



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

June 9, 2006

Bonnie Scott Jones, Esq.  
Simon Heller, Esq.  
Center for Reproductive Rights  
120 Wall Street, 14<sup>th</sup> FL  
New York, NY 10005

Re: Docket No. 2001P-0075/CP1

Dear Ms. Jones and Mr. Heller:

This letter responds to your citizen petition dated February 14, 2001, with supplements submitted on August 7, 2001 and February 13, 2002, on behalf of more than 60 family planning and health organizations. You requested that the Food and Drug Administration (FDA or we) exempt from prescription dispensing requirements two emergency contraceptive drug products, Preven (no longer marketed but formerly marketed by Gynetics, Inc.<sup>1</sup>), and Plan B (now marketed by Duramed Research, Inc. (Duramed), a wholly-owned subsidiary of Barr Pharmaceuticals, Inc. (Barr)), as well as any new drug eligible for filing an abbreviated new drug application using Preven or Plan B as the reference listed product. Your petition contends that the prescription dispensing requirements for Plan B are not necessary to protect the public health and that a prescription-only (Rx) to over-the-counter (OTC) switch for consumers of all ages is authorized under 21 U.S.C. 353(b)(3) and 21 CFR 310.200.

## I. SUMMARY OF DECISION

After considering your petition and the thousands of comments to it that we received, we are denying your petition for the reasons discussed below. It should be immediately noted, however, that FDA's denial of your citizen petition has no bearing on Barr's Supplemental New Drug Application (SNDA) seeking an Rx to OTC switch for Plan B. The SNDA is still pending. FDA has not made a final decision whether emergency contraception will be switched to OTC status and, if an OTC switch occurs, which age groups would be involved.

Soon after your petition was filed, we made a preliminary determination that your petition and its supporting information did not provide sufficient data to satisfy the statutory requirements to approve an OTC switch for emergency contraceptives, as documented in memoranda dated February 28, 2001 and April 12, 2001. However, as we have done on other occasions, we deferred responding to your petition because we anticipated that the then-sponsor of Plan B (Barr's predecessor) would submit additional

<sup>1</sup> Hereafter, we discuss your petition requests only as they relate to Plan B.

data and information to us relating to the proposed OTC switch for its drug product. Even before your petition was filed, we had been engaged in discussions with the then-sponsor of Plan B regarding a potential SNDA seeking an OTC switch for Plan B; in fact, in the month before we received your petition, we had received study proposals from that sponsor, and we continued to receive proposals and information from the sponsor -- and continued to meet with the sponsor -- until as late as September 2002. In September 2001, pursuant to our authority under 21 CFR 10.30(e)(2)(iii), and based on the need for additional information supporting OTC status for Plan B, we provided you with a tentative response to your petition, explaining that we had not yet resolved the issues raised in your petition because it raised significant issues requiring extensive review and analysis by agency officials. Thereafter, we received tens of thousands of public comments on your petition -- some of which supported and some of which opposed making Plan B available OTC. However, neither your petition nor any of the public comments contained sufficient data to satisfy the statutory requirements for FDA to remove the Rx requirements for emergency contraceptives.

In April 2003, we received an SNDA from the then-sponsor of Plan B. We analyzed that application carefully, and, in May 2004, advised Barr (which had, by that time, purchased the rights to the application) that the SNDA lacked sufficient data and information for approval at that time. In July 2004, Barr submitted an amended SNDA to address some of our concerns. However, even though you were aware of our May 2004 letter to Barr, and of Barr's submission of the amended SNDA, neither you nor any of the public commenters on your petition submitted to FDA data or information sufficient to address our concerns or sufficient to warrant the action requested by your petition, namely, promulgation of a regulation removing the Rx requirements for Plan B for users of all ages.

On August 26, 2005, we informed Barr by letter that, as a scientific matter, the Center for Drug Evaluation and Research (CDER or Center) had determined that Plan B had been shown safe for OTC use only for women 17 years of age and older, but that FDA was unable to reach a final decision on the approvability of the amended supplemental new drug application because of unresolved regulatory issues raised by that application, including issues related to whether the identical drug product can be simultaneously marketed as an Rx-only product and an OTC product based on the age of the individual using the drug (see Docket No. 2001P-0075/Petition Response References (Reference(s)), Reference #1, at page 1). On the same day, we placed on public display an advance notice of proposed rulemaking (the ANPRM) seeking public comment on issues regarding Rx and OTC switches -- issues which relate to the regulatory issues raised by Barr's amended application (see Docket No. 2001P-0075/Reference #2). The public comment period on the ANPRM closed on November 1, 2005, and we have received approximately 47,000 comments. FDA is still reviewing those public comments and evaluating what steps to take with regard to the ANPRM.

In light of your request that we issue a final decision on your petition forthwith,<sup>2</sup> and in light of the significant public interest in the issues raised by your petition, we have decided to issue a response to your citizen petition now, based on the evidence in the record of this citizen petition proceeding, rather than continue to defer responding to the petition until the issues raised in the amended SNDA are resolved, which would be our normal practice.

We are denying the citizen petition because it did not contain sufficient data to satisfy the statutory and regulatory requirements for an Rx-only to OTC switch for Plan B. Your petition seeks OTC status for emergency contraceptives for women of all age groups, but you have failed to provide sufficient data or information to meet the statutory and regulatory requirements for an OTC switch for any age group. Further, you may not rely on the data in the pending SNDA, insist on a final decision on the pending SNDA, nor circumvent the SNDA processes and the substantive issues that have arisen in that proceeding. In any event, the issues raised by the amended SNDA have not yet been finally resolved.

## **II. BACKGROUND**

### **A. Legal Framework for Rx-OTC Switches**

FDA's authority to exempt a drug from prescription-only requirements is based on section 503(b) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 353(b)). Under section 503(b)(1) of the Act, we restrict a drug to prescription-only status when we determine that the drug is not safe for use except under the supervision of a practitioner licensed by law to administer the drug. A drug will be restricted to Rx-only status when FDA finds that "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug" (21 U.S.C. 353(b)(1)). In addition, section 503(b)(3) of the Act provides that a drug subject to section 505 of the Act (21 U.S.C. 355, governing approval of new drugs) may be removed by regulation from prescription-only status when such requirements are deemed not necessary for the protection of the public health. For a drug to be legally marketed (whether Rx-only or OTC), the safety and efficacy standards set forth in section 505 of the Act must be met.

There are two different mechanisms under the Act for FDA to make an Rx to OTC switch. First, the Act explicitly provides us with the authority to issue a regulation changing the status of an Rx drug to an OTC drug (see 21 U.S.C. 353(b)(3) ("The Secretary may by regulation remove drugs [under NDAs] from the requirements of [Rx-only restrictions] when such requirements are not necessary for the protection of the

---

<sup>2</sup> On January 21, 2005, a group of individuals and reproductive health groups, including the Association of Reproductive Health Professionals (ARHP), one of the petitioners here, sued FDA seeking a court order requiring FDA to approve the OTC switch for Plan B for women of all ages (see *Tummino v. Crawford*, No. 05-CV-366 (E.D.N.Y.) (ERK/VVP)). In November 2005, the plaintiffs amended their complaint to allege that FDA had unreasonably delayed its response to your citizen petition.

public health.”)). Second, the Act grants us the authority to approve and reject drug applications (see 21 U.S.C. 355(c), (d)), and FDA has by regulation construed that authority to apply to supplements to approved drug applications (see 21 CFR 314.71(c)).

FDA regulations at 21 CFR 310.200(b) identify processes for initiating consideration of an Rx to OTC switch. A proposal under this regulation to exempt a drug from prescription-only requirements may be initiated by the Commissioner or by “any interested person” in the form of a sponsor submitting a supplement to an approved new drug application (NDA) or, as in your case, by a third party petitioning FDA (see 21 CFR 310.200(b)) (“Any interested person may file a petition *seeking* such exemption . . .”) (emphasis added)).<sup>3</sup> Regardless of who initiates a request for an OTC switch, however, the evidence must demonstrate that the prescription-only dispensing requirements are no longer necessary to protect the public health by reason of the drug’s toxicity or other potentiality for harmful effect, or by reason of the method of the drug’s use, and must also demonstrate that the drug is safe and effective for use in self-medication as directed in proposed labeling (see *id.*).

## **B. History of FDA’s Consideration of an OTC Switch for Plan B.**

On July 28, 1999, we approved an NDA for Plan B (levonorgestrel, 0.75 mg) for Rx-only use as an emergency contraceptive. This drug is approved for use to prevent pregnancy after known or suspected contraceptive failure or after unprotected intercourse. The sponsor of Plan B at that time was the Women’s Capital Corporation (WCC). Since its 1999 approval by FDA, the drug has been widely available for sale and use by prescription.

### *1. Discussions Between WCC and FDA Regarding the OTC Switch Application Begin.*

In 2000, WCC requested a meeting with us to discuss a possible switch from Rx to OTC use for Plan B. On December 19, 2000, we agreed to meet with WCC to discuss the potential for OTC use of Plan B. We met with WCC on February 5, 2001, to discuss the plan for developing an OTC switch application (i.e., an SNDA) including study design, additional data, and labeling. The participants discussed the design of actual use and label comprehension studies.<sup>4</sup> WCC stated that it planned to submit an SNDA seeking an OTC switch for Plan B within 12 months.

### *2. Citizen Petition is Submitted.*

---

<sup>3</sup> Contrary to the suggestion in your citizen petition (see Docket No. 2001P-0075/CP1 at page 2), FDA cannot cause a product to be switched from Rx-only to OTC status simply by declaring it to be switched in response to a citizen petition. Rather, an OTC switch can be accomplished only through an SNDA or through notice-and-comment rulemaking.

<sup>4</sup> Actual use studies are trials designed to assess how consumers actually use the product in an OTC setting. These trials are usually open-label and are designed specifically to assess consumer use, but they may also provide information about safety. Label comprehension studies are designed to assess understanding of proposed OTC labeling.

On February 14, 2001, you submitted your citizen petition (see Docket No. 2001P-0075/CP1). The contents of your petition are summarized in part II.C below. In accordance with our standard practice, we established a docket for the citizen petition and began to receive what ultimately became tens of thousands of public comments on the issues raised by the petition.

The petition was immediately reviewed by FDA's Division of Reproductive and Urologic Drug Products (DRUDP). By memorandum dated February 28, 2001, that Division noted that, although the petition contained two expert declarations and citations to medical literature, FDA's Division of OTC Drug Products (DOTCDP) "typically requires an evaluation of data from both a labeling comprehension study and an actual use study prior to an Rx-to-OTC switch for a drug product" (see Docket No. 2001P-0075/Reference #3 at page 2).

3. *WCC Submits Study Protocol.*

In March 2001, WCC submitted to FDA a protocol for a labeling study. Thereafter, FDA and WCC engaged in regular communications and meetings regarding WCC's potential OTC-switch application for Plan B.

4. *OTC Division of FDA Concludes Citizen Petition Lacks Necessary Studies for Approval.*

By memorandum dated April 12, 2001, DOTCDP concluded that your citizen petition had insufficient data to support a switch approval because actual use and label comprehension studies were needed: "[A]ctual use and label comprehension studies to demonstrate if consumers can use ECP [emergency contraceptive pills] safely and effectively without a learned intermediary are necessary. . . . There are several potential safety issues that need to be examined through Actual Use Studies before a recommendation can be made to switch either or both ECP from prescription to OTC availability" (see Docket No. 2001P-0075/Reference #4).<sup>5</sup>

5. *FDA Issues Tentative Response to Citizen Petition and Petitioner Supplements the Petition.*

On August 7, 2001, you supplemented your petition with a document showing that an emergency contraceptive drug called Norlevo is registered in Belgium by the Belgian

---

<sup>5</sup> As further discussed below (see Part IV.A), FDA may require actual use and label comprehension studies for an OTC switch of any drug for which the efficacy and safety of OTC use cannot be shown by prior OTC approval or an established monograph. Label comprehension studies, which test whether consumers can understand the directions, and actual use studies, which test how consumers use the drug, may be required when there is a new OTC indication, when there is a new method of use for the OTC drug, when there is a new OTC warning, when there are new OTC medical follow-up recommendations, and when there are specific concerns about self-medication.

Minister of Public Health as distributed without a prescription (see Docket No. 2001P-0075/SUP1). This supplement also contained a new list of petitioners.

On September 6, 2001, we provided a tentative response to the citizen petition, explaining that FDA “has not yet resolved the issues raised in your Citizen Petition because it raises significant issues requiring extensive review and analysis by Agency officials. . . . We will respond to your petition as soon as we have reached a decision on your request” (see Docket No. 2001P-0075/LET2).

You filed your second supplement on February 13, 2002 (see Docket No. 2001P-0075/SUP2). That supplement included documentation that the countries of Finland, Israel, Norway, and Sweden allow emergency contraceptive products to be sold without a prescription. It should be noted, however, that European countries have different systems for selling non-prescription medication that are not necessarily equivalent to the general open-shelf availability of OTC drugs in the United States.

#### 6. *FDA Considers SNDA for OTC Switch.*

During the following eighteen months, there were many communications between FDA and WCC about the design of WCC’s actual use and label comprehension studies.<sup>6</sup> In April 2003, WCC submitted an SNDA seeking to switch Plan B from Rx-only to OTC status. Subsequently, Barr purchased the patent rights for Plan B, and it assumed responsibility for the SNDA.

On November 25, 2003, we published a notice in the *Federal Register* announcing a joint meeting of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs (Joint Committee), to be held on December 16, 2003 (see 68 FR 66113 (Nov. 25, 2003)). The meeting concerned WCC’s SNDA to switch Plan B to OTC status. At the meeting, questions were raised about the adequacy of the data regarding adolescent use of the product. In particular, some members of the Joint Committee, including the Chair, raised questions concerning whether the actual use data submitted by the sponsor could be generalized to the overall population of nonprescription users, chiefly because of inadequate sampling of younger age groups. At the conclusion of the meeting, the Joint Committee voted 23 to 4 in favor of recommending to FDA that Plan B be allowed to be sold without a prescription (see

---

<sup>6</sup> Review of a drug application (including supplements and amendments) typically involves extensive direct and private communications between FDA and the sponsor in which FDA reviewers raise issues and concerns that the sponsor may then try to address. This is generally a confidential process that is closed to public participation. Although we do on occasion invite public participation in significant regulatory issues related to a drug application, for example through an advisory committee meeting, that process does not in any way replace the direct, confidential relationship between FDA and the applicant. We did not engage (and were not required to engage) in the same type of discussions with you, however, because the citizen petition process involves different procedures and interests. The citizen petition process is a public process that allows interested members of the public to raise issues of concern to them and that allows other members of the public to comment on those issues. Although we do not typically engage in a direct dialogue with the petitioner, the petitioner is free to review all comments sent to the public docket, and to supplement its initial submission at any time.

Transcript of Joint Session Advisory Committee Meeting (Dec. 16, 2003) at 262,  
available at [www.fda.gov/ohrms/dockets/ac/03/transcripts/4015T1.htm](http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4015T1.htm).)

In the months that then followed, the CDER review staff and FDA management reviewed and analyzed the available data, met repeatedly, and drafted comprehensive reviews.

7. *FDA Issues Non-Approvable Letter.*

On May 6, 2004, Dr. Steven Galson, then the Acting Director (now the Director) of CDER, issued a letter to Barr, stating that the SNDA was “not approvable *at this time* under section 505(d) of the Act and 21 CFR § 314.125(b)” (see Docket No. 2001P-0075/Reference #5 at page 1). Dr. Galson concluded that Barr had “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” (see *id.*).<sup>7</sup> Among other things, Dr. Galson noted that only 29 of the 585 subjects enrolled in Barr’s actual use study were between the ages of 14 and 16, and none were under the age of 14 (see *id.*). Dr. Galson believed that it was inappropriate to extrapolate data regarding older women to young adolescents because of the “rapid and profound physical and emotional change” that occurs during adolescence (see Docket No. 2001P-0075/Reference #6 at page 1). For example, early adolescence is often characterized by the emergence of impulsive behavior and mid-adolescence by an immature and incomplete ability to integrate emerging cognitive skills into real-life experiences (see *id.*). Because extrapolation was inappropriate, Barr needed to submit sufficient direct data regarding adolescents (see *id.*). Barr did not have a sufficient number of adolescents who participated in the study to reach valid conclusions from the study for that group (see *id.* at page 2). Dr. Galson differentiated the data needed to show safe *OTC* use for Plan B and safe *prescription* use for other contraceptive products: because prescription products involve monitoring by health care practitioners and, in many cases, parents, the same safety concerns, particularly regarding misuse of the product, do not arise (see *id.*).

Dr. Galson advised Barr that, before its SNDA for Plan B could be approved, Barr would have to either: (1) submit data demonstrating that the product could be used safely by women under 16 years of age without professional supervision by a licensed practitioner,<sup>8</sup> or (2) provide further information in support of its alternate proposal to allow for marketing of Plan B as an Rx-only product for women under 16 years of age and as an OTC product for women age 16 years and older.<sup>9</sup> Dr. Galson concluded that the latter

---

<sup>7</sup> Although Barr’s SNDA and your citizen petition are distinct administrative proceedings, Dr. Galson’s analysis of Barr’s data shows the type of data that would be required for FDA to approve an OTC switch for Plan B, regardless of whether FDA considers the switch in an SNDA or in a petition for rulemaking.

<sup>8</sup> The data in the actual use and label comprehension studies which Barr submitted in support of its SNDA were stratified by age in the following categories: 12-16 years, 17-25 years, and 26 years and older. Dr. Galson later clarified that the data were insufficient to establish that women 16 years of age and younger can use Plan B safely as an OTC product.

<sup>9</sup> We made Dr. Galson’s May 6, 2004 letter to Barr available to the public. Thus, you were on notice that we did not believe that even the applicant had submitted sufficient data to support an OTC switch.

proposal was only preliminary in nature and was not sufficiently complete to permit FDA review at that time. For example, such a proposal would require Barr to submit draft product labeling and packaging, as well as details of how Barr proposed to educate consumers, pharmacists, and physicians about the dual marketing of Plan B. Dr. Galson advised Barr that, whichever option it chose, it was also required to submit updated safety information concerning the drug, consisting of seven specified categories of information. He further stated that “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” (see Docket No. 2001P-0075/Reference #5 at page 2).

On July 22, 2004, Barr filed an amended SNDA, proposing to market Plan B as a non-prescription product for women age 16 and older and as an Rx-only product for women under age 16. In the months following that submission, the CDER review staff and CDER management reviewed the amended application, engaged the sponsor in further communications, debated the issues internally, and drafted reviews. FDA decision-makers also continued to discuss and consider the complex issues raised by the application. In the meantime, the docket on the citizen petition remained open, and comments continued to be submitted.

8. *Director of CDER Reviews Citizen Petition.*

On August 26, 2005, Dr. Galson completed a memorandum that included a review of the citizen petitions then pending before FDA, including your petition, that related to emergency contraceptive products. He explained in his memorandum that, for this type of request for an Rx-only to OTC switch, FDA requires actual use and label comprehension studies (see Docket No. 2001P-0075/Reference #7 at page 2). Dr. Galson further explained that neither your “petition nor the comments supporting that petition have provided any additional data on which I could rely to make the finding that Plan B will be used safely and effectively by adolescents under the age of 17” (see *id.* at page 4). He therefore concluded that the data submitted in relation to your citizen petition were insufficient to meet the statutory requirements for an OTC switch (see *id.*).

9. *FDA Issues Letter to Barr and ANPRM.*

Dr. Galson’s August 26, 2005 memorandum also set forth his conclusions regarding Barr’s amended SNDA. With respect to the population of consumers age 17 and older, Dr. Galson found that data provided in support of the SNDA showed that this population could use Plan B safely and effectively for emergency contraception in an OTC setting. With respect to the population of consumers ages 12 to 16, Dr. Galson found that the data were inadequate. More specifically, the label comprehension study submitted with Barr’s SNDA showed that the younger age groups were less likely to comprehend Plan B’s labeling instructions than were the older age groups. The actual use study, which had enrolled few subjects under age 17, also raised safety concerns. For example, the

---

However, you neither submitted additional data nor amended your citizen petition to request an age-bifurcated OTC switch for Plan B as Barr then chose to do.

younger age groups were less compliant with the study protocol's four-week follow-up period with the study investigator than were the older women (see *id.* at page 3). Dr. Galson also found that it would be inappropriate to extrapolate the actual use data regarding OTC use by women 17 and older to the younger population because of the nature of the product, the risks associated with inappropriate use, and the characteristics of the younger population (see *id.* at page 5).

Also on August 26, 2005, then-FDA Commissioner Lester Crawford wrote to Barr in response to its amended SNDA with respect to Plan B. In the letter, FDA advised Barr that 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 the SNDA for Plan B (see Docket No. 2001P-0075/Reference #1 at page 1).

The letter identified "three difficult and novel issues" presented by the Plan B SNDA: (1) whether the identical drug product can be simultaneously marketed as an Rx-only product and an OTC product based on the age of the individual using the drug (as opposed to Rx and OTC marketing based on the indication, strength, dosage form, or route of administration of the drug); (2) how, as a practical matter, such an age-based limitation could be enforced; and (3) whether Rx-only and OTC versions of the same active ingredient can be marketed in the same packaging (see *id.*). The letter advised Barr that "*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" (see *id.* at page 2 (emphasis added)). Since August 2005, we have not issued a final decision on Barr's SNDA.

Also on August 26, 2005, we placed the ANPRM on public display (see Docket No. 2001P-0075/Reference #2), and published it in the Federal Register on September 1, 2005 (see 70 FR 52050). The ANPRM requested public comment on the following issues:

1.
  - A. Should FDA initiate a rulemaking to codify its interpretation of section 503(b) of the [A]ct regarding when an active ingredient can be simultaneously marketed in both a prescription drug product and an OTC drug product?
  - B. Is there significant confusion regarding FDA's interpretation of section 503(b) of the [A]ct ?
  - C. If so, would a rulemaking on this issue help dispel that confusion?

2.

A. If FDA limited sale of an OTC product to a particular subpopulation, *e.g.*, by making the product available to the subpopulation by prescription only, would FDA be able to enforce such a limitation as a matter of law?

B. If it could, would it be able to do so as a practical matter and, if so, how?

3.

A. Assuming it is legal to market the same active ingredient in both a prescription and OTC product, may the different products be legally sold in the same package?

B. If the two products may be lawfully sold in a single package, under what circumstances would it be inappropriate to do so?

70 Fed. Reg. at 52051. We requested public comment on the ANPRM by November 1, 2005.

We have received approximately 47,000 comments on the ANPRM and are continuing to review and consider those comments.

**C. Content of Your Petition and the Comments in the Petition Docket.**

Your petition, filed on February 14, 2001, stated the reasons you believe emergency contraception should be considered safe and effective for OTC use. You assert (see Petition at pages 3-4) that emergency contraceptive drugs are appropriate for OTC use because:

1. They are safe for self-medication and have a low risk of abuse or overdose;
2. They are effective and easily self-administered based on a woman's assessment of time elapsed since intercourse;
3. The condition the drugs treat — contraceptive failure or failure to use contraception during intercourse — is one that is readily diagnosable by a woman, and the drug has no contraindications that would pose a danger to the patient;
4. Existing patient labeling for Plan B is suitable for self-administration in that it is simple, clear, and comprehensive; and
5. It affords women the opportunity to obtain the drug in a timely fashion (without needing to schedule a physician visit and fill a prescription), thereby enabling women to prevent unwanted pregnancies, which benefits the public health.

You have also submitted documents to support your petition. In particular, you included a declaration from David Grimes, M.D., statements from the American Medical

Association and the American College of Obstetricians and Gynecologists supporting OTC availability of emergency contraception, FDA-approved Rx-only product labeling for Preven and Plan B, and several references from the medical and legal literature. Your two petition supplements, dated August 7, 2001 and February 13, 2002, included the names of additional petitioners and information about non-prescription marketing of emergency contraception in other countries (although, as noted, these systems are not equivalent to OTC availability in the United States).

We received thousands of comments both in support of, and in opposition to, the petition.<sup>10</sup> In brief, those who supported the petition opined that:

- Plan B's current prescription-only status creates barriers to access;
- An OTC switch would be good public health policy because it would reduce unintended pregnancies and save scarce public health dollars;
- There is no evidence that, if available OTC, women will overuse or abuse Plan B or use it as a substitute for regular birth control;
- Access to emergency contraceptives in college/university health clinics is limited;
- Emergency contraceptives differ from mifepristone in that they do not cause an abortion (i.e., they are not abortifacients);<sup>11</sup>
- There is no evidence that the OTC availability of Plan B will lead to more sexual activity or increase the incidence of sexually transmitted diseases (STDs); and
- There is no evidence that refusal to provide contraception to adolescents results in abstinence.

In brief, those who opposed a switch as urged by the petition stated that:

- Emergency contraceptives are powerful hormonal treatments requiring appropriate medical supervision;
- OTC availability would eliminate needed clinical monitoring to address ectopic pregnancy risk;<sup>12</sup>
- Emergency contraceptives are abortifacients, and marketing them as contraceptives is misleading;
- Women who are unaware that emergency contraceptives can have an abortifacient effect are effectively denied informed consent, making physician participation a necessity;
- Making emergency contraceptives available OTC may affect the sexual behavior of adolescents and may affect adolescent sexual health (such as by increasing the incidence of STDs);
- OTC availability of Plan B would increase the potential for misuse; and

---

<sup>10</sup> Although we summarize some of the comments we received, this is by no means a comprehensive summary of all comments submitted, nor do we mean to suggest that the positions expressed in those comments would necessarily be relevant to the decision whether to switch a drug from Rx to OTC status.

<sup>11</sup> Mifepristone, when used together with another drug called misoprostol, is used to end an early pregnancy (49 days or less since a woman's last menstrual period began).

<sup>12</sup> An ectopic pregnancy occurs when the fertilized egg implants in a fallopian tube instead of the uterus.

- OTC availability of Plan B would conflict with the moral or religious objections of pharmacists and others.

As noted, on September 6, 2001, we provided a tentative response to your citizen petition, explaining that we had not yet resolved the issues raised in the petition because those issues required extensive review and analysis (see Docket No. 2001P-0075/LET2). There are many safety and regulatory issues presented by a request for an OTC switch, particularly where, as here, the drug is the first in this class of drugs to be switched. That is, FDA had not previously approved for OTC use any emergency contraceptive product, or, for that matter, any hormonal contraceptive of any kind. Thus, the agency was required to analyze data on safety and effectiveness and assess the benefit-to-risk ratio related to use of the product without the intervention of a health professional. One of the benefits of the intervention of a health care practitioner is, of course, to educate the patient on the proper use of a medication. For example, as subsequent consideration of Barr's SNDA shows, our review considered whether consumers properly understood how to safely use the product, such as not using it for regular contraception and not foregoing safe-sex practices. Because we had never previously examined these issues for OTC use of a hormonal contraceptive, we knew that this process would require more data. The tentative response noted that we would respond to the petition as soon as we reached a decision. Even before your petition was filed, we were discussing a potential SNDA with the then-sponsor of Plan B that would raise the same issues you raised in your petition. However, we are still in the process of considering issues raised by the SNDA and have not issued a final decision on that application.

### **III. FDA'S DEFERRAL OF YOUR PETITION RESPONSE**

#### **A. Regulations on Responding to Citizen Petitions**

FDA regulations govern our responses to citizen petitions. When a citizen petition is submitted to FDA, we have the discretion to grant or deny the petition, or alternatively to defer consideration of the petition because of the existence of other agency priorities or of the need for additional information (see 21 CFR 10.30(e)). This regulation provides, in pertinent part, that, upon the filing of a citizen petition, the Commissioner may

Provide a tentative response, indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency priorities, or a need for additional information. The tentative response may also indicate the likely ultimate agency response, and may specify when a final response may be furnished.

See 21 CFR 10.30(e)(2)(iii); see also 21 CFR 10.30(h) (providing that the Commissioner may use a variety of procedures in reviewing the petition). As we stated earlier, we did provide a tentative response to you on September 6, 2001, thereby complying with 21 CFR 10.30(e)(2). When we issue a tentative response to a citizen petition, nothing in our regulations provides an additional time limit on when the final response must issue. It is not unusual for citizen petitions raising novel or complex issues to remain pending at

FDA for several years. CDER, one of five agency centers, alone receives over fifty citizen petitions each year, and as of June 1, 2006 had a backlog of over 170 petitions. In addition, as of June 1, 2006, CDER's backlog included 31 petitions that were submitted before your petition was filed in February 2001 and that were still pending.

Our regulations further provide that the administrative record of a citizen petition proceeding consists of the following documents:

- (1) The petition, including all information on which it relies, filed by the Division of Dockets Management.
- (2) All comments received on the petition, including all information submitted as part of the comments.
- (3) If the petition resulted in a proposal to issue, amend, or revoke a regulation, all of the documents specified in [21 CFR] § 10.40(g).
- (4) The record, consisting of any transcripts, minutes of meetings, reports, Federal Register notices, and other documents resulting from the optional procedures specified in [21 CFR 10.30(h)], except a transcript of a closed portion of a public advisory committee meeting.
- (5) The Commissioner's decision on the petition, including all information identified or filed by the Commissioner with the Division of Dockets Management as part of the record supporting the decision.
- (6) All documents filed with the Division of Dockets Management under [21 CFR] § 10.65(h).
- (7) If a petition for reconsideration or for a stay of action is filed under paragraph [21 CFR] § 10.30(j) of this section, the administrative record specified in [21 CFR] § 10.33(k) or 10.35(h).

See 21 CFR 10.30(i); see also 21 CFR 10.3 (“administrative record means the documents in the administrative file of a particular administrative action on which the Commissioner relies to support the action.”); 21 CFR 10.20(c) (“[i]nformation referred to or relied upon in a submission is to be included in full and may not be incorporated by reference, unless previously submitted in the same proceeding”).

#### **B. FDA's Consideration of Your Citizen Petition**

The information contained in your petition did not meet the statutory and regulatory criteria to support an OTC switch. Nevertheless, at the time that you filed your petition, we exercised our discretion to defer issuing a full response to the petition because we were aware that the drug sponsor planned to conduct research to obtain scientific data on the same issues. As a result, we expected that some or all of the issues you raised in your petition would be resolved in the then-anticipated SNDA proceeding; in fact, they might still be resolved in that proceeding. As we have done with other petitions, we determined that it would be more prudent and efficient to defer consideration of your petition pending the outcome of the SNDA proceeding (see *Natural Resources Defense Council, Inc. v. SEC*, 606 F.2d 1031, 1046 (D.C. Cir. 1979) (An agency “may determine for reasons lying within its special expertise that the time for [issuing a regulation] has not

yet arrived.” For example, “the scientific state of the art may be such that sufficient data are not yet available on which to premise adequate regulations, . . . or the agency may still be developing the expertise necessary for effective regulation.”) (citations omitted)).

As a general matter, there are two main reasons why FDA has exercised its discretion to defer responding to a citizen petition that raises the same or similar issues that are being considered (or that we expect will be considered) in the context of a drug application. First, when we anticipate multiple, roughly contemporaneous submissions on similar issues in separate proceedings, we prefer to refrain from issuing a final response to a citizen petition because data in the other proceedings, e.g., an SNDA submission, may result in a different outcome concerning the same issues. Here, we delayed responding to your petition because, although it lacked adequate data, we fully expected that the SNDA would contain data potentially relevant to the issues you raised (see *Sierra Club v. Thomas*, 828 F.2d 783, 799 (D.C. Cir. 1987) (“additional time spent reviewing a rulemaking proposal . . . may well ensure earlier, not later, implementation of any eventual regulatory scheme’’)).

Second, particularly given our extremely limited resources, when it is possible to answer similar questions at the same time, we do so to maximize efficiency (see *Vermont Yankee Nuclear Power Corp. v. NRDC*, 435 U.S. 519, 543 (1978) (“administrative agencies should be free to fashion their own rules of procedure and to pursue methods of inquiry capable of permitting them to discharge their multitudinous duties’’) (citations and quotation marks omitted); *Mobil Oil Exploration & Producing Southeast, Inc. v. United Distribution Cos.*, 498 U.S. 211, 230 (1991) (“An agency enjoys broad discretion in determining how best to handle related, yet discrete, issues in terms of procedures and priorities.’’) (citations omitted); *Cutler v. Hayes*, 818 F.2d 879, 896 (D.C. Cir. 1987) (“An agency has broad discretion to set its agenda and to first apply its limited resources to the regulatory tasks its deems most pressing’’)). As noted above, the agency has a tremendous backlog of pending citizen petitions, including 31 petitions pending as of June 1, 2006, regarding matters regulated by CDER that were submitted before your petition was filed in February of 2001.

The timing of the issuance of our responses to citizen petitions varies, based in part on the complexities of the issues raised in the petitions and in part on whether similar matters are already under consideration (or expected to be under consideration) elsewhere in the Center. When a citizen petition requires review by multiple components within CDER and elsewhere in FDA, it makes administrative sense to defer consideration of a particular substantive question raised by the citizen petition if the same issue is expected to arise in another proceeding. Consideration of the issue in the other proceeding may moot the need to consider the same issue in the context of the citizen petition.<sup>13</sup>

---

<sup>13</sup> For example, we have also deferred responding to citizen petitions filed by third parties who request labeling changes while separate NDA discussions involving the same or similar issues are occurring. When Public Citizen submitted a petition to change the labeling of Versed (midazolam) (docket number 88P-0059), we responded several years later with a letter indicating that in the intervening years, substantial revisions to the labeling had occurred after significant interaction between the Agency and the drug’s sponsor that addressed the same issues separately raised in the petition. Another petition (docket number 86P-0450) also filed by Public Citizen requested a labeling change for Piroxicam. We issued a final

In this case, because we anticipated and eventually received submissions of scientific data from the Plan B sponsor seeking to switch Plan B to OTC status, and because such submissions involved the same issues as the ones you raised in the citizen petition, we decided to defer answering the petition while we evaluated the issues in the context of the SNDA. Not only have these submissions contained data and information that are relevant to the statutory and regulatory requirements for an OTC switch, but these data were and continue to be absent from your petition. As noted, however, FDA has not yet fully resolved all of the complex issues presented by the SNDA and therefore has not yet made a final determination on the SNDA.

Because you have made it clear in a variety of settings that you do not wish to wait for the resolution of the SNDA, we have decided to issue a response to explain why we cannot grant your petition.

#### **IV. ANALYSIS OF DATA SUBMITTED IN THE PETITION**

We are construing your petition as requesting that FDA engage in rulemaking to switch all emergency contraceptives from Rx-only to OTC status for users of all ages pursuant to 21 U.S.C. 353(b)(3) and 21 CFR. 310.200(b).<sup>14</sup> For the reasons discussed below, we find that the petition and supplements you submitted to us were incomplete and inadequate in that they did not provide sufficient data to support the granting of your request, nor did the comments filed by the public in response to your citizen petition contain sufficient data.

##### **A. Your Citizen Petition Lacks the Requisite Data.**

In order for FDA to respond to your petition by initiating a notice-and-comment rulemaking proceeding with regard to making emergency contraceptives available OTC for users, the burden is on you, as the petitioners, to provide FDA with sufficient evidence to demonstrate that Plan B is safe and effective for OTC use, and that all of the statutory and regulatory requirements for an Rx-to-OTC switch of this nature have been met. As discussed below, you have not submitted adequate data to satisfy the Rx-to-OTC switch requirements with respect to users of any age. Data to support an Rx-to-OTC switch generally come from the following sources: safety and efficacy data in an original NDA for the prescription drug; safety and efficacy data from trials conducted to support

---

response years later noting that we had addressed the issues in other proceedings by changing the labeling with the sponsor during that time, in addition to having held a public hearing and advisory committee meetings.

<sup>14</sup> Although your petition does not explicitly state that you are requesting FDA initiate notice-and-comment rulemaking, the Act, as discussed above, authorizes only two mechanisms for FDA to make an Rx to OTC switch: notice-and-comment rulemaking and approval of a drug application (see 21 U.S.C. 353(b)(3), 355(c), (d)). You are not yourselves applicants for drug approval, and you are not permitted to submit a supplement to another company's application. 21 CFR 314.71(a). Accordingly, your petition can only be construed as a request that we initiate notice-and-comment rulemaking proceedings pursuant to which a rule would be promulgated allowing Plan B and other emergency contraceptives to be made available OTC.

the OTC use; other available safety data;<sup>15</sup> actual use trials; and label comprehension trials. As a general matter, actual use and label comprehension data are generally required when relevant safety data are not otherwise available because the drug's indication: 1) is not the subject of an OTC monograph which includes OTC labeling; or 2) has not been previously approved by FDA for OTC use. More particularly, these studies are generally required where, as here, the drug is first in its class to enter the OTC market. The less that is known about use of a medication without the intervention of a health care practitioner, the more data will be required to show safety.

Thus, to obtain the administrative action sought by your petition, either you as the petitioners or the public commenters to the petition needed to submit actual use and label comprehension data to address issues such as the following about the safety and effectiveness of Plan B when labeled for use as an OTC product for consumers of all ages:

- Can consumers of all ages use Plan B safely and effectively in accordance with information on the label or other information tools?
- Would consumers who are already pregnant use Plan B?
- Could sexually active girls under age 18 effectively comprehend the labeling of the product and appropriately use Plan B both in terms of timing and selection, even in the absence of parental or other adult involvement in the procurement and use of the drug?<sup>16</sup>
- Could consumers of all ages use Plan B within the proper time intervals without the assistance of a health care practitioner?
- Would consumers of all ages know what to do if they had an adverse reaction (such as vomiting) shortly after taking a dose of Plan B?
- Would consumers of all ages know what to do if they develop unexpected vaginal bleeding prior to or after using Plan B?
- What, if any, changes in sexual/contraceptive behaviors are evident due to Plan B use?
- What are the rates of unintended pregnancies and STDs associated with Plan B use?
- Are there any safety or efficacy concerns associated with repeat use of Plan B?

---

<sup>15</sup> Safety assessments typically rely on information presented in an NDA, worldwide databases, FDA's Adverse Event Reporting System (AERS) database (postmarketing), and/or literature.

<sup>16</sup> The data submitted in support of the SNDA used 17 as the cut-off instead of 18.

Although your petition and its attachments and supplements contained several studies and references, including examples of foreign OTC use, they did not contain the type of data that FDA requires before granting a switch from Rx-only to OTC status. Because the administrative record compiled with regard to the citizen petition proceeding (as defined in 21 CFR 10.30(i)) does not contain data and information that would justify an OTC switch, you have failed to meet your burden of establishing a basis to grant your petition. Consequently, we are denying your petition.

**B. You Are Not A Party to the SNDA Proceeding.**

As discussed above, we have been engaged in a thorough evaluation of the scientific and regulatory issues posed by Barr's SNDA, and we had intended to defer our response to your petition until we could issue a response contemporaneously with our issuance of a final decision on Barr's SNDA. However, our analysis and evaluation of the SNDA are not yet complete. Because you have asked us to issue a final decision on your citizen petition before completion of our evaluation of the SNDA, there is not now a final decision on the SNDA that resolves the issues raised in your petition.

You cannot require, by means of your citizen petition, that the agency render a final decision on the pending SNDA based on the information which the sponsor has submitted to FDA. Nothing in FDA's regulations permits a member of the public to obtain, in a separate petition proceeding, a final decision on a pending SNDA by relying on the data the sponsor submitted in support of its application. Although FDA regulations permit an interested person to submit a petition requesting that FDA effect an OTC switch through notice-and-comment rulemaking (see 21 CFR 310.200(b)), they do not authorize a petitioner to participate directly in a related SNDA proceeding or to incorporate portions of the record from a pending SNDA proceeding into the record for the citizen petition proceeding.

As you lack any commercial, financial, associational, fiduciary, or confidential relationship with Barr, you are not privy to Barr's legal, business, or scientific concerns, and therefore cannot represent its interests, which may well be in conflict with your own.<sup>17</sup> Furthermore, without express authorization from Barr, which you do not have, you may not step into Barr's shoes, rely on Barr's data (be it proprietary or otherwise), or assert your own interests with respect to Barr's application.

You also cannot deny the sponsor the benefit of the specific procedures that apply to sponsors seeking review of drug applications, and you cannot seek, in effect, to expedite agency review of a sponsor's drug application. The procedures afforded sponsors, among other things, are designed to further the exchange of information between sponsors and FDA with regard to the drug application before a sponsor can obtain judicial review. For example, if FDA were to issue a Not Approvable letter, the sponsor may request a meeting with FDA under 21 CFR 314.102(d) or a hearing under 21 CFR 314.120(a)(3). Likewise, before we can make a final decision refusing to approve a drug application, we

---

<sup>17</sup> For example, whereas you have petitioned to make Plan B available OTC without any age restriction, Barr currently seeks only to sell its product OTC to women 16 years of age and older.

must provide the sponsor with notice and an opportunity for a hearing (see 21 U.S.C. 355(c)(1), (d); 21 CFR 314.200). After the hearing, or after notice is provided and the time for requesting a hearing has elapsed, we may issue an order refusing to approve an application (see 21 U.S.C. 355(d)). If that were to happen, and if the drug sponsor were to desire judicial review of that decision, jurisdiction would lie exclusively in the United States court of appeals where the sponsor resides or has its principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit (see 21 U.S.C. 355(h)). As noted above, the administrative proceedings surrounding your citizen petition are subject to an entirely different set of regulatory and administrative proceedings. You may not, through the vehicle of your citizen petition, circumvent the SNDA process to which the sponsor of the drug is entitled.

Finally, *even if* you believed you were authorized to support your citizen petition by relying on the data submitted to FDA in connection with Barr's SNDA, you failed to supplement your petition with any additional data, even after learning as early as May 2004, that CDER determined Barr's data to be inadequate to support OTC use for women of all ages.

In the course of the SNDA proceeding, CDER has concluded that the data and information currently before the agency do not sufficiently demonstrate that consumers under age 17 can be expected to use Plan B appropriately in self-medication as directed in the proposed labeling. CDER made that determination in Dr. Galson's May 6, 2004 letter to Barr, which we made public shortly thereafter (see Docket No. 2001P-0075/Reference #5). Dr. Galson further elaborated on his analysis in his August 26, 2005 memorandum. In that memorandum, Dr. Galson explained that, although the actual use and labeling comprehension studies submitted with the SNDA were well designed, there were too few women under 17 who took part in those studies. What little data there were with regard to this age group raised questions about whether this age group could use the product safely and effectively (see Docket No. 2001P-0075/Reference #7 at page 3). Dr. Galson also discussed the literature submitted, particularly the literature discussing studies of emergency contraceptives conducted in clinical settings. However, he found that these studies, in which the participants had already contacted clinics, were of limited value because they did not accurately approximate OTC use in the general population (see *id.* at page 4).

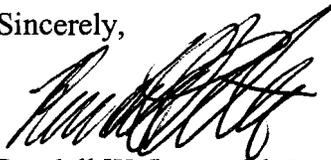
Dr. Galson further explained that the agency will sometimes extrapolate to children data regarding adult use of a drug product, but that this extrapolation is appropriate only when the disease course and the drugs' effects are similar in adults and children, as is the case for drugs treating seasonal allergies and reflux disease (see *id.* at page 5). However, it would be inappropriate to extrapolate data regarding older women to this age group given the nature of the product, the risks associated with its use, and the cognitive and behavioral differences between adolescents and older age groups (see *id.*). Young adolescence is characterized by more impulsive behavior that is less controlled by balancing risks and benefits. These characteristics may impact decision-making regarding birth control. Risks from inappropriate use of Plan B include: failure to understand that the product is for non-routine use, and routine use would result in a

higher than appropriate dose of systemically-absorbed hormone product with possible serious side-effects; failure to understand that Plan B is not a substitute for other forms of birth control that offer protection against sexually transmitted diseases including HIV; and failure to understand the required dosing regimen for Plan B (see *id.*). All of these matters could be clarified by consulting with a health care professional (see *id.* at page 6). In order to establish that younger adolescents can use Plan B safely without consulting with a health care professional, there needs to be more data from actual use and label comprehension studies conducted with younger adolescent participants (see *id.* at page 5).

It should have been apparent that, if the SNDA lacked sufficient data to support the agency action that you sought, then your petition, which referenced far less data in comparison to the SNDA, was also deficient. Yet, you have never provided any additional data in support of your petition.

Accordingly, for all of the reasons discussed above, your petition is denied.

Sincerely,



Randall W. Lutter, Ph.D.  
Associate Commissioner  
for Policy and Planning

cc: Steven Galson, MD, MPH, Director, CDER, HFD-001  
Docket No. 2001P-0075/CP1