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July 24, 2006

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Supplement to Citizen's Petition in Docket No. 2006P-0223 seeking a switch of *Plan B*® and equivalent drugs

Dear Division of Dockets Management:

Please find enclosed four copies of a Supplement to the Citizen's Petition in Docket No. 2006P-0223, seeking a switch of *Plan B*® and equivalent drugs, being submitted by the State of Wisconsin. 21 C.F.R. §§ 10.20 and 10.30. The Citizen's Petition seeks a switch of *Plan B*®, an emergency contraceptive drug approved in 1999 for sale and use on a prescription basis, to over-the-counter status and also a switch of any drugs equivalent to *Plan B*® from prescription to over-the-counter status. This Supplement adds to, rather than supercedes, that Citizen's Petition.

Attached to each copy of the Supplement are: (1) Photocopies of current *Plan B*® packaging as purchased in July 2006 and (2) "COMPLETE CITATIONS TO DOCUMENTS CITED IN 5/22/06 PETITION OR 7/24/06 SUPPLEMENT IN FDA DOCKET NO. 2006P-0223".

If you have any questions or concerns about the format of these submissions, or their compliance with applicable requirements, please contact Sally Mueller at 608-267-2238 or muellersa@doj.state.wi.us. Thank you.

Sincerely,

Richard Briles Moriarty
Assistant Attorney General
State Bar No. 1017190

RBM:
Encls. (four copies of Citizen's Petition and attachments)

2006P-0223

SUP 1

July 24, 2006

DOCKET NUMBER 2006P-0223

Division of Dockets Management
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5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUPPLEMENT TO CITIZEN PETITION IN DOCKET NUMBER 2006P-0223

Petitioner, the State of Wisconsin, by its attorneys, Peggy A. Lautenschlager, Attorney General, and Richard Briles Moriarty and Nelle R. Rohlich, Assistant Attorneys General, (Wisconsin), supplements its May 22, 2006 Citizen Petition in Docket Number 2006P-0223, that was received by FDA on May 24, 2006 (http://www.fda.gov/OHRMS/DOCKETS/dockets/06p0223/06p0223.htm). The purpose of this Supplement is to address selected points noted by FDA in its June 9, 2006 letter denying the Citizen Petition filed on February 14, 2001 in Docket Number 2001P-0075 (http://www.fda.gov/ohrms/dockets/dockets/01p0075/01p-0075-pdn001-vol348.pdf; http://www.fda.gov/ohrms/dockets/dockets/01p0075/01p0075.htm.)[1]

This Supplement addresses only selected points noted in the 6/9/06 denial letter, and then only as a supplement to how the 5/22/06 Petition addressed those selected points. No inference should be drawn from some points being addressed while others

[1]Over-the-counter is referred to as "OTC", the emergency contraception drugs marketed as *Plan B®* as "*Plan B®*", and all drugs equivalent to *Plan B®* currently available only by prescription, whether marketed as emergency contraception drugs or not, as "equivalent EC drugs." The term "EC" includes *Plan B®* and equivalent EC drugs. The May 22, 2006 Citizen's Petition in this docket is referred to as the "5/22/06 Petition", the June 9, 2001 denial letter in Docket Number 2001P-0075 as the "6/9/06 denial letter", and this Supplement as the "7/24/06 Supplement".

Abbreviated references to citations in the 5/22/06 Petition and in this 7/24/06 Supplement are to the lead or institutional author, year and page, e.g., "(Ashby 2005, p. 37)" and "(DHHS 2001, p. 9-4)", except where extra descriptors distinguish publications in the same year, e.g., "FDA Action 2005" and FDA Draft 2005". Attached is "Complete Citations to Documents Cited in 5/22/06 Petition or Supplement," which provides full citations to materials other than laws, regulations and federal decisions cited in either the 5/22/06 Petition **or** this 7/24/06 Supplement.

are not, or from discussion of those points being limited to supplementation of the 5/22/06 Petition.

The State of Wisconsin pro-actively undertakes to address, through this Supplement, selected points in the 6/9/06 denial letter now, rather than wait for the FDA to respond to the 5/22/06 Petition and encounter any delay regarding those points, because substantial detrimental effects are occurring daily, in Wisconsin and elsewhere in this country, from *Plan B®* not being available OTC. Each day that passes without *Plan B®* or equivalent EC drugs being available OTC is another day that thousands of unwanted pregnancies – often ending in abortions or unwanted births - occur in Wisconsin in this country that OTC access could have prevented. (Ellertson, 2003. p. 1160 ("Emergency contraceptives ... could eliminate up to half of the 3.0 million annual unintended pregnancies [citations omitted]").

More than five **years** after the Citizen Petition in Docket Number 2001P-0075 was filed in 2001, the 6/9/06 denial letter posed nine questions that, it asserted, the petitioners in that Docket bore the burden of answering, namely:

- 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?
- 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?

(6/9/06 denial letter, p. 16.) Contending that the petitioners in FDA Docket Number 2001P-0075 had not answered these questions, FDA expressly denied their Citizen Petition in June 2006. (6/9/06 denial letter, pp. 16-19.)

The 5/22/06 Petition confirms that any questions that FDA may, in the past, have legitimately had about whether to switch *Plan B®* to OTC status were long ago overwhelmingly answered in favor of an OTC switch by, among many other things, (a) the deliberations and votes of the Nonprescription Drugs Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD) in December 2003 regarding this switch; (b) the recommendations of FDA review staff that *Plan B®* should be granted OTC status; (c) the 2005 Policy Statement of the Committee on Adolescence of the American Academy of Pediatrics, based on relevant, peer-reviewed scientific literature (Committee 2005); and (d) other relevant peer-reviewed scientific literature. (5/22/06 Petition, pp. 3-26.)

Nonetheless, the State of Wisconsin seeks to avoid any delays in the relief requested in the 5/22/06 Petition by expressly noting the nine questions quoted above and, going beyond what was noted in the 5/22/06 Petition, confirming that none of those questions raises any legitimate reason to delay granting that relief.

A. **"Can consumers of all ages use Plan B safely and effectively in accordance with information on the label or other information tools?"**

"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?"

"Could consumers of all ages use Plan B within the proper time intervals without the assistance of a health care practitioner?"

Under the circumstances created by FDA in considering whether to approve OTC status for *Plan B®* (5/22/06 Petition, pp. 3-26), the first, third and fourth questions in the 6/9/06 denial letter are essentially the same questions, stated differently. In August

2005, FDA definitively answered all three of these questions in the affirmative regarding **all** consumers who are 17 or older. (FDA Action 2005; see also FDA Decision 2004.) In August 2005, FDA declared that *Plan B®* was "safe" and "effective" for OTC sale and use by older adolescents (i.e., adolescents 17 or older) and adult women. (FDA Action 2005.) Nonetheless, it has continued to refuse OTC access to **all** women by claiming to be concerned about the sufficiency of studies addressing how increased EC access might alter sexual behavior by younger adolescents (i.e., adolescents 16 or younger) (FDA Action 2005; see also FDA Decision 2004).

In other words, based on purported concerns about making *Plan B®* accessible OTC to a small fraction of women in child-bearing years, FDA is actively depriving nearly all women in that group, those over 16 years of age, from OTC access that FDA itself admits to be mandated. (FDA Action 2005; see also FDA Decision 2004). FDA's action in this regard is analogous to jailing 100,000 people because a handful of those people may have committed a crime – except that the analogy improperly disparages menarchal adolescents 16 or younger. It is inexcusable for FDA to have delayed OTC approval for the vast number of menarchal adolescents and women as to whom it expressly found OTC use to be safe and effective due to alleged – and transparently groundless - concerns about a small fraction of menarchal females who may be engaging in sexual activities.

Nonetheless, given the admission by FDA that there is no valid reason to deny OTC access to *Plan B®* to women in child-bearing years who are older than 16 (FDA Action 2005), the first, third and fourth questions in the 6/9/06 denial letter must necessarily be limited to concerns about whether consumers who are 16 or younger can use *Plan B®* safely and effectively, in accordance with information on the label or other information tools, if it is available OTC. The 5/22/06 Petition conveyed numerous reasons why these are improper inquiries, wholly inconsistent with prior FDA actions and practice and, regardless, that relevant, peer-reviewed scientific literature confirmed

that switching *Plan B®* and equivalent EC drugs to OTC status was as safe and effective for menarchal adolescents 16 and younger as for older females (5/22/06 Petition, pp. 9-16).[2]

In 1999, FDA concluded, by making *Plan B®* available on a prescription basis to all women in child-bearing years, that consumers of all ages – including consumers who are 16 or younger - could use *Plan B®* safely and effectively, in accordance with information on the label or other information tools, in a prescription drug setting. (5/22/06 Petition, p. 6.) The 6/9/06 denial letter contended that the data presented regarding potential consumers who were younger than 16 was insufficient to show that "the product could be used safely by women under 16 years of age without professional supervision by a licensed practitioner" (6/9/06 denial letter, p. 7).

A document that FDA placed on its website with the 6/9/05 denial letter, a memorandum from Dr. Steven Galson to "NDA 21-045, S-011" dated August 26, 2005 helps frame the issue.[3] Dr. Galson – who signed the May 2004 non-approvable letter – stated in August 2005, based on the label study (Raymond, 2002), that potential consumers between 12 and 16 were, , when compared to "older adolescents", "less likely to specifically comprehend Plan B's labeling instructions" (8/26/05 Galson memo, p. 3). As examples, he noted that, in the label study:

> women ages 12-16 did not understand as often as women 17 years and older that Plan B's indication is to prevent pregnancy after unprotected sex (86% for ages 12-16, 93% for ages 17-25, 95% for ages 26-50), that Plan B is not for routine use (57% for ages 12-16, 67% for ages 17-25, 71% for ages 26-50), that the first pill should be taken within 72 hours after intercourse (77% for ages 12-16, 86% for ages 17-25, 87% for ages 26-50),

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[2] The third question in the 6/9/06 denial letter – ""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? – is incomprehensible in this context since the FDA has already determined that sale to and use by menarchal adolescents who are 16 and 17 of *Plan B®* on an OTC status is safe and effective. (FDA Action 2005.)

[3] This document, now available on the FDA website in connection with the 6/9/06 denial letter (http://www.fda.gov/ohrms/dockets/dockets/01p0075/01p-0075-ref0001-08-082605-SGalson.pdf), is referred to as "the 8/26/05 Galson memo."

> and that the second pill should be taken 12 hours after the first pill (77% for ages 12-16, 90% for ages 17-25, 82% for ages 26-50).

(8/26/05 Galson memo, p. 3.) The FDA focus on this relatively minor, but noticeable, disparity in understanding the label loses any significance, in analyzing whether the intervention of prescribers is necessary before menarchal females under 16 could obtain *Plan B®*, when the knowledge base of the participants 16 and younger is compared not to older menarchal females but to the knowledge base of prescribers.

New York pediatricians, for example, responding to mail-in questionnaires in 1999 had substantially **less** understanding about *Plan B®* than the adolescents 16 and younger who participated in the label study in 2001 and 2002. (*Compare* Golden, 2001, pp. 288-89 with 8/26/05 Galson memo, pp. 3 and 5.) In a 1999 survey conducted anonymously by the American Academy of Pediatrics of New York State members, 233 pediatricians in active practice replied (Golden, 2001, p. 288). Amazingly, "[o]nly **27.9%** of [those] respondents answered correctly that the maximum time within which to prescribe EC is 72 hours after unprotected intercourse" and "**40.1% answered that they did not know the time limit**" (Golden, 2001, p. 289 (emphasis added)).

By contrast, in the label study, 77% of the participants who were 16 or younger, after reviewing the label, knew **both** that "the first pill should be taken within 72 hours after intercourse" and "that the second pill should be taken 12 hours after the first pill." (8/26/05 Galson memo, p. 3.) As the label study noted, however, knowledge of these two facts – high as they are – understate the level of acceptable comprehension, since the

> more important message is that almost all women (97%) understood the overall time frame for product use (*either* within 72 hours *or* as soon as possible after sex.)

(Raymond 2002, p. 346.)

Yet Dr. Galson cited only the level of knowledge that younger menarchal adolescents had about these details (77%) and then propounded it as a reason to require

all menarchal females to undergo a prescriber/pharmacist gauntlet before they could obtain *Plan B®*. (8/26/05 Galson memo, pp. 3 and 5.) Ironically, Dr. Galson concluded, from this very information that:

> if a young adolescent does not understand that the first dose of Plan B should be taken within 72 hours of unprotected intercourse, and the second pill 12 hours later, the effectiveness of the product will be compromised, **and she may be at greater risk of having an unwanted pregnancy**.

(8/26/05 Galson memo, p. 5 (emphasis added).) There are several problems with this conclusion.

First, after the 2001-2002 label study, and before Dr. Galson wrote that memorandum, it was becoming apparent that the 12 hour delay was unnecessary, i.e., that taking both pills at the start of the *Plan B®* regimen was just as effective as spacing them by 12 hours. (Lahka 2004, p. 302. *See also* Sambol 2006.) If so, then taking both pills together at the start of the regimen was more likely to lower the risk of unwanted pregnancy even further – since the occasions when the 12 hour delay resulted in the second pill being forgotten would be eliminated.

Second, Dr. Galson in August 2005 – and the FDA in the 6/9/06 denial letter - ignored studies subsequent to the label study that overwhelmingly confirmed that younger menarchal adolescents both understand and use *Plan B®* as directed by the labels without any prescriber/pharmacist interventions. (5/26/06 Petition, pp. 14-15; *see esp.* Harper, 2005, p. 490; Clements 2006, 149 (summarizing the Harper results).)

Third, and more important, what places younger adolescents at far greater risk of unwanted pregnancies than less than perfect knowledge about when to commence *Plan B®* is requiring them – for no valid scientific reason – to obtain a prescription and have it filled. The prescriber may well have dramatically lower knowledge of when *Plan B®* must be commenced (Golden, 2001, p. 289) and it could be quite difficult to locate a willing pharmacist who actually stocks *Plan B®* (Espey 2003, p. 918; Chuang

2006; Pradhan 2006; Lewington 2006; Soon 2005, p. 881; Jackson 2003, pp. 8, 11-15) and will not, based on their own inadequate training or biases, scare off the younger adolescent (Conard 2003). If available OTC, those delays – resulting in substantially more unwanted pregnancies – could be avoided.

Hypothetically, however, assume that, in 1999, a 15 year old female had engaged in unprotected intercourse, was unaware of when *Plan B®* should be commenced and found her way to a New York State pediatrician's office. That hypothetical 15 year old would be far more likely to determine the correct information about when *Plan B®* should be commenced – and to avoid an unwanted pregnancy – by ignoring whatever the hypothetical pediatrician told her and simply reading, and relying on, the label for *Plan B®*. (*Compare* Golden, 2001, pp. 288-89 with 8/26/05 Galson memo, pp. 3 and 5.)

The misinformation, or misdirection, that menarchal adolescents might obtain from pediatricians, and pharmacists, about emergency contraception is not limited to when *Plan B®* should be commenced. In 1997, FDA had, in an announcement that garnered considerable attention, expressly identified several regimens of drugs that, although not marketed as such, were approved as ones that physicians could prescribe for emergency contraceptive purposes. (FDA 1997). Yet in that 1999 New York State study of pediatricians' knowledge base regarding emergency contraception, "[a]lmost 73% of [those New York pediatrician] respondents were unable to identify **any** of the FDA-approved methods of EC" (Golden, 2001, pp. 289 (emphasis added)). Also, while over "50% of [those] respondents answered correctly that in a mature adolescent known to the physician, a physical examination or a pelvic examination are not necessary before prescribing EC," 46.8% erroneously believed that a physical examination was necessary, and 35.7% erroneously believed that a pelvic examination was necessary, in those circumstances. (Golden, 2001, pp. 289.)

The knowledge base of pediatricians about EC has likely increased since the Golden study – just as the knowledge base of menarchal adolescents 15 and younger about EC has likely increased since the Raymond label study. Indeed, there is clear evidence supporting the latter, if not the former, assumption. (Harper 2005.) But consultations that pediatricians may have with adolescents regarding sexual issues may be unhelpful not just due to poor knowledge bases regarding *Plan B®* and other forms of emergency contraception (Golden, 2001, pp. 289) but because pediatricians may feel uncomfortable with, and inadequately prepared, to provide adolescents with routine gynecological care (Korczak 2006).

In that context, how does it increase potential understanding regarding *Plan B®* amongst younger menarchal adolescents, in ways that are at all significant to the safety and efficacy of *Plan B®* for that age group, to continue requiring those females to consult with prescribing physicians rather than allowing them to obtain *Plan B®* OTC and read the labels for themselves? The participants in the label study who were females 16 or younger may have been – by comparison with pediatricians and pharmacists – remarkably well informed about the proper use of *Plan B®*. (Raymond, 2002. See also discussion and citations at 5/22/06 Petition, pp. 9-16.)

Studying the label is likely to be far more educational than listening to a pediatrician or pharmacist. A review of the current label approved by FDA for Rx use of *Plan B®* confirms that is remarkably clear and understandable (*Plan B®* Rx packaging, 2006) – particularly when compared with the labels of drugs that FDA approved for OTC sale and use to adolescents as young as 12 years of age (5/22/06 Petition, pp. 9-11). If anything, the labels now used for Rx use of *Plan B®* are substantially easier to understand and comprehend than the simulated OTC labels used in the 2002 label study. (Compare *Plan B®* Rx packaging, 2006 with Raymond, 2002, p. 347 (simulated OTC labels).)

It is perverse to deny younger menarchal adolescents the significantly increased access to *Plan B®* that would accompany an OTC switch (5/22/06 Petition, pp. 16-17) – essentially condemning many of them to the severe adverse consequences of unwanted pregnancies, abortions and unwanted births long before they become adults (5/22/06 Petition, p. 18) – because younger menarchal adolescents may know somewhat less than older menarchal adolescents about *Plan B®*.

Any disparity in knowledge between those two subgroups, after all, is far more likely to be cured by providing genuine sex education than by requiring younger menarchal adolescents to run the gauntlet of obtaining prescriptions and searching around for a pharmacist willing and able to fill the prescriptions. Relevant, peer-reviewed scientific literature has established that, when menarchal adolescents aged 14 or 15 were given a single lesson by the teachers at school about emergency contraception, following in-service training of those teachers, the knowledge of those adolescents about the correct time limits for commencing emergency contraception substantially improved. (Graham 2002, pp. 1183, text & Table 7.)[4]

It is doubly perverse to use the fact that menarchal adolescents 16 or younger in the label study were somewhat less familiar with the correct time limits for commencing *Plan B®* than older adolescents as an excuse to require them to continue running the prescriber gauntlet when so many pharmacies do not carry *Plan B®* and, even when willing to order it, would obtain it only long after *Plan B®* should be commenced. (Chuang, 2006; Pradhan, 2006; Lewington, 2006.) As noted in the 5/22/06 Petition:

> Because there "is an inverse relationship between pregnancy and time since unprotected intercourse" (Weismiller 2004, p. 709), any delay between unprotected intercourse and commencing the regimen - such as delays caused by locating a willing physician, obtaining a prescription and

[4] It is ironic that, in Britain where this study occurred, EC is available OTC to menarchal adolescents 16 and older but that younger adolescents, the very ones most at risk in the event of sexual activity, continue to have "substantial limitations" placed on EC access through prescription/pharmacist requirements. (Tripp 2005, p. 392).

then having that prescription filled – substantially reduces the effectiveness of *Plan B®*. (Weismiller 2004, p. 709.)

(5/22/06 Petition, p. 17.)

It is triply perverse to deny OTC access to **all** menarchal women 17 and older because the FDA has unfounded concerns about younger menarchal adolescents in the label study being somewhat less familiar with relevant information about *Plan B®*.

The answers to the first, third and fourth questions in the 6/9/06 denial letter are clearly affirmative.

B. "Would consumers who are already pregnant use Plan B?"

The second question in the 6/9/06 denial letter - "Would consumers who are already pregnant use Plan B?" – is best answered: "While a neglible percentage consumers may use *Plan B®* after becoming pregnant, that is irrelevant to evaluating whether *Plan B®* should be approved for OTC use." The label study confirmed that 98% of the participants, after reviewing the label, knew that *Plan B®* "should not be used by women who are already pregnant." (Raymond 2002, p. 342.) Since that was less than 100%, and nothing physical informs a woman of the moment when she has become pregnant, the potential exists that women may, no matter how much they may know about *Plan B®*, take it after becoming pregnant.

But requiring women to undergo the physician/pharmacist gauntlet would, if anything, substantially **increase** the likelihood that women will have become pregnant by the time they commence *Plan B®* regimens. Research is now indicating that *Plan B®* prevents pregnancy not by blocking implantation, but by blocking or delaying ovulation, i.e., the release of the egg from the ovary, such that fertilization never occurs. (Ortiz 2004; Marions 2004; Gemzell-Danielsson 2006; Ackerman 2006.) If so, it is even more critical to assure that *Plan B®* regimens are commenced as soon after contraceptive failure as practicable. If, however, as prior researchers have assumed, that *Plan B®*

blocks implantation, imposing the physician/pharmacist gauntlet rather than allowing OTC access still substantially increases the likelihood that women will have become pregnant by the time they commence *Plan B®* regimens. To the extent that maintaining *Plan B®* in prescription status delays the time when women would have commenced *Plan B®* regimens, the refusal to approve an OTC switch substantially **increases** the occasions when "consumers who are already pregnant [would] use Plan B." (6/9/06 denial letter, p. 16.)

Addressing the question as asked - "Would consumers who are already pregnant use Plan B?" – the label study confirms that women, left to their own devises, would plainly avoid using *Plan B®* if they knew, or suspected that they were already pregnant. Why would women who know they are already pregnant pay a high cost for, and take, a drug that they know could well make them nauseous and have absolutely no positive effects? The label currently used for Rx packaging of *Plan B®* is even clearer, in conveying that *Plan B®* is ineffective after a woman becomes pregnant, than the simulated OTC label used in the 2002 label study. (*Compare Plan B®* Rx packaging, 2006 with Raymond 2002, p. 347 (simulated OTC label).) Presumably, FDA would call for the clearest labeling, if *Plan B®* is approved for OTC sale and use, so it is worth considering the current Rx packaging of *Plan B®*. The inside of the current package, in the panel right next to the pills themselves states:

> **Who should not take Plan B?**
>
> ***Plan B*** should not be taken if you are already pregnant....
>
> **What if I am already pregnant and take Plan B?**
>
> ***Plan B*** is not appropriate if you are already pregnant; it will not work. ...

(*Plan B®* Rx packaging, 2006, p. 3.) The more detailed explanatory sheet that is inserted into that packaging also expressly warns against taking *Plan B®* as a response to becoming pregnant:

CONTRAINDICATIONS

Progestin-only contraceptive pills (POPs) ... are not recommended for use in the following conditions:

- Known or suspected pregnancy

WARNINGS

....
Plan B® is not effective in terminating an existing pregnancy.

(*Plan B®* Rx packaging, 2006, p. 7.)

The highly speculative fear that a woman who was already pregnant would take *Plan B®* despite these clear warnings is no reason to bar OTC approval. Even if a woman, despite these warnings, takes *Plan B®* after becoming pregnant, relevant peer-reviewed scientific literature confirms that it would have no health effects on either the woman or a fetus, except perhaps making the woman nauseous. (Camp, 2003, pp. 313-14.) And as the FDA-approved label itself states,

> After taking ***Plan B***, most women (87%) get their next period within one week of when it is expected. If your period is more than a week late, you should check with your health care provider to see if you are pregnant.

(*Plan B®* Rx packaging, 2006, p. 2.) In the label study, nearly 89% of the participants responded appropriately to comprehension questions regarding similar information that was conveyed in the simulated OTC label. (Raymond, 2002, p. 345 (Table 2, No. 21).)

People can, of course, always act irrationally, but FDA has never grounded its OTC decisions on such assumptions. There is considerably more potential that adolescents 16 and younger would use other drugs approved by FDA for OTC status in 2004 improperly (*see* 5/22/06 Petition, pp. 9-11) than that adolescents 16 and younger would use *Plan B®* after becoming pregnant.

There are, in other words, numerous reasons why it is inappropriate to any evaluation of whether *Plan B®* should be approved for OTC status to ask "Would consumers who are already pregnant use Plan B?" (6/9/06 denial letter, p. 16.)

Speculation is no substitute for science. Science overwhelmingly confirms that numerous unwanted pregnancies would be prevented each day if FDA had, when required, approved OTC status for *Plan B®*. (5/22/06 Petition, pp. 3-26.) Science also confirms that menarchal women of all ages, simply from reviewing the label, overwhelmingly understand that *Plan B®* should not be used after becoming pregnant. (Raymond 2002, p. 342.) Science also confirms that, even if a particular woman should take *Plan B®* while pregnant, that would have no health effects on either the woman or a fetus, except perhaps making the woman nauseous. (Camp, 2003, pp. 313-14.)

C. "Could 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?"

The fifth question in the 6/9/06 denial letter is an invalid question to pose in the evaluation of whether to switch *Plan B®* to OTC status. Vomiting is among the potential side effects of taking *Plan B®* - as 89% of the participants in the label study understood from reviewing the simulated OTC label used there. (Raymond 2002, pp. 345 (Table 3, No. 11) and 347 (simulated OTC label).) As that simulated OTC label – reviewed by FDA as part of its review of the protocol – stated, merely experiencing vomiting shortly after taking a dose of *Plan B®* would not be a signal to a consumer to "do" anything. Instead, that simulated OTC label instructed immediately after listing the side effects, "Talk to a doctor if side effects are severe or last more than 48 hours." (Raymond 2002, p. 347 (simulated OTC label).) So it is meaningless, and misdirected, to ask whether "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?"

Regardless, "there are no documented tetragenic effects in the 48 known patients in whom treatment failed and who went on to term after receiving EC." (Golden, 2001, p. 290.) A woman who took *Plan B®* and, in response to experiencing any level of vomiting, consulted a physician who was an informed practitioner, may well be

counseled according to the messages conveyed in a 2004 article entitled "Emergency Contraception: What Primary Care Clinicians Need to Know":

> Women are often concerned that they may vomit after taking EC. Although antiemetics can be given at the same time, they can cause adverse effects of their own (eg. drowsiness). Given that only about 6% of women vomit using Plan B [footnote 7 omitted], routine use of antiemetics is unnecessary; clinicians should instead recommend that EC not be taken on an empty stomach and instruct the patient to return for more EC if she does vomit.

(Lahka, 2004, p. 303.) Most antiemetics, parenthetically, are OTC. (FDA Drug Interactions 2006, p. 6.)

But it may well be that a physician would have no better idea than the woman about what to "do" if she "had an adverse reaction (such as vomiting) shortly after taking a dose of Plan B" (6/9/06 denial letter, p. 16), since the "preferred management of vomiting shortly after taking emergency contraception is **unknown**" (Grimes, 2002, p. E-185 (emphasis added).)

Conceivably, vomiting after taking *Plan B®* could signal some other condition that the taking of *Plan B®* could, coincidentally mask as attributable to that drug. But, if so, it is improper for the FDA to ground a safety conclusion regarding a drug on the fear, even if justified, that the person taking the drug may be lulled into thinking there is no need to consult with a physician regarding conditions the drug is not designed to cure. *Cf., e.g., U.S. v. Articles of Drug Labeled "Quick-O-Ver"*, 274 F.Supp. 443, 449 (D.Md. 1967) (rejecting this position regarding a drug that "may relieve headache, nausea and upset stomach, and help restore some measure of alertness," and thereby "prevent persons from consulting a doctor even though they have serious aftereffects as a result of alcoholism or prolonged excessive drinking" because the "same argument could be made against any over-the-counter remedy which relieves pain or a cough, but does not undertake to cure the cause of such pain or cough"). Safety inquiries by the FDA must be grounded on science, not speculation or fears unassociated with the matter at hand. *Id.*

The fifth question in the 6/9/06 denial letter - "Could 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?" - is simply not a valid question in the evaluation of whether to switch *Plan B®* to OTC status.

D. "Would consumers of all ages know what to do if they develop unexpected vaginal bleeding prior to or after using Plan B?"

The State of Wisconsin is unaware of any valid scientific reason to pose this question in the evaluation of whether to switch *Plan B®* to OTC status. The published results of the label study expressed similar bewilderment over why FDA focuses on this issue – to the point of requiring that a notice be included in the simulated OTC label:

> Only three-quarters of subjects understood that the product should not be used by women with unexplained vaginal bleeding. The questionnaire included just one question to test this objective, which in retrospect would have been too few to test an important concept. However, the rationale for the Food and Drug Administration's requirement that this contraindication be included on the prescription label is unknown. To our knowledge no published medical guidelines for use of emergency contraceptive pills include unexplained bleeding as a contraindication.[4,5]
>
> [4] American College of Obstetricians and Gynecologists. ACOG practice patterns. Emergency oral contraception. Number 25. Washington, DC: American College of Obstetricians and Gynecologists, 2001.
>
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(Raymond, 2002, p. 346.) There continues to be no apparent basis for this expressed concern by FDA. (Webb 2004; Arowojolu 2004.) Once again, this question, as posed in the 6/9/06 denial letter, can only be focused on menarchal adolescents 16 and younger – since FDA already determined in August 2005 that was *Plan B®* was both safe and effective for OTC sale to and use by all menarchal females 17 and older. (FDA Action 2005.) If anything, however, studies have shown that unusual bleeding patterns is even less associated with *Plan B®* use by younger menarchal adolescents than by older females. (Clements 2006, p. 149.)

The FDA insistence that *Plan B®* labels warn consumers regarding vaginal bleeding – for reasons that escape explanation - may have created unfounded fears in the populace that actually push consumers away from EC use. (Wynn 2005.) Nonetheless, at FDA's insistence, the Rx labeling for *Plan B®* - for no apparent scientific reason - continues to warn consumers as follows:

> **Who should not take Plan B?**
>
> ... Do not take ***Plan B*** if you have any unexplained vaginal bleeding.

(*Plan B®* Rx packaging, 2006, p. 3.) The more detailed explanatory sheet that is inserted into that packaging also expressly warns against taking *Plan B®* as a response to becoming pregnant:

> **CONTRAINDICATIONS**
>
> Progestin-only contraceptive pills (POPs) ... are not recommended for use in the following conditions:
>
> ...
> - undiagnosed abnormal genital bleeding

(*Plan B®* Rx packaging, 2006, p. 7.) And as the label study confirmed, three-quarters of the participants absorbed and comprehended this information – no matter how groundless it may be – as part of what they drew from reviewing the simulated OTC label. (Raymond, 2002, p. 346.)

A separate issue implied by the question "Would consumers of all ages know what to do if they develop unexpected vaginal bleeding prior to or after using Plan B?" is that consumers should "do" something if they experience unexpected vaginal bleeding after using *Plan B®*. The FDA-approved Rx label only addresses this issue in this way:

> **What are the risks and side effects of taking Plan B?**
>
> Menstrual bleeding is sometimes heavier and sometimes lighter than usual after women take ***Plan B***. After taking ***Plan B***, most women (87%) get their next period within one week of when it is expected. If your period is more than one

week late, you should check with your health care provider to see if you are pregnant.

(*Plan B®* Rx packaging, 2006, p. 2.) The CDER Medical Review of the 1999 application for approval of *Plan B®* on a prescription basis (FDA Dkt. No. 21-045) contains no hint of FDA concern about unexpected vaginal bleeding either before or after *Plan B®* is taken. (http://www.fda.gov/cder/foi/nda/99/21-045_Plan%20B_medr.pdf.)

The State of Wisconsin is unaware of any valid scientific reason to pose this question in the evaluation of whether to switch *Plan B®* to OTC status. It stands ready, however, to address this question further if, in response to the 5/22/06 Petition, FDA provides some viable rationale for posing the question.

E. "What, if any, changes in sexual/contraceptive behaviors are evident due to Plan B use?"

As noted in the 5/22/06 Petition, FDA's unprecedented concerns about potential sexual behavior – or misbehavior – from a moralistic viewpoint is a wholly inappropriate consideration in FDA decision-making regarding whether *Plan B®* should be switched to OTC status. (5/22/06 Petition, pp. 8-9, 12 & 25. *See also* Davidoff 2006.) Indeed, the injection of those concerns into the decision-making process raises serious constitutional issues. (5/22/06 Petition, p. 25.)

But addressing the question as if it were valid, relevant, peer-reviewed scientific literature has confirmed, uniformly and repeatedly, that increasing access to EC does not either increase sexual activity or diminish the use of other contraceptive methods. (5/22/06 Petition, pp. 13-15; Harper, 2005; Walker, 2006; Gold, 2004; Raine 2005; Raymond 2003; Ellertson 2001; Hoggart 2006; Jackson 2003; Larsson 2006; London 2006; Nursing Standard 2005; Pierce 2005; Walker 2006.) Beyond being a wholly invalid inquiry, therefore, relevant, peer-reviewed scientific literature confirms that the improper moralistic fears that underlie this question are also factually unfounded.

F. "What are the rates of unintended pregnancies and STDs associated with Plan B use?"

It is unclear what is meant by the question in the 6/9/06 denial letter that states "What are the rates of unintended pregnancies ... associated with Plan B use?" (6/9/06 denial letter, p. 16.) Since the question also seems to ask about rates of STDs that result from *Plan B®* use, the first part of the question could be asking about rates of unintended pregnancies that result from *Plan B®* use. If so, it is merely another way of asking the improper moralistic question just discussed, i.e., whether increased access to *Plan B®* would increase sexual behavior and, speculatively, result in some additional unintended pregnancies. Although the question is improper for FDA to pose in evaluating whether to approve an OTC switch of *Plan B®*, the answer is, definitively, that usage, or increased usage through increased access, of *Plan B®* does not increase risky sexual behavior. (5/22/06 Petition, pp. 13-15; Harper, 2005; Walker, 2006; Gold, 2004; Raine 2005; Raymond 2003; Ellertson 2001; Hoggart 2006; Jackson 2003; Larsson 2006; London 2006; Nursing Standard 2005; Pierce 2005; Walker 2006.)

Relevant peer-reviewed scientific evidence also establishes that the rates of unintended pregnancies are dramatically reduced when emergency contraception is used. (Raymond 2003; Gold 2004; Ellertson 2001; Hoggart 2006; Jackson 2003; Larsson 2006; London 2006; Harper 2005; Nursing Standard 2005; Pierce 2005; Raine 2005; Walker 2006). Research is now pointing towards the mechanism of *Plan B®* not being to prevent implantation, as was earlier assumed, but instead to block or delay the release of the egg from the ovaries, such that viable sperm does not interact with the egg. (Ortiz 2004; Marions 2004; Gemzell-Danielsson 2006; Ackerman 2006.) As a result, assuring access to *Plan B®* is not obstructed by unnecessary delays, such as time-consuming efforts to obtain and fill a prescription, is likely to be even more vital than earlier assumed. If this mechanism is established to be how *Plan B®* works, this should

also confirm even more clearly that *Plan B®* does not cause abortion – since it acts before fertilization even occurs. (Ortiz 2004; Marions 2004; Gemzell-Danielsson 2006; Ackerman 2006.)

The question "What are the rates of unintended pregnancies ... associated with Plan B use?" (6/9/06 denial letter, p. 16) could, as an alternate meaning, be asking how many times *Plan B®* is used in response to unintended pregnancies. If so, the question would relate to efficacy issues. But since FDA has already determined that *Plan B®* is effective for OTC sale and use regarding all menarchal women 17 or older for its intended use of ending unintended pregnancies (FDA Action 2005), there seems no point to having asked that question in the 6/9/06 denial letter. Relevant peer-reviewed scientific literature confirms that approving *Plan B®* for OTC use would dramatically reduce unwanted pregnancies. (Raymond 2003; Gold 2004; Ellertson 2001; Hoggart 2006; Jackson 2003; Larsson 2006; London 2006; Harper 2005; Nursing Standard 2005; Pierce 2005; Raine 2005; Walker 2006). The number of times that *Plan B®* may actually now be used in response to unwanted pregnancies and then successfully have avoided unwanted pregnancies is almost impossible to determine. In any event, given the prescriber/pharmacist gauntlet that women must now undergo, it would be improper, in evaluating whether *Plan B®* should be granted OTC status, to require petitioners to prove with any precision how many unwanted pregnancies *Plan B®* actually prevented while on prescription status.

Rather than speculate on what FDA could possibly mean by this aspect of the question, the State of Wisconsin invites FDA to promptly clarify that meaning – or drop the inquiry – so that it will not stand in the way of a speedy disposition of the 5/22/06 Petition.

The question contains another subquestion, namely, "What are the rates of ... STDs associated with Plan B use?" Presumably, this subquestion is another way to

pursue the improper focus on feared sexual misbehavior by menarchal adolescents 16 or younger who may take *Plan B®*. Once again, relevant, peer-reviewed scientific literature has confirmed, uniformly and repeatedly, that increasing access to EC does not either increase sexual activity or diminish the use of other contraceptive methods. (5/22/06 Petition, pp. 13-15; Harper, 2005; Walker, 2006; Gold, 2004; Raine 2005; Raymond 2003; Ellertson 2001; Hoggart 2006; Jackson 2003; Larsson 2006; London 2006; Nursing Standard 2005; Pierce 2005; Walker 2006.) Numerous studies have confirmed that women do not change their decrease their reliance on condoms, for example, when they take *Plan B®*. (Ellertson 2001,; Jackson 2003; Hoggart 2006; London 2006; Nursing Standard 2005; Pierce 2005.)

FDA's continuing arguments that increasing access to *Plan B®* would diminish condom use – in this case by expressing concerns about STDs – fly in the face of not just all available evidence but FDA's own actions in 2004 in approving vaginal infection drugs for OTC use that can clearly damage condoms and expose users to increased STD risk at the same time FDA was denying OTC status to *Plan B®*. (5/22/06 Petition, pp. 9-10.) All available evidence confirms that using *Plan B®* substantially diminishes unwanted pregnancies and do not in any way increase risks of STDs.

G. "Are there any safety or efficacy concerns associated with repeat use of Plan B?"

If there were "any safety or efficacy concerns associated with repeat use of Plan B" that were relevant to whether *Plan B®* should be approved for OTC status, then FDA would never have concluded that it was safe for OTC sale to and use by all menarchal females 17 or older. (FDA Action 2005.) There certainly are no perceivable distinctions between menarchal adolescents 16 and younger and any other menarchal females regarding that issue.

Setting that aside, however, it is difficult to understand what FDA's current concern is as to this issue. It is clear from the labeling and all relevant studies that *Plan B®* is not effective as a regular contraceptive – which is precisely why it was approved, is marketed and is very clearly labeled as an "emergency contraceptive." (*Plan B®* Rx packaging, 2006.) The name of the drug itself, as then CDER Director and now FDA Deputy Commissioner Janet Woodcock confirmed in 1999 in reversing a "denial of the trade name 'Plan B' for the emergency contraceptive product levenogrestrel (NDA 21-045)", is a crystal clear message that *Plan B®* is not to be used as a primary contraceptive method:

> ...
>
> The phrase "plan B" in ordinary usage denotes an emergency or backup plan – something to employ when "plan A" fails. This common usage does not connote superiority or inferiority; rather it implies a sequence or order. That emergency contraception should be a backup or emergency plan, not the primary method, is a useful public health message that is reinforced by the name of the product.
>
> Many therapies in medicine have a sequential component to their indications, i.e., "indicated in patients who have failed ..." While the failure is usually a judgement of the physician managing the patient, the emergency contraception scenario is unusual in that only the individual woman is in a position to recognize when "plan A" has failed and the need for emergency contraception is triggered. Therefore it is of the utmost importance that the individual consumer thoroughly understand the role and timing of this intervention.
>
> I think this name will be helpful to women, and do not believe it will mislead those who, due to cultural factors, do not understand the vernacular usage.

(Woodcock 1999.)

If anything, the labeling approved by FDA for *Plan B®* on a prescription basis convey a scary message, to anyone considering using *Plan B®* as a routine contraceptive, that is not supported by relevant, peer-reviewed literature:

What are the risks and side effects of taking Plan B?

...

Progestrin contraceptive pills used for routine daily contraception can increase your risk for a tubal (ectopic) pregnancy. ...

(*Plan B*® Rx packaging, 2006, p. 2.) The labeling contains numerous other warnings about tubal or ectopic pregnancies and that women should promptly consult health care providers if the symptoms associated with tubal or ectopic pregnancies arise. (*Plan B*® Rx packaging, 2006.) But no relevant, peer-reviewed literature actually supports the conclusion that any use of *Plan B*®, as an EC, as a routine contraceptive, or otherwise, would result in any increased risk of tubal or ectopic pregnancy. (Trussell 2003.)

Regardless, studies of the fear that women would use *Plan B*® as a routine contraceptive have not substantiated that fear. (Ziebland 2005.)

By concluding, in 2005, that there were no safety or efficacy bars to approving *Plan B*® for OTC sale to, and use by, all menarchal females 17 or older, FDA answered its own question later posed in the 6/9/06 denial letter - "Are there any safety or efficacy concerns associated with repeat use of Plan B?" The answer that necessarily flows from this FDA conclusion in 2005 – "No" – remains as clear today as it did then.

The State of Wisconsin requests that FDA promptly address the 5/22/06 Petition, and this 7/24/06 Supplement, and approve OTC status for *Plan B*® and equivalent drugs. The State of Wisconsin stands ready to reply to any specific questions or inquiries that FDA might pose, while noting that it is vital - given the daily adverse consequences resulting from unwanted pregnancies, abortions and unwanted births that could have been avoided through EC access to *Plan B*® - to restrict those questions or inquiries to ones that genuinely matter.

Dated this 24th day of July, 2006.

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