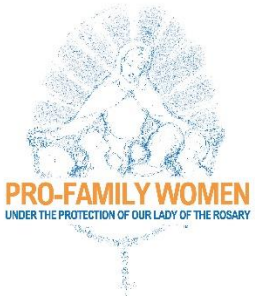

May 6, 2023

U.S. Food and Drug Administration
Washington, D.C.

RE: **FDA-2022-N-1959**. "Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments."

Dear U.S. Food and Drug Administration:

Pro-Family Women respectfully submits these comments in opposition to the proposal to allow over-the-counter nonprescription access to the Opill progestin-only contraceptive pill, especially the potential allowing of access to minors without parental consent. If the FDA approves the application, it will be the first time in America that women will purchase a daily oral contraceptive pill over the counter, without first getting a prescription from a health care provider.

Over-the-counter access to the progestin-only contraceptive pill presents an infringement on the rights of parents (assuming that minors are granted access), the potential of serious health risks, unexpected pregnancy, and an overall detrimental impact on the flourishing of women and minor girls.

Parental Rights and "Over-the-Counter" Access for Minor Girls

A key issue is whether the FDA will allow minor girls over-the-counter access to Opill without their parents' permission. The clinical trial[1] conducted for purposes of this application included 200 adolescent girls, ages 12-17.[2] Sixty percent of the adolescents were using no method of birth control prior to enrolling in the clinical trial.[3]

If an adolescent has not used birth control, it would mean that their first exposure to a birth control pill, with all of its potential side effects and strict criteria for proper use to avoid pregnancy, would be by picking up a package of pills off the store shelf.

What exactly is meant by "over-the-counter access?" One study described it this way to its participants: "With 'over-the-counter' access, birth control pills would be available on the shelf at a pharmacy or grocery store just like cough medicine or some allergy pills. You would not need a prescription from a doctor or nurse. You would not need to talk to anyone about buying birth control pills (not a doctor, pharmacist, or parent) unless you wanted to."[4]

Parents should always be involved in their minor daughter's medical care, especially when a medication presents potentially serious side effects, which is the case with a progestin-only contraceptive. Research has shown that one of the most serious side-effects of a progestin-only contraceptive for adolescent girls is depression and suicide. A 2016 Danish study, *Association of Hormonal Contraception With Depression*,[5] found evidence that "[u]se of hormonal contraception, especially among adolescents, was associated with subsequent use of antidepressants and a first diagnosis of depression, suggesting depression as a potential adverse effect of hormonal contraceptive use." The study found that adolescent girls using a progestin-only contraceptive pill were twice as likely to be prescribed an antidepressant than girls who were nonusers. This was a large-scale study involving over a million Danish women.

Two years later, four of the same researchers produced a study which focused on suicide, *Association of Hormonal Contraception with Suicide Attempts and Suicide*.[6] This study involved close to half a million women and concluded that "[u]se of hormonal contraception was positively associated with subsequent suicide attempt and suicide. Adolescent women experienced the highest relative risk." With respect to a progestin-only contraceptive, the study found that "[u]se of all types of oral progestin-only products was also positively associated with the risk of suicide attempt."

If parents are unaware that their daughter has begun to use this hormonal contraception, they won't be able to connect their child's use of this new drug to any new symptoms of depression, suicidal thoughts, or other potential side effects (see discussion below regarding other side effects).

Likewise, without a health care provider to monitor the young girl's use of the contraceptive, there will be no monitoring for an ectopic pregnancy or sexually transmitted disease (which left untreated can lead to infertility).

Some people may argue that the benefit of preventing teen pregnancy outweighs the risk of side effects, and that allowing adolescents access to over-the-counter contraceptives will further reduce teen pregnancy. But Professor Helen Alvare, a preeminent scholar in family law, has noted that there is a "body of research showing that while declines in teen pregnancies may occur after contraception is rendered more accessible to teens who were *already* sexually active but not using it, with respect to teens who were *not* sexually active, increased access to contraception is associated with the normalization of nonmarital sex and an increase in teen sexual behaviors leading to *more* teen pregnancies and abortions overall."[7]

A study conducted by Professor Peter Arcidiacono of Duke University revealed that increased access to contraception decreased teen pregnancy in the short term, but increased it in the long term due to the increased rate of sexual activity.[8]

The U.S. Supreme Court has identified three reasons why the constitutional rights of children are not equal to that of adults: "the peculiar vulnerability of children; their inability to make critical decisions in an informed, mature manner; and the importance of the parental role in child rearing." *Bellotti v. Baird*, 443 U.S. 622, 634 (1979). The vulnerability of children is especially present in this instance where they are expected to read and follow very strict criteria for the proper use of this progestin-only contraceptive or else increase the risk of pregnancy (see discussion below). Moreover, since this contraceptive will be available to them over-the-counter, they need not be counseled on its proper use or screened for contraindications, as would be the case if they were required to first obtain a prescription. Screening and counseling are two of the very reasons why prescriptions are often required for medication.

It is particularly in the area of sexuality that parental involvement must be respected. Facilitating sexual promiscuity by minors through access to contraception is in direct opposition to the belief of Christians and many other people of faith that sexual relations are to be reserved for marriage. Some tend to minimize this effect on the parent-child relationship, but premarital sexual activity is of great concern not only because it can lead to pregnancy, but because it is directly related to how one views the human person. A key component of the Christian faith is its view of the human person (which encompasses the human body). Namely, that human beings are different from any other species because a person is created in the very image of God, with a soul that lives on throughout eternity. That is why the human person (and the human body) is deserving of respect and dignity.

America's Women and "Over-the-Counter" Access

At the outset, it is important to point out that the vast majority of American women using oral contraceptive pills do not use progestin-only contraceptive pills. It is estimated that only 4%[9] of American women using an oral contraceptive pill use a progestin-only pill. Therefore, if this proposal to provide over-the-counter access to the Opill progestin-only pill goes into effect, many of America's women and young girls will be introduced to a new contraceptive method that they literally just take off the store shelf without any prior counseling or advice from a medical provider.

Health Risks: Contraindications and Potential Side-Effects

Unlike other over-the-counter drugs that are meant to provide temporary relief of symptoms, contraception is meant to be used by a woman for decades. It is hard to imagine any set of documents or protocols that could replace sitting down with a medical provider to learn about the side-effects[10] and contraindications for a drug that a woman may be on for decades.

The "FDA Briefing Document"[11] describes very serious potential health risks that numerous American women could face if they don't understand and deselect themselves from using Opill, specifically:

> The ability of consumers to appropriately deselect is vital because this product has important risks that are different from the risks associated with currently available nonprescription contraceptive methods, including risks associated with a history of breast cancer or other progestin-sensitive cancers, vaginal bleeding of undiagnosed etiology, and use of medications that may interact with norgestrel (drug-drug interactions). Norgestrel use in consumers with a history of breast cancer and other progestin-sensitive cancers may stimulate growth of progesterone-receptor positive tumor cells and can increase the risk of recurrence in breast cancer survivors with a history of progesterone-receptor positive tumors. Abnormal uterine bleeding can be a sign of a medical condition such as malignancy, ectopic pregnancy, thyroid 10 disorders, or bleeding diathesis that requires medical evaluation and treatment. Using medications that interact with norgestrel can result in decreased efficacy of norgestrel or the other medication or both. The consequences of this can be severe, potentially resulting in unintended pregnancy or seizures in an individual with a seizure disorder. Therefore, FDA emphasizes deselection as the critical endpoint in self-selection studies.[12]

Contraindications listed in the **2017** Opill manufacturer information included: "known or suspected carcinoma of the breast, or other progestin-sensitive cancer, now or in the past; undiagnosed abnormal uterine bleeding; hypersensitivity to any component of [Opill]; benign or malignant liver tumors; acute liver disease."[13] After becoming a user, possible side effects listed in the **2017** Opill manufacturer information included ectopic pregnancy, ovarian cysts, and allergies.

Unexpected Pregnancy

The effectiveness of an oral contraceptive is dependent on a woman's diligence in using it properly, as the "typical use" failure rates are often higher than the "perfect use" failure rates. A woman's vigilance in following the manufacturer's instructions is especially important with regards to the Opill progestin-only contraceptive pill, as it must be taken at the same time each day. If she does not do so within a three-hour window, or misses a pill on one or more days, she is instructed to use a backup method of contraception during sex for the next 48 hours. The HRA Pharma Sponsor Briefing Document asserts that Pharma's recent Delayed Pill Intake Study shows that "taking Opill late or missing one pill would be unlikely to result in an increased risk of pregnancy."[14] Nevertheless, the **2017** Opill Patient Information stated "If you take a pill late, and especially if you miss a pill, you are more likely to get pregnant."[15]

Women and girls participating in a trial would likely be much more diligent and motivated to follow the manufacturer's instructions, knowing that they are part of a trial.

Moreover, based on a summary of the trial methodology, participants in the clinical trial were given time and encouraged to read the package labeling:

> In the Self-Selection Phase, participants first reviewed the OTC labeling and were asked to decide whether Opill was right for them to use, per the label, and whether they would purchase it for their own use (referred to as the selection decision). After making their selection decision, participants were asked a series of health and medical history questions to evaluate whether use of Opill was appropriate for them based on the proposed OTC label.[16]

Therefore, unlike a woman who may grab Opill off the shelf in the future, all trial participants had most assuredly carefully read the package information before beginning use.

It remains to be seen what the unintended pregnancy rate will be for American women's over-the-counter use of a progestin-only contraceptive issued without a prescription.

Numerous circumstances can reduce the efficacy of the Opill progestin-only pill, increasing the risk of pregnancy, including the following:

- If the woman experiences vomiting or diarrhea within 4 hours of taking the pill, she is instructed to use a backup method of contraception during sex for 48 hours.[17]

- The proposed Consumer Information Leaflet instructs the reader to talk to her doctor or pharmacist if she is taking any of the following medicines, as **"these may make Opilll less effective:"** "Certain drugs to treat Seizures (barbiturates, carbamazepine, oxcarbazepine, phenytoin, topiramate, primidone); Tuberculosis (rifampin, rifabutin); Pulmonary hypertension (bosentan); HIV/AIDS (efavirenz)." Also listed is "St. John's Wort (or any herbal products containing hypericum perforatum)." (emphasis added).[18]

Without the benefit of having seen a medical provider to learn of these strict requirements for patient compliance, how many women and girls are going to know that they must use a backup contraceptive if they are late in taking the pill that day? Or if they vomit within four hours of taking the pill that day? Without having seen a provider, will she know that St. John's Wort can reduce the effectiveness of Opill?

Today's women are constantly inundated with fine print – when they download new software, when they open a new bottle of cleaner for their eye contacts.

Currently, close to half of women (48%) who experience an unintended pregnancy are already using contraception during the month they become pregnant,[19] and about half of women undergoing an abortion were using contraception.[20] Clearly, American women's typical use of contraceptives, when put into real-world practice, often do not prevent pregnancy.

For the above reasons, as well as the concerns raised in the FDA Briefing Document, Pro-Family Women urges the FDA to reject the application for approval of over-the-counter access to this progestin-only contraceptive pill.

Sincerely,

Susan T. Muskett, J.D., President
Pro-Family Women
P.O. Box 41891
Arlington, VA 22204

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[1] Clinicaltrials.gov. Adherence With Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS). See https://clinicaltrials.gov/ct2/show/NCT04112095

[2] HRA Pharma, Sponsor Briefing Document, Executive Summary, p. 24. Available at https://www.fda.gov/media/167893/download.

[3] Guillard H, Laurora I, Sober S, Karapet A, Brass EP, Glasier A. "Modeling the potential benefit of an over-the-counter progestin-only pill in preventing unintended pregnancies in the U.S." *Contraception*. 2023 117:7–12, Table 1.

[4] Grindlay K, Key K, Zuniga C, Wollum A, Blanchard K, Grossman D (2022) "Interest in continued use after participation in a study of over-the-counter progestin-only pills in the United States," *Women's Health Reports* 2022 3:1, 904-914, DOI: 10.1089/whr.2022.0056.

[5] Skovlund CW, Morch LS, Kessing LV, and Lidegaard O. "Association of Hormonal Contraception with Depression." *JAMA Psychiatry* 2016; 73:1154-1162.

[6] Skovlund CW, Morch LS, Kessing LV, Lange T, and Lidegaard O, "Association of Hormonal Contraception with Suicide Attempts and Suicides," *Am. J. Psychiatry* 2018; 175:4:336-342.

[7] Alvare, Helen M., "No Compelling Interest: The 'Birth Control' Mandate and Religious Freedom" (2013). *Villanova Law Review*, Vol. 58, No. 3, pp. 379-436, 401. Available at SSRN: https://ssrn.com/abstract=2272821.

[8] P. Arcidiacono et al., "Habit Persistence and Teen Sex: Could Increased Access to Contraception Have Unintended Consequences for Teen Pregnancies?" *Journal of Business & Economic Statistics* (2012) Vol. 30, No. 2: 312-25 at https://www.researchgate.net/publication/239793126_Habit_Persistence_and_Teen_Sex_Could_Increased_Access_to_Contraception_Have_Unintended_Consequences_for_Teen_Pregnancies.

[9] Grindlay K, Key K, Zuniga C, Wollum A, Blanchard K, Grossman D (2022) "Interest in continued use after participation in a study of over-the-counter progestin-only pills in the United States," *Women's Health Reports* 3:1, 904-914 DOI: 10.1089/whr.2022.0056.

[10] For information about the side effects of hormonal contraception, in general, including progestin-only contraceptives, see Williams WV, Brind J, Manhart M, Klaus H, Lanfranchi A, Migeon G, Seman E, Ruppersberger L, and Raviele K, "Hormonally Active Contraceptives Part I: Risks Acknowledged and Unacknowledged," *The Linacre Quarterly* 2021, Vol. 88(2) 126-148. Available at https://pubmed.ncbi.nlm.nih.gov/33897046/

[11] https://www.fda.gov/media/167892/download

[12] FDA Briefing Document, Executive Summary, pp. 9-10 at https://www.fda.gov/media/167892/download

[13] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017031s035s036lbl.pdf (Aug, 2017).

[14] HRA Pharma, Sponsor Briefing Document, p. 118. Available at https://www.fda.gov/media/167893/download

[15] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017031s035s036lbl.pdf (Aug, 2017).

[16] HRA Pharma, Sponsor Briefing Document, Executive Summary, pp. 17-18. Available at https://www.fda.gov/media/167893/download

[17] See Proposed Drug Facts Label for OTC Opill, HRA Pharma, Sponsor Briefing Document, p. 50.

[18] HRA Pharma, Sponsor Briefing Document, p. 133.

[19] A. Sundaram et al., "Contraceptive Failure in the United States: Estimates from the 2006-2010 National Survey of Family Growth," 49.1 *Perspectives on Sexual and Reproductive Health* (March 2017) 7-16 at 7.

[20] A. Sundaram et al., "Contraceptive Failure in the United States: Estimates from the 2006-2010 National Survey of Family Growth," 49.1 *Perspectives on Sexual and Reproductive Health* (March 2017) 7-16 at 8-9.