

Micro ICU Project

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Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2001P-0075 ("Switch Status of Emergency Contraceptives from Rx to OTC")

To Whom It May Concern:

It has been reported that the U.S. Food and Drug Administration will decide by Sept. 1 whether Barr Laboratories can sell its morning-after pill brand Plan B without a prescription. The announcement was contained in a letter from Department of Health and Human Services Secretary Michael Leavitt to high-ranking senators.

The purpose of this brief report is to outline important facts concerning Plan B so that the most healthful decision can be arrived at.

A. Typical Use Data is Unavailable

- Dr. Duane Alexander, Director of the National Institute of Child Health and Human Development, states in a letter of November 8, 2004, "We are unaware of any studies of typical use rates for the morning-after pill."
- Typical use includes the phenomenon of non-use after planned use.
- Typical use rates prevail with on-the-shelf distribution.
- Typical use rates of pregnancy reduction are less than perfect rates, and some methods experience a greater decline in effectiveness with typical use than others. For example, relying only on perfect use rates, the male condom and withdrawal methods appear similarly effective, but based on typical use rates, it is evident that the withdrawal method is grossly inferior.

B. The Brand Name "Plan B" is Suggestive of Substituted Reliance

- Substituted reliance occurs when a couple foregoes a traditional "Plan A" method, e.g., the male condom, in favor of "Plan B".
- In a typical use scenario, substituted reliance may also include non-use after planned use, since there may be no follow through on plans to take Plan B.
- The brand name "Plan B" is suggestive of substitution for "Plan A" methods.

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C. The Labeling of Plan B Overstates Average Natural Pregnancy Expectation

- There are four weeks (28 days) in a typical menstrual cycle. On average the two mid-cycle weeks are fertile to the extent that during this time eight out of 100 women are expected to get pregnant after a single act of intercourse, assuming no method is used to reduce pregnancy. From this it follows that even for an idealized morning-after pill no fewer than 92% of uses will be taken for nothing, since pregnancy is a relatively unlikely event at any rate.
- For a real morning-after pill, the fraction of uses that will be taken for nothing is calculated using the formula $N=1-XY$, where X is the fraction of women expected to get pregnant after a single act of intercourse using no method, and Y is the fraction of those pregnancies expected to be reduced using the morning-after pill.
- The prescription label for Plan B states values of $X=0.08$ (8%) and $Y=0.89$ (89%). This implies $N=0.93$, meaning 93% of uses will be taken for nothing. In other words, $1-X$ of the time pregnancy will not have occurred using no method, and $X(1-Y)$ of the time Plan B will not eliminate a possible pregnancy.
- The labeling of Plan B overstates natural pregnancy expectation because the value of $X=0.08$ (8%) is only valid based on the assumption that the act of intercourse takes place during the two mid-cycle weeks, when pregnancy expectation is highest. But averaged over the whole cycle, natural pregnancy expectation is less. In other words, averaged over the whole cycle, $X<0.08$ per act.
- Plan B's label does not limit its indications of use to specific days of the cycle on the basis of varying natural rates of pregnancy expectation. So women using Plan B outside the two mid-cycle weeks will end up taking it for nothing at a rate even greater than the rate of 93% determined for mid-cycle use. By overstating the average rate of natural pregnancy expectation per act of intercourse, Plan B's label implicitly masks the overall rate at which Plan B will be used for nothing.
- Plan B's label does nothing to inform that 100% of uses on infertile days will be taken for nothing. This statistic also includes infertile women.
- Unlike most traditional treatments that are administered based exclusively on symptoms, Plan B is administered merely on the basis of a potential for symptoms, in this case pregnancy. An example is helpful to clarify this distinction. For example, antacids are traditionally administered based on symptoms of indigestion. In contrast, a non-traditional approach would be to take antacids after every meal, based simply on the potential for indigestion. In this scenario, even a highly effective antacid may be taken for nothing, simply because the user may not have experienced indigestion anyway. Plan B's label does nothing to inform of this distinction.

D. Plan B Contains High Levels of Progestin

- One use of Plan B contains the active progestin equivalent (1.5 mg) of a 40-day supply of the progestin-only birth control pill (the "minipill"), marketed under the brand name Ovrette by Wyeth Pharmaceuticals.
- Combined with the potential for sporadic use, there is no indication that this level of progestin exposure will not be harmful to girls and women.

E. “Per Act” Data has been Grossly Misleading to Experts

- Table 1 shows a comparison of rates. The first year rate gives the pregnancies per 100 women expected in the first year of use for the given method when relying on no other method to reduce pregnancy. The per act rate gives the percent of pregnancies that would be reduced when using the given method after a single act of intercourse compared to using no method. In a typical use scenario, the notion of a single use is an average that includes non-use after planned use.

Table 1. Comparison of Rates

	----- Perfect Use -----		----- Typical Use -----		
	First Year Rate	Per Act Rate	First Year Rate	Per Act Rate	Lapse Rate ^e
Condom	2 ^a	99% ^c	15 ^a	91.5% ^c	7-8 %
Withdrawal	4 ^a	98% ^c	27 ^a	83.5% ^c	15%
Diaphragm	6 ^a	97% ^c	16 ^a	91% ^c	6%
Plan B	19 ^b	89% ^b	? ^d	? ^d	?
Preven	38 ^b	75% ^b	? ^d	? ^d	?

References and Notes: a) Contraceptive Use. The Alan Guttmacher Institute. http://www.agi-usa.org/pubs/fb_contr_use.html (accessed 7/30/2005); b) Emergency Contraception. Princeton University. <http://ec.princeton.edu/questions/eceffect.html> (accessed 7/31/2005); c) The method of estimating per act rates from first year rates has been described in a Micro ICU Project report to the U.S. Food and Drug Administration docketed as 2001P-0075-C2044, Vol. 300 (Switch Status of Emergency Contraceptives from Rx to OTC, entered Dec. 22, 2004), <http://www.fda.gov/ohrms/dockets/dockets/01p0075/01p-0075-c002044-01-vol300.pdf> (accessed 7/31/2005); d) Though specific data is unavailable, it is understood that the typical use rates must in any case be worse than perfect use rates; e) The rate of non-use after planned use, discussed later.

- For a pregnancy reduction method, there is an *exponential* relationship between first year pregnancy rates and rates of reduction per act. Mathematically, this is due to the cumulative effect of repetition—in this case, of intercourse—on probability. Statistically, the cumulative effect is irrespective of whether the repetition is individual or collective. In short, to be reasonable, the percent effectiveness of a “per act” rate must be in the 90s with *typical* use; also, as the effectiveness per act tends towards 100%, the added reduction in the first year rate increases exponentially, so that each percentage point added to the per act rate becomes more and more significant as the rate approaches 100%.
- Even though the relationship between first year and per act rates is exponential, the *order* among rates must be the same in either case. Thus, a method with a more favorable first year rate will also have the more favorable per act rate, and vice versa.
- At first glance, the morning-after pill Preven appears to boast a 75% rate of reduction in pregnancy per act with perfect use. But to emphasize the misleading nature of the per act rate, it is noted that even mere typical use the withdrawal method offers a better rate, i.e., 83.5%!
- At first glance, the per act rates of Preven (75%) and Plan B (89%) with perfect use may seem similar. However, based on the exponential relationship between

per act rates and first year rates, it is noted that with perfect use the first year rate of pregnancy for Preven (38 pregnancies per 100 women) is actually twice as high as the first year rate for Plan B (19 pregnancies per 100 women). For this reason, it would be terribly misleading to consumers to equate the two, because one is actually twice as ineffective as the other on a first year basis of perfect use.

Unfortunately, evidence of this grossly misleading situation is observed in the American Medical Association House of Delegates Resolution 443 (A-04), which employs “Plan B” as a generic name to refer equally to the combination pill form (Preven) of the morning-after pill, which combines estrogen and progestin, and progestin-only form (Plan B). In this manner, the Resolution reads: “The Plan B pill is a post-coital contraception method which transiently provides a high dose of (1) combined estrogen and progestin or (2) progestin-only...”¹

- In another example of being grossly misled, a writer for a British periodical, clearly a supporter of the morning-after pill, reports on what she feels is the complete ignorance of people who fail to support it. But sadly unaware that the opposite is true—and that there is a statistical basis for the result—she is left alone to puzzle: “Astonishingly, the greater availability of the morning-after pill over the past five years has had no real impact on teenage conception or abortion rates... And in the 13 local authorities with the highest rates, 11 have seen the numbers of teenage pregnancies increase.”² If this miserable effect is already seen with pharmacist-controlled over-the-counter distribution of the progestin-only morning-after pill, just think of the terrible epidemic of unplanned pregnancies that will result from typical use with open distribution on-the-shelf. Indeed, if even our medical community has had big illusions, just think of the fanciful expectations that boys and ordinary men will have, and the unjust impact it will have on girls and women!
- Chart 1 on the next page gives a graphical comparison of rates. Note especially the exponential nature of the curve. This curve is known as the Pregnancy Reduction Curve.
- Looking at Chart 1, it is clear that even with perfect use the morning-after pill is relatively ineffective. Although typical use rates for the morning-after pill have not been determined or estimated, it is understood that typical use rates are worse than perfect use rates. Therefore, typical use rates for Plan B and Preven will fall back compared to perfect use rates on the Pregnancy Reduction Curve.
- A comparison of perfect use rates focuses more on differences in the effectiveness of the underlying mechanism of pregnancy reduction, whereas typical use rates incorporate the behavioral aspects of non-use after planned use. With perfect use the condom allows two pregnancies per 100 women in the first year of use. Relying instead on Plan B, this figure rises to 19 pregnancies; relying on Preven, it rises to 38 pregnancies. Thus, for a gross comparison, one may ask how many pin pricks it would take to make a condom leaky enough to allow the added 17-36 pregnancies allowed for by perfect use of the morning-after pill.

¹ American Medical Association House of Delegates. Resolution 443 (A-04) Re: FDA Rejection of Over-The-Counter Status for Emergency Contraception Pills. June 12, 2004. <http://www.ama-assn.org/meetings/public/annual04/443a04.rtf> (accessed 07/31/2005).

² The Observer Magazine, Guardian Unlimited, May 15, 2005, Waking Up to the Morning After Pill, by Geraldine Bedell.

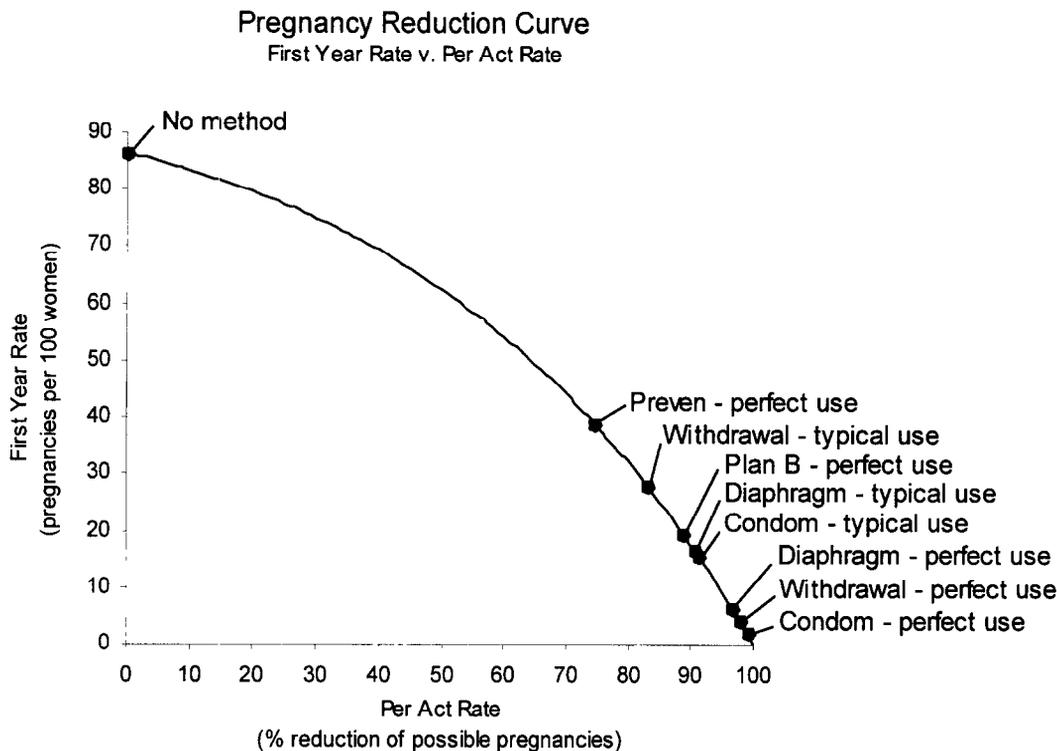


Chart 1. First Year Rate of Pregnancy v. Per Act Rate of Pregnancy Reduction

F. Post-Coital Methods are Contraindicated for Typical Use

- As mentioned earlier, typical use rates prevail in an on-the-shelf environment. Thus, the move from prescription use to over-the-counter use must be viewed as a move towards typical use rates and away from perfect use rates. Although prescription use does not guarantee perfect use, it is reasonable to anticipate that typical use will add greater departure from perfect use rates when compared to rates observed in the context of strictly regulated prescription use.
- When properly understood, “per act” rates are actually quite informative. For example, with perfect use the withdrawal method reduces roughly 98% of the pregnancies expected using no method. But with typical use this figure falls back to 83.5%. With some approximation, typical use averages instances of perfect use with times of non-use after planned use. The fraction of times L (“ L ” is for “lapse”) in which non-use occurs can be calculated as $L=(P-T)/P$ where P is the perfect use rate per act and T is the typical use rate. For typical use of the withdrawal method, the lapse rate is 15%. In other words, the typical use rate for the withdrawal method can be viewed as a combination of perfect use 85% of the time (at the perfect use rate) along with non-use 15% of the time (at the rate of zero). In contrast, the lapse rate for typical use of the condom is roughly half of that for the withdrawal method. A plausible explanation is that the condom is a pre-coital method, whereas the withdrawal method is an inter-coital method—its practice takes place during intercourse. Arguably, it makes better sense to take care of matters *before* intercourse begins, rather than to chance matters later on. This perspective appears to be confirmed by the above comparison.

- In contrast to the condom, which is a pre-coital method, and the withdrawal method, which is an inter-coital method, the morning-after pill is a post-coital method—its practice takes place after intercourse. Since attitudes about responsibility before intercourse can change widely after intercourse, and since behaviors after intercourse are not readily predictable, there is a notable risk of non-use after planned use involved when relying on post-coital methods in a typical use scenario. Because the risk of non-use after planned use distinguishes typical use from perfect use, it cannot be overlooked or underestimated.
- For example, a girl may be grounded by her mother after staying out too late with her boyfriend. But in this scenario, the girl may be afraid to tell her mother that she needs permission to go out and purchase Plan B. This is because she knows her mother will be upset to find out she had intercourse.
- For example, a boy may hear that the morning-after pill can be taken within three days (72 hours) after intercourse. He may then tell his girlfriend to forestall plans to take Plan B, in case they decide to have intercourse again within the three day period taken from when the first instance of intercourse occurred.
- For example, a man may convince a girl to let him forget condom use because he says he will pay for Plan B when he gets paid tomorrow. But he does not show up with the money or call her, and she gets upset and does not take Plan B on her own. This is an example of non-use after planned use following substituted reliance. In this case, the couple experiences the rates of pregnancy and sexually transmitted diseases corresponding to the use of no method at all!
- An informative question to ask is, “What rate of non-use after planned use in a typical use scenario would be required to make a morning-after pill less effective than typical use of the condom, even if it were an idealized morning-after pill that offers a per act rate of pregnancy reduction of 100% with perfect use?” The answer is a lapse rate of 8-9% or greater. The lapse rate is the rate of non-use after planned use. In other words, even for a morning-after pill that is 100% effective with perfect use, a lapse rate of 8-9% or greater would render it less effective with typical use than the male condom is with typical use.
- Although typical use rates have not been estimated for the morning-after pill, there are a number of reasons why the expected lapse rate should be anticipated to be much greater than 8-9%. For one thing, the morning-after pill is a post-coital method. Procrastination, forgetfulness, and social and economic reasons will all come into play. It is already seen that the withdrawal method has a much higher lapse rate than the condom, presumably because it is not a pre-coital method. Thus, planning to take care of matters after intercourse introduces notable risks, because those plans may succumb to non-use afterwards. An additional source includes the fact that the morning-after pill can cause sickness. This in turn can create negative reinforcement, leading to non-use after planned use at future occasions. It is noted that the long term effect of negative reinforcement has not been explored. Other problems include economic expense, the burden of access, and worries that the pills will probably be used for nothing anyway since in itself pregnancy is a relatively unlikely event. Another problem concerns matters of conscience since some authorities believe the morning-after pill has a possible concepticidal component. Concepticide is the taking of the life of a conceptus. All of these problems will combine to inhibit use even despite planned use.

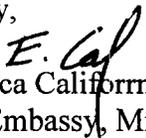
- Needless to say, many drugs can be used with the desired results. But this in itself does not provide sufficient grounds for over-the-counter status. For if the mere possibility that someone out there may be able to use a drug with the desired results in some particular situation were the only condition for over-the-counter status, then no drug would require a prescription! Instead, we must duly account for typical use and the overall effects on the population as a whole.

G. Conclusions

- It is unconscionable to recommend a drug for over-the-counter use without a reasonable analysis of typical use.
- In the future, the U.S. Food and Drug Administration should require experts to state whether they have personally made a direct analysis of relevant matters, or whether they are relying indirectly on their impressions of the conclusions of others, which they themselves have not directly analyzed. For, in the present case, one can only assume that a general lack of direct analysis is responsible for the greatly overlooked problems associated with the morning-after pill.
- The application of Barr Laboratories to switch the status of Plan B from prescription use to over-the-counter use should be denied.

It is hoped that this outline will be of help in your review.

Sincerely,


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