U.S. FOOD & DRUG
ADMINISTRATION

DEC 28 2016

Larry R. Pilot, Esq.
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Re: Docket No. FDA-2014-P-1685

Dear Mr. Pilot:

This letter responds to your citizen petition (Petition) received by the Food and Drug Administration (FDA or Agency) on September 22, 2014. The Petition requests that FDA "authorize acquisition of oral contraceptive drug products" (OCs) through nonprescription (often referred to as over-the-counter or OTC) purchase, eliminating the current prescription-only requirement.[1] You suggest that "FDA authorization for OTC purchase and use" of OCs is appropriate in light of "user awareness . . . coupled with product refinements over time [that] have established that these oral contraceptives, when used as instructed in accordance with approved labeling, are safe and effective for informed purchase and use by women."[2] You also note the nonprescription availability of OCs in other countries and support for making OCs available without a prescription (Rx) by health care organizations and public figures.[3] Further, you indicate that making OCs available for purchase without a prescription would eliminate or reduce certain costs and could lessen "the confusion associated with the implementation of the Affordable Care Act."[4]

For the reasons set forth below, your Petition is denied. We note, however, that we evaluate marketing applications for drug products for nonprescription use on a case-by-case basis. Sponsors interested in exploring the development of nonprescription OCs can meet with us to discuss development of the data necessary to support such applications.

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[1] Petition at 1.

[2] Id. at 1-2.

[3] Id.

[4] Id. at 2. As set forth below, consideration of costs or potential effects on the implementation of the Affordable Care Act (Public Law 111-148) is not among the relevant statutory and regulatory obligations governing the prescription or nonprescription status of oral contraceptive drug products. This response does not address these considerations.

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I. BACKGROUND

The Petition broadly requests nonprescription status for "oral contraceptive drug products."[5] In assessing a request for nonprescription status for OCs, however, it is important to distinguish between the different types of OCs because their safety and efficacy profiles vary substantially. The two major types of OCs marketed today are progestin-only oral contraceptives (progestin-only pills or POPs) and combination oral contraceptives (COCs).

First approved in 1973, POPs do not include an estrogen component.[6] POPs prevent pregnancy through suppressing ovulation (in about 50 percent of users), thickening cervical mucus to prevent sperm penetration, slowing transport of the egg through the fallopian tubes, and altering the endometrium. The correct use of POPs can be challenging because they require near-perfect adherence to the dose schedule. To ensure maximum effectiveness for contraception, POPs must be taken at precise 24-hour intervals on a very regular schedule. Even a delay of dosing by a matter of hours can have an adverse effect on the effectiveness of POPs.

COCs were first approved in 1960 and include both estrogen and a progestin. COCs have a similar mechanism of action to POPs.[7] The estrogen component improves cycle control (menstrual and breakthrough bleeding) and may contribute somewhat to ovulation suppression. A number of COC products are currently marketed. Different products vary in estrogen dose, specific progestin, and dosing regimen (including multiphasic products, in which the hormone doses vary over the course of the 28-day dosing cycle; extended cycle products, in which the hormonal component is taken continuously for 84 days; and variations on the duration of the hormone-free interval).

Both POPs and COCs should not be used by women (i.e., are contraindicated) in a number of clinical situations. The contraindications listed in the labeling for POPs and for COCs are generally similar, except that certain thrombogenic conditions are contraindicated for COCs and not for POPs. This difference in contraindications reflects the venous thromboembolism (VTE) and arterial thrombotic event (ATE) risks for COCs. POPs are not associated with an increased risk of VTEs or with the rarer risk of ATEs.[8, 9]

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[5] Id. at 1.

[6] Micronor (NDA 016954) was approved in January 1973 and is currently manufactured by Janssen Pharmaceuticals. Nor-QD (NDA 017060) was approved on the same date in January 1973, and is currently manufactured by Watson Labs. The reference listed drug for the generic products is Nor-QD in some cases and Micronor in others. Both innovator products contain 350 micrograms (µg) of norethindrone and are administered continuously.

[7] Hatcher RA et al., *Contraceptive Technology*, 20th Revised Edition, 2011, 257-58.

[8] World Health Organization collaborative study of cardiovascular disease and steroid contraception, "Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives: Results of an international, multicenter, case-control study," *Contraception*, 1998, 57:315-24.

VTEs and ATEs are serious risks associated with COC use. The risk of an ATE is of particular concern for older women who smoke, and this risk is reflected in a boxed warning included in COC labeling that states:

> Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See *Contraindications (4)*]

Other important risk information specific to particular OCs is reflected in the labeling for each drug product.

II. LEGAL FRAMEWORK

As set forth in section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353(b)(1)), a prescription drug is:

> a drug intended for use by man which (a) 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; or (b) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug . . . .

Under section 503(b), a drug that is not safe for use except under the supervision of a practitioner licensed by law to administer the drug may be dispensed by prescription only. Drugs that do not meet the description set forth in section 503(b)(1) are nonprescription drugs. To be nonprescription, a particular drug must be determined by FDA to be safe and effective for use without the supervision of a licensed healthcare practitioner.[10]

A. Marketing Nonprescription Drug Products

Under the FD&C Act and FDA's regulations, a drug product can be made available without a prescription pursuant to an approved new drug application (NDA) under section 505 of the FD&C Act (21 U.S.C. 355).[11, 12] As part of such an application, the applicant must submit data

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[9] Lidegaard O et al., "Hormonal contraception and risk of venous thromboembolism: National follow-up study," *Br Med J*, 2009, 339:b2890.

[10] See section 503(b) of the FD&C Act.

[11] See section 505(b) and (j) of the FD&C Act.

to satisfy the applicable statutory and regulatory requirements for approval of a new drug application. An NDA must include adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling,[13] and there must be substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.[14] A drug product may be approved as an Rx or nonprescription product, or may be switched from Rx to nonprescription status, under the applicable legal and regulatory standards. The Rx-to-nonprescription switch process is described in further detail below.

B. Rx-to-Nonprescription Switch

Section 503(b)(3) of the FD&C Act states, "The Secretary may by regulation remove drugs subject to section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health." FDA's regulations in 21 CFR 310.200 identify processes for initiating consideration of an Rx-to-nonprescription switch. That regulation requires that the Commissioner make a twofold finding before removing a drug product with an approved NDA from prescription status. First, the Commissioner must find that "the prescription-dispensing requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use."[15] Second, the Commissioner must find that the drug is "safe and effective for use in self-medication as directed in proposed labeling."[16] A proposal to exempt an Rx drug from Rx-only requirements can be initiated by the drug sponsor submitting an application or by a third party petitioning FDA to initiate rulemaking pursuant to section 503(b)(3) of the FD&C Act.[17]

III. DISCUSSION

In order to initiate a classwide switch of the type requested by your Petition, sufficient data would need to be before the Agency to support the safe and effective OTC use of these products. Your Petition, however, does not present such data. Moreover, the arguments in your Petition are insufficient to persuade FDA to initiate rulemaking for a classwide switch of OCs at this time. Consequently, your Petition is denied.

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[12] We also note that products marketed in compliance with an OTC monograph and all other applicable regulations are not required to have approved NDAs.

[13] See section 505(d)(1) and (2) of the FD&C Act.

[14] See section 505(d)(5) of the FD&C Act.

[15] 21 CFR 310.200(b).

[16] Id.

[17] Id.; 21 U.S.C. 353(b)(3).

FDA will continue to monitor and review new studies and data, as they become available. We are open to evaluating marketing applications for drug products for nonprescription use. Sponsors seeking to make a particular OC available without a prescription can consult with the Agency to discuss a development program for a nonprescription OC drug, including the specific evidence and labeling that would be required.

A. Evidence Needed to Support a Switch

Data to support an Rx-to-nonprescription switch generally come from the following sources: (1) safety and efficacy data in an original NDA for the prescription drug; (2) other available safety and efficacy data;[18] and (3) data from trials conducted to support an NDA supplement for nonprescription use (e.g., actual use, self-selection, and label comprehension studies). Often, consumer studies are required to demonstrate that products can be used safely and effectively in a nonprescription setting. Actual use, self-selection, and label comprehension studies may be required to evaluate proposed OTC drug product labeling and to demonstrate that the drug is safe and effective for use in self-medication, as directed in proposed labeling as required under 21 CFR 310.200(b).[19] More particularly, consumer studies are generally required when, as here, the drugs at issue would be the first in their class to enter the OTC market. The less that is known about the use of a medication without the intervention of a health care professional (HCP), the more data typically will be required.

The current prescription requirement for initiation and continuation of OC use allows prescribers, on a regular basis, to address and reinforce a number of issues related to the safe and effective use of OCs, including:

- The importance of taking the OCs correctly without missing any pills, to minimize the chances of getting pregnant
- The importance of recognizing pre-existing or new medical conditions or personal characteristics, such as age and smoking status, that could preclude the use of OCs for safety reasons
- The understanding that, if taken concomitantly with certain drugs, vitamins, and herbal supplements, OCs have the potential for drug interactions that may affect the safety and effectiveness of the OC or the concomitantly used drug(s)

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[18] Safety assessments typically rely on information presented in an NDA, worldwide databases, FDA's Adverse Event Reporting System (AERS) database (postmarketing), and/or literature.

[19] See, e.g., guidance for industry *Self-Selection Studies for Nonprescription Drug Products*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM272122.pdf; guidance for industry *Label Comprehension Studies for Nonprescription Drug Products*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf.

Currently, patient information is provided for prescription OCs in lengthy patient package inserts (PPIs) and instructions for use (IFUs).[20] Converting the necessary information into appropriate OTC labeling could present challenges. Further, demonstrating that an OC could be used safely and effectively without prescriber oversight would likely require testing to address numerous considerations. For example:

- Consumer ability to recognize warnings and contraindications that would require them to consult with an HCP before use or to avoid use altogether. This consideration is particularly important not only among women who are unfamiliar with OCs and are initiating use for the first time, but also among women seeking to continue OC use who have developed one or more contraindications. This awareness is particularly critical for women over the age of 35 years who smoke, because in this population, COC use is associated with an increased risk of serious cardiovascular events.

- Consumer understanding of when to initiate OC use based on their last menstrual period or postpartum status, and how to adjust the dose if a dose is missed.

- Consumer understanding of serious side effects that may be associated with the use of OCs, including symptoms of those side effects and the need to seek prompt medical attention.

- Consumer understanding of the importance of ongoing routine healthcare with a healthcare provider.

In sum, marketing applications or rulemaking to switch OCs to nonprescription use would likely need to be supported by results from adequately designed consumer studies that address the adequacy of OTC labeling, and whether consumers can adequately self-select and safely and effectively use the particular product(s) being proposed.

B. Your Petition's Arguments and Evidence Supporting a Classwide Switch

At this time, the arguments set forth in your Petition, in view of the evidence available to FDA, are insufficient to persuade the FDA to initiate rulemaking for a classwide switch of OCs. You suggest that "access to the patient package insert" described in 21 CFR 310.501 has increased awareness of the risks and benefits of OCs.[21] According to the Petition, this increased awareness, "coupled with product refinements over time[,] have established that these oral

[20] See 21 CFR 310.501.

[21] Petition at 1.

contraceptives, when used as instructed in accordance with approved labeling, are safe and effective for informed [nonprescription] purchase and use by women."[22]

We agree that there is evidence of broadened user awareness of the risks and benefits of OCs in general since approval of the first OC products. As discussed above, however, an application for nonprescription marketing for an OC product or products would require considerably more specific information than a statement claiming an increased awareness of the risks and benefits of OCs. Moreover, general increased awareness of the risks and benefits of OCs does not support a sweeping approach that would allow nonprescription access to all OC products, because particular OC products have specific, and often complex, benefit-and-risk profiles. Without data from consumer studies, and without proposed OTC labeling, FDA cannot evaluate whether particular products can be used safely and effectively in the nonprescription setting.

The product refinements you reference do not suffice to support a change to the nonprescription status of OCs. The doses of hormones included in COCs have decreased markedly since they were first approved.[23] Early COCs typically contained ≥ 50 µg of ethinyl estradiol (EE); today's products most commonly contain from 20 to 35 µg of EE.[24] There are data demonstrating a reduction in the VTE and ATE risk as the EE dose is reduced from 50 µg to 30-40 µg.[25] However, risk factors for VTE, such as obesity and older age, are now more prevalent in the U.S. population and in the population of COC users. Specifically, the obesity rate has risen considerably since the 1960s,[26] and COC use by older women may be more common now that women are delaying childbearing.

Further, while the benefit-risk profile for COCs is favorable for the prevention of pregnancy,[27] there are a number of contraindications to use, as well as serious, life-threatening adverse

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[22] Id. at 1-2.

[23] The POPs marketed today, however, are identical in progestin component and dose to the POP originally approved in 1973.

[24] Two COCs that contain 50 µg of EE are still marketed, but they are little-used.

[25] Meade TW, Greenberg G, and Thompson SG, "Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30-microgram oestrogen preparations," *Br Med J*, 1980, 280 (6224):1157-61; Lidegaard O, Edstrom B, and Kreiner S, "Oral contraceptives and venous thromboembolism: A five-year national case-control study," *Contraception*, 2002, 65:187-196; Pettiti D et al., "Stroke in users of low-dose oral contraceptives," *N Engl J Med*, 1996, 335:8-15; Lidegaard O and Kreiner S, "Contraceptives and cerebral thrombosis: A five-year national case-control study," *Contraception*, 2002, 65:197-205.

[26] Dietz W, "The response of the US Centers for Disease Control and Prevention to the obesity epidemic," *Ann Rev Pub Health*, 2015, 36:17.1-17.22.

[27] Certain COCs have secondary indications for noncontraceptive actions, including treatment of acne, premenstrual dysphoric disorder (PMDD), and folate supplementation. These indications are secondary, i.e., indicated for additional uses only in women who already need the drug for the primary indication, because of the concern about the benefit-risk ratio for indications other than contraception. Consideration of these COC products for potential

reactions associated with COC use. These risks are discussed extensively in both the prescribing information and the patient labeling for COCs.

In the Petition, you state that "[w]omen in other countries are able to make an informed purchase [of OCs] without the costly and possibly onerous intermediary of a physician and/or third party payers."[28] A recently published online survey of global OC availability targeted to government officials and pharmaceutical and reproductive health specialists found OCs are legally available without a prescription in 46 countries, of which 11 countries require a health screening by a trained HCP when getting the OCs (presumably at the point of purchase), and 35 countries have no health screening requirement.[29] Countries where OCs are legally available without a prescription and without screening include China, India, and Greece.[30] Countries where OCs are legally available without a prescription but which require screening include South Africa and Jamaica.[31] Other countries' allowance of nonprescription access to OCs, however, is not determinative of FDA's judgment regarding whether or not these products can be used safely and effectively in a nonprescription setting. Further, OCs have Rx-only status in many places, including Canada, Japan, and most of Western Europe.[32]

In the Petition, you indicate that "[s]ome health care organizations and public figures" support switching OCs to nonprescription status, including the American Congress of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP).[33] Support by these organizations, however, does not establish that OCs can be used safely and effectively in a nonprescription setting. Moreover, health organizations that are generally supportive of nonprescription access to OCs have highlighted the need for further "studies relevant to over-the-

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nonprescription sale would necessitate additional testing to ensure that women can appropriately self-identify their need for these additional, secondary, indications, as well.

[28] Petition at 2.

[29] Grindlay K, Burns B, and Grossman D, "Prescription requirements and over-the-counter access to oral contraceptives: a global review," *Contraception*, 2013, 88:91-96.

[30] Id.

[31] Id.

[32] Id.

[33] Petition at 2. These organizations have indicated support for nonprescription access to OCs with checklists to assist in self-screening for contraindications. See ACOG, "Over-the-Counter Access to Oral Contraceptives," Committee Opinion #544, December 2012, reaffirmed 2014, available at http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Gynecologic_Practice/Over-the-Counter_Access_to_Oral_Contraceptives ; AAFP, "Over-the-Counter Oral Contraceptives," available at http://www.aafp.org/about/policies/all/otc-oral-contraceptives.html. The Petition does not discuss the use of checklists or otherwise discuss the mechanism of providing OTC access to OCs.

counter access for oral contraceptives" and have encouraged manufacturers of OCs to "submit the required application and supporting evidence."[34]

IV. CONCLUSION

For the reasons stated above, your Petition is denied. FDA will evaluate applications for OC products for nonprescription use on a case-by-case basis should such applications be received, and the Agency is available to meet with interested parties to discuss initiating a program to develop the data necessary to support such an application.

Sincerely,

for Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[34] American Medical Association, Resolution 507 – Support for Over-the-Counter Sales of Oral Contraceptives, http://ocsotc.org/wp-content/uploads/2013/07/AMAresolution5071.pdf, accessed March 11, 2015; see also February 18, 2015, Letter from American Academy of Pediatrics to Dr. Woodcock (stressing the need for "robust adolescent-specific research prior to OTC labeling for this population").