues in an open, public process.

Through this process, all interested parties can weigh in on the questions of whether a drug may be both prescription and over the counter based on uses by different subpopulations and whether the prescription and over the counter versions of the drug may be marketed in a single package.

There is precedent for this kind of careful, public policy making inside FDA and inside many federal agencies. This action ensures that the rules that an Agency like ours sets are done so in an open fashion. These rules have lots of implications that aren't always easy to anticipate at first blush.

Today I am making the commitment that we will work with our stakeholders to make sure that this process is expeditious and thorough.

Before I close, I want to step back and give you a little more detail on the regulatory pathway that led us to our current action.

And I want to help explain why the question of whether a drug can be sold simultaneously both over the counter and as a prescription product, in the same dosage, for the same indication, and in the same package, and with age as the only deciding criteria, is so profound.

FDA used to prohibit products from being both over the counter and prescription at the same time. They had to be one or the other. The idea was that if an active ingredient was safe and effective without a practitioner's supervision it had to be over-the-counter. If it needed a prescription for one group of people, then it needed a prescription for all people.

That was FDA's practice for a very long time.

In the late 1970s, FDA formed a task force to undertake a formal process to consider changing that policy, to determine whether a drug could be sold prescription and over-the-counter in different settings, for example, for different medical indications.

But ultimately, this task force rejected changing the policy, and so the policy continued. And from the 1950s until the 1980s, drugs were either only prescription or only over-the-counter.

There was no molecule that existed on the market as both a prescription drug and an over-the-counter product.

Then in the 1980s, the agency was challenged on an application. FDA decided to allow the molecule to be sold as a prescription product for one use and an over-the-counter product for another.

Since then, there have been only a small number of ingredients approved as both prescription and over-the-counter and in these cases there was a meaningful difference in the way the two products are used.

In the Plan B application, we are grappling not with the same question but with a different question: whether we can have the same molecule exist as both a prescription and over-the-counter product for the SAME indication?

And if FDA were to attempt to limit sale of an over-the-counter product to a particular sub population, would FDA be able to enforce such a limitation as matter of law, and could it do so as practical matter and then how?

Moreover, we are being asked to determine whether a product can be labeled for over-the-counter and prescription use and be sold in the same package.

I am committed to expediting this rule-making process, and in order to do so, I have ordered a 60-day comment period instead of the usual 90 to 120 day comment period. FDA will process and post the comments as they come in to us and finalization of this regulatory and policymaking process will be a personal priority of mine.

The action FDA took today underscores the Agency's commitment to public health and safety.

As an agency and as its Commissioner personally, I want to say that FDA remains committed to making safe and effective contraceptive products available to women and men who choose to use them.

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[FDA Letter to Sponsor](#)
[Federal Register Document \[PDF 17KB\]](#)
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

Barr Research, Inc.

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

Senior Director, Regulatory Affairs

One Bala Plaza, Suite 324

Bala Cynwyd, PA 19004-1401

Dear Dr. Carrado:

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

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

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

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

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

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

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

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

Before this application can be approved, you would have to provide data demonstrating that Plan B can be used safely by women under 16 years of age without the professional supervision of a practitioner licensed by law to administer the drug. Alternatively, you could supply additional information in support of the revised indication to allow for marketing of Plan B as a prescription-only product for women under the age of 16 years and a nonprescription product for women 16 years and older, including draft product labeling. If you take the latter approach, your response to this letter would have to include details of how you propose to implement simultaneous prescription and nonprescription marketing of Plan B for women of different ages in a single packaging configuration while complying with all relevant statutory and regulatory requirements for labeling and marketing of this product. We will have to assure ourselves that your proposed approach is consistent with our statutory authority. If you pursue the alternative approach, we also would request details of your proposed program to educate consumers, pharmacists, and physicians about the dual marketing of Plan B as both a prescription and nonprescription product, as well as your proposed program to monitor implementation of this novel approach.

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

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Steven Galson
5/6/04 04:56:02 PM



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Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20587

NDA 21-045/S-011

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