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. 2005N–0345 and RIN 0910–AF72 ("Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-The-Counter Drug Product")

To Whom It May Concern:

The Micro ICU Project is an interdisciplinary project in micro-biomedical engineering working to create neonatal-type incubators for pre-implantation infants using microfabrication technology, a field that has considerably advanced in recent years.[1-2] Such incubators have been dubbed "micro ICUs" (micro intensive care units). As the world leader in developing incubator systems for the patient care of pre-implantation infants using microfabrication technology, the Micro ICU Project opposes products such as the morning-after pill that may harm a pre-implantation infant.

In a statement of Aug. 26, 2005 ("FDA Takes Action on Plan B"), FDA Commissioner Lester M. Crawford raises important questions concerning the impact that liberalized distribution of the morning-after pill "Plan B" will have on public health. The Commissioner is thanked for the opportunity to comment on these questions.

In the language of the FDA, a "molecule" refers to a composition of matter comprising a drug treatment. The FDA has approved two different molecules for prescription use as a morning-after pill. The molecule known by the brand name Preven consists of a combined estrogen and progestin composition. The molecule known by the brand name Plan B consists of a progestin-only composition.

The two molecules differ widely in their side effects and effectiveness. The short term side effects of Preven are significantly more unpleasant than those of Plan B. Regarding differences in effectiveness, according to Dr. James Trussell and colleagues at Princeton University, using no other method if women made perfect use of Preven after

[1] Californiaa, E. Method of monitoring the body temperature of human embryos and hatchlings. U.S. Patent No. 6,694,175. Feb. 17, 2004. Prior to this teaching practitioners failed to grasp the biophysical distinction between an incubator thermostat reading and the patient's own body temperature!

[2] Californiaa, E. Thermoregulation of human embryos and hatchlings in a prenidial incubator using infrared microthermography. Trends in Reproductive Biology. 2005;1:63-67 (in press). A preprint of the article is available online at http://www.juridic.org/images/preprint.pdf. This is the founding paper on the subject of competent incubator care for pre-implantation infants, and it offers ethically relevant insights.

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every act of intercourse, 38% would experience a post-implantation pregnancy in the first year of use, compared to half as many (19%) using Plan B.[3]

Barr Laboratories, which owns marketing rights to both molecules in the United States, quietly withdrew Preven from the U.S. market approximately one year ago. The exact reasoning behind this decision has not been publicly disclosed.

The FDA is cautioned to recognize that whatever the reasons Barr Laboratories may have had for withdrawing prescription use of Preven, the FDA's own analysis failed to anticipate these reasons in allowing prescription use of Preven in the first place. For unlike the FDA, it appears even Barr Laboratories eventually realized that Preven should not be on the U.S. market. In view of these developments the importance of caution should not be underestimated because the FDA has a responsibility to avoid making the same mistakes with Plan B such as were evidently made with Preven.

Although questions raised by Commissioner Crawford in his recent statement do recognize the need for caution, they do so only in minor part. For those questions do not make available for comment the major determination by the Center for Drug Evaluation and Research (CDER)—namely, that Plan B is safe as an over-the-counter product for women who are 17 years of age and older—as if that finding were a done deal. In an effort to promote thorough responsibility, and to invite recognition for the possibility of oversight, the Commissioner is strongly urged to open up a lengthy period of comment so as to enable an open, public process to respond to the credibility of this finding.

The criticism that may be offered for such a finding is so strong and certain that one is wary that its expression may be mistaken for an *ad hominem* attack. For this reason, it seems preferable to introduce the possibility of such criticism indirectly in the form of a couple of questions.

1) Would it be unprofessional for a medical body to employ the brand name of one molecule as a generic name for two different molecules?
2) As consumers begin to learn that one molecule is more effective than another, would it serve to defraud consumers for a medical body to employ the brand name of the more effective molecule as a generic name for both?

In this case, the medical body in question is the American Medical Association (AMA) House of Delegates. Though integrity demands that both of these questions be answered in the affirmative, the AMA demonstrated unprofessional resolve by employing the brand name "Plan B" as a generic name to refer to both the combination and progestin-only molecules of the morning-after pill. In evidence of this act of consumer fraud, AMA House of Delegates Resolution 443 (A-04) reads in part: "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..."[4] Note that Barr Laboratories voluntarily withdrew Preven from the U.S. market shortly after the AMA resolution. From the perspective of social analysis, it stands to reason that the members of the AMA House of Delegates did not make credible analysis of either morning-after pill regimen, else presumably they would not have made the mistake of equating the two different

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[3] "How effective is emergency contraception?" http://ec.princeton.edu/questions/eceffect.html

[4] 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

molecules using the brand name of the least ineffective of the two. If the credibility of a medical body as distinguished as even the AMA can be drawn into question, certainly the conclusions of the CDER should not be made exempt from public comment.

At any rate, the questions raised by the Commissioner in his recent statement are pertinent, and he should be commended for bringing them to our attention. But his approach to the question of whether the same molecule can exist in both prescription and over-the-counter forms for the same indication still deserves a note of criticism. For in accepting the finding of the CDER that Plan B is safe as an over-the-counter product for women who are 17 years of age and older, he appears to have contradicted his own question by overlooking the fact that Barr Laboratories' Plan B is the same molecule as Wyeth's prescription-only brand Ovrette, but in a different dosage. For this reason the question should be broadened to address whether prescription and over-the-counter forms of the same molecule can exist to straddle different dosages and/or ages.

Each of two tablets in the Plan B regimen contains the active progestin equivalent of 20 tablets in the Ovrette regimen—a 40 tablet total. Both regimens are indicated by their labels to reduce unplanned pregnancy. Both regimens suggest suppressing ovulation as a mode of action. The molecular equivalence is confirmed by Dr. Trussell and colleagues at Princeton University, who recommend substituting 40 tablets of Ovrette for the two tablets of Plan B.[5] So why would the FDA accept the finding of the CDER that the same molecule is safe in high dosage form as an over-the-counter product for women who are 17 years of age and older, but not in low dosage form? Since it is particularly odd to conclude that the higher dosage of the same molecule should exist in over-the-counter form and the lower dosage in prescription form, by circumstances alone one must conclude that the determinations of the CDER are highly questionable. For although the FDA might consider whether different dosages can be straddled, it is hard to believe that the *higher* dosage would be the one relegated to over-the-counter status!

It is noted that important clarification is needed regarding the Commissioner's recent statement. The statement reports that the CDER determined that Plan B is safe as an over-the-counter product, "but only for women who are 17 [sic] years of age and older." If this is not a misprint, then the Commissioner appears to have independently concluded that Plan B is safe for women who are specifically 16 years of age. For according to the Commissioner's statement, the FDA is now considering whether to allow over-the-counter use of Plan B for women as young as 16 years of age and older, rather than for women at least 17 years and older.

In considering whether Plan B should be made available in age-straddled prescription and over-the-counter forms, the reasoning the FDA appears to have used is that 1) the research on Plan B has left out women of the younger age group, 2) the CDER is satisfied with the research regarding the older age group, and 3) the line between the younger and older age groups should serve to distinguish prescription and over-the-counter forms. Of note, comments C 2044 and C 2092 of the Micro ICU Project in Vol. 300 of Docket No. 2001P-0075 demonstrate with absolute certainty the invalidity of the CDER's finding. But even aside from this paramount issue, an unqualified assumption is made in presuming that the age differences between research groups should automatically draw the line between prescription and over-the-counter forms.

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[5] "Twenty-one brands of oral contraceptives that can be used for emergency contraception in the United States." http://ec.princeton.edu/questions/dose.html

This is an extremely important but subtle point. The CDER did not specifically validate the safety of Plan B for women who are, for example, 17, 18, and 19 years old. Instead, these women were included in an overall group, and the CDER was satisfied with the results for the group as a whole. But the CDER failed to investigate the possibility that unacceptable values for the lower aged women in the group (e.g., women aged 17-19) may have averaged in with better values for older women in the group. For this reason, even if the results for the overall group had been acceptable, there would still be the possibility that the age limit used to distinguish prescription and over-the-counter forms may still need to be set higher (e.g., to 20 years of age) than the age of the youngest members of the group. This means even if the FDA were to accept the CDER's finding that liberalized distribution of Plan B is safe for older women, it would still be scientifically premature to define a specific age range of safety.

Yet if the FDA is to consider age-straddling the availability of a given molecule between prescription and non-prescription forms, then the issue of age specificity is of critical importance. However, at present the CDER lacks sufficient age-specific data to make such a determination regarding Plan B. Instead, for the most part the CDER only has data to rely upon that has been averaged over a range of ages regarding women in the group 17 years and older. No age cutoff has been scientifically established within the group of women 17 years and older. It is spurious to rely on the lowest aged members of that group as the cutoff point without detailed, age-specific data to back it up.

As a word of extreme caution, it may be recalled that after Sweden introduced liberalized distribution of the morning-after pill in 1995, teen abortions rose an epidemic 32% between 1995 and 2001. As reported by a researcher at the Karolinska Institute in Stockholm, "Teenage abortion rates have gone up, from 17/1000 in 1995 to 22.5/1000 in 2001. Genital chlamydial infections have increased from 14,000 cases in 1994 to 22,263 cases in 2001, 60% occurring among young people, and with the steepest increase among teenagers."[6] As the American Association for Pro-Life Obstetricians and Gynecologists (AAPLOG) points out in comment C 2042 in Vol. 295 of Docket No. 2001P-0075, "It would seem to us that the association of an increased induced abortion rate among teens corresponding to the availability of OTC EC [over-the-counter emergency contraception] in Sweden is a very red flag." The basis for the predictable effect of liberalized distribution is examined statistically in the above-stated Micro ICU Project comments. In a nutshell, the morning-after pill is ineffective in a liberalized atmosphere. This problem appears especially evident in teenagers, and not just in women under 16 years of age. Though the average typical use patterns of women may improve with age, women of any age group are not immune to the ineffectiveness based on statistical reality.

Even if the FDA were to attempt age-straddled distribution of the morning-after pill between prescription and over-the-counter forms, there is no doubt that some of those eligible for non-prescription Plan B would in effect become the prescribers to ineligibly young women. Consequently, the FDA must question the ability of these would-be physicians to assess the risks to their would-be patients. The enforceability of discipline in this regard is evidently very low, for even a number of states have disregarded the process of drug evaluation by going ahead of the FDA, on their own incentives, and allowing over-the-counter distribution of Plan B to women of any age. If even a number

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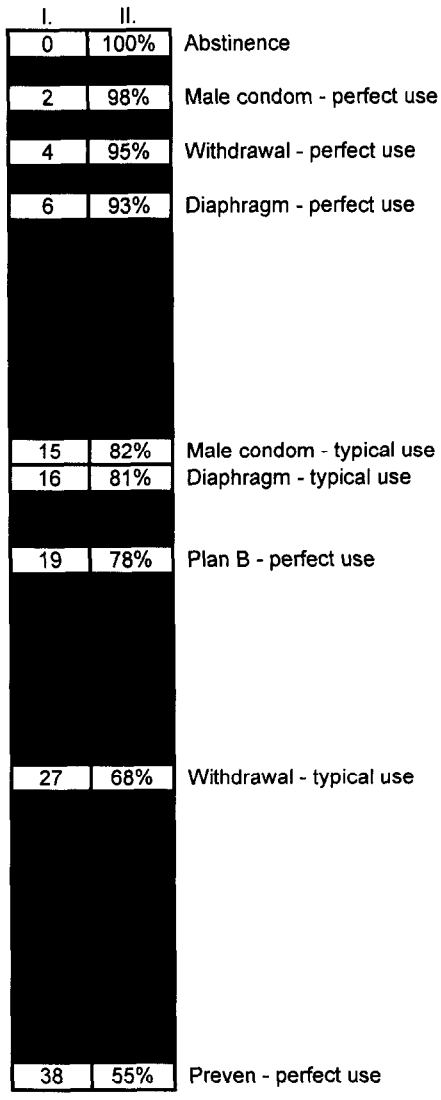
[6] Edgardh, K. Adolescent sexual health in Sweden. Sex Transm Infect. 2002;78:352-356. Online at: http://sti.bmjjournals.com/cgi/content/full/78/5/352

of states have disregarded discipline, the same problem can certainly be expected from individuals, especially since public opinion is volatile in the United States when it comes to reproductive rights issues.



Pregnancy Reduction Totem Pole

Col. I: Pregnancies per 100 women in the first year of use are paired with given methods of reducing pregnancy. Data from the Alan Guttmacher Institute and Not-2-Late.com.
Col. II: Percentage of possible pregnancies reduced by the given method in the first year of use, assuming 85 pregnancies per 100 women in the first year using no method of reduction.
Important: These percentages calculated for the first year of use are not to be confused with reduction percentages determined with respect to a single act of intercourse.
Note: The totem pole has been truncated. At the bottom of the full totem pole is "No method" with its corresponding 85 pregnancies per 100 women in the first year—a 0% reduction.

In considering whether would-be physicians will be able to assess the risks to their would-be patients, it suffices to show that even distinguished medical bodies have been unable to appreciate the risks correctly. In other words, if even top medical bodies throughout the world have been unable to appreciate the risks, then clearly street physicians will be unable to appreciate the risks for their ineligibly young patients. To give an example, the Karolinska Institute is Sweden's top medical institute and is highly respected throughout the world. As a notable distinction, members of the Institute determine who will receive the Nobel Prize for medicine. But tragically, the Institute decided in favor of what became Sweden's policy in 1995 of instituting liberalized distribution of the combined estrogen and progestin molecule of the morning-after pill, which in the United States is marketed under the brand name Preven.

Examining the "Pregnancy Reduction Totem Pole" on the previous page, given that the molecule branded as Preven in this country is at the low end of the totem pole even with perfect use, it is not surprising that liberalized distribution resulted in an epidemic of unplanned pregnancies in Sweden. This is especially true since typical use rates will be much worse than perfect use rates. In 2001 Sweden liberalized distribution of the progestin-only molecule marketed in this country as Plan B. Yet unlike the voluntary actions of Barr Laboratories in this country regarding its brand Preven, Sweden did not remove the combined estrogen and progestin molecule from the Swedish market despite its greater ineffectiveness. This goes to show that even a medical body as distinguished as the Karolinska Institute did not appreciate the risks that liberalized distribution of either morning-after pill would have on public health. The miserable consequence, as is now known, was an epidemic of unplanned pregnancies and sexually transmitted diseases that proper discipline in this country would do well to avoid.

In assessing the epidemiology of this tragedy, a strong driving force was provided by none other than the admirably strong intentions of Swedish teens to take responsibility for their fertile capacity by listening to authorities who offered them the morning-after pill as if a respectable new means. But like a dog being cruelly made to chase its own tail in a miserably humiliating fashion, the more they relied upon the morning-after pill the higher their rates of unplanned pregnancy and abortion went up—and as their rates went higher, their authorities became all the more determined to impose the morning-after pill on them. Because this is truly one of the cruelest tragedies in world memory, even though it did not transpire in this country the U.S. Congress should investigate it.

Other countries, such as England, have experienced similar results, though such experiences have been largely damped compared to the Swedish tragedy due to relatively tight controls on the over-the-counter distribution. Noted is that concerned citizens have been similarly bewildered by the results. For example, as one bewildered advocate of the morning-after pill writes for a British periodical, "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."[7] So clearly if the FDA were to allow older women to get Plan B over-the-counter, they would be unlikely to understand the tragic risks posed in giving it to ineligibly younger women, since even distinguished medical bodies and concerned citizens remain bewildered.

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

At the heart of the bewilderment appears to be an inability to appreciate three considerations: 1) the exponential (i.e., non-linear) distinction between first year rates and per act rates, 2) the distinction between perfect use and typical use, and 3) the problem of substituted reliance. In addition to these considerations, it is also helpful to appreciate the meaning of acquiescence and coitivity ("co-it-TIV-it-t").

Coitivity is the rate at which a sexually active woman experiences coitus. Acquiescence is the rate at which non-sexually active women become sexually active. To understand the importance of coitivity, suppose Method X reduces a *greater* percentage of possible pregnancies per act than Method Y, but Method X seems so sophisticated and wonderful that users increase their coitivity in relationship to its use. On this basis, first year pregnancy rates for users of Method X could actually be *higher* than rates for Method Y. When it comes to teen sexuality, this problem presents a special concern because individual teenagers may be especially subject to increases in coitivity inasmuch as their comparatively low coitivity rates leave them plenty of room for increase. To understand the importance of acquiescence, suppose Method 1 reduces first year pregnancy rates for its users to a greater extent than Method 2 does. But the boys hear about Method 1 and think science has solved everything, so they put more pressure on the girls to acquiesce. Even though Method 1 has lower first year pregnancy rates per user than Method 2, popularization of Method 1 could actually result in an increase in the total number of pregnancies in the population, based on increased acquiescence.

When it comes to the problem of substituted reliance, even the brand name "Plan B" is cleverly suggestive in the marketing sense of substitution for traditional "Plan A" methods of pregnancy reduction. However, advocates note that studies submitted to the FDA on this subject found no decrease in the use of traditional methods. Actually, what those short studies found was a tremendous *increase* in the use of traditional methods. Obviously, what is happening here is that researchers have failed to distinguish between the short term effects of counseling on the use of traditional methods from the impact of Plan B on the problem of substituted reliance. For by introducing a variable that will not be present in over-the-counter use, namely, counseling, researchers failed to control the variable they attempted to study. However, since literacy tests show clearly that many women fail to grasp the suggestion that Plan B should not be relied upon in place of "Plan A" methods, there can be no question that substituted reliance is a major problem with Plan B. The rate of sexually transmitted diseases experienced in Sweden is clearly a "red flag" as to what can be expected from liberalized distribution. But even the literacy studies mask the overall problem, because in many situations it is actually the male's impression that is most controlling, not the female's. For this reason, the literacy of males should also have been tested, to learn their thoughts on reliance possibilities.

In a table entitled "Pregnancy Rates for Birth Control Methods", the FDA defines "typical use" to include non-use after planned use.[8] Noted is that perhaps "typical reliance" would be better, since in some cases there is no actual use. Perfect use includes times of correct use and excludes times of non-use and times of incorrect use, whereas typical use includes all of these times. Non-use means couples and individuals who consider themselves users of a method may lapse in its use. Typical use rates have not been estimated for either Plan B or Preven.

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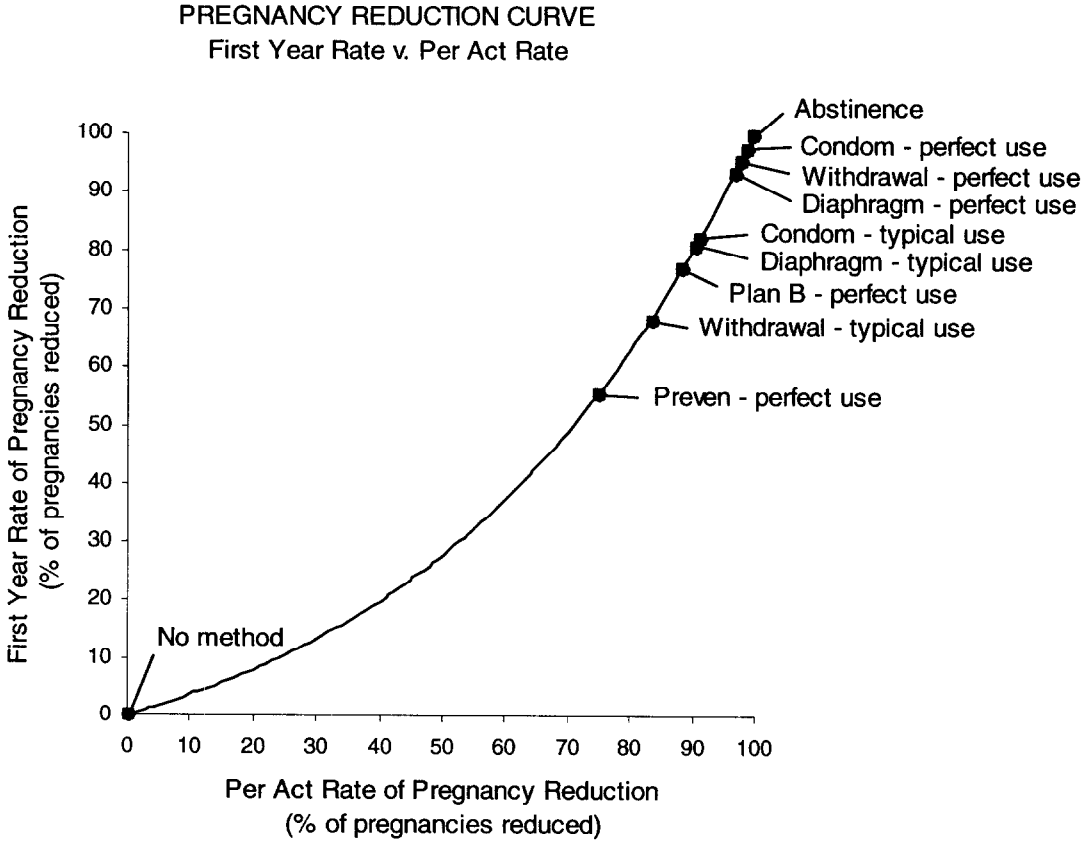
[8] U.S. Food and Drug Administration. Center for Devices and Radiological Health. Uniform Contraceptive Labeling. CDRH Facts on Demand Document Shelf No. 1251. Issued July 23, 1998. Table prepared by FDA: 5/13/97, revised 9/17/98. http://www.fda.gov/cdrh/ode/contrlab.pdf

Suppose every time a woman seeks Plan B her doctor administers it to her according to the prescription label and makes a house call to ensure she takes the two doses. It would be a mistake to assume this woman will necessarily experience the rate of pregnancy associated with perfect use. For example, suppose the woman lets her boyfriend skip condom use thinking she will go to the doctor the next day. But the next day she forgets about her plans. In such a case she exhibits non-use after planned use, even though on other occasions she follows through and goes to her doctor. This means her rate of pregnancy will be higher than the perfect use rate. We cannot assume prescription use necessarily implies a perfect use scenario. Instead, even prescription use can include non-use after planned use. Thus, the FDA is faulted for allowing even prescription use without an estimate of typical use rates; moreover, it is unconscionable to consider over-the-counter use without a typical use estimate.

Comments C 2044 and C 2092 of the Micro ICU Project in Vol. 300 of Docket No. 2001P-0075 have explained the exponential difference between first year pregnancy rates, known elsewhere as "first year contraceptive failure rates", versus "per act" rates of pregnancy reduction, meaning per act of intercourse. For example, the difference between an 89% per act rate and a 75% per act rate is actually a two-fold increase in terms of first year pregnancy rates; the difference between per act rates of 99% and 97% is a three-fold increase in first year rates; and the difference between per act rates of 99% and 75% is a nineteen-fold increase in first year rates. The following graph depicts this exponential relationship using the data of Table 1 in comment C 2092. As explained in comment C 2044, the form of this graph differs from Chart 1 in comment C 2092 in that the first year rate is expressed as a percentage of pregnancies reduced, on the basis of an expected rate of 85 pregnancies per 100 women in the first year of using no method.



It may be noted that the typical use rate for the withdrawal method of 27 pregnancies per 100 women in the first year of use is taken from the Alan Guttmacher Institute, which relied on a report from Fu et al.[9] In contrast, Dr. James Trussell, whose work the FDA relied upon to compile its table entitled "Pregnancy Rates for Birth Control Methods", states a typical use rate of 19 pregnancies per 100 women.[10] Trussell's own rate for typical use of the withdrawal method is identical to the perfect use rate he and his colleagues have determined for Plan B and which the FDA relied upon. Typical use rates for Plan B will be worse than perfect use rates.

In contemplating the extent to which typical use rates will worsen compared to perfect use rates, the rate of non-use after planned use L ("L" is for lapse) and incorrect use M ("M" is for misapplication or misuse) must be considered. With relatively straightforward methods such as the condom or withdrawal methods, it may be valid to presume that M is relatively small. This may also be the case with methods such as the diaphragm, given that patients are instructed to proficiency on correct use. In contrast, the use of a method such as Plan B is not so straightforward and therefore may involve higher rates of M, particularly in the context of over-the-counter use. This appears to have been confirmed by literacy studies and other experience. Another problem is that uneducated women with over-the-counter access may fail to propagate accurate information about use when in effect "prescribing" Plan B to ineligibly younger women. Thus, in estimating the typical use rate, it is reasonable to expect that the value for M will be unusually large for the morning-after pill compared to a method like the condom.

Comment C 2092 of the Micro ICU Project in Vol. 300 of Docket No. 2001P-0075 has considered the increasing trend of the lapse rate L associated with a comparison of pre-coital, inter-coital, and post-coital methods of pregnancy reduction. Inter-coital means the practice of the method takes place during intercourse. Noted is that the lapse rate for the withdrawal method—an inter-coital method—is roughly twice as high as that for the condom—a pre-coital method. Even without having the results from Swedish experience before us, it stands to reason that the lapse rate for a post-coital method will be even higher still, simply because behaviors after intercourse can differ widely compared to behaviors planned for before intercourse, based on a large variety of circumstances, some of which are not under individual control. Thus, in estimating the typical use rate, values for both M and L will likely be much larger for a post-coital method such as Plan B compared to values for other methods. <u>This means Plan B's typical use rate will fall back dramatically compared to the perfect use rate, which is already on the low end of the scale</u>.

In addition to failure to estimate the typical use rate, it appears the FDA has not fully applied the meaning of typical use. For example, it has been mistakenly reported that the high price of Plan B will inhibit reliance. On the contrary, what the high price means is that women <u>planning to rely</u> on Plan B will be less likely to experience actual use. One thing is reliance; another thing is the experience of use. The high price will serve to increase the typical use occurrence of non-use after planned use. Another factor concerns negative reinforcement. Since Plan B and Preven offer unpleasant side effects

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[9] Fu, H., Darroch, J.E., Haas, T., and Ranjit, N. Contraceptive failure rates: new estimates from the 1995 National Survey of Family Growth. Fam Plann Perspect. 1999;31:56-63.

[10] Trussell, J. Contraceptive efficacy. In Hatcher, R.A., Trussell, J., Stewart, F., Cates, W., Stewart, G.K., Kowel, D., and Guest, F. Contraceptive Technology: 17th Rev. Ed. New York, NY: Ardent Media, 1998.

as well as problems of conscience, past users may be inhibited from following through on future plans of use. This highly important area has not been investigated.

In addressing the issue of safety, it is imperative to apply a coherent standard. For example, it would not be "safe" for teens to be unwittingly exposed to increases in unplanned pregnancy and sexually transmitted diseases after being misled to believe that Plan B is effective. It may be noted that FDA research on sexually transmitted diseases has been obscured by the short term effect of counseling, which not only showed an increase in the use of traditional methods, but preference for the condom. For this reason, unlike the real-life results experienced in Sweden, it is not surprising that these studies appear to indicate no increase in sexually transmitted diseases.

In addressing the issue of safety, it is imperative to apply a coherent standard. Some contend that Plan B is as safe as aspirin. But if anything is "as safe as aspirin" it must be aspirin itself. So in consideration of the drug safety issue, suppose a woman visits her doctor and says, "Sometimes I have trouble with my partner and he gives me a headache. So I decided to take 20 aspirin, followed by another 20 aspirin 12 hours later—not because I had a headache, but because I had contact with him and I was afraid I might get a headache later on." Obviously it would not be reasonable for the FDA to conclude that this practice is safe for women simply because millions of women have used aspirin safely. Yet the FDA has adopted the similar assumption that Plan B is safe simply because it believes many users of Ovrette have been largely free from safety problems. However, to review the above comparison, each tablet of Plan B contains the active progestin equivalent of 20 tablets of Ovrette—a 40 tablet total.

To review the analogy further, women are instructed to take this phenomenal dosage of progestin, not because they know they have an impending pregnancy to avoid, but simply out of fear that a possible pregnancy might be on their horizon after contact with their partners. Comment C 2053 of the Micro ICU Project in Vol. 300 of Docket No. 2001P-0075 examines the inefficiency of this practice, and Comment 2092 of the same docket elaborates on it further. In a nutshell, with perfect use limited to the two mid-cycle weeks, 93% of the time a woman will take Plan B for nothing. Looked at another way, with perfect use limited to the two mid-cycle weeks, for every 14 times women take Plan B, one pregnancy will have been reduced. This does not mean one pregnancy in net; it simply means to reduce a single pregnancy at all. By comparison this total represents the progestin equivalent of taking 1½ years worth of Ovrette. Outside the two mid-cycle weeks, when fertility is greatly decreased, the figure of inefficiency will be even higher still, and the sky is the limit regarding women who are infertile to begin with. With typical use, the inefficiency will climb even further due to misapplication or misuse. Despite this phenomenal use of progestin, net pregnancy rates will actually increase due to the typical use ineffectiveness of the regimen under liberalized distribution.

Notably, AMA Resolution 443 (A-04) begins by saying that widespread use of the morning-after pill could reduce 1.7 million unplanned pregnancies in the United States annually. According to the Alan Guttmacher Institute, there are about three million unintended pregnancies in the U.S. annually. So reducing 1.7 million unplanned pregnancies would mean a 57% annual reduction. But even with perfect use of Preven, assuming no increase in coitivity or acquiescence, only 55% of pregnancies would be reduced annually—a very low value compared to perfect or even typical use of other methods. In other words, even if the definition of "widespread use" meant that all women who are not planning to get pregnant will make perfect use of Preven after every act of

intercourse in addition to their usual methods, with absolutely no increase in coitivity or acquiescence, the AMA's expectations still would not be fulfilled!

Instead, as has been evidenced in Sweden, something along the lines of the complete opposite happens. Women do not use the morning-after pill in addition to their usual methods, they substitute it for their usual methods. Instead of making perfect use, they exhibit non-use after planned use in a typical use scenario. Also, the rates of coitivity and acquiescence increase. And so with liberalized distribution the predictable result is an epidemic of unplanned pregnancies, with no net reduction in unplanned pregnancies at all. So clearly the members of the AMA House of Delegates did not make a credible analysis of the morning-after pill in offering us their consensus.

The bias physicians have for presuming the effectiveness of pills predates the double-blind study. Indeed, it is with great irony that the logic of the double-blind study still escapes the medical community even today. For example, a research director at a psychiatric medical association, responding to researcher claims that antidepressants do not work, was recently quoted in the news as saying, "The interesting issue is that it is now medical malpractice not to treat major depression with medication. If in fact there were nonsignificant differences (between antidepressants and placebo), that would not be the standard of care."[11] But contrary to this assumption, if a trial medication can be distinguished from a placebo based on its spectrum of side effects, doctors may single out the trial medication and apply the biased presumption that the pill works.

Identifying positive results for a trial medication as often as a placebo signals problems in a study of its effects on a condition unlikely to improve spontaneously. But logically the reverse is not true: Choosing a trial medication over the placebo does not imply it works! For example, doctors may have been alerted to the trial medication's identity based on the side effects it produces; in turn they may have associated positive results with it, due purely to their biased belief that the "real" pill works.

A breed of psychotropic drugs has capitalized on this design flaw in drug tests, which allows various useless drugs to pass their clinical trials. These psychotropics have withdrawal patterns, the symptoms of which are relieved by re-administering the drug. Mental illnesses, anxiety disorders, and learning difficulties have been targets because the symptoms of withdrawal mimic the disorder under treatment. Unaware that this is the case, doctors, patients, and their families may become loyal to the drug once they witness its apparent power to relieve symptoms. In other words, it appears to them that the drug is relieving symptoms of the disorder under treatment, when really it is relieving symptoms caused by an attempt to withdraw from the drug. This side note underscores the need for the medical community to review its undisciplined infatuation with pills.

No doubt, many a young man would be infatuated with the notion that science had somehow created the chemical equivalent of the "undo" button on your computer in pill form—and that it sends the stork packing back to the cabbage patch, with no pregnancy or abortion to worry about. Two weeks away from his high school graduation, a young man with right-wing roots responded with a gleam in his eye to let it be known where even he departs from traditional conservatives, saying, "But the morning-after pill—I think that's a really good thing." It did not take much to remember what it was like to be 18 years old, nor did it take much to realize that the morning-after pill is poised

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[11] Reuters Health, "Antidepressant Efficacy May Be Overblown – Experts", by Karla Gale. Jul. 15, 2005 (correction Jul. 19, 2005).

to create an epidemic of unplanned pregnancies. More so than any data on the morning-after pill, the gleam in his eye provided the best tip on the epidemic to come.

The infatuation with pills is so strong in our medical community that it may be virtually impossible, psychologically, to break the biased belief that the pills work very well and that a whole consensus of experts has already validated them.[12] So to get the point across concerning the dangerous ineffectiveness of Plan B in a liberalized scenario, it may be necessary to use a different example of a post-coital method—namely, one that does not involve any kind of pill. For example, Casanova's lovers are reported to have used a lemon juice douche post-coitally to reduce pregnancy.

In general, if people have intercourse independently of their knowledge of a given method or its availability (i.e., knowledge of the method does not increase coitivity or acquiescence), then the use of the method will—under controlled circumstances—serve to reduce some amount of pregnancy compared to using nothing at all. The slight of hand played on the mind in considering a post-coital method is that the notion that intercourse has already occurred creates a sense of comparison to using nothing at all. For example, if a woman experiences condom breakage, and then she uses a lemon juice douche in response to the problem, some might conclude, "It's better than nothing at all." But what happens when the method, like the morning-after pill, is ineffective compared to other methods on the totem pole? And what happens if the method is advertised like something really great—something that even Casanova would use?

What happens is that when the boy forgets his condom, and the girl does not want to give him a hard time, she will think it is okay just to use "that lemon juice thing" after sex. In pill form, this is what happened in Sweden. Teens started relying on "that morning-after pill thing". They thought it was something great that doctors and scientists had recently invented to keep them from getting pregnant. Instead, they ended up with an epidemic increase in unplanned teen pregnancies and sexually transmitted diseases.

If one is not to be terribly naive it must be admitted that there are those among us who reap their fortunes of social, political, and financial currency based on women's dependency on abortion. Looked at from a business perspective, the most significant statistic relating to the abortion industry is the annual number of abortions. According to the Centers for Disease Control and Prevention (CDC), "Overall, the annual number of legal induced abortions in the United States increased gradually from 1973 until it peaked in 1990, and it generally declined thereafter."[13] As one can imagine it would for any business, a downward trend in abortion may have sounded the alarm for those whose very fortunes rely on the dependency women have on abortions. This consideration may provide insight into what otherwise might seem like a puzzling contradiction.

Namely, reproductive choice advocates like Planned Parenthood waited until 1994—amid declining abortion rates—to push for urgent FDA backing of the morning-after pill, as if America's best kept secret. But the "secret" was known since the 1960s. So if reducing unplanned pregnancies was truly their aim, and they truly believed the morning-after pill would have this effect, why didn't they push for it back when abortion rates were increasing? But on the other hand, if they knew the morning-after pill would actually increase abortion rates like it did in Sweden, this might solve the puzzle. For if

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[12] If one reviews *Sell v. United States*, 539 US 166 (2003), it is evident that our legal system has had such an infatuation with pills and those who prescribe them that one may even be forced to take them.

[13] Strauss, L.T., Herndon, J., Chang, J., Parker, W.Y., Levy, D.A., Bowens, S.B., Zane, S.B., and Berg, C.J.; CDC. Abortion surveillance—United States, 2001. MMWR Surveill Summ. 2004;53:1-32.

they knew deploying the morning-after pill would actually reverse falling abortion rates, this might explain why the abortion industry's support for it is now so adamant.

A recent news story attributed to Jim Sedlak, director of STOPP International, a group that monitors Planned Parenthood, alleges that documents made public in a court trial have revealed a "sweetheart deal" between Planned Parenthood Federation of America, Inc. (PPFA) and Barr Laboratories (Barr). The story reads:[14]

> One of the documents is a February 9, 2004 e-mail from the PPFA vice president of medical affairs, Vanessa Cullins, M.D., to all Planned Parenthood affiliate CEOs. The executives were told that Planned Parenthood was "in the midst of confidential discussions" with Barr and that Planned Parenthood's "immediate interest is to develop and protect our market base."

According to Sedlak's allegations, Barr Laboratories agreed to sell Plan B to Planned Parenthood at $0.25 less than the $4.50 price given to the public sector. The average sale price, Sedlak noted, was $25 at Planned Parenthood clinics—hardly a "sweetheart deal" for women seeking help to reduce unplanned pregnancy.

No doubt, maintaining women's dependency on abortion would indeed protect the "market base" of the abortion industry. But it would be unwise to allow the abortion industry to "develop" this market base by promoting a method of pregnancy reduction that with liberalized distribution will have the unwitting effect of actually increasing abortion rates, and to allow the abortion industry to profit additionally by selling women the very pills that in effect make the dog chase its own tail, as in Sweden.

Presumably Barr Laboratories realized that the liabilities of the two morning-after pill regimens would be more easily exposed, by comparison of the differences in their ineffectiveness for liberalized distribution, if Preven, the more ineffective of the two, were allowed to stay on the U.S. market. This would explain the product's removal from the U.S. market, even despite the support Preven received from authorities such as the AMA House of Delegates. The remaining question is whether Barr Laboratories felt it could somehow gain protection from the liabilities associated with Plan B by maintaining a "sweetheart" relationship with the powerful abortion industry lobby.

The FDA should be cautioned to reflect that unlike real medical procedures, it is not mandatory to report abortions to the CDC. Voluntary reporting to the CDC is largely under the control of the abortion industry. Although the CDC has enumerated the importance to public health of accurate reporting of abortions, the reliability and completeness of voluntary reporting has been limited. Additionally, CDC reports on abortion surveillance become available only several years after the year for which the data has been collected. Consequently, this means that the FDA would have to wait years before assessing the impact of Plan B on abortion rates. Because abortion rates are notoriously subject to underreporting in this country, it is plausible to believe that the rates may even be tampered with to mask the true impact of Plan B. Alarmingly, California, the nation's most populous state, and one of the states that decided to abandon the FDA's drug evaluation process by instituting over-the-counter access on its own to Plan B for girls and women of all ages, does not even report abortions at all. Similarly,

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[14] Lifenews.com, "Planned Parenthood Turns Sweetheart Deal on Morning After Pill Sales", by Jim Sedlak. Aug. 24, 2005. http://www.lifenews.com/nat1563.html

teen pregnancies are only casually monitored in this country. Thus, the FDA's real ability to assess Plan B's effect on pregnancy and abortion will be badly limited.

Comments C 2044 and C 2092 of the Micro ICU Project in Vol. 300 of Docket No. 2001P-0075 underscore the statistical reasons why post-coital methods, being subject to a large lapse rate L, are contraindicated for popularization in a typical use scenario, no matter how effective they may be with perfect use. So when someone says, "The condom broke," we must have the discipline not to fall prey to the presumption that a post-coital approach to the problem should be liberally popularized. Instead, looking ahead, a pre-coital discipline should always be emphasized. This might include engineering better standards for condoms. It also means teaching people that the technology best suited for those who wish to completely separate sex and responsibility is abstinence.

Because it will be administered in a controlled setting, a method of preventing fertilization post-coitally would be desirable for rape victims, provided the method does not have a concepticidal component. Concepticide is the taking of the life of a conceptus. Methods with a concepticidal component would be especially problematic for women who have been actively seeking pregnancy, because the method would be more likely to harm a child conceived by her partner than by the offender. In cases where conception by rape does occur, and the victim is unable to continue her pregnancy, the technology is now feasible to 1) detect and locate the conceptus prior to implantation, 2) separate him or her from the victim, 3) transfer the conceptus to an incubator (micro ICU), and 4) transfer her or him to an adoptive or surrogate mother within the timeframe associated with pre-implantation events. Importantly, this separation procedure is medically distinct from an abortion in which no effort is made to preserve the life of the child.

If preventing fertilization post-coitally would be desirable for rape victims, why not for women with other reasons? The tough answer is that life is not based on what is desirable. You have to take real life into account. In the case of rape, use of a post-coital method would satisfy the condition that the act of intercourse took place independently of knowledge of the method. Without this condition being satisfied, women will substitute the post-coital method for other methods, and sometimes they will not even follow through on their plans of reliance. The former problem is of special importance when the post-coital method is inferior to the other methods. The latter problem will be true of any post-coital mechanism that is not permanently in place or otherwise independent of the woman's actions. It takes discipline to account for these factors. Like sex, life is not always based on what is desirable; instead you have to take practical considerations into account. Otherwise, you will end up with a tragedy like Sweden did.

When people dream unrealistic figures it is good to take out a calculator and do a quick reality check. For example, did Barr Laboratories ever tell the FDA it has plans to sell in excess of 23.8 million units of Plan B per year? At minimum, 14 units of Plan B will be taken on average for every one pregnancy reduced. So to fulfill the AMA's morning-after pill fantasy of reducing 1.7 million pregnancies annually, it would take no less than 23.8 million units. At $25 per unit, this would put revenues for Plan B at $595 million per year, with Planned Parenthood taking a piece of the cake. Recall also that this lavish expenditure to reduce pregnancies will not reduce pregnancies in net, since in net liberalized access to the morning-after pill serves to increase pregnancies. Instead, it simply means that to reduce 1.7 million pregnancies, on an individual basis, it would take 23.8 million units of Plan B at absolute minimum.

The figure of 14 units of Plan B per pregnancy reduced is determined by first multiplying the odds of pregnancy (0.08) by the fraction of them reduced (0.89) per use of Plan B, which gives the odds of actual pregnancy reduction per use, and then taking the reciprocal. This minimum figure is based on the unrealistic assumption that all women will make perfect use of Plan B during the two mid-cycle weeks and will not combine it with other methods that have some effect. Otherwise, the likelihood that an instance of use will actually have the effect of reducing a pregnancy will be less, because the odds of pregnancy are less at other times of the cycle as well as when women are simultaneously using other methods that have some effectiveness.

In a subtle way, Plan B's prescription label actually serves to mask the overall rate at which women will be taking the drug for nothing. To be clear, "for nothing" means times of taking Plan B when either they would not have gotten pregnant anyway, or when Plan B does not reduce a pregnancy anyway because they ended up with one even despite taking the drug. The label is faulted for masking the problem of the overall rate at which women will be using the drug for nothing because it quotes a value for natural pregnancy expectation of 8% that is only valid during the two mid-cycle weeks, when pregnancy expectation is highest. But the label does not limit the indications of use to specific weeks of the cycle. Yet women who take Plan B during the infertile portions of their cycles, like women who are infertile, will always be taking it for nothing.

According to MedlinePlus drug information, a service of the U.S. National Library of Medicine and the National Institutes of Health, "Combined estrogen and progestin oral contraceptives may increase the risk of getting breast cancer, endometrial cancer, and liver tumors. It is not known whether progestin-only oral contraceptives also increase the risks of these conditions."[15] Recalling that one unit of Plan B contains the active progestin equivalent of a 40-day supply of Ovrette—an enormously large dosage—one seriously questions the epidemiological impact that taking Plan B may have on women's risk of getting cancer. Especially alarming is that women will be taking Plan B for nothing at such a high rate, and that Plan B's net effect of increasing unplanned pregnancies with liberal access will be counterproductive to begin with.

Unfortunately, the medical community behaves in an odd way when it comes to an evaluation of the health effects of matters that implicate concepticide. For example, the unqualified claim persists that abortions are safer for women than birth. The claim is unqualified because it does nothing to rule out the possibility that abortions, whatever their risks, present a compounding risk factor. Women who have abortions do so predominately before they complete their lifetime number of births. For this reason, abortions may largely tend to forestall the completion of a woman's desired birth pattern, thereby subjecting her to added risks by enabling her to balk at the child-bearing process via abortion. In other words, abortion risks may largely be additive.

Another example concerns evaluation of the impact abortion has on breast cancer. For example, contrary to general assumption, the famous study of Melbye et al. did not eliminate recall bias, because the study failed to "recall" abortions for some of the older women.[16] In other words, as far as figures go, the numbers do not care who is failing to do the recalling, whether it is the researchers or the women under study. This makes it

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[15] "Progestin-only oral contraceptives" http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a602008.html

[16] Melbye, M., Wohlfahrt, J., Olsen, J.H., Frisch, M., Westergaard, T., Helweg-Larsen, K., and Andersen, P.K. Induced abortion and the risk of breast cancer. N Engl J Med. 1997;336:81-85.

seem all the more amazing that the study managed to pull a one-point-zero-zero figure for relative risk out of its hat. Analysis of the range of uncertainties associated with crude and adjusted figures also suggests that the latter's range is too narrow to have undergone proper error propagation in adjusting the former's value of 1.44.[17] Yet as with support for Plan B, we are told everything has been validated by an expert consensus.

Evidently some element of reform is needed in our medical community, which seems to be living in a time warp. Even new medical students are not receiving the most up-to-date education. For example, despite being introduced by the Medical Students Section, AMA House of Delegates Resolution 443 (A-04) makes reference to "ovum implantation", underscoring the problem that even our new students of medicine are not being familiarized with the fact that ovum implantation is known to be a complete myth. Instead, human babies must literally hatch from their eggs before implantation.

Of medical concern, Plan B may have a concepticidal ("conceptus-killing") component, particularly during the pre-implantation stages of life. These stages include what are properly known as the embryo and hatchling stages. As shown in the photo below, the transition between embryo and hatchling stages occurs at hatching time, taking place about 5-6 days after fertilization. The baby below is hatching in the two o'clock direction through a hole in the eggshell. The baby's body is surrounded by a fluid-filled precursor of the birth sac in primordial form, which serves as a protective spacesuit. Despite the ignorance of our medical profession, these babies hatching are every bit as important as the ones you see crawling across the floor.

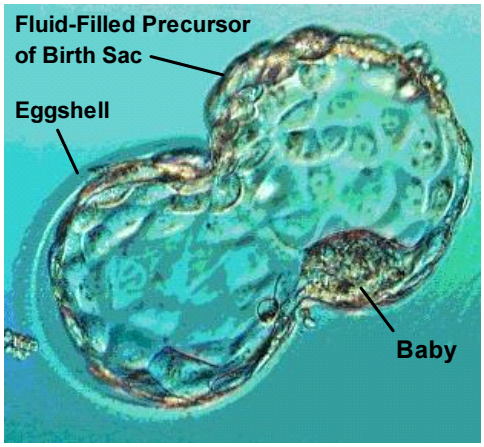

Photo credit: Georgia Reproductive Specialists, IVF.com

A Human Baby Hatching

Because of the problem of concepticide, legality presents a consideration regarding over-the-counter status for Plan B. Notably the definitions of "pregnancy" and "abortion" used in Dorland's Illustrated Medical Dictionary are broad enough to include the conceptus during the pre-implantation stages of gestational life. Although some authorities may beg to differ with these definitions, it appears nonetheless that the U.S.

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[17] Brind et al. state the value of the crude figure but not the corresponding range of uncertainty. In response Melbye et al. manage to give a partially adjusted figure with an upper range that is *narrower* (in parts per million) than that of the corresponding crude figure on which it is based! Brind, J., Chinchilli, V. M., Senghas, R. E., Dolan, M. F., Melbye, M., Wohlfahrt, J., and Andersen, P. K. Induced abortion and the risk of breast cancer. N Engl J Med. 1997;336:1834-1835.

Supreme Court has traditionally relied upon Dorland's. In *Roe v. Wade*, 410 U.S. 113 (1973), the Supreme Court made expressly clear that a woman may neither decide nor effectuate an abortion on her own; instead, as stressed in *Roe*, "the abortion decision and its effectuation must be left to the medical judgment of the pregnant woman's attending physician." 410 U.S., at 164. Yet based on its concepticidal potential, over-the-counter distribution of Plan B would violate that ruling by enabling a woman to decide and effectuate an abortion herself. Similarly, section 503(b)(1)(A) of the Federal Food, Drug, and Cosmetic act does not limit the concerns of a drug's "toxicity or other potentiality for harmful effect" to the woman herself, thus providing further indication that unsupervised use of Plan B is strictly illegal based on the adverse implications the drug may have for her conceptus.

As a technology, if Plan B did not have a concepticidal component, but instead only prevented fertilization, an application for over-the-counter status would still face the broad standards of inquiry posed by the Commissioner's notable questions. But Plan B presents additional legal complexities based on its concepticidal potential. For it would be unprecedented for the FDA to enable a woman to decide and effectuate her own abortion, in any form, apart from the medical judgment of an attending physician. For example, birth control pills and intrauterine devices, which some believe may have a concepticidal component, require an attending physician because they are only available as prescription products. Notably, all concepticidal products would be banned outright if the Government were to protect the person by outlawing concepticide altogether.

From the photo on the previous page, it is clear that hatching is a very intelligent human behavior, and one that defies the traditional neurological paradigm. Instead, we have to think of brain power based on molecular computing inside the cells, and that the neurons formed later represent specific interconnects. Understandably, many users of Plan B would be shocked to learn that they may have caused the demise of an intelligent human baby engaged in behaviors such as hatching prior to implantation.

Early pregnancy tests are evolving to detect conception prior to implantation. However, apart from an early pregnancy test, there will be uncertainty as to whether or not a given use of Plan B prevented fertilization, destroyed a conceptus, or was taken for nothing due to infertility at the time of use. From an emotional and psychological perspective, uncertainty about the possible destruction of a conceptus may present cause for morbidity. Consequently, states require abortion providers to perform a pregnancy test in advance of an abortion. But with Plan B this compliance will generally be lacking, particularly with over-the-counter use. In this regard, the FDA has an obligation to research and consider the facts thoroughly in an effort to protect a woman's conscience from serious harm. Though some would keep women in the dark under the pretense of protecting them, the potential for awareness about the lives of pre-implantation infants is rapidly evolving thanks to medical programs like the Micro ICU Project.

Obviously the application to liberalize access to Plan B should be denied. But most of all, the FDA should evaluate the concepticidal potential of its regulated products and reject their approval accordingly.

Sincerely,

E. G

Mr. Eurica Californiaa, Amb.
Juridic Embassy, Micro ICU Project