Kirkpatrick & Lockhart Nicholson Graham LLP

1800 Massachusetts Avenue, N.W.
Suite 200
Washington, DC 20036-1221
202.778.9000
Fax 202.778.9100
www.klng.com

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Via Hand Delivery

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
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Re: Comment to Docket No. 2005N-0345; RIN 0910-AF72
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:

Kirkpatrick & Lockhart Nicholson Graham (K&LNG) submits these Comments to Docket No. 2005N-0345 on behalf of four groups that oppose the dual marketing of the same drug product in both the prescription (Rx) and over-the-counter (OTC) markets. For the legal, medical, and public health reasons set forth below, Concerned Women for America (CWA), the Family Research Council (FRC), the Christian Medical and Dental Associations (CMDA), and the American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) oppose the simultaneous marketing of an active ingredient in both an Rx drug product and an OTC drug product. The groups also oppose the Rx-to-OTC switch of Plan B® (levonorgestrel) tablets, 0.75 mg, an emergency contraceptive (EC) drug product, also referred to as the "morning after" pill (MAP).

CWA, FRC, CMDA and AAPLOG are non-profit organizations that share a great concern about women's health issues in general, and safe contraception use in particular. CWA represents a membership of 500,000 women in 50 states across the USA. CWA seeks to represent women before Congress and U.S. and International governmental bodies on issues of specific interest to women, including the sanctity of human life from conception until natural death. CWA has been active in contraception-related issues for over 25 years. FRC is a non-profit organization formed in the 1980's that formulates public policy recommendations that value human life. CMDA is a professional organization with thousands of physician members representing every medical specialty. AAPLOG is a recognized interest group of the American College of Obstetricians and Gynecologists, currently representing over 2,000 physicians throughout the USA.

BACKGROUND

On September 1, 2005, the U.S. Food and Drug Administration (FDA) published an Advance Notice of Proposed Rulemaking requesting public comment on whether, under the Federal Food, Drug, and Cosmetic Act (FDC Act), an active ingredient may be simultaneously marketed in both an Rx and OTC drug product. *See* 70 Fed. Reg. 52,050 (2005). FDA presented three questions, which we answer briefly as follows:

(1) Should FDA initiate a rulemaking to codify its interpretation of when simultaneous marketing is permitted under the law? Yes.
(2) Would FDA be able to enforce an age-related limitation for Rx vs. OTC sales? No.
(3) May the same drug be sold in the same packaging to both the Rx and OTC markets? No.

In these Comments, we provide detailed legal, medical and public-health-protection analyses to support the brief answers set forth above. We make particular note that in a related action, FDA denied approval to a New Drug Application (NDA) Supplement for Plan B® (levonorgestrel) tablets, 0.75 mg, in which the Sponsor requested a switch from Rx-only status to OTC status for women ages 16 years and older. Women under age 16 would have prescription-only access to Plan B®. The undersigned support FDA's denial of the NDA Supplement, and we provide evidence herein that this EC product should not be made available OTC to any age group, primarily because physician involvement is paramount to the safe use of the product.

DISCUSSION

I. FDA Lacks The Statutory Authority To Permit The Simultaneous Dual Marketing Of The Same Drug As An Rx And An OTC Product

FDA lacks legal authority under the FDC Act, as amended by the Durham-Humphrey Amendments (Public Law 82-215, 65 Stat. 648), to allow the dual marketing of an active ingredient simultaneously in an Rx drug product and an OTC drug product. The statutory language, the legislative history, the implementing regulations, and the Agency's past interpretations all preclude such dual marketing of an active ingredient.

A. Dual Marketing Runs Counter to the Statutory Language and Congressional Intent

The FDC Act defines a prescription drug as a drug which "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug." 21 U.S.C. § 353(b)(1)(A). The concern is the safety of the drug product, and drug products that are not safe to use except under the supervision of a licensed physician are to be dispensed by prescription only.

The legislative history of the Durham-Humphrey Amendments, as recorded in Senate Report No. 946, notes that the "not safe" language in the statute is intended to have its ordinary meaning. *See* 1951 U.S.C.C.A.N. 2,454 at 2,457 and 2,461. If the Agency has determined that a certain drug product is "not safe" for use except under the supervision of a licensed physician, then carving out a subpopulation (by age, for example) would run counter to this "ordinary meaning" – not safe is not safe, regardless of age. Drugs would not be safe for self-medication if "their unsupervised use may indirectly cause injury," as in the case of drug products that contain potent steroid hormones which affect many organ systems. 1951 U.S.C.C.A.N. 2,454, 2,457. *See also* 35 Fed. Reg. 9,001 (June 11, 1970). In fact, courts have historically noted the safety risks particular to oral contraceptive prescription drug products. *Cf. Turner v. Edwards*, 1969-1974 FDLI Jud. Rec. 471, 472 (D.D.C. 1970) (stating that "oral contraceptives are prescription drugs, and therefore subject to different requirements as to their use and dispensation than over-the-counter products").

We further note that the legislative history supports the broad applicability of classifying a drug as an Rx product due to the concerns of safety for such drug products. In addressing the concerns in relation to the Durham-Humphrey Amendments, our legislatures made clear that "the broad language of the definition contained in [these provisions] is intended to comprehend *all drugs* that in fact should be administered under medical supervision in order to insure [sic] their safe use." 1951 U.S.C.C.A.N. 2,454, 2,462 (emphasis added). This Congressional intent on making the definition of a prescription drug apply as broadly as possible is precisely why the statutory language makes sweeping reference to "toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use." *See* 21 U.S.C. § 353(b)(1)(A). Allowing the marketing of a drug product as OTC based solely on the age of a subpopulation would run counter to the Congressional intent of drafting the statutory language in this broad way.

Indeed, the language of the statutory definition for a prescription drug "clearly shows that toxicity is only one fact to be considered" in determining whether a particular drug is safe for use without medical supervision. 1951 U.S.C.C.A.N. 2,454, 2,457. Given the overarching purpose of the FDC Act to protect the public health, the breadth of this statutory definition serves to "effectively restrict to prescription sale *all drugs* that require professional supervision for their use." 1951 U.S.C.C.A.N. 2,454, 2,457 (emphasis added).

Thus, the concerns for safety, as well as the breadth of the statutory language, indicate that Congress intended the reach of the definition of a "prescription drug" to be as wide as possible. To carve out an OTC exception for a drug product currently approved for prescription use would run counter to this legislative intent set forth in the Congressional record for the Durham-Humphrey Amendments.

B. Dual Marketing Runs Counter to the Dichotomous Classification of Drug Products

A plain-meaning interpretation of the statutory language indicates that the Agency may not allow the dual marketing of a drug as both Rx and OTC. The statute states that FDA may "*remove drugs*…from the requirements of [21 U.S.C. § 353(b)(1)] when such requirements are not necessary for the protection of the public health." 21 U.S.C. § 353(b)(3) (emphasis added). The statutory language allows for the Agency to "remove drugs" from one classification (Rx) and into another (OTC). The statutory language, in essence, provides for the requisite conditions to market a drug as an OTC drug product by noting inapplicability as an Rx product. *Cf.* 70 Fed. Reg. 52,050 at 52,051 (stating that the term "OTC drug" has been adopted to refer to any drug that does not meet the definition of a prescription drug in 21 U.S.C. § 353(b)(1)). Thus, a dichotomy exists between the prescription and OTC drug "classification." *See id.; see also* 21 C.F.R. § 310.200 (describing FDA's prescription exemption procedure).

If one "removes" a drug from regulation as an Rx drug, then that drug becomes an OTC drug. One cannot "remove" a drug from the prescription classification and still regulate that drug product as an Rx drug. Either the drug is "removed" from the prescription drug regulatory rubric and is therefore an OTC drug, or the drug remains under the Rx rubric and is *not* an OTC drug. The mutually exclusive nature of the dichotomous classification of a drug product as either Rx or OTC is manifest in the statutory language. *Cf.* 21 U.S.C. 353(b)(4). The dual marketing of the same drug as Rx and OTC therefore runs contrary to the plain-language meaning of the statute.

C. Dual Marketing Causes Confusion Between Drug Products

The underlying concern both for FDA and Congress in the statutorily-required dichotomous classification is the potential for confusion that would arise if the statute did not provide for this bifurcation between Rx and OTC drugs. *See, e.g.*, 21 U.S.C. §§ 353(b)(4)(A) and (B) (stating, in essence, that a prescription drug must have the "Rx" symbol on its label, whereas an OTC drug must *not* have this symbol on its label, to avoid the potential for confusion). In fact, courts have noted historically that if birth control pills were extensively disseminated outside distribution channels for prescription drug products, different standards of labeling might be applicable. *See, e.g., Turner v. Edwards*, 1969-1974 FDLI Jud. Rec. 493, 494 (D.D.C. 1971).

Likewise, the legislative history of the statutory language at hand underscores the concern for labeling confusion by stating:

> …the interstate label on [prescription] drugs must bear the statement "Caution: Federal law prohibits dispensing without prescription." On the other hand, over-the-counter drugs are forbidden to bear a label containing this caution statement. A

> prescription drug, the label on which does not bear the specified caution statement, is deemed to be misbranded. So, too, is an over-the-counter drug, the label on which bears this or a substantially similar statement.

See 1951 U.S.C.C.A.N. 2,454, 2,463. *Cf.* 1951 U.S.C.C.A.N. 2,454, 2,457 (stating that the statutory definition of a prescription drug "could bring an end to the existing confusion in drug labeling and that uniformity can be achieved"). *See also* 70 Fed. Reg. at 52,051 (noting the resulting confusion and uncertainty that arose due to a lack of criteria in determining when to limit a drug product's approval to prescription use).

The dual marketing of an active ingredient both as an Rx drug and as an OTC drug would only exacerbate this previously-identified confusion, especially if the product was sold in the same package to both markets, or differed only in age-limited dispensing. In order to avoid this confusion, the statutory provisions of the FDC Act prohibit the marketing of the same drug product in an identical package in both the Rx and OTC markets. Instead the law requires, at the very least, labeling with or without the "Rx" symbol. Thus, the inclusion (or exclusion) of the "Rx" symbol on a label would preclude the marketing of a drug product in that package for both the Rx and the OTC markets. Likewise, the FDA's labeling requirements differ substantially for the Rx and OTC markets, such that the labels on the packages could not be the same. *See* 21 C.F.R. Part 201, subpart B (Rx labeling) and Subpart C (OTC labeling).

Moreover, even if a firm attempted to market two different packages, with one package including the "Rx" symbol and the other excluding this symbol, the administrative task of ensuring this dual marketing would be burdensome at best, infeasible at worst. During the approval process, the Agency would need to pass judgment on the Sponsor's plans for utilizing both marketing avenues for the product. During post-approval marketing, the Agency would have to expend its limited resources to ensure that, among other tasks, (1) the manufacturer printed two labels with information appropriate to the distinct markets (i.e., health care providers or consumers), (2) the distributor shipped the packages to the correct retailer, and (3) the pharmacist stocked the relevant shelves with the correct package and dispensed it properly. This extensive regulation of the dual marketed product would be antithetical to the purposes of the FDC Act, which sought precisely to eliminate this type of confusion through the definition of a prescription drug.

D. FDA Regulations Demonstrate the Separation of Rx and OTC Marketing Avenues

The regulatory provisions governing oral contraceptives further demonstrate the difficulty that the Agency would face in allowing the dual marketing of an active ingredient both as an Rx drug and as an OTC drug. The regulations stipulate that "the safe and effective use of oral contraceptive drug products requires that patients be fully informed of the benefits and the

risks involved in their use." 21 C.F.R. § 310.501(a). Furthermore, the requirements for the requisite patient package inserts for oral contraceptives are both extensive in reach and exhaustive in content. *See* 21 C.F.R. § 310.501 (noting the wide-ranging requirements for oral contraceptive patient package inserts).

In contrast, the Drug Facts Panel of an OTC drug product is intended to be comprehended by the layperson without need for medical supervision. By allowing the dual marketing of an active ingredient both as an Rx drug and as an OTC drug, the Agency would be conflating the concerns of safety underlying a prescription package insert with the purposes of simplicity underlying an OTC drug label. Such a decision by the Agency would only add to the confusion that the statutory language and legislative history of the FFDCA precisely sought to avoid.

This dichotomy between Rx and OTC drug products is made clear by the fact that FDA has numerous implementing regulations specific to Rx drug products, as well as regulations specific to OTC drug products.

For example, FDA regulates Rx labeling in 21 C.F.R. §§ 201.50-201.59, whereas FDA regulates OTC labeling in 21 C.F.R. §§ 201.60-201.72. Furthermore, under the labeling provisions, with regard to exemptions from adequate directions for use, 21 C.F.R. §§ 201.100 and 201.120 are specific to Rx drug products. In addition, for specific labeling requirements for specific drug products, FDA again makes this distinction between Rx and OTC drug products. *See* 21 C.F.R. §§ 201.300-201.323.

FDA further delineates the distinction between Rx and OTC drug products by limiting to Rx drugs the Agency's regulations as to advertising (21 C.F.R. § 202), as well as its regulations as to marketing restrictions (21 C.F.R. § 203). Furthermore, FDA regulations as to the guidelines for state licensing of wholesale drug distributors are limited to Rx drugs. *See* 21 C.F.R. § 205. In addition, the medication guide regulations in 21 C.F.R. § 208 are limited to Rx drug products.

The Agency implements the Rx-exemption procedures, as well as the exemption for certain drugs limited by NDAs to Rx sale, through its regulations in 21 C.F.R. § 310.200 and 21 C.F.R. § 310.201, respectively.

In addition, FDA's requirements for specific new drugs in 21 C.F.R. §§ 310.501-310.518 are for Rx, whereas the requirements for specific new drugs in 21 C.F.R. §§ 310.519-310.548 are for OTC. Likewise, the FDA regulations in 21 C.F.R. §§ 328-358 are limited to OTC monographs. In contrast, 21 C.F.R. § 361 is limited to Rx drugs used in research. Yet the regulations in 21 C.F.R. § 369 pertain to interpretative statements regarding warnings on OTC drugs. This regulatory separation supports the statutory dichotomy of Rx and OTC drug products.

E. Past Agency Position Precludes Dual Marketing Without Meaningful Difference

According to FDA's present regulatory interpretation of the Durham-Humphrey Amendments, the marketing of the same active ingredient in different drug products in both the Rx and OTC markets *assumes some meaningful difference exists* between the two marketed drug products. *See, e.g.*, 70 Fed. Reg. at 52,051 (emphasis added). Historically, FDA has concluded that the meaningful difference relates to five parameters – the product's active ingredient, indication, strength, route of administration, or dosage form. *See id.* Even so, however, FDA has been reticent to acknowledge a "meaningful difference" in a drug product, determining instead that physician supervision is still necessary when a drug product's strength or dosage form, for instance, is distinct. Only in a few cases in the past 50 years has FDA determined that a change in one of the five drug product parameters provided enough of a difference to support the safe use of the product without physician supervision. *See* 70 Fed. Reg. 52,050 (citing specific product differences in indication, dosage form, and strength). And most of those cases involved two separate indications, for which one of the indications a layperson could clearly self-diagnose and self-treat, but the other indication required a physician diagnosis and supervision (e.g., prescription for ulcers vs. OTC for heartburn). In other words, only rarely can a drug product with one parameter (e.g., lower strength) be used safely without physician supervision, when that physician supervision is required for the safe use of the product with a different parameter (e.g., higher strength).

Furthermore, there is no legal support for an FDA conclusion that a difference in a subpopulation, related to age, constitutes the type of "meaningful difference" that would negate the concerns of safety associated with a drug product that is marketed as a prescription drug and, thus, support dual marketing. A distinction by age subpopulation does not alleviate the safety concerns associated with the drug product's "toxicity or other potentiality for harmful effect"; if a drug product is not safe for use by one age group except under the supervision of a licensed physician, those same safety concerns apply to all subpopulations, regardless of age. In sum, the dual marketing of a drug product as prescription-only for one age group and OTC for another age group represents an arbitrary agency action without legal support.

II. FDA Lacks The Statutory Authority To Create A Pharmacist-Dispensed "Behind The Counter" Class or "Third Class" Of Drugs

A. A Third Class of Drugs Runs Counter to the Durham-Humphrey Amendments

By considering the dual Rx and OTC marketing of Plan B based on an age limitation, FDA is necessarily contemplating the creation of a third class of drugs intended for sale "behind-the-counter" (BTC) by pharmacists. This third class would be inevitable because the product's labeling would have an age-related limitation for OTC sale (i.e., 17 years and above). In all

likelihood, then, pharmacists would need to control access to the drug to enforce the age limitation.

FDA itself does not have the authority to ensure that this age limitation is enforced. Furthermore, the creation of a "third class" of drugs beyond the Rx and OTC markets is unlawful without legislative changes to the FDC Act because, as discussed above, the distribution of medicine in the United States is based on a two-class system – prescription and OTC – that was formalized by Congress in 1951. The goals of the prescription-nonprescription distinction were to protect the public from abuses in the sale of potent prescription drugs, and to relieve pharmacists and the public from burdensome and unnecessary restrictions on the dispensing of safe OTC medicines. This law directed FDA to distinguish between drugs that were too dangerous for use without professional supervision and those that were safe on an OTC basis with adequate directions and warnings on the label. The statute provides no authority for FDA to establish a new class, i.e., a third class of drugs – whether because the labeling needs to be supplemented by a pharmacist's instructions, or because a certain subpopulation might misuse the drug with direct access.[1] Moroever, at least one court has questioned FDA's authority in this area. In *APhA v. Weinberger*,[2] the court held that FDA lacked statutory authority to impose or authorize the

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[1] Some have suggested that Plan B's proposed age distinction is no different from age restrictions for alcohol or tobacco sales. These proponents of the age distinction assume incorrectly that enforcement of the age restrictions for the sale of alcohol and tobacco is successful. In 1998, underage buyers were able to buy alcohol in 97% of purchase attempts in Washington, DC, 82% of attempts in Westchester County, NY, 44% of attempts in Schenectady, NY, and 59% of attempts in northwestern New Jersey. *See* Preusser, D.F., and A.F. Williams, Sales of alcohol to underage purchasers in three New York counties and Washington D.C., Journal of Public Health Policy 13(3):306-317 (1992). For every 100,000 occasions of youth drinking, only 5 alcohol outlets incur actions by a state Alcohol Beverage Control Agency. *See* Wagenaar, A.C., and M. Wolfson, Enforcement of the legal minimum drinking age in the United States, Journal of Public Health Policy 15(1):37-58 (1994). Certain state police forces have instituted effective compliance check programs; however, successful enforcement of the minimum drinking age requires the enactment of laws prohibiting such action, implementing regulations that prevent adults from buying alcohol for minors, and enclosing areas for alcohol sales and consumption to make it more difficult for adults to pass alcohol to minors. The framework for enforcement of tobacco and alcohol age restrictions may be theoretically present, but the reality is, enforcement is difficult and often not realized. In addition, since there is no statutory enforcement provision in the context of age limits for approved drugs, the framework cannot be easily translated to a BTC drug class.

[2] *APhA v. Weinberger*, 377 F. Supp. 824 (D.D.C. 1974).

imposition of certain post-approval controls on methadone and declared the regulations invalid to the extent that they prohibited or restricted shipment to, or receipt or dispensing by, a duly-licensed pharmacy. Similarly, the U.S. Justice Department and the National Association of Attorneys General have opposed a third class of drugs, calling such proposals anti-competitive and anti-consumer because they create a monopoly in the distribution of nonprescription drugs.[3]

B. FDA Does Not Have The Authority or the Resources To Enforce An Age Restriction for the Same Drug to be Marketed as Rx and OTC

Because FDA does not have the statutory authority or the economic or personnel resources to enforce an age restriction for Plan B sales, enforcement activities would fall to the states, local governments, or pharmacies. Yet, FDA has no regulations to instruct third parties in appropriate enforcement activities, nor is there any mechanism for FDA to ensure that enforcement is carried out.

Some states have shown a willingness to create a framework for BTC drugs. Alaska, California, Hawaii, Maine, New Mexico, and Washington currently offer emergency contraception behind the counter. However, other states, such as Louisiana, are unable or unwilling to expend the financial resources necessary to promulgate pharmacy access laws and enforce the regulation's restrictions. This uneven regional enforcement illustrates the imprudent and illegal nature of a dual marketing approval for Plan B. It is also unclear that FDA has the requisite legal authority to supervise and correct the states' efforts, or lack thereof.

Furthermore, previous attempts to restrict consumer access to nonprescription substances have effectively failed. Some states restrict consumer access to Schedule V (e.g., cough medicines with codeine) nonprescription controlled substances to pharmacist-only sales. These restrictions were imposed under state controlled substance laws, not federal law. The original intent of the restrictions was to prevent abuse, but many states that originally placed Schedule V nonprescription drugs behind the counter realized that the restrictions did not achieve their intended purpose. As a result, roughly half of the states placed these nonprescription drugs on prescription status under the states' controlled substance laws.[4]

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[3] Consumer Healthcare Products Association (CHPA) comment to FDA, Docket No. 00N-1256: Over-the-Counter Drug Products, August 25, 2000, p. 19, footnote 16.

[4] Among others, these include California, Colorado, Louisiana, Montana, Nebraska, New Hampshire, North Dakota, Oregon, Rhode Island, and Texas. *See* R. William Soller, Eve E Bachrach, Doc. No. 00N-1256: Over-The-Counter (OTC) Drug Products: Request for Comments; 65 Fed. Reg. 24704, April 27, 2000 (August 25, 2000), *available at* www.chpa-info.org/web/advocacy/submissions/08_25_00_OTC_comments.pdf.

Some proponents of a third class of drugs have offered as precedent certain restrictive drug distribution models in the United States. Upon closer examination, however, these examples do not provide a basis for pharmacist-only third class distribution of nonprescription drugs. For example, the state of Florida initiated an experiment in 1985 under the Pharmacist Self-Care Consultant Law to permit pharmacists to prescribe a limited number of *prescription* drugs without physician supervision. The GAO Report, described below, found that the authority was rarely used because pharmacists and/or pharmacies were unwilling to assume the liability risks.[5] When the prescribing authority was used, the law's record-keeping requirements were seldom followed because pharmacists were already burdened by time pressures to address other responsibilities. Given that there is currently a shortage of pharmacists, the time-pressures that a pharmacy-only class of nonprescription drugs would add make such a plan even less appealing.

C. From Both Practical and Public Policy Standpoints, the Health Care System in the U.S. Does Not Support a Third Class of Drugs

In addition to the legal impediments, the U.S. health care system as a practical matter does not have the necessary infrastructure to support a BTC class of drugs. With respect to pharmacy practice, pharmacists in the U.S. and elsewhere often do not perform the roles on which the benefits of the third class are premised, even when such roles are expected or required. Pharmacists are expected, among other things, to provide complete counseling, report adverse drug events, and maintain patient profiles, but often do not.[6]

A third class of BTC drugs in the U.S. will necessitate the active participation of pharmacists. Pharmacists will be forced to provide meaningful advice and counseling before offering products from behind the counter. The education of pharmacists would have to include training on retail patient counseling, which, for the most part, is currently lacking. Pharmacies would also have to grant their pharmacists time away from dispensing drugs to meet with patients. The burden of this financial cost will not be willingly absorbed by the pharmacies, and will most likely be borne by the patients themselves. The push for BTC drugs to reduce the cost of prescription drugs may ironically result in inflation of drug costs. At this time, there is nothing available from insurance companies or other sources for reimbursement for patient drug counseling.

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[5] *See* Nonprescription Drugs: Value of a Pharmacist-Controlled Class Has Yet to Be Determined, Report GAO/PEMD-95-12. Washington, D.C.: U.S. General Accounting Office, Program Evaluation and Methodology Division, August 1995 at 57-59, 65, 79 [hereinafter, GAO Report].

[6] *See* GAO Report at 28.

As a public policy matter, evidence of the need for or benefit of a third class of drugs is lacking. In 1995, the U.S. General Accounting Office (now called the Government Accountability Office) researched other countries that use the BTC drug avenue and found that use of a pharmacy only class to prevent abuse met with similarly poor results in other countries. In a study performed in Germany, for instance, children between 10 and 14 were directed to purchase medicines containing alcohol from pharmacies. In all 54 pharmacies visited, the children were allowed to purchase the drugs, and in only one instance was the child questioned intensively.[7] The GAO also found that safeguards against abuse are easily circumvented and that actual counseling of patients by pharmacists is infrequent and incomplete.[8] The GAO stated specifically that other countries' experiences "do not support a fundamental change in the drug distribution of the United States such as creating an intermediate class of drugs . . . . The evidence that does exist tends to undermine the contention that major benefits are being obtained in countries with a pharmacist or pharmacy only class."[9] Among the organizations opposing a third class of drugs are the American Medical Association, Interamerican College of Physicians and Surgeons, National Black Caucus of State Legislators, National League of Nursing, Food Marketing Institute, Consumer Alert, National Black Women's Health Project, National Coalition of Hispanic Health and Human Services Organizations, National Grange, National Council on Aging, Food Industry Association Executives, and many others.[10] Regardless of the public policy issues associated with a BTC class of drugs, the existing dichotomy of prescription and OTC drugs is well-established in the FDC Act and any alterations would require explicit action by Congress.

The existence of third class drugs in other countries does not support establishing the same in the United States. No public health advantages have been identified to justify creating a third class of drugs, nor to provide patients with better access to medicines. In its 1995 report to Congress, the GAO concluded that "the existence of a third class does not make regulatory officials more or less likely to approve new OTC products or switch prescription drugs to unrestricted nonprescription status."[11]

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[7] *See* GAO Report at 28.

[8] *Id.*

[9] *Id.*

[10] *See* Third Class of Drugs, CHPA, available at http://www.chpa-info.org/web/advocacy/general_issues/third_class.aspx.

[11] *See* GAO Report at 42-43, 78.

D. Without A Third Class of Drugs, OTC Sale Is Unregulated and Uncontrolled

Whether Congress creates a third class, or FDA by regulation creates a third class, without such a creation the Plan B product will be freely available to all consumers. Presently in the U.S., an OTC drug can be sold anywhere to any consumer unless restricted by state law. Thus, if FDA approves Plan B for OTC sale and a state does not restrict the sale to pharmacies, the drug would be available at any gas station, 7-11, or other business that wanted to sell the drug. In such a setting, does anyone believe the under-17 age limit will be observed, much less enforceable?[12] FDA has been given the statutory tools to protect the public health for the nation, and the switch of Plan B without a regulatory framework to control the drug's use in under-age children is without precedent. It may be that some statutory plan can be created to provide this drug OTC to adults, but the current statutes and regulatory scheme do not provide them. Moreover, FDA should not usurp the role of Congress by creating a marketing exception to the laws and regulations currently on the books.

III. FDA Must Initiate And Complete Full Rulemaking Proceedings In Order To Institute The Simultaneous Dual Marketing Of The Same Rx/OTC Drug Product

FDA has asked whether it should proceed with notice and comment rulemaking to codify the FDA's interpretation of Section 503(b) as to when a drug can be dually marketed as OTC and by prescription, since FDA historically has not allowed marketing of the same active ingredient in a prescription for one population and OTC for another. The brief answer is yes.

Agency "rules" are broadly defined in Section 551 of the Administrative Procedures Act (APA) as the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy, or describing the organization, procedure, or practice requirements of an agency.[13] Agency rules include the approval or prescription for the future of rates, wages, corporate or financial structures or reorganizations thereof, prices, facilities, appliances, services or allowances therefor or of valuations, costs, or accounting, or practices bearing on any of the foregoing. Given the magnitude of the regulatory change that FDA would be enacting despite the DurhamHumphrey Amendments, any FDA approval of an active ingredient for simultaneous Rx and OTC marketing is a new Agency "rule" that triggers notice and comment rulemaking.

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[12] For the remainder of these Comments, we will refer to the proposed age restriction for Plan B OTC sales as 17-and-over and under-17, as delineated by FDA, though we acknowledge that the Sponsor's NDA Supplement requested a restriction at age 16. *See* Not Approvable Letter, Lester M. Crawford, DVM, Ph.D., Commissioner, FDA, to Duramed Research, Inc. (Aug. 26, 2005).

[13] *See* 5 U.S.C. § 551.

In order to issue a rule, an agency must complete a three step process – issuance of a notice of proposed rulemaking, receipt and consideration of comments on the proposed rule, and issuance of a final rule incorporating a statement of its basis and purpose. Section 553(b)(A) of the APA exempts several types of rules from the rulemaking process. The exemptions cover interpretative rules, general statements of policy, procedural rules, rules the agency has "good cause" to issue without the rulemaking process, and rules that apply to particular subject matters – e.g. military or foreign affairs. However, none of these apply to the Plan B dual marketing.

In particular, if the Agency issues a general statement of policy, it need not go through notice and comment. However, the task of distinguishing between a rule and a general statement of policy is complicated by the reality that many rules are also general statements of policy. To determine what procedures an agency must use, courts distinguish between rules and policy statements based on whether the agency statement has binding effect on members of the public. Thus, if a general statement of policy binds the public, the agency must issue the statement using notice and comment procedures. *See Pacific Gas and Electric v. FERC*, 506 F.2d 33 (D.C. Cir. 1974). The issue of simultaneous marketing would bind the public in the case of Plan B, as well as establish Agency precedent for future Rx-to-OTC switch decisions. Consequently, the issue is not merely a general statement of policy.

An additional exemption to the notice and comment procedures is issuance of an interpretative rule. A majority of the Circuits, the DC Circuit included, utilize the following factors to determine when an agency action is legislative, requiring notice and comment, or interpretative, which is exempt from notice and comment: (1) whether in the absence of the rule, there would not be a basis for enforcement action, (2) whether the legislative rule claimed to be interpretative is too vague or open ended to support the interpretative rule, (3) whether the agency has explicitly invoked its general legislative authority, or (4) whether the rule effectively amends a prior legislative rule. *See Health Insurance Association v. Shalala*, 23 F.3d 412 (D.C. Cir. 1994) and *ANR Pipeline v. FERC*, 205 F.3d 403 (D.C. Cir. 2000). Interpretative rules which do not require notice and comment are those which merely clarify or explain existing law or regulations. *Malone v. BIA*, 38 F.3d 433 (9th Cir. 1994). As argued above, simultaneous dual marketing presents a new and about-face interpretation of the FDC Act, not a mere clarification.

Any claim of exemption from the rulemaking requirements of the APA will be narrowly construed. Further, when rules to be adopted by an agency will have a broad impact not merely on the regulated industry but also on the general public in a matter which concerns the public and transcends economic issues, the notice requirements of the APA must be interpreted liberally. *See NRDC V. SEC*, 389 F. Supp. 689 (D.D.C. 1974). Also, when an agency statement effects a change in existing law or policy, it will be considered a substantive rule requiring notice and comment even if the agency labels the action as interpretative. *D&W*

Food v. Block, 786 F.2d 751 (6th Cir. 1986). Similarly, if a rule constitutes a change in prior agency position and has a substantial impact on the rights and obligations of members of the public, the rule is invalid if there has not been compliance with notice and comment procedures. *NRTA v. USPS*, 430 F. Supp. 141 (D.D.C. 1977), *affirmed* 593 F.2d 1360. *See also Benten v. Kessler*, 799 F. Supp. 281 (E.D.N.Y. 1992). Notice and comment rulemaking is required before FDA can approve an NDA Supplement that would produce the kind of sea-change presented by simultaneous dual marketing of an Rx and OTC drug product.

With regard to the matter at hand, we question whether the current Rx labeling for Plan B can be simplified to the extent necessary to present information in the OTC-required Drug Facts Format (21 CFR § 201.66), while also adequately warning patients of risks, side effects, and contraindications. For example, the labeling of human prescription drugs requires not only a summary of the essential scientific information needed for the safe and effective use of the drug, but also specific information required under 21 CFR § 201.57 including clinical pharmacology, and detailed contraindications, drug interactions and warnings. This information on prescription labeling consists of concise, yet still dense paragraphs of detailed drug information.

In contrast, during the rulemaking process for OTC drug labeling, FDA cited literature studies confirming that OTC drug product labeling requires short statements and clear graphical features and visual cues to ensure readability and comprehension. *See* 64 Fed. Reg. 13254 (March 17, 1999). These and other studies described the importance of adherence to directions for use, and reported on a number of preventable adverse drug reactions from OTC drug products with confusing labeling. *Id.* Accordingly, for certain drugs it is not possible to convey the amount of information needed to adequately inform consumers of the required directions for use and safety information using the simplified OTC labeling requirements.[14] Plan B is such a drug.

Moreover, FDA promulgated a regulation acknowledging that the safe and effective use of contraceptives requires that patients be fully informed of the benefits and risks involved in their use. *See* 21 CFR § 310.501. To provide full information, a patient package insert must be distributed. *Id.* That package insert must include a number of warnings including: information on medical conditions that are not contraindications to use but deserve special consideration in connection with oral contraceptive use and about which the patient should inform the prescriber; a warning regarding the most serious side effects of oral contraceptives; a statement of other serious adverse reactions and potential safety hazards that may result from the use of an oral contraceptive; a statement concerning common, but less serious side effects which may help the

[14] In the proposed rule making for OTC labeling, the FDA stated "information …presented in a paragraph format … is unappealing to the eye and may cause the reader to lose interest." 62 Fed. Reg. 9,024, 9,028 (February 27, 1997).

patient evaluate the benefits and risks from the use of an oral contraceptive; as well as eight additional areas of information. *Id.*

These two rulemakings are in direct conflict with each other in the case of the Plan B oral contraceptive product. We assert that the conflict may only be resolved by FDA adherence to the most comprehensive set of labeling – the patient package insert which, in turn, requires physician interpretation and prescription-only sale. Nevertheless, even in the alternative, it is clear that FDA cannot approve OTC labeling in the Drug Facts Format for Plan B without complying with APA notice and comment rulemaking to fully examine this regulatory conflict. Thus, FDA must initiate and complete full rulemaking proceedings in order to institute the simultaneous dual marketing of the same drug product as Rx and OTC.

IV. The FDA Approval Of An NDA Supplement Permitting The Simultaneous Dual Marketing Of Plan B (Levonorgestrel) Tablets As An Rx And An OTC Product Would Be Arbitrary, Capricious And Unlawful Agency Action

A. The Safety Profile and Method of Use of Plan B Requires the Supervision of a Physician and, Thus, an Rx Classification

As explained above, the FDC Act, FDA regulations, and Agency precedent all dictate that, in order for a drug to be approved for an OTC switch, it must be proven safe and effective for use by the lay public without the involvement of a physician. For Plan B, however, physician supervision is paramount to the safe use of the drug, for physical, emotional, and societal reasons. According to the drug's approved labeling, Plan B is used "to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse", and not for routine birth control. Consequently, its proper method of use involves a certain degree of knowledge of birth control options, failure rates of those options, and female biological cycles. To our knowledge, the Sponsor has provided no data on a woman's age-related or maturity-related ability to assess these items and appropriately choose Plan B as her contraception option without physician involvement. A physician/patient conversation on the proper use, risks, warnings, and range of birth control and emergency contraceptives, no matter how brief, is beneficial for women's health.

1. The FDA Lacks Proof that Plan B is Safe and Effective for OTC Use By Patients Ages 17 Years and Older

Health Risks Identified In the Approved Labeling of Plan B

An Rx-to-OTC switch may occur only when the prescription marketing of particular drug is not necessary for the protection of the public health. *See* 21 U.S.C. § 353(b)(3). Yet, the Plan B switch fails to meet this statutory requirement. In fact, at least four health risks are inherent in Plan B use, including serious drug interactions, increase in known risks, adverse reactions, and

lack of patient compliance. These risks will only be heightened by the drug's OTC marketing, with the likely result of increased adverse health events.

First, because Plan B interacts with other drugs and has the propensity to cause serious adverse events from drug interactions, the public health would be jeopardized if FDA permitted its OTC marketing. Specifically, the approved labeling warns against taking Plan B with nevirapine, rifampin or St. John's wort. These therapies are used to treat HIV-1, tuberculosis, and mild to moderate depression – diseases that affect more than 20 million people nationwide.[15] The amount of women who are taking these drugs to treat these diseases and, thus, should not take Plan B, is numerous and must be considered by FDA. Does FDA have evidence that, without physician involvement, women in these disease categories will understand the drug interaction risks and refrain from using Plan B? The OTC switch would remove the supervisory activity provided routinely by physicians and pharmacists who monitor and evaluate a patient's drug profile for drug/drug interactions. The combination of serious drug interactions with the lack of physician/pharmacist supervision inherent in the OTC marketplace supports the necessity of prescription dispensing to ensure the safe use of Plan B.

Second, without physician involvement, there is likely to be an increase in the known/expected risks described in the approved labeling. Oral contraceptives are associated with DVT's, ectopic pregnancies, dysplasia, liver hemangiomas, and other risks. An increase in these risks would be caused by a lack of screening for medical contraindications. The group Alabama Physicians For Life, Inc. (APFLI) noted in comments to FDA that in order for a patient to receive low hormone dose oral contraceptives, the patient is typically given a physical examination before receiving a prescription, while for a high dose of hormones as supplied in Plan B, the OTC use would not require a medical examination, medical history, or other physician counseling.[16]

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[15] According to the Centers for Disease Control (CDC), at the end of 2003, an estimated 1,039,000 to 1,185,000 persons in the U.S. were living with HIV/AIDS. *See* CDC National Center for HIV, STD and TB Prevention, Division of HIV/AIDS Prevention, Basic Statistics, at http://www.cdc.gov/hiv/stats.htm. More than 14,000 cases of tuberculosis were reported in 2003 in the United States. *See* CDC National Center for HIV, STD and TB Prevention, Division of Tuberculosis Elimination, Questions and Answers About TB, 2005, at http://www.cdc.gov/nchstp/tb/faqs/qu_introduction.htm. According to the National Institutes of Health (NIH), depression affects nearly 19 million Americans each year. *See* NIH National Center for Complementary and Alternative Medicine, St. John's Wort and the Treatment of Depression, at http://www.nih.gov/health/stjohnswort.

[16] *See* APFLI letters to FDA dated Sept. 20, 2004, Jan. 14, 2005, and Aug. 22, 2005, available at http://www.physiciansforlife.org/content/view/793/36/.

Ectopic pregnancies can lead to rupture and internal bleeding and may damage fertility. AAPLOG notes that in World Health Organization (WHO) EC Task Force trials, the ectopic pregnancy rate for EC users was triple the regular rate.[17] Another doctor commented to CWA that it is possible that a woman could have an ectopic pregnancy and believe that it was aborted when in fact, the pregnancy was not terminated, only to find out that the EC did not work when the pregnancy ruptures.[18] Schering Health Care, the makers of the morning-after-pill in the UK, was ordered to change the wording of patient information leaflets to make clear the potential risk of ectopic pregnancy. Does FDA have a plan to include a pre- and post-usage pregnancy test in the packaging to prevent or identify ectopic pregnancies?

In Australia, of the women who have remained pregnant despite taking a morning-after-pill, more than 1 in 20 have suffered an ectopic pregnancy. (Beezy Marsh, Anna Patty, Ectopic Pregnancy Linked to Morning-After Pill, Nationwide News Pty Lmt., The Daily Telegraph, January 31, 2003.) It is important that women be aware of risks and to seek medical assessment if their period does not return to normal after taking the morning-after pill. Ordinarily, a doctor prescribing Plan B would advise the patient of these risks before giving the prescription. To prevent delay in the diagnosis of ectopic pregnancy, FDA should require an OTC Plan B label to advise women that ectopic gestation can occur with emergency contraceptive pill failure. *See also* Nielsen, C.L., Miller L., Ectopic Gestation Following Emergency Contraceptive Pill Administration, Contraception, 2000 November, 62(5): 275-276; Galit Sheffer-Mimouni, et al., Ectopic Pregnancies following Emergency Levonorgestrel Contraception, Contraception, 2003. Without adequate labeling and pregnancy tests, Plan B must remain in the Rx-only category for all age groups.

Numerous studies have shown that more research is needed to improve tolerance of progestin-only contraceptives and identify alternative techniques that will not interfere with the endocrine events of the cycle. Outstanding research issues include the mechanisms of

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[17] CMO Update 35A [communication to all doctors from the Chief Medical Officer] January 2003; Department of Health, Published 04/02/2003. Overseas Post-marketing Surveillance of EC use (Levonelle, reported to the Committee on Safety of Medicines from the WHO Task Force trial) showed a reported ectopic pregnancy rate of 6%, three times the usual rate. The UK Dept of Health even issued a warning to its doctors to be aware of this. http://www.dh.gov.uk/PublicationsAndStatistics/LettersAndCirculars/CMOUpdate/CMOUpdateArticle/fs/en?CONTENT_ID=4003844&chk=2uZJEX.

[18] *See* Letter from Chris Kahlenborn, MD, Oct. 24, 2005, referencing Testimony before the FDA, December 16, 2003, re: Plan B, on file with the authors.

endometrial bleeding, definition of molecular and cellular targets for an endometrial approach to contraception, progesterone action, integrins, placental protein 14, insulin growth factor binding protein-1, and plasminogen activators. Emergency contraception has been found to suppress progesterone-associated endometrial protein in the midluteal uterus, potentially altering the endometrial environment unfavorably and affecting the survival of the early embryo. (Young, D.C., et al., Emergency Contraception Alters Progesterone-Associated Endometrial Protein in Serum and Uterine Luminal Fluid, Obstet Gynecol, 1994 August, 84(2):266-271.)

Other hormonal treatments have noted damage to the delicate balance of reproductive hormones. A study published in 2000 found that the Yuzpe regimen of emergency contraception reduced endometrial MUC-1 expression, increased endometrial oestrogen receptors, lowered luteal phase serum oestrogen concentrations, reduced endometrial thickness, and increased proportion of glandular supranuclear vacuoles in a statistically significant way. (Raymond, E.G., Lovely, L.P., Chen-Mok, M., Seppala, M., Kurman, R.J., Lessey, B.A., Effect of the Yuzpe Regimen of Emergency Contraception on Markers of Endometrial Receptivity, Hum. Reprod., 2000 Nov, 15(11): 2351-2355).

Third, FDA must further analyze the propensity for and severity of adverse events for Plan B, accumulated since the Agency's Oct. 31, 2003 Office of Drug Safety Postmarketing Safety Review. The signatories below maintain that this data supports the Rx-only sale of Plan B. Also, CWA has received comments from an OB/GYN who works with middle school students, regarding the possible steroidal abuse of Plan B by young athletes who believe that ingesting Plan B will help them delay epiphyseal closure.[19] The Physicians Desk Reference lists post-marketing reports demonstrating myocardial infarctions and strokes coincident with Norplant System (75 mg levonorgestrel implant). "Plasma concentrations average approximately 0.03 ng/mL over 5 years but are highly variable as a function of individual metabolism and body weight. Diffusion of levonorgestrel through the wall of each capsule provides a continuous low dose of the progestin. Resulting blood levels are substantially below those generally observed among users of combination oral contraceptives containing the progestins norgestrel or levonorgestrel." (1999 Physicians Desk Reference, 53rd Edition, pg. 3344-3345.) The physician argues that higher doses of levonorgestrel in Plan B, if used on a regular basis, would quite likely result in myocardial infarctions, particularly with the lipid profile of males. Is FDA prepared to study the effects of Plan B in males and require the addition of a specific warning before approving Plan B for OTC?

Fourth, FDA must consider, but does not have data on, the potential extent of a lack of patient compliance with the approved labeling for Plan B in the OTC setting. The approved labeling calls for limited usage, on an "emergency" basis, with two pills to be used per "dosage". If the product is misused in frequency or extent, either by taking it 10 days in a row or 12 times

[19] Physician comments are on file with the author.

per year or 5 pills instead of two, FDA should have data to support the safe use of the product in these foreseable ways. For example, Plan B is a progestin which is linked to breast cancer and repeated use could lead to an increase in the risk of breast cancer. Data on the safety and efficacy of Plan B for long term or frequent use must be further explored before the product is switched to the OTC market for any age group.

No Doctor/Patient Relationship for Addressing Complications (Physical and Emotional)

The American Academy of Pediatrics' (AAP) Policy Statement on Emergency Contraception given by the Committee on Adolescence (Ped 116:1026-1035 (Sept. 1, 2005)) recommends that teens who receive prescription EC via telephone receive a follow-up appointment to exclude an already existing pregnancy and/or to deal with issues of contraception and screening for sexually transmitted diseases. The statement also recommends doing an appropriate medical history analysis of the patient before prescribing EC. The policy statement further recommends pregnancy testing, antibiotic prophylaxis, and counseling for rape victims. These policies to ensure appropriate usage and adequate provision of aftercare assume a relationship between the doctor and the patient. Although recognizing "social pressures" to make EC more readily available, the AAP does not conclude that EC should be made available OTC. Indeed, doing so would undermine the doctor-patient relationship that provides a safety net for the patient and ensures that EC is used safely and effectively.

AAPLOG observes that the proposed Plan B OTC status would result in lack of physician oversight for patients at risk of failed MAP treatment and potential ectopic pregnancy. Furthermore, patients who elect to use MAP are generally also at high risk of getting STDs, and without physician oversight, undiagnosed and untreated STD's lead to infertility and cervical disease. AAPLOG maintains that use of the MAP is attendant with very serious long-term risks for the health of the women involved. AAPLOG insists that physician oversight, with STD testing, pap smears, and pregnancy tests as indicated, is essential for the well-being of women's health, as discussed in more detail below.

2. The FDA Lacks Proof that Plan B is Safe and Effective for OTC Use By Patients Under 17 Years of Age

In addition to the specific safety-related and public health concerns described above – all of which would apply to the use of Plan B in both the 17-and-over and under-17 patient subpopulations, CWA and its physician contacts have specific concerns about the safe use of Plan B by children and adolescents under 17 years of age.

Lack of Control with OTC Sale / Black Market to Underage Adolescents and Children

CWA has received multiple comments from doctors citing a concern over the ease with which underage adolescents and children will be able to obtain Plan B from their older friends, boyfriends, or relatives, based on currently insufficient age restriction mechanisms (e.g., age restriction mechanisms for cigarettes and alcohol have little effect on preventing underaged minors from obtaining cigarettes and alcohol).[20] The unintended creation of a "black market" for Plan B mitigates against an OTC age bifurcation for Plan B.

Physical and Biological Changes in Pre-Pubescent and Early Pubescent Girls

Dr. Harold Wallis, a Texas-based OB/GYN, has observed that the MAP primarily inhibits ovulation, disrupts follicular development, and produces other pathophysiological symptoms in pre-pubescent and early pubescent girls.[21] He notes that teenagers with abnormal menstrual cycles are commonly treated for the same kind of pathophysiological problems. Thus, without adequate age restriction enforcement to support Rx sales and physician supervision for this subpopulation, girls in this variable "biological" age range may create the same pathophysiological problems through the use of Plan B that necessitate common treatment by OB/GYNs.

Furthermore, this age group's general lack of understanding and experience with monthly biological cycles and the cause of pregnancy may lead to the misuse of Plan B. One study concludes that risk-taking behavior and poor assessment of the future consequences of their actions are common characteristics of 15 – 17 year olds. (Burgis, J. and J. Bacon, Communicating with the Adolescent Gynecology Patient, Obstetrics and Gynecology Clinics of North America, 30:251-260, 2003.) Similarly, the AAP's Policy Statement on Emergency Contraception given by the Committee on Adolescence notes: "Teens may not be able to give sufficiently adequate menstrual histories to exclude a preexisting pregnancy, and some teens already pregnant may try to use EC as an abortifacient." (Ped 116:1026-1035 (Sept. 1, 2005).)

Connection Between Plan B and STDs

APFLI noted in a letter to FDA that there has been a demonstrated link between the availability of MAP and exposure to STDs. APFLI cited data from the Swedish Institute for Disease Control and the Washington State Health Department demonstrating a significant

[20] Physician comments are on file with the author.

[21] Physician comments are on file with the author.

increase in chlamydia infection in women, especially teens, in the five years following OTC availability of MAP.

AAPLOG comments that in the five years following a Washington State pilot program to provide OTC MAP, teenage women showed a 23% increase in chlamydia infections. (Sexually Transmitted Disease Morbidity, Washington, State, Infection, Disease, and Reproductive Health, STD/TB Services & IDRH Assessment Unit, Washington State Dept. of Health 1997, available at http://www.doh.wa.gov/cfg/STD/mobidity.htm.) AAPLOG comments that these increases may well be associated with the increased and unprotected sexual activity facilitated by OTC MAP. Chlamydia causes infertility in a quarter of women and can reduce men's chances of becoming a father by 33%. As untreated chlamydia is a major cause for infertility, the availability of MAP OTC could lead to many women, especially teens, becoming infertile after several years of untreated and asymptomatic chlamydia.

Plan B offers no protection against STDs. In the UK where EC has been OTC for five years, figures show that over the past four years there has been a 76% increase in chlamydia diagnoses, a 55% increase in gonorrhea, a 54% increase in syphilis, and a 20% increase in genital warts. In all of these infections, the highest rates and the fastest increases were found in the 16-24 age group. (The Observer, May 15, 2005, available at http://observer.guardian.co.uk/magazine/story/0,11913,1482669,00.html.) In Scotland, rates of chlamydia rose by 106 percent between 1998 and 2004. Scottish Executive figures reveal almost half of all chlamydia cases diagnosed in 2002 were in people under 25, and there has been a 66% increase in cases involving youth under 16. A possible reason for this increase is that teenagers comforted by the idea of a contraceptive pill use condoms less. "Too often teens think that by taking the contraceptive pill, or ensuring their partner is taking the pill, that's all the protection they need…The pill can protect against pregnancy, but it's the ever increasing numbers of nasty diseases that will do your health more long-term harm." (Julia Hunt, Experts Fear Rise In Infertility as Chlamydia Cases Soar by 66 Percent, Scottish Daily Record & Sunday Mail, May 2, 2004, pg. 40, 41.)

A Swedish study published in 2002 reported that STDs were on the rise among adolescents who had OTC access to emergency contraception and other forms of contraception. (January W. Payne, Is Plan B Unsafe? Current Research Does Not Support Fears of Day-After Pill Dangers, September 6, 2005, Page HE01.) From 1999-2002, the cases of genital chlamydial infections increased between 20-28% in the teenage population, and 14-20% among 20-25 year olds. (K. Edgardh, Adolescent Sexual Health in Sweden, Sexually Transmitted Infections, 2002. 78:352-356.)

B. <u>The Risk/Benefit Profile of Plan B is Enhanced by Physician Involvement</u>

As discussed below, the Sponsor's label comprehension study – conducted specifically to support the OTC switch of Plan B – reveals significant label comprehension problems with the

medical information that should be provided to patients for this drug product. A proper understanding of the risks, warnings, contraindications, and benefits can be provided only through physician involvement in the prescribing of Plan B. Only by marketing Plan B as a precription product can proper patient education be undertaken.

Furthermore, physician involvement is necessary for patient counseling on the extra-label considerations related to contraception choices in the U.S., including physical, medical, emotional, and moral questions. Plan B should not be placed in the same category as an aspirin, a Tylenol, or an antacid. Use of Plan B without a prescription will lead to fewer or no follow up visits with doctors, no STD testing, pap smears, pregnancy tests and/or counseling about the effects of unprotected intercourse. AAPLOG notes that the most common reason young women visit a physician is to obtain contraception. The Association comments that it is in that environment where women have the best chance to be properly counseled, have detection of STDs, and make their best selections for family planning. FDA should not approve Plan B for OTC use but continue to require the use of a prescription so women of all ages will be provided the necessary medical care they deserve.

A physician contact shared his experience with providing emergency contraceptives to CWA. He maintains that most women and teenage girls are uneducated about the risks associated with being sexually active, including cervical cancer, human papilloma viral (HPV) infection, and other sexually transmitted diseases. Women under the age of 17 are at high risk for cervical cancer because the cells on the cervix are more sensitive to HPV infection. About the age of 17, these cells become covered with more protective cells. HPV infections cause cancer that can sterilize the woman, increase the risk of miscarriages in the future, or death. Because of the prevalent ignorance of the risks of HPV and cervical cancer, clinical standard of care requires a pap smear for cervical cancer screening before patients may receive a prescription for birth control pills. This physician argues that if birth control pills or MAP are ever made available OTC, cervical cancer rates will skyrocket, since the incentive to have pap smears done will largely cease in this at risk population. The physician reasons that when a shortcut is created for women to obtain contraceptive services without seeing a healthcare professional, women who are ignorant of STDs and their long-term effects, will remain ignorant.[22]

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[22] Physician comments are on file with the author, by Donald F. Thompson, MD, MPh, TM, Colonel, USAF, MC, SFS, National Defense University, Fort McNair, Washington, DC, (the comments reflect this physician's personal experiences and do not represent the views of the NDU or the federal government). His anecdotal experiences are as follows:
"I was caring for a 20 year old woman who was a junior in college, where I was performing periodic pap smears and microscopic examinations (colposcopy) of her cervix after her outpatient cryosurgery to treat the precancerous changes discovered on an earlier pap smear. As part of my evaluation, I always identify risk factors that help identify which patients are at high risk versus lower risk so treatment and counseling can be directed most

Published studies support this concern. A study published in 2001 found that EC users were more likely than controls to have never had a pelvic examination (26% vs. 6%, P<0.002) or a Pap smear (24% vs. 6%, P<0.002) (Stewart H.E., et. al., The Impact of Using Emergency Contraception on Reproductive Health Outcomes: A Retrospective Review in an Urban Adolescent Clinic, J. Pediatric Adolescent Gynecology, 2001 Nov, 14(4): 163-9). A Washington State Pharmacy study published in 2001 found that among 126 adolescents who obtained EC directly from a pharmacist without a prescription, 81% needed a new method of ongoing contraception, an evaluation for sexually transmitted disease, or both. The study concluded that many adolescents using EC need additional medical care and recommended that programs designed to increase EC access should use opportunities to link adolescents with more comprehensive reproductive health care services. (Sucato, G.S., Adolescent's Use of Emergency Contraception Provided by Washington State Pharmacists, Contraception, 2001 March; 63(3):123-129.)

An article from the International Peace Maternity and Child Health Hospital of the China Welfare Institute stated that although reported ectopic gestation after failed EC have been rare, clinicians should be aware of the possibility of an ectopic gestation when an EC pill fails. The

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appropriately. This young lady was at high risk because she had had over three lifetime sexual partners (she had had four), and she had first had sex at age 15 (anytime before age 17 is high risk because of HPV sensitivity). When I asked her what she had been taught in high school about sex and its risks, she said that the risks were just glossed over and that the message was that if you are going to have sex, then you just needed to use birth control to avoid getting pregnant. No one had ever explained the other risks of sex, like cervical cancer and other sexually transmitted infections.

Another patient was a 17 year old who had only started having sex in the previous year and had only had one sexual partner. She was referred for evaluation of an abnormal pap smear that was discovered during her first exam when she was prescribed birth control pills for the first time. Her colposcopic exam was abnormal, and I did several biopsies of her cervix. When I tried to schedule her for a follow-up exam two weeks later, her main concern (and that of her mother) was that the appointment not conflict with her high school graduation celebration. Her biopsies came back highly abnormal, with a result of carcinoma in situ, a condition that required urgent surgery to remove the cancer before it spread. Instead of celebrating the major step of graduating high school with her classmates, she was faced with a diagnosis of cancer and the anxiety of wondering if the cone biopsy of her cervix was able to get all the cancer, and if she was ever going to be able to get pregnant and carry a baby to term. She and her mother were totally ignorant of the risks of sexually transmitted infections and cervical cancer and had only come into the clinic to get birth control pills so she would not get pregnant. If she had been able to get the MAP without seeing a healthcare professional, she probably would have gone on to develop invasive cervical cancer in the next year because of the aggressive strain of human papilloma virus with which she was infected.

I had another 18 year old patient who suffered from anorexia nervosa. She had an insatiable need for reassurance from others, and moved from one dependant relationship to another, using sex as the foundation for her relationships. I treated her and one boyfriend for Chlamydia and worked closely with our counseling center to provide supportive services for her issues with her distorted body image. Despite cautions about sexual activity and sexually transmitted diseases, she continued in self destructive relationships. Our clinic had a policy that the MAP must be provided to anyone who requested it, and she was a regular client on Monday mornings. Despite counseling, she refused to think ahead and use other forms of birth control, but instead continued to engage in "spontaneous" sexual activity since she had easy access to the morning after pill.

department recommended women use the established service networks to enhance education and dissemination of information on emergency contraception. The department also urgently advised that health care providers should advise women very clearly that ectopic gestation is possible after failed EC treatment. (Jian, Z., Linan, C., Ectopic Gestation Following Emergency Contraception with Levonorgestrel, Contraception 2002 December, 66()6: 433-437).

A discussion of the medical/societal discourse on whether life begins at fertilization, conception, implantation or the embryo stage is beyond the scope of these Comments. FDA would be remiss, however, if it did not acknowledge that women's views differ on this point in the U.S. At least one national survey shows that almost half of American women believe that human life and pregnancy begin at fertilization. (Zogby J., American values, vol. V: Zogby International, 2000.) Similarly, a 1998 survey of physicians who were predominantly ACOG members noted that 50% indicated that pregnancy begins with fertilization. (Spinnato JA., Informed consent and redefining of conception: a decision ill-conceived?, J. Matern. Fetal Med. 1998; 7:264-268.) Likewise, whether a "therapeutic" effect of Plan B that may occur after fertilization but before implantation could be consistent with the term abortifacient will not be discussed here. Given these facts, however, the Rx-to-OTC switch of Plan B and resultant removal of physician involvement from the use of this drug has negative implications for patient informed consent. Specifically, via informed consent, patients should fully understand the risks and benefits of the drugs they take. Even strong proponents of EC agree that women should be informed about its mechanisms of effect for adequate consent. *See* Drazen, J.M., Green, M.F. Wood, A.J.J., The FDA, politics, and Plan B [letter]. N. Engl. J. Med 2004; 350:2414. Only through the physician/patient relationship can a patient's philosophical or religious convictions and Plan B's contraceptive mechanisms be addressed. OTC labeling alone cannot adequately describe these biologically-sophisticated and morally controversial issues. *See, e.g.,* Letters to the Editor, Contraception 72 (2005) 394-395.

C. FDA's Jurisdiction Over the "Safety and Efficacy" of Drugs Provides it With Sufficient Authority to Consider Potentially Negative Societal Ramifications Related to the OTC Sale of Plan B

FDA's jurisdiction over the "safety and efficacy" of drugs provides it with legal authority to consider morality, misuse, age-appropriate sexual behavior, and related social issues in the context of the Plan B approval for OTC marketing.[23] There is no question that FDA can and

[23] Those who argue that morality should not affect FDA's decision-making hypocritically cite moral judgments in support of the OTC approval of Plan B. For example, certain Congressional representatives have asserted that "Public health experts have estimated that over-the-counter sales of the emergency contraception pill Plan B would cut the rate of unintended pregnancies in half and reduce the number of abortions by more than 500,000 per year." U.S. Reps. Henry

should, as a matter of law, take issues of morality and social conscience into account when those issues relate directly to the drug's risk/benefit analysis or safety/efficacy profile – two concepts with which FDA has decades of experience and for which the courts provide deference to the Agency. If there is evidence that the expected patient population is likely to use the drug in a way that decreases the drug's safety, negatively impacts the patient's health, or tips the risk/benefit balance toward greater risk, FDA must consider this evidence when addressing the approval decision. FDA routinely takes potentially harmful patient use scenarios into account in its NDA approval decisions, whether for potent pain drugs (for which abuse and misuse are Agency considerations), for obesity drugs (for which preferences for nutrition and exercise are Agency considerations), or for HIV home test kits (for which the patient's mental well-being and need for a learned intermediary or counselor was an Agency consideration). OTC emergency contraceptives fall squarely within this listing of drugs in which self-destructive patient actions may cause more harm than good.[24]

Waxman, D-CA, and Louise Slaughter, D-NY, circulated a "Dear Colleague" letter and Fact Sheet on October 12, 2005, referencing these factors as a reason that FDA should approve the OTC sale of Plan B. FDA cannot take the societal concern of unintended pregnancies into account, while refusing to consider the societal concerns of an increase in unprotected sex and STDs, off-label over-use/repeat use of Plan B, and sexual abuse.

[24] FDA should reject the argument posited by some that an FDA decision denying OTC approval to Plan B is too paternalistic. FDA has ample precedent over the years where it has made an "unpopular" decision for reasons that were arguably paternalistic. FDA's mission is to protect the public health by assuring the safety, efficacy, and security of human drugs. FDA has viewed this mission broadly over the years to include the "blocking" of access to certain drug products that, while safe and effective on a scientific basis, were not appropriate for OTC use for broader public health reasons. For example, the FDA removed phenacetin from the market after use as an ingredient in OTC drug products for over 80 years. In the FDA's notice of the withdrawal of phenacetin from the market, the basis cited for approval was "phenacetin's *high potential for misuse* and its unfavorable benefit-to-risk ratio when incorporated in analgesic combinations which are then subject to excessive chronic use." (Emphasis in original.) 48 Fed. Reg. 45486 (Oct. 5, 1983). In the proposed rule, the FDA stated that phenacetin was not alone among analgesics in its ability to cause nephropathy, but because of its greater likelihood for abuse, the agency believed other safe and effective analgesics would be sufficient for consumers. 47 Fed. Reg. 34636, 34638 (Aug. 10, 1982). Similarly, in 1972 the FDA severely restricted the allowable OTC uses for the drug hexachlorophene as an antibacterial product. The restrictions on the use of hexachlorophene followed the deaths of a number of infants in France due to the use of a baby powder contaminated with six percent hexachlorophene. 37 Fed. Reg. 20160 (Sept. 27, 1972). Although hexachlorophene was recognized as a safe and effective bacterio-

1. OTC Sale of Plan B Would Further the Interests of Sexual Predators

Evidence suggests that making Plan B available OTC would serve to further the predatory interests of sexual offenders who molest family members, children of friends, or students, as well as adult "boyfriends" who commit statutory rape. Namely, rapists and sexual predators could "stock up" on emergency contraceptives and keep a ready supply in, for example, their bedroom drawers or pockets to give to their victims after committing each sexual crime.[25] *Cf.* Press Release for Congressman Don Manzullo, 16th District of Illinois, entitled "Manzullo's Title X Statutory Rape Reporting Provision Will Become Law" (Oct. 21, 1998) (noting the incident of a 37-year-old teacher having his 14-year-old student take birth control injections so that he could "continue molesting her at will"). *See also* Paul Bissell & Claire Anderson, Supplying Emergency Contraception Via Community Pharmacies in the UK: Reflections on the Experiences of Users and Providers, 57 Social Science & Medicine 2,367 (2003) (noting the concern that the widened availability of EC might provide an opportunity for men to coerce women into having unprotected sexual intercourse against their will).

In fact, several studies have shown that men are the most frequent buyers of MAP and that many learn about these drug products from advertisements in men's magazines. *See* Karnjariya Sukrung, *Morning-After Blues*, Bangkok Post, June 10, 2002. The Bangkok Post further states that "[sexual predators] buy pills for their girlfriends or wives so that they don't have to wear condoms….Some women…said they that they didn't even know what they were taking; that the guy just said it was a health supplement." *See id*. The Bangkok Post continues, "Although many feminists believe that the morning-after pill gives them more control over their own bodies, it would seem, judging from the few studies conducted so far, that it is actually being used by men to exploit women." *See id.* Thus, the unrestricted access of Plan B would give these sexual predators another method to shield their abusive behavior. OTC Plan B opens the door farther to sexual predators by reducing a woman's bargaining power at the critical moment when the decision is made whether or not to have sex.

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static skin cleanser, FDA concluded that a "risk to benefit ratio" analysis justified restriction of the availability of the drug even though the at-risk population was extremely small. *Id.*

[25] For our discussion on the societal ramifications of OTC marketing for emergency contraceptives, we draw on the Written Testimony of Jill L. Stanek, on behalf of CWA of Illinois, regarding the MAP, presented at the Joint Meeting of the FDA Nonprescription Drugs Advisory Committee and the FDA Advisory Committee for Reproductive Health Drugs (Docket No. 01P-0075) (Dec. 16, 2003). This written testimony can be found at http://www.cwfa.org/articles/4998/CWA/life/index.htm (last accessed October 29, 2005).

The OTC availability of the MAP would in fact only increase this likelihood of sexual abuse of young girls by adult men. Without a link to medical services for emergency contraceptives, the likelihood is much greater that a sexual predator will continue to commit his crime without detection and with greater frequency if he can find a way to keep his victim from seeing a licensed physician to seek contraception. *Cf.* Cathy O'Leary, *Abbott Wants Clamp on Morning-After Pill*, The West Australian, June 8, 2004. How much more will minor girls be exploited if emergency contraceptives are available OTC? OTC access to emergency contraception will increase the likelihood that sexual perpetrators will go undetected and that young girls will be sexually abused. Switching Plan B to OTC would thwart Congressional attempts to protect minors from sexual abuse.

Conversely, if Plan B remains in the Rx-only category, physicians will remain involved with its prescribing and the potential for proper reporting of sexual predators will be increased. CWA has received comments from a physician advocating that victims of sexual abuse need medical consultation, not quick fixes in complete secrecy and isolation. According to APFLI, public health policy dictates that victims of rape or incest should be encouraged by medical professionals to go to a hospital emergency room where equipment and training advances the collection of forensic evidence and the provision of victim care. Similarly, AAPLOG comments that there is no question that Plan B OTC will become the leading "rape" drug in the country. AAPLOG is apprehensive of the "benefits" of Plan B OTC for sexual predators; namely, quietly hiding the rape, leading to "covering up" of crime, and the victim's perception of a second societal abuse, since rapes are criminal matters that require medical examination to assess injury, collect forensic evidence, get baseline STD testing, and possibly treat infections.

2. OTC Sale of Plan B Would Exacerbate the Abuse of Teenage Girls

Evidence also suggests a relationship between the age of a woman, the risk of abuse, and the likelihood of pregnancy. For example, Planned Parenthood[26] reported that teenage girls with older partners are more likely to become pregnant than those with partners closer in age. Among women younger than 18, the pregnancy rate among those with a partner who is six or more years older is 3.7 times as high as the rate among those whose partner is no more than two years older. *See* M. Joycelyn Elders, *Adolescent Pregnancy and Sexual Abuse,* 280 Journal of Amer. Med. Assoc. 648 (1998) (noting that "coercive sex acts against adolescent girls are frequently perpetrated by their boyfriends….Boyfriends who are considerably older than their adolescent girlfriends have been found to be responsible for a majority of teen pregnancies"). Furthermore, Planned Parenthood also reported that teenagers who have been raped or abused also experience higher rates of pregnancy – in a sample of 500 teen mothers, two-thirds had histories of sexual and physical abuse, primarily by adult men averaging age 27. *Cf.* M. Joycelyn Elders,

[26] As noted in the Written Testimony of Jill L. Stanek.

Adolescent Pregnancy and Sexual Abuse, 280 Journal of Amer. Med. Assoc. 648 (1998) (noting that sexual abuse is a common antecedent of adolescent pregnancy, with up to 66% of pregnant teens reporting histories of abuse). Thus, evidence indicates that sexually active young girls are likely to be the victims of sexual abuse and carry a higher risk for pregnancy.

This relationship between age and abuse suggests the particular vulnerability of young girls to sexual abuse. If FDA approves Plan B for OTC use, this medication will be more readily available, and sexual predators will in effect have lower barriers to restrain their actions – they will have less fear of impregnating a woman, and the patterns of abuse will become more prevalent. This abuse will in turn target younger victims, as indicated by the correlation discussed above.

3. OTC Sale of Plan B Will Not Reduce the Number of Abortions and Unintended Pregnancies

A potential reduction in the number of abortions and unintended pregnancies is not a sufficient reason to allow the OTC marketing of Plan B, and evidence exists to the contrary. While some argue that Plan B OTC status is desirable because the unwanted pregnancy rate and abortion rate would decrease, studies indicate that this relationship may not be true. One study showed that the advanced provision of emergency contraceptives had no effect on abortion rates. *See* Anna Glasier, Karen Fairhurst, et al., *Advanced Provision of Emergency Contraception Does Not Reduce Abortion Rates*, 69 Contraception 361 (2004). *See also* Stuart Nicolson, *Morning-After Pill Campaign Fails to Stem Abortion Rate*, Daily Mail (London), December 3, 2004 (noting that new research indicates that distributing EC more freely does nothing to reduce the number of abortions).

Further research, released on January 5, 2005, also fails to support the contention that OTC marketing of Plan B would decrease the number of pregnancies. A study of 2,117 young women ages 15-24 reported in the Journal of the American Medical Association (JAMA) demonstrated that providing young women with non-prescription access to emergency contraception did not lead to any decrease in the pregnancy rate. Even women provided with an advance supply of EC did not have a decreased pregnancy rate. The study demonstrates that readily available EC does not lead to a reduction in unintended pregnancies, despite erroneous claims to the contrary by the study's conclusion and other EC proponents. *See* Raine, TR, et al, Direct Access to Emergency Contraception Through Pharmacies and Effect on Unintended Pregnancy and STIs, JAMA 2005, 293:54-62, at www.jama.com.[27]

[27] CWA has received comments questioning whether the author's conflict of interest dilutes the significance of certain studies. CWA understands that Dr. Tina R. Raine served on the expert advisory panel for the Sponsor for the OTC application of Plan B to the FDA. She did so while

Dr. Raine previously published a study that ostensibly refutes any concerns about possible increased STDs and risky sexual behavior in women with EC availability (Emergency Contraception: Advance Provision in a Young, High-Risk Clinic Population, Obstetrics & Gynecology 2000; 96:1-7). Interestingly enough, her study cites data that women in the treatment group (those that had access to EC) were more likely than those in the control group to report using less effective contraception. Furthermore, the women who did not have access to EC were more likely than the treatment group to report consistent birth control pill use. Raine's study demonstrates that easier access did not lead to changes in risky sexual behavior or routine contraception use. The Raine study clearly shows that there was no difference in pregnancy rates between those women who had access to EC, and those who did not. In other words, the very justification for proving EC, namely decreased unintended pregnancies, was lacking.[28] Furthermore, the adolescents in this study stated themselves that they would have more unprotected intercourse with the availability of EC. The examination of behavior in the study's short time frame of six months could not confirm this but, with the passage of time, and with the increased comfort and familiarity with EC, CWA's physician contacts believe that this increased unprotected intercourse would likely occur.

Other CWA physician contacts have commented that, in a review of all studies relating to the topic of OTC MAP and its effects on the sexual activity of women, there has not been found to be a difference in either abortion rates or pregnancy rates. The groups in the studies are actually given advance provision of the MAP, which is more aggressive than actually having access to the drug OTC. The women were also in a clinical study setting, knowing they were under observation, and were educated and instructed regarding the drug's use. Presumably, the physicians note, this setting should be optimal to observe a decrease in abortions and unintended pregnancies. Instead, the studies reflect no change, and in fact, demonstrate increased risky sexual behaviors after experience with MAP access. Furthermore, to our knowledge, there has never been a randomized study with a control group not utilizing MAP; therefore, the comparative number studies used to prove efficacy over using nothing is simply anecdotal and not a generally acceptable manner in which to determine the efficacy of a product.

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at the same time arranging to conduct two studies designed to directly counter the concerns raised by opponents of Plan B's OTC status.

[28] If the rebuttal to this concern is that the study was not large enough to find a difference in this young age group, the same argument can be made regarding the lack of differences they found in teens' sexual behavior or the rate of acquiring new STDs. In other words, if one argues that it will take time for pregnancy rates to decrease, or a larger population studied to see the benefit, then one can just as properly argue that with time or a larger population size, one will also see an increase in risk-taking behavior and an increase in STDs among these individuals.

AAPLOG highlights the UK study above and a separate San Francisco study, referenced herein, showing that there is no difference in the abortion rate or in the unintended pregnancy rate between women who are given the MAP free to take home for immediate use and women who have to obtain prescriptions for MAP.

A CMDA member comments that there are multiple studies that show that easier access to contraception increases sexual activity rates, decreases the age of onset of sexual activity, and increases the incidence of STDs. One study found that pregnancy rates are unaffected by readily available MAP; that increasing the availability of birth control to teenagers increases STD rates, especially when MAP is made available; and that teens make rational decisions based on available options (i.e., when contraception is less available, they have sex less frequently). (David Paton, Random Behavior or Rational Choice? Family Planning, Teenage Pregnancy and STIs, Nottingham University Business School, UK, presented at the Royal Economic Society Conference, April, 2004.) Another study shows that widespread distribution of advanced supplies of MAP did not reduce unintended pregnancy, and MAP may be less effective than believed; namely, efficacy is based on unreliable data and a great number of assumptions that have been questioned both in the past and more recently. (Anna Glasier et al, Advanced Provision of Emergency Contraception does not Reduce Abortion Rates, Contraception 69 (5): 361-366, May 2004).

While it has been argued that OTC MAP would reduce abortion rates by up to 50%, the evidence presented does not support this contention. As noted above, a 2004 study showed that there was no effect on abortion rates with the advanced provision of MAP. (Anna Glasier, et al., Advanced Provision of Emergency Contraception Does Not Reduce Abortion Rates, Contraception 69 (2004) 361-366.) The study suggested that widespread distribution of advanced supplies of MAP may not be an effective way to reduce the incidence of unintended pregnancy. Indeed, in Great Britain, abortion rates have increased for teenagers in the years since OTC availability. A UK article reports that there were 2.1 % more abortions performed in England and Wales in 2004 than 2003. In the last three years, abortions in the UK have increased from 176,000 in 2002, to 181,000 in 2003, to 185,400 in 2004. (Steven Ertelt, British Abortion Figures Show Increase of Two Percent in 2004, LifeNews Editor, July 27, 2005, London England.) The number of abortions increased despite the government's spending £40 million to promote contraception. *Id.* An article in the Observer, a British publication, states that since the morning-after-pill was made available without prescription five years ago, there has been little change in teenage conception rates. Teenage conceptions have fallen by about 10 percent, but in 13 local authorities with the highest rates, 11 have seen the numbers of teenage pregnancies increase. (The Observer, May 15, 2005, available at http://observer.guardian.co.uk/magazine/story/0,11913,1482669,00.html.)

Similarly, while the sales of emergency contraceptives have risen sharply in Belgium, there appears to be no signs of a reduction in the number of abortions. *See Abortions "Rise" Despite Morning After Pill*, Expatica, August 27, 2004 (stating that some "estimate that the number of abortions has gone up, despite the morning after pill").

In Scotland, one in five 16 year old girls takes the morning-after pill each year. However, the birthrate for 16-19 year olds rose from 63.6/1000 in 1983 to 68.1/1000 in 2004. (Julia Hunt, Experts Fear Rise In Infertility as Chlamydia Cases Soar by 66 Percent, Scottish Daily Record & Sunday Mail, May 2, 2004, pg. 40, 41.)

In Sweden, teenage pregnancies declined from 1975-1985; abortions decreased as well. However, in the late 1980s, abortions increased. A changing pattern of contraceptive use was discussed as a contributing factor (e.g., less use of oral contraceptives due to fear of adverse effects). Since then, subsidies for oral contraceptives have emerged, and emergency hormonal contraception has become easily available. In spite of these factors, teenage abortion rates have been increasing, from 17/1000 in 1995 to 22.5/1000 in 2001. Furthermore, widespread availability of sexual education, contraception, and abortion services does not protect teenagers from STDs, pregnancy, and sexual victimization. (K. Edgardh, Adolescent Sexual Health in Sweden, Sexually Transmitted Infections: 2002; 78:352-356.) AAPLOG notes that in the 5 years following non-prescription EC availability, Sweden experienced a 31% increase in teen abortion. (K. Edgardh, Adolescent Sexual Health in Sweden, Sexually Transmitted Infections, 2002, 78: 352-356.) A Swedish study assessing the short- and long- term risk of unintended pregnancy in women receiving emergency contraception (and contraceptive counseling) found that in a long-term follow up, 10 of 134 women experienced an unplanned pregnancy, 9 of which resulted in abortions. All these women had either started and terminated oral contraceptives or had never commenced the prescribed oral contraceptives. The study concluded that women who request emergency contraception are, despite a planned follow-up with contraceptive counseling, a high risk group for new unintended pregnancies. (Falk, G. et al, *Young Women Requesting Emergency Contraception Are, Despite Contraceptive Counseling, a High Risk Group for New Unintended Pregnancies*, Contraception, 64(1):23-27 (July 2001)).

Given that accumulating sound scientific evidence that OTC access to EC doesn't decrease unintended pregnancy or abortion rates, any claim that OTC access will cut these social ills betrays the public trust.[29] Moreover, any FDA reliance on such argument is improper and unsupportable.

[29] *See* AAPLOG News Release, Statement of the American Association of Pro-Life Obstetricians and Gynecologists on JAMA Emergency Contraception Study, January 12, 2005.

D. It Is Unlawful For FDA To Approve the Plan B NDA Supplement Without Data from a Clinical Study Involving the Relevant Pediatric Subpopulation

In a case where the Sponsor intends to label a drug for use in the pediatric population, FDA has only limited authority to cede the requirement for pediatric testing.[30] FDA cannot approve an NDA or an NDA Supplement without the submission of data that are adequate (1) to assess the safety and effectiveness of a drug product in pediatric subpopulations and (2) to support dosing and administration in these subpopulations. *See* 21 U.S.C. § 355c(a)(2).

The Pediatric Research Equity Act (Public Law 108-155) (PREA), which amended the FDC Act, requires the conduct of pediatric studies for NDAs and NDA Supplements requesting approval for a new indication and a new dosing regimen, among other items. *See* 21 U.S.C. § 355c(a)(1); *see also* Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (2005), p. 3 (hereafter, "Pediatric Research Guidance") (stating that PREA requires all NDAs or NDA supplements to contain a pediatric assessment). Because PREA makes this legislation retroactive, all NDAs submitted on or after April 1, 1999 are subject to PREA. *See id.* The Plan B NDA Supplement was submitted after April 1, 1999 and requested approval for

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[30] We note that Plan B is not eligible for a waiver of the pediatric requirements. FDA may grant a full waiver of the requirement to submit pediatric assessments only if the applicant certifies and FDA finds one or more of the following:

> (a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).
>
> (b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act).
>
> (c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

See Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (2005), pp. 9-10. Plan B does not fulfill any of these conditions. First, studies are both possible and practicable. Secondly, the Sponsor of OTC marketing for Plan B seeks the Rx-to-OTC switch precisely because it presumes that Plan B would be safe and effective in pediatric age groups. Lastly, the intention of marketing Plan B OTC specifically contemplates the drug's use in a substantial number of pediatric patients. Thus, Plan B does not meet any of the criteria for a full waiver of pediatric requirements.

the new indication/dosing regimen of OTC use by women 16 years and older for pregnancy prevention and, thus, is subject to the PREA requirements.

PREA requires the submission of a pediatric assessment "in *all* relevant pediatric populations." PREA requires a pediatric assessment for each age group in which the drug product is expected to provide a meaningful therapeutic benefit over existing therapies for pediatric patients or is likely to be used in a substantial number of pediatric patients. *See* Pediatric Research Guidance (emphasis added). A "pediatric assessment" consists of data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, as well as other data that are adequate to assess the safety and effectiveness of the drug product in pediatric subpopulations and to support dosing and administration for each pediatric subpopulation. *See* 21 U.S.C. § 355c(a)(2). *See also* Pediatric Research Guidance.

In the case of Plan B, a pediatric assessment should have been required for two pediatric subpopulations: Children, ages 2 to 12, and adolescents, ages 12 to16. Given its indication as an emergency contraceptive, the Plan B patient population logically includes all females who can become pregnant – that is, as of the age their first menstrual period begins (i.e., "menarche") until they no longer have a menstrual period (i.e., "menopause"). According to FDA, the average age of menarche in the United States is 12 years, although menstruation may commence in healthy females as early as age 10.[31] In the past, the Agency defined "pediatric population(s)" and "pediatric patient(s)" as the age group "from birth to 16 years, including age groups often called … adolescents."[32] Therefore, the population of menstruating females (i.e., 10 or 12 and older) and the pediatric population (i.e., up to 16) overlap by up to 6 years. Because Plan B will be used by some number of adolescent girls who become pregnant, FDA should have required the Sponsor to produce specific and statistically relevant safety and effectiveness data for the pediatric population. Extrapolation from adult data alone is not appropriate for this product because of the broad range of "normal" physiologic issues experienced by the subpopulation of adolescent girls. The safety and effectiveness data in adults would not be sufficiently similar to the under-17 subpopulation to support such extrapolation. *See* Pediatric Research Guidance, at 5-6.

If a pediatric assessment is not submitted by an applicant in accordance with PREA, not only may FDA deny approval to the drug application, but also the drug product may be

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[31] *See On the Teen Scene: A Balanced Look at the Menstrual Cycle*, FDA Consumer Magazine (Dec. 1993) (available at http://www.fda.gov/fdac/reprints/ots_mens.html). In the U.S., the average age of the start of menopause is 51. *See Taking Charge of Menopause*, FDA Consumer Magazine (Nov.-Dec. 1999) (available at http://www.fda.gov/fdac/features/1999/699_meno.html).

[32] *See*, formerly, 21 C.F.R. § 201.57(f)(9).

considered misbranded solely because of that failure to submit a pediatric assessment. *See* Pediatric Research Guidance. Thus, if a firm submits a supplemental NDA providing for a switch of a drug product from Rx-only status to OTC status (for a certain subpopulation based on age, for example), that firm would need to submit a pediatric assessment in order to comply with the provisions of PREA. The need for such an assessment is especially salient for a drug product intended to be sold OTC (even if just for adults) because of the high likelihood of such a drug product to be used in a substantial number of pediatric patients – whether access is obtained improperly through a "black market" scenario or lawfully with physician supervision.

After more than a decade of supporting "the legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling" that culminated in the PREA, it is curious that, here, FDA failed to require a pediatric study for a drug that is being marketed specifically to the under-16 patient subpopulation. Pediatric Research Guidance, at 2.

E. It Is Unlawful for FDA to Approve the Plan B NDA Supplement on The Basis of the Sponsor's Label Comprehension/Actual Use Study

FDA balances numerous factors when considering a drug sponsor's application for an R_x-to-OTC switch. First and foremost, patients using an OTC drug should be able to self-medicate after reading the drug's labeling. Consequently, FDA expends considerable effort to analyze the results of label comprehension studies conducted by the drug sponsor. FDA's review of the Sponsor's label comprehension study was presented on December 16, 2003, by Dr. Karen Lechter at a joint meeting of the FDA's Nonprescription Drugs Advisory Committee and its Advisory Committee for Reproductive Health Drugs,[33] and shows that the Sponsor's study is not adequate to support the Rx-to-OTC switch of Plan B.

The information presented casts considerable doubt on FDA's conclusion that Plan B can be safely self-administered by adults – not to mention by adolescent girls.[34] Only 75% of all respondents answered that Plan B should not be taken in the presence of unexplained vaginal bleeding. Among the low-level literacy group that figure declined to 69%; with high-literacy respondents answering correctly only 81% of the time. Thus, one-quarter of all respondents failed to understand this crucial fact.[35] Only 67% of all respondents answered correctly that Plan B is designed to serve as a backup for regular contraception methods – not as a replacement for

[33] FDA, Center for Drug Evaluation and Research, Nonprescription Drugs Advisory Committee (NDAC) in Joint Session with the Advisory Committee for Reproductive Health Drugs (Dec. 16, 2003) ("Joint Hearing"), at 118-124. Dr. Lechter (J.D., Ph.D) is an FDA social scientist.

[34] http://www.fda.gov/ohrms/dockets/ac/03/slides/4015s1.htm.

[35] http://www.fda.gov/ohrms/dockets/ac/03/slides/4015S1_04_FDA-Lechter_files/frame.htm.

them. Among those of low-literacy this figure dropped to 46%; whereas for women of high literacy the figure was 78%.[36] Accordingly, one-third of all respondents failed to understand that Plan B is not a typical method of contraception.

Given results like these it is not surprising that Dr. Louis Cantilena (M.D., Ph.D.), Plan B Joint Hearing, noted that "if you look at other studies that … we've heard about in the past for statins and the heartburn drugs, the overall success of the [Plan B] comprehension study was really not that good[.]"[37] Later, Dr. Cantilena observed, "The label comprehensi[on] study was, I think, an overall failure."[38]

Furthermore, Dr. David Hager asked the FDA panelists about data received from Washington State pharmacists who had participated in Plan B's actual use studies. The pharmacists indicated that 85% of the Plan B patients required medical follow-up – usually consisting of medical evaluation and counseling. Dr. Hager asked whether there was any concern about a potential failure to diagnose ectopic pregnancies in this population if the drug were made available OTC.[39] Dr. Hager does not appear to have received an answer to his question during the hearing. The question needs to be asked: if 85% of a population of women using Plan B needed medical follow-up, how will those patients receive the care and information they need in an OTC environment?

FDA improperly focused its concerns on whether Plan B could be safely used by young teenage girls, rather than considering also women with pathophysiological issues. In FDA's 2004 "Not Approvable Letter" to the Sponsor, Dr. Steven Galson noted that FDA had "concluded that you have not provided adequate data to support a conclusion that Plan B can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug."[40] The Sponsor chose not to propose new label comprehension and actual use studies designed to demonstrate Plan B's safety

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[36] http://www.fda.gov/ohrms/dockets/ac/03/slides/4015S1_04_FDA-Lechter_files/frame.htm.

[37] Joint Hearing at 136.

[38] Joint Hearing at 411.

[39] Joint Hearing at 137.

[40] Not Approvable Letter, Steven Galson, M.D., Acting Director of the Center for Drug Evaluation and Research, FDA, to Barr Research, Inc. (May 6, 2004) at 1. Galson noted the small sampling of adolescent women in Barr's actual use study: "You propose OTC status for *Plan B* for both adults and children based primarily on an *actual use study* in 585 subjects. Only 29 of the 585 subjects enrolled in the study were 14-16 years of age, and none was under 14 years of age." *Id.*

in this younger population. Rather, the Sponsor redoubled its efforts to advance a proposal it had made to FDA on March 11, 2004 in an amendment to its application that called for a dual approach for Plan B in which the drug would be available OTC to women 16 and older and as a prescription drug for women under age 16.[41]

As stated above, we believe that FDA lacks the legal authority under section 503(b) of the FDC Act to allow this drug product to be sold OTC to women 17 years old and over while requiring a prescription for girls under 17. With that in mind, FDA should reexamine the abysmal results produced by Plan B's proposed labeling in the Sponsor's label comprehension study. It is our contention that FDA erred in concluding that the drug could be safely distributed even to adults OTC, and we ask FDA to reconsider that decision. If it does not reconsider that decision, the Agency should state what standards it uses to evaluate when label comprehension failure becomes so great that OTC sale is not supportable.

[41] *See* Not Approvable Letter, Lester M. Crawford, DVM, Ph.D., Commissioner, FDA, to Duramed Research, Inc. (Auguust 26, 2005), referencing Sponsor's Research Submission of July 21, 2004.

CONCLUSION

There can be no legal or scientific doubt that Plan B is unsafe for women under age 16 as an OTC product, since the Sponsor's July 21, 2004 submission admits this explicitly. Since the Plan B label comprehension study, actual use study, and FDA's safety analysis have not been altered by any new evidence presented by the Sponsor, the Agency must conclude that even on the Sponsor's terms Plan B is not safe for girls under 16 years of age for OTC sale. Furthermore, because FDA lacks the legal authority to approve the simultaneous dual marketing of an active ingredient in the Rx and OTC distribution regimes, Plan B cannot legally be sold as an OTC product to any age group.

Sincerely,

Gary L. Yingling, J.D., M.S. Rebecca L. Dandeker, J.D.

On Behalf Of:

Wendy Wright
Executive Vice President
Concerned Women for America

Joseph L. DeCook, M.D., FACOG
Vice President
American Association of Pro-Life Obstetricians & Gynecologists

Christopher M. Gacek, J.D., Ph.D.
Senior Fellow for Regulatory Affairs
Family Research Council

David Stevens, M.D., M.A. (Ethics)
Executive Director
Christian Medical and Dental Associations